EFFECTS OF AURICULAR ACUPRESSURE ON CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN BREAST CANCER PATIENTS: A PRELIMINARY RANDOMIZED CONTROLLED TRIAL

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TAN JINGYU

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

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CERTIFICATE OF ORIGINALITY

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TAN JINGYU (Name of student)

ABSTRACT

Background

Chemotherapy-induced nausea and vomiting (CINV) is regarded as one of the most upsetting and frequently seen adverse reactions during antineoplastic therapies. Given the fact that using antiemetic medications alone cannot completely manage CINV, different non-pharmacological treatments have therefore been utilized in research and practice to be used in combination with conventional antiemetics to deal with nausea and vomiting during cancer chemotherapy. Among these treatments, auricular therapy (AT) is a promising candidate but relevant research evidence is scarce at present.

Aim and objectives

The aim of this study was to evaluate the feasibility of an evidence-based AT treatment protocol for CINV management in female breast cancer patients receiving chemotherapy and preliminarily examine the effects of AT on CINV and quality of life (QoL) via a pilot randomized controlled trial (RCT). The study objectives were: **(1)** to develop an evidence-based AT treatment protocol for CINV management; **(2)** to pilot the methodological procedures of the RCT; **(3)** to determine the eligibility rate, recruitment rate, retention rate, and attrition rate during the pilot RCT subject recruitment and follow-up process; **(4)** to determine the feasibility and acceptability of the study questionnaires and the AT treatment protocol administered to the participants; **(5)** to identify potential adverse events associated with AT; **(6)** to preliminarily examine the effects of AT on CINV and QoL; **(7)** to explore the participants' experiences of participating in the pilot RCT and receiving the AT treatment; and **(8)** to refine the study protocol for a future multicenter large-scale RCT to examine the definite effects of AT on CINV and QoL in female breast cancer patients.

Methods

The *Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions* was employed to guide the research design. An evidence-based AT treatment protocol was developed first based on several recent systematic reviews, relevant AT theories and handbooks, the Chinese standard ear acupoint chart, and characteristics of the CINV symptoms. The AT treatment protocol was then evaluated by a group of experts to determine its content validity. A

pilot RCT was utilized afterward. A total of 114 female breast cancer patients scheduled to be treated with the first cycle of chemotherapy were recruited from three medical centers in Fuzhou and were randomly assigned to the true AT group, the sham AT group, or the standard care group. The participants in the true AT group received a five-day true AT plus standard antiemetic treatment and care, the participants in the sham AT group received a five-day sham AT plus standard antiemetic treatment and care, and the participants in the standard care group received standard antiemetic treatment and care only. The MASCC Antiemesis Tool (MAT) was employed to measure CINV. The Functional Assessment of Cancer Therapy-Breast (FACT-B) was utilized to measure QoL. The likelihood of causality between AT and the reported adverse events was assessed using the *WHO-Uppsala Monitoring Centre (UMC) System for Standardized Case Causality Assessment*. In addition, anticipatory CINV was also evaluated using the Index of Nausea, Vomiting, and Retching (INVR). After completing the RCT, semi-structured interviews were conducted to explore the participants' experiences of participating in the pilot trial and receiving the AT treatment.

Results

A total of 114 patients were recruited to participate in the pilot RCT and 110 of them completed the outcome assessment (completion rate: 96.5%). Acceptability of the study questionnaires was adequate, with missing values identified in only a few FACT-B questionnaire items. The AT treatment protocol was found to be feasible for use, as the majority of participants (80.3%) from the true AT group and the sham AT group followed the study protocol to complete the five-day AT treatment. Adverse events associated with AT, such as minor pain and discomfort, were identified by a few participants but the reactions were generally mild, tolerable, and transient.

The participants in the true AT group and the sham AT group had higher complete response (CR) rates of CINV symptoms than those in the standard care group, with the among-group difference in the CR of acute CINV reaching statistical significance (p=0.03). The occurrence and severity of acute CINV in the true AT group were lower than in the sham AT group, and both the true AT group and the sham AT group reported a lower occurrence and severity of acute CINV than that of the standard care group. Statistically significant among-group differences were identified for the occurrence of acute nausea (p=0.04) and the severity of acute nausea (p=0.001). Delayed CINV

was also lower in the true AT group and the sham AT group than in the standard care group, but no statistically significant differences were found among the groups. The MAT total and domain scores in the true AT group and the sham AT group were all lower than those in the standard care group. Statistically significant differences in the MAT overall total (p=0.004), MAT total nausea (p=0.003), MAT acute CINV (p=0.002), and MAT acute nausea (p=0.001) scores were found among the groups. There were no statistically significant differences in anticipatory CINV and QoL among the groups at post-intervention (follow-up) assessment.

Twenty-seven participants took part in the semi-structured interviews. The interviewees generally viewed that complementary healthcare approaches (CHAs) could be used as convenient and safe adjuvant approaches to conventional medicine. The majority of the interviewees felt that the study questionnaires were easy to understand and the MAT questionnaire accurately recorded their CINV symptoms. Most of the interviewees from the true AT group and the sham AT group strictly followed the study protocol to complete the five-day AT treatment, and the majority of the interviewees viewed AT as a safe and convenient approach. Most of the interviewees from the true AT group and the sham AT group perceived that AT produced some beneficial effects in relieving their CINV symptoms, while a few of them believed that AT did not have specific treatment effects for CINV but did provide some "psychological comfort."

Conclusion

The evidence-based AT treatment protocol demonstrated that it is a safe, feasible, and convenient non-pharmacological intervention for use among female breast cancer patients. The use of AT plus standard antiemetic medication and care showed superiority over the use of standard antiemetic medication and care alone in managing acute and delayed CINV, and the antiemetic effects of AT were found to be more profound in alleviating acute CINV symptoms, particularly acute nausea. However, it should be noted that the antiemetic effects of AT were a mixture of specific treatment (true) effects and non-specific treatment (placebo) effects. The preliminary research evidence from this study supports the hypothesis that AT is a safe, convenient, and promising non-pharmacological intervention for alleviating CINV in breast cancer patients undergoing chemotherapy, and future practice is encouraged to utilize AT as a promising complementary treatment approach to assisting

CINV management in cancer patients. A future multicenter large-scale RCT is needed to examine the definite effects of AT on CINV and QoL in cancer patients receiving chemotherapy.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE PH.D STUDY

Refereed journal articles arising from the thesis

1. Tan, J. Y., Suen, L. K. P., & Molassiotis, A. (2016). Psychometric assessment of the Chinese version of the MASCC Antiemesis Tool (MAT) for measuring chemotherapy-induced nausea and vomiting. *Supportive Care in Cancer, 24*(9), 3729-3737.

2. Tan, J. Y., Suen, L. K. P., Wang, T., & Molassiotis, A. (2015). Sham acupressure controls used in randomized controlled trials: A systematic review and critique. *PLoS ONE, 10*(7), e0132989.

3. Tan, J. Y., Molassiotis, A., Wang, T., & Suen, L. K. P. (2014). Adverse events of auricular therapy: A systematic review. *Evidence-Based Complementary and Alternative Medicine,* 2014, Article ID 506758.

4. Tan, J. Y., Molassiotis, A., Wang, T., & Suen, L. K. P. (2014). Current evidence on auricular therapy for chemotherapy-induced nausea and vomiting in cancer patients: A systematic review of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine,* 2014, Article ID 430796.

Refereed journal articles arising from other research trainings during the Ph.D study

1. Tan, J. Y., Molassiotis, A., Lloyd-Williams, M., & Yorke, J. (2017). Burden, emotional distress and quality of life among informal caregivers of lung cancer patients: An exploratory study. *European Journal of Cancer Care,* e12691. https://doi.org/10.1111/ecc.12691 (In Press).

2. Tan, J. Y., Yorke, J., Harle, A., Smith, J., Blackhall, F., Pilling, M., & Molassiotis, A. (2017). Assessment of breathlessness in lung cancer: Psychometric properties of the Dyspnea-12 questionnaire. *Journal of Pain and Symptom Management, 53*(2), 208-215.

3. Liu, X. L., Tan, J. Y., Molassiotis, A., Suen, L. K. P., & Shi, Y. (2015). Acupuncture-point stimulation for postoperative pain control: A systematic review and meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine,* 2015, Article ID 657809.

4. Molassiotis, A., Bailey, C., Caress, A., & Tan, J. Y. (2015). Interventions for cough in cancer. *Cochrane Database of Systematic Reviews, 5*, Article No. CD007881.

Conference and research forum presentations

1. Tan, J. Y. (2017). Effects of auricular acupressure on chemotherapy-induced nausea and vomiting in breast cancer patients: A preliminary randomized controlled trial [Abstract and Oral Presentation]. Bloomberg Emerging Nurse Scholars Forum (May 8–9, 2017), University of Toronto, Toronto, ON, CANADA.
2. Tan, J. Y., Suen, L. K. P., & Molassiotis, A. (2016). Validation of the Chinese version of the MASCC Antiemesis Tool [Abstract and Oral Presentation]. The 19th East Asian Forum of Nursing Scholars (March 14–15, 2016), Chiba, JAPAN.
3. Tan, J. Y., Molassiotis, A., Wang, T., & Suen, L. K. P. (2015). Auricular therapy for chemotherapy-induced nausea and vomiting in cancer patients: Current evidence and directions for future research and practice [Abstract and Oral Presentation]. PhD Student Research Forum (July 9, 2015), School of Nursing, The Hong Kong Polytechnic University, Kowloon, HONG KONG.

Institutional presentations

1. Tan, J. Y. Psychometric assessment of the Chinese version of the MASCC Antiemesis Tool (MAT) for measuring chemotherapy-induced nausea and vomiting. School Research Seminar (November 2016), School of Nursing, The Hong Kong Polytechnic University, Kowloon, HONG KONG.
2. Tan, J. Y. Sham acupressure controls used in randomized controlled trials: A critical literature analysis. School Research Seminar (March 2016), School of Nursing, The Hong Kong Polytechnic University, Kowloon, HONG KONG.
3. Tan, J. Y. The effects of auricular acupressure on chemotherapy-induced nausea and vomiting in female breast cancer patients: A pilot and feasibility randomized controlled trial. School Research Seminar (June 2015), School of Nursing, The Hong Kong Polytechnic University, Kowloon, HONG KONG.

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AC	Doxorubicin plus Cyclophosphamide
AE	Adverse Events
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASCO	American Society of Clinical Oncology
AT	Auricular Therapy
BCS	Breast Cancer Subscale
BOCF	Baseline Observation Carried Forward
CAAM	Chinese Association of Acupuncture-Moxibustion
CBM	Chinese Biomedical Literature Database
CENTRAL	Cochrane Central Register of Controlled Trials
CHA	Complementary Health Approach
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CINV	Chemotherapy-induced Nausea and Vomiting
CNKI	China National Knowledge Infrastructure
CNS	Central Nervous System
CNY	Chinese Yuan
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CSBTS	China State Bureau of Technical Supervision
CSO	Chief Scientist Office
CTZ	Chemoreceptor Trigger Zone
CVI	Content Validity Index
EC	Epirubicin plus Cyclophosphamide
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ	EORTC Quality of Life Questionnaire
ESMO	European Society for Medical Oncology

EWB	Emotional Well-Being
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
FLIC	Functional Living Index-Cancer
FLIE	Functional Living Index-Emesis
FWB	Functional Well-Being
GEE	Generalized Estimating Equation
GIT	Gastrointestinal Tract
HADS	Hospital Anxiety and Depression Scale
INVR	Index of Nausea, Vomiting, and Retching
ITT	Intention-to-Treat
LOCF	Last Observation Carried Forward
MANE	Morrow Assessment of Nausea and Emesis
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemesis Tool
MeSH	Medical Subject Headings
MRC	Medical Research Council
MRC CBSU	Medical Research Council Cognition and Brain Sciences Unit
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NETSCC	National Institute for Health Research Evaluation, Trials and Studies Coordinating Center
NK_1	$Neurokinin_1$
NLM	National Library of Medicine
NRS	Numeric Rating Scale
ONS	Oncology Nursing Society
PEP	Putting Evidence into Practice
PMRT	Progressive Muscle Relaxation Technique
PWB	Physical Well-Being

QoL	Quality of Life
RCT	Randomized Controlled Trial
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form (36) Health Survey
SNS	Sympathetic Nervous System
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
SWB	Social/Family Well-Being
TC	Cyclophosphamide plus Docetaxel
TCM	Traditional Chinese Medicine
TOI	Trial Outcome Index
UMC	Uppsala Monitoring Center
VIP	Chinese Scientific Journal Database
WHO	World Health Organization
WMA	World Medical Association
5-HT$_3$	5-hydroxytryptamine$_3$

CHAPTER ONE: INTRODUCTION

1.1 Introduction

This chapter will present a general introduction of this doctoral research project, which includes the background and study procedures of the doctoral project and the organization of the doctoral thesis.

1.2 Background and procedures of the study

Chemotherapy has been viewed as one of the most effective antineoplastic treatment approaches to better treatment outcomes that can help cancer patients extend their life expectancy (Hawkins & Grunberg, 2009). However, despite the positive health outcomes gained from chemotherapy, different undesirable side effects can also be introduced by the use of chemotherapeutic agents (Hawkins & Grunberg, 2009). Among these side effects, one of the most upsetting and frequently seen during antineoplastic therapies is chemotherapy-induced nausea and vomiting (CINV) (Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; Kottschade et al., 2016). In cancer patients with unmanaged nausea and vomiting, their physical and mental functions as well as quality of life (QoL) are gradually deteriorated by these unpleasant gastrointestinal symptoms (Hawkins & Grunberg, 2009). Previous research has documented clear evidence that inadequate management of nausea and emesis during cancer treatment can result in a series of physical impairments, such as dehydration, eating disorders, subnutrition, gastrointestinal bleeding, sleep problems, dyspnea, electrolyte and acid-based disorders, dehisced wounds, physical tiredness, aspiration pneumonia, etc. (Hamadani et al., 2007; Lohr, 2008; Osoba et al., 1997; Schnell, 2003). Meanwhile, uncontrolled CINV and its related physical and psychological impairments can place significant unpleasant impacts on cancer patients' QoL and deteriorate their functional status for maintaining routine activities (Lindley, Hirsch, O'Neill, Transau, Gilbert, & Osterhaus, 1992; Lohr, 2008). Doherty (1999), Hesketh (2000), and the Italian Multicenter Study Group (1999) (as cited in Schnell, 2003) once pointed out that many cancer patients may even withdraw from their routine antineoplastic therapies because of uncontrolled CINV and its related impairments to their physical and psychological functions; thus, their chances of recovery from cancer become minimal.

Different antiemetic medications have been developed and introduced to control CINV, and currently the most frequently used antiemetics in clinical practice include 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and corticosteroids (Aapro, Gralla, Herrstedt, Molassiotis, &

Roila, 2016; Chan & Yeo, 2011; National Comprehensive Cancer Network [NCCN], 2015). However, research and practice evidence has indicated that complete management of CINV is still challenging, regardless of the assistance offered by standard antiemetic medications (American Cancer Society, 2016). Given the fact that the use of antiemetic medications alone is unable to completely manage CINV, different non-pharmacological treatment methods have therefore been utilized in research and practice to be used in combination with conventional antiemetics to deal with nausea and vomiting during cancer chemotherapy. Among these treatment methods, the most frequently adopted approaches include acupuncture, acupressure, relaxation, music therapy, guided imagery, massage, ginger, exercise, and hypnosis (Oncology Nursing Society [ONS], 2017; Tipton, McDaniel, Barbour, & Johnston, 2007). During the past few decades, a great deal of research has been performed to examine the antiemetic effects of non-pharmacological interventions on CINV symptoms, and different levels of evidence have been concluded accordingly (ONS, 2017; Tipton et al., 2007).

Acupuncture-point stimulation techniques, including body acupuncture and acupressure, are currently the most popular non-pharmacological interventions for CINV management. A number of clinical studies have demonstrated a promising role of acupuncture for CINV management (Reindl et al., 2006; Rithirangsriroj, Manchana, & Akkayagorn, 2015; Tas, Uncu, Sendur, Koca, & Zengin, 2014; Zhou et al., 2017), but the research evidence must be interpreted with caution given that different methodological flaws haven been identified in those studies, including a limited sample size and unclear information in terms of randomization and allocation concealment. The antiemetic effects of acupressure on CINV were also explored, with contradictory research findings identified in current literature (Dibble et al., 2007; Genç & Tan, 2015; Molassiotis, Helin et al., 2007; Molassiotis, Russell et al., 2014; Suh, 2012). The effects of acupuncture and acupressure on nausea and vomiting in cancer patients with chemotherapy have been inconclusive, and the latest guideline developed by the ONS listed them at the level of "effectiveness not established" (ONS, 2017). For other non-pharmacological interventions, a large number of clinical studies have also been performed, with contradictory research findings reported, and relevant rigorously-designed high-quality research has been scanty. Meanwhile, it has been emphasized that additional intensive training for cancer patients, healthcare professionals (e.g., oncologists and nurses), and/or caregivers is often required for most of the frequently utilized non-pharmacological

techniques for controlling CINV, such as guided imagery, exercise, hypnosis, and relaxation. Specific equipment and settings are also necessary for the implementation of some approaches, including relaxation, acupuncture, and guided imagery. All of these approaches are deemed to be time- and energy-consuming for cancer patients and their caregivers as well as healthcare professionals. In addition, it should be noted that some approaches have been identified as being associated with potential side reactions, but relevant safety assessment and management have not been fully addressed yet in current research and practice.

Considering all the issues above, more high-quality research is needed in the future to attain more concrete evidence on the use of non-pharmacological approaches to alleviate CINV. At the same time, other non-pharmacological methods with promising antiemetic potential and established safety and convenience should also be introduced to provide new antiemetic options for cancer patients in clinical practice. The optimal candidates may be those approaches with promising potential in antiemetic effects and less burden and harm to cancer patients, of which auricular therapy (AT) could be a good option. As advocated by the World Health Organization (WHO), AT has been viewed as a minimal version of traditional acupuncture in the ear (WHO, 1999), and its underpinning mechanisms have mostly been explained by the homuncular reflex theory and Chinese *zang-fu* organs and meridians theory, which both indicate a close linkage between auricular acupoints and other parts of the body. The stimulation of certain auricular acupoints can produce some beneficial effects on dysfunctions occurring in corresponding parts of the body or internal organs (Abbate, 2004, p. 2; Bai, 1994; Shan, 1996; Suen et al., 2001). AT is convenient and safe for use and it has been used as a popular non-pharmacological treatment approach to managing different health conditions. The beneficial effects of AT have been demonstrated in various types of pain (Murakami, Fox, & Dijkers, 2017; Yeh, Chiang et al., 2014; Zhao, Tan, Wang, & Jin, 2015), sleep disturbance (Chen, 2007; Lan et al., 2015; Lee, Shin, Suen, Park, & Ernst, 2008), constipation (Li, Lee, & Suen, 2014; Shin & Park, 2016), and emotional problems, including anxiety and depression (Gagliardi, Meneghetti, Ceccherelli, Giommi, & Romoli, 2014; Michalek-Sauberer, Gusenleitner, Gleiss, Tepper, & Deusch, 2012; Zhang et al., 2016). From a theoretical perspective, AT can also be used as an effective approach to CINV management, but relevant research evidence is rare at present.

The doctoral researcher therefore conducted a systematic review to identify current research evidence on AT for CINV management (Tan, Molassiotis, Wang, & Suen, 2014a). This systematic review demonstrated positive antiemetic effects of AT among different cancer patients with various chemotherapy combinations; however, the research evidence was deemed to be very low as a number of significant methodological flaws were found in the included studies (Tan et al., 2014a). The systematic review concluded that more rigorously-designed studies are necessary in the future to provide more reliable evidence regarding the antiemetic role of AT in cancer patients. Meanwhile, a number of research gaps were also located in the systematic review as important implications for further research, including poor methodological quality, non-standardized AT intervention protocols, the lack of sham AT comparisons, and unsatisfactory CINV outcome assessments. The doctoral research project was therefore designed to address these research gaps.

The overall aim of this doctoral research project was to test the feasibility of a standard AT protocol for managing CINV in female breast cancer patients with moderately to highly emetogenic chemotherapy and to preliminarily explore the effects of AT on patients' CINV and QoL through a three-parallel-arm sham-AT-controlled randomized pilot trial. The *Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions* was employed to guide the research design to achieve the study's aim. An evidence-based AT treatment protocol was developed first based on several recent systematic reviews, relevant AT theories and handbooks, the widely-accepted Chinese standard ear acupoint chart, and the characteristics of cancer symptoms. The AT treatment protocol was then evaluated by a group of experts specialized in AT and Traditional Chinese Medicine (TCM) to determine its content validity. A preliminary randomized controlled trial (RCT) with a pilot study design was utilized afterward to examine the feasibility of the AT treatment protocol, pilot the methodological procedures of the RCT, and preliminarily examine the effects of AT on patients' CINV symptoms and QoL. Following the completion of the pilot RCT, semi-structured interviews were conducted to explore the participants' experience of participating in the pilot RCT and receiving the AT treatment. In addition, as the Chinese version of the CINV outcome assessment tool (Multinational Association of Supportive Care in Cancer [MASCC] Antiemesis Tool [MAT]) had not been formally validated before the commencement of the doctoral research project, a preparatory study on the psychometric

assessment of the MAT, Chinese version, was also performed and included in this doctoral research project.

1.3 Organization of the thesis

This doctoral thesis consists of eight chapters. This first chapter gave a brief introduction of the doctoral research project. The second and third chapters will detail comprehensive literature reviews on CINV and AT, respectively. In the fourth chapter, the research gaps will be identified through a comprehensive systematic review. Details of the research methodology, including the research aim and objectives, research questions and hypotheses, and research design for different stages of the doctoral research project, will be presented in the fifth chapter. The sixth chapter will describe the preparatory work on the psychometric assessment of the MAT, Chinese version, while the study results of the doctoral research project will be shown in the seventh chapter. The final chapter (Chapter Eight) will present the discussion and conclusion of the doctoral research project.

CHAPTER TWO: LITERATURE REVIEW: CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

2.1 Introduction

This chapter will provide details on a comprehensive literature review, with a focus on CINV. Nine major sections are included in this chapter, and the first five sections (Section 2.2 to Section 2.6) will generally review the definition, classification, mechanism, risk factors, and incidence of CINV, respectively. The impacts of CINV on cancer patients' physical and psychosocial functions and QoL will be presented in Section 2.7, and the current treatments of CINV, including both pharmacological and non-pharmacological approaches, will be introduced in Section 2.8. Available guidelines and recommendations for CINV management, and the limitations of current pharmacological and non-pharmacological approaches to alleviating CINV, will also be described in Section 2.8. A summary of the chapter will be presented in Section 2.9.

2.2 Definition of nausea, vomiting, and CINV

According to the Medical Subject Headings (MeSH) classification proposed by the United States National Library of Medicine (NLM), nausea is defined as "an unpleasant sensation in the stomach usually accompanied by the urge to vomit" (National Library of Medicine [NLM], 2017a), and the frequent causes of nausea include "early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses" (NLM, 2017a). Vomiting is defined by the NLM as "the forcible expulsion of the contents of the stomach through the mouth" (NLM, 2017b), while CINV can generally be referred to as "a broad term used to describe the many types of nausea and vomiting that can occur in patients with cancer" (Rao & Faso, 2012, p. 233).

2.3 Classification of CINV

The classification of CINV is generally based on the time of onset of nausea and vomiting symptoms, and there are three major types of CINV: (1) acute CINV: nausea and emesis that occur within the first 24 hours after receiving chemotherapeutic agents (day 1 of chemotherapy), and the worst symptoms are usually identified five to six hours post-chemotherapy; (2) delayed CINV: nausea and emesis that occur after the first 24 hours of the administration of chemotherapeutic agents, with the most severe episodes emerging at 48 to 72 hours post-chemotherapy; and (3) anticipatory CINV: nausea and vomiting that occur before receiving

current chemotherapy, which is one kind of "conditioned response" triggered by previous emesis experiences associated with antineoplastic therapies or other conditions (American Cancer Society, 2016; Hesketh, 2005; Navari & Aapro, 2016; Rao & Faso, 2012). In addition, there is another type of nausea and vomiting related to chemotherapy called breakthrough/refractory CINV (American Cancer Society, 2016; Navari & Aapro, 2016; Rao & Faso, 2012). Breakthrough/refractory nausea and vomiting happen during chemotherapy regardless of the use of adequate antiemetics, and rescue treatments are necessary to deal with this type of CINV (American Cancer Society, 2016; Navari & Aapro, 2016; Rao & Faso, 2012).

2.4 Mechanism of CINV

Current evidence regarding the pathophysiological mechanisms of CINV is not fully conclusive (Hesketh, 2008). Studies in recent years have highlighted the roles of the emetic center and neurotransmitters in the development of nausea and vomiting during chemotherapy (Girish & Manikandan, 2007; Grunberg & Hesketh, 1993; Hesketh, 2008; Middleton & Lennan, 2011; Navari & Aapro, 2016; Rao & Faso, 2012). CINV responses are now commonly believed to be coordinated by the central emetic center, which can be found in the lateral reticular formation of the medulla (Grunberg & Hesketh, 1993; Middleton & Lennan, 2011; Rao & Faso, 2012). A number of pathways have been recognized that send nerve impulses to the emetic center to introduce gastrointestinal reactions, including the chemoreceptor trigger zone (CTZ), the gastrointestinal tract (GIT), the vestibular nerve system, and the brain stem and cortex (Grunberg & Hesketh, 1993; Middleton & Lennan, 2011; Rao & Faso, 2012).

The CTZ consists of a cluster of neurons that lie in the fourth ventricle of the brain and is mainly responsible for exploring potentially emetic toxins in the cardiovascular system (Grunberg & Hesketh, 1993; Middleton & Lennan, 2011; Rao & Faso, 2012). Neurotransmitters, including 5-hydroxytryptamine$_3$ (5-HT$_3$) and substance P, are the major mediators of the GIT pathway (note: the GIT pathway is also referred to as the peripheral pathway in some literature), which can further bind to their respective receptors (e.g., 5-HT$_3$ receptors and neurokinin$_1$ [NK$_1$] receptors) to evoke nausea and vomiting responses via the emetic center (Hesketh, 2008; Middleton & Lennan, 2011; Rao & Faso, 2012). The vestibular nerve system is mainly related to motion sickness (e.g., travel sickness), while the higher brain stem and cortex are potentially associated

with anticipatory nausea and vomiting (Grunberg & Hesketh, 1993; Middleton & Lennan, 2011; Rao & Faso, 2012).

During antineoplastic treatments, the normal gastrointestinal functions are usually impeded by the chemotherapeutic agents via either direct damage of the local gastrointestinal mucosa or indirect blood-borne actions (Hesketh, 2008). The damaged gastrointestinal mucosa and enterochromaffin cells are subsequently stimulated by the antineoplastic agents to release a variety of neurotransmitters (e.g., 5-HT_3 and NK_1), which can bind to their corresponding receptors to further generate increased nerve impulses to the CTZ and central emetic center, and, finally, evoke a series of gastrointestinal reactions, including nausea and emesis (Girish & Manikandan, 2007; Grunberg & Hesketh, 1993; Hesketh, 2008; Navari & Aapro, 2016). Chemotherapeutic agents can also directly act on the higher brain stem and cortex to evoke emesis (Grunberg & Hesketh, 1993; Hesketh, 2008). **Figure 2.1** below presents the potential pathophysiological mechanism of CINV based on the roles of the emetic center and neurotransmitters:

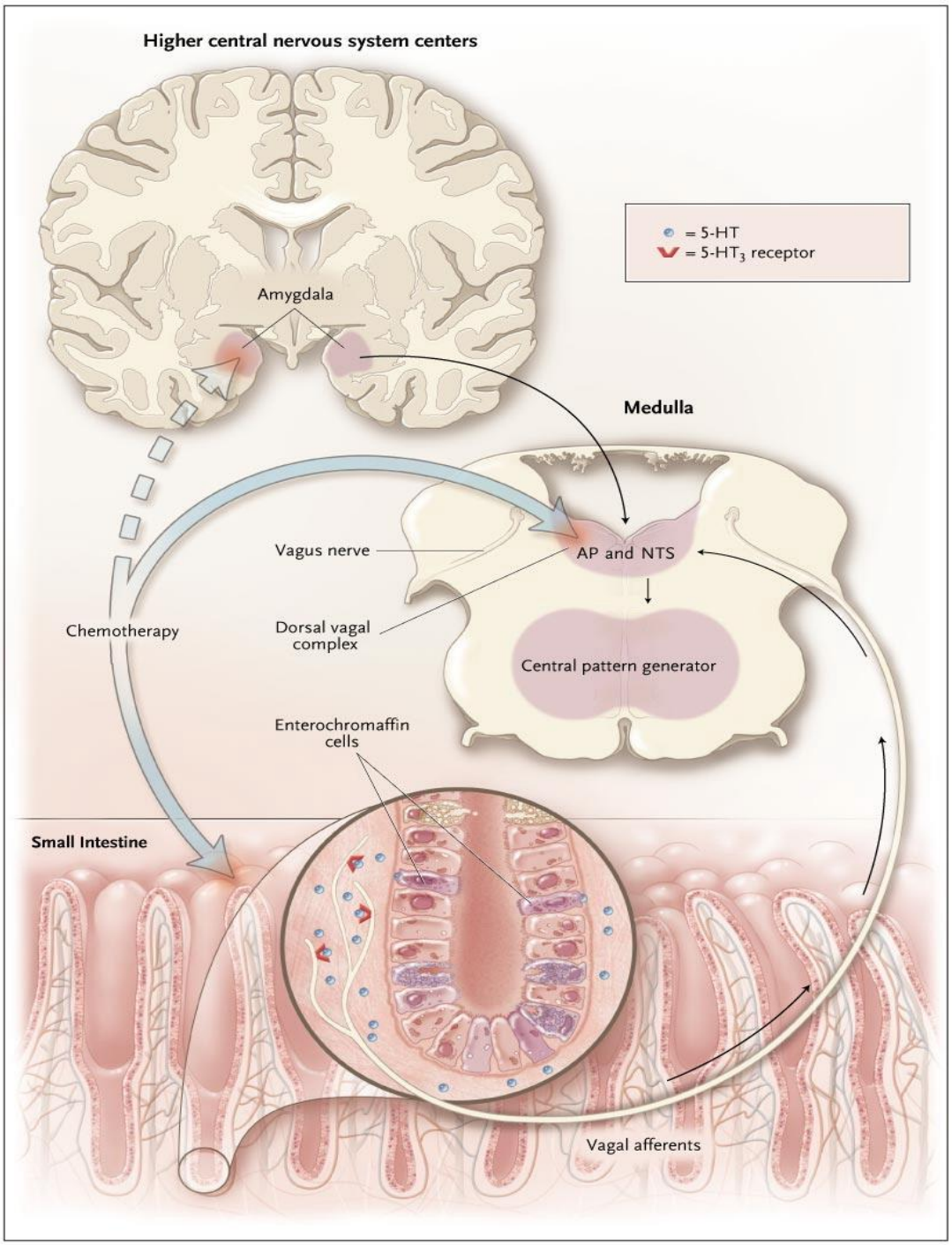


Figure 2.1 Potential mechanism of CINV based on the roles of the emetic center and neurotransmitters

Note: Reproduced with permission from Hesketh, P. J. (2008). Chemotherapy-induced nausea and vomiting. *New England Journal of Medicine*, *358*(23), 2482-2494. Copyright Massachusetts Medical Society.

2.5 Risk factors associated with CINV

Emetogenic potential of the administered antineoplastic treatment protocols and cancer patients' own characteristics are two major aspects in determining the occurrence, frequency, and severity of nausea and emesis during chemotherapy, which can generally be referred to as treatment-related risk factors and patient-related risk factors, respectively, for CINV (Chan & Yeo, 2011; Inrhaoun, Kullmann, Elghissassi, Mrabti, & Errihani, 2012).

Treatment-related risk factors usually include the specific type of cytostatic drugs, dosage and course of the particular antineoplastic agents, duration and approach of administration of the agents, and combinations with other antineoplastic regimens or cancer treatment protocols (American Cancer Society, 2016; Chan & Yeo, 2011; Inrhaoun et al., 2012; Lohr, 2008; Thompson, 2012). According to the latest antiemetic guideline co-developed by the MASCC and the European Society for Medical Oncology (ESMO) (Aapro et al., 2016) and the *Clinical Practice Guideline in Oncology-Antiemesis* recommended by the NCCN (2015), the emetogenic potential of frequently used intravenous and oral antineoplastic drugs in clinical practice can generally be classified into four major categories, as follows: **(1)** high risk: the majority of cancer patients (>90%) receiving antineoplastic treatment would present nausea and emesis if no antiemetics were given; **(2)** moderate risk: more than 30%, but less than 90%, of cancer patients receiving antineoplastic treatment would have nausea and emesis if no antiemetics were provided; **(3)** low risk: around 10% to 30% of cancer patients undergoing antineoplastic therapy would present nausea and emesis if no antiemetics were taken; and **(4)** minimal risk: fewer than 10% of cancer patients receiving antineoplastic treatment would experience nausea and emesis if no antiemetics were given. Among the commonly adopted intravenous cytostatic drugs in cancer treatment, the anthracycline/cyclophosphamide combination, carmustine, cisplatin, cyclophosphamide with a dosage of >1500 mg/m^2, dacarbazine, mechlorethamine, and streptozocin are regarded as having the highest risks for introducing nausea and vomiting (Aapro et al., 2016). With regard to other treatment-related risk factors, higher doses of antineoplastic regiments are believed to be associated with more frequent and severe CINV symptoms, and multiple chemotherapeutic agent combinations, treatment days, and cycles can also make the CINV symptoms worse (American Cancer Society, 2016; Lohr, 2008; Thompson, 2012). **Figures 2.2** to **2.5** below summarize the commonly used

intravenous and oral cytostatic agents based on the categories of different emetogenic potentials as proposed by MASCC/ESMO (Aapro et al., 2016):

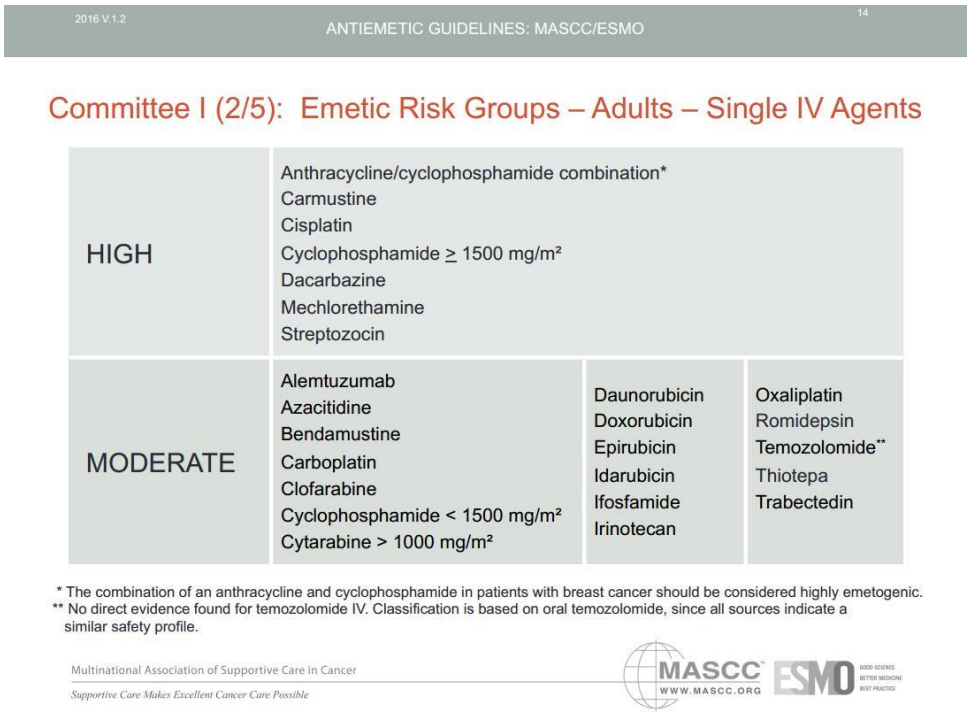


Figure2.2 Emetogenic risks of intravenous chemotherapeutic agents (high and moderate)

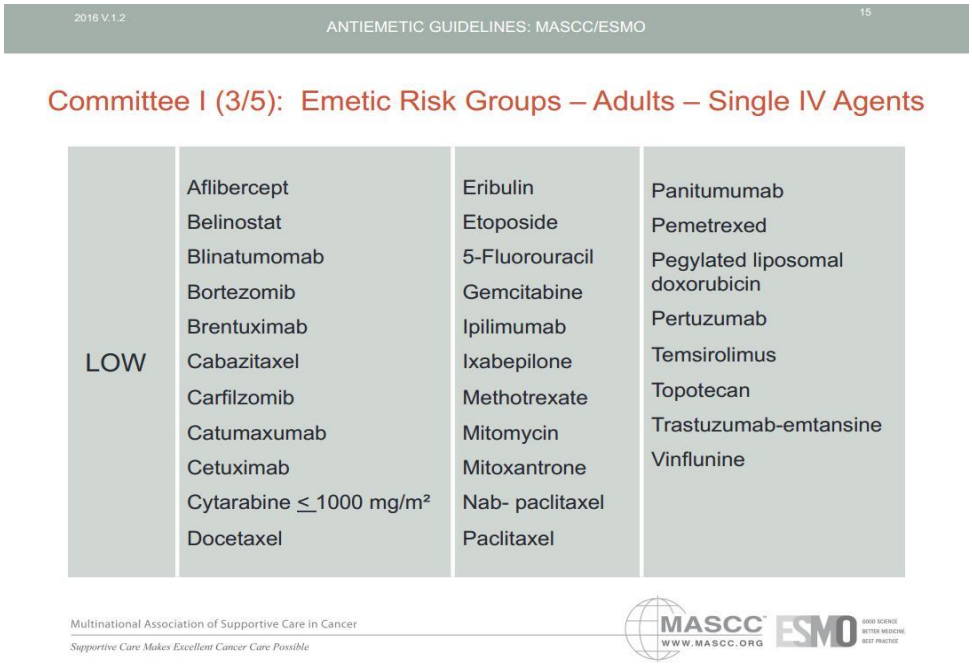


Figure 2.3 Emetogenic risks of intravenous chemotherapeutic agents (low)

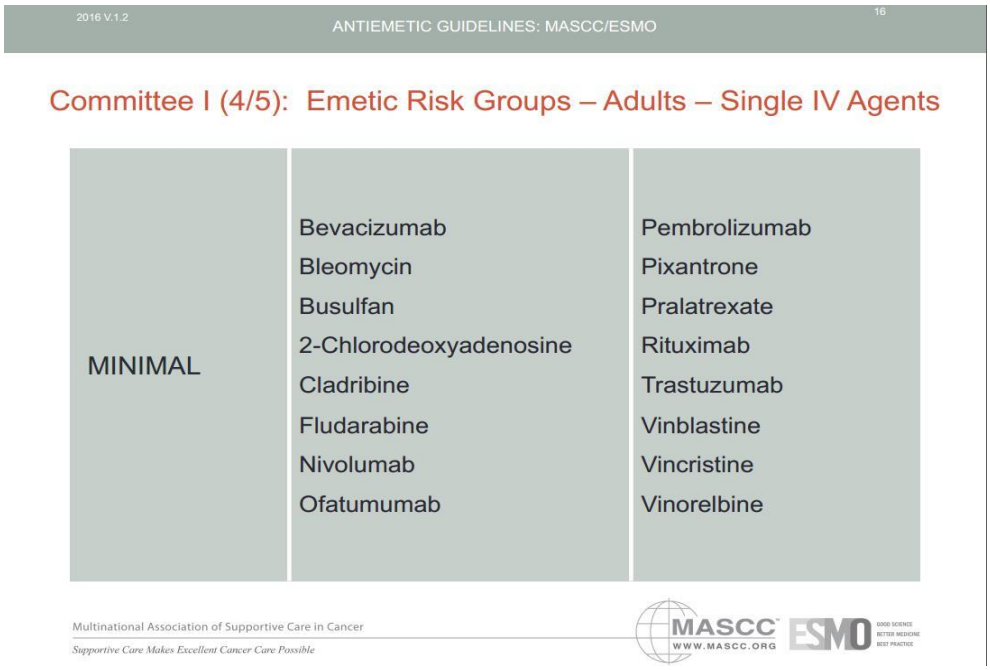


Figure 2.4 Emetogenic risks of intravenous chemotherapeutic agents (minimal)

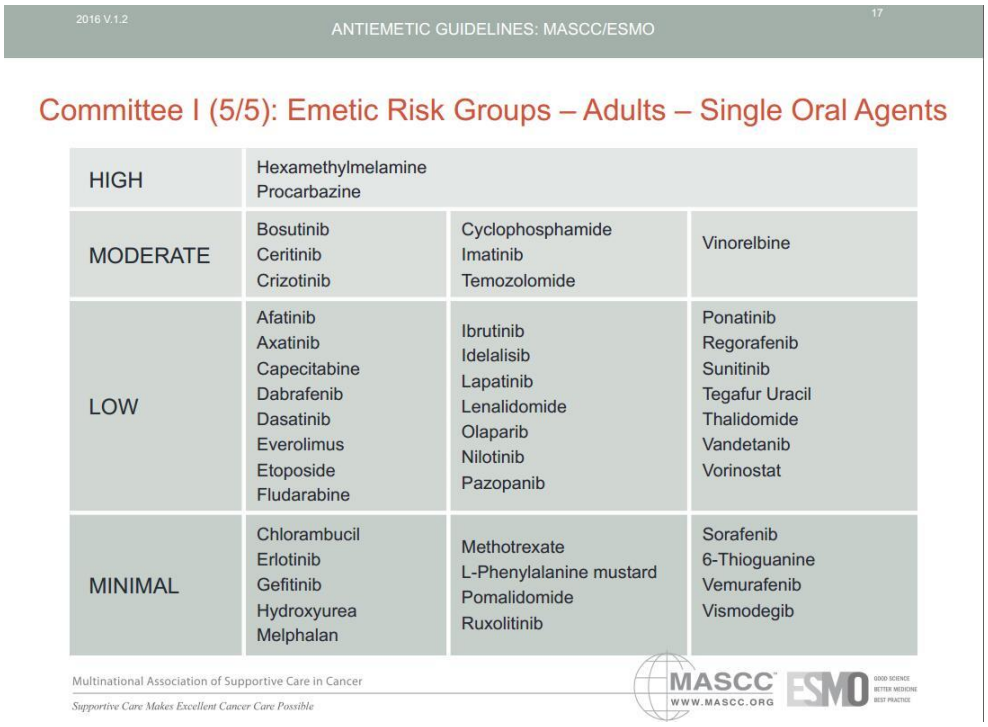


Figure 2.5 Emetogenic risks of oral chemotherapeutic agents (high to minimal)

Note: Figures 2.2 to 2.5 reproduced with the permission of the Multinational Association of Supportive Care in Cancer (MASCC). Source: Aapro, M., Gralla, R. J., Herrstedt, J., Molassiotis, A., & Roila, F. (2016). MASCC/ESMO Antiemetic Guideline 2016. MASCC. Retrieved from http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_2016_v.1.2.pdf. Copyright MASCC.

In terms of patient-related risk factors, cancer patients with a younger age of less than 50 years old, female gender, a history of travel sickness (motion sickness) associated with vestibular system problems, a history of morning sickness associated with pregnancy, psychological distress (e.g., anxiety and depression), less use of alcohol, experience of nausea and vomiting during previous antineoplastic treatments, or inappropriate use of antiemetic medications are more likely to have chemotherapy-associated nausea and emesis than those without such factors (American Cancer Society, 2016; Chan et al., 2015; Chan & Yeo, 2011; Hawkins & Grunberg, 2009; Inrhaoun et al., 2012; Lohr, 2008; Molassiotis, Aapro et al., 2014; Molassiotis et al., 2016; Rha, Park, Song, Lee, & Lee, 2016).

Younger age (<50 years old) has been a well-recognized risk factor contributing to CINV (American Cancer Society, 2016; Chan & Yeo, 2011; Hawkins & Grunberg, 2009; Inrhaoun et al., 2012; Lohr, 2008; Molassiotis, Aapro et al., 2014; Molassiotis, Lee et al., 2016; Rha et al., 2016). A multisite prospective study conducted in eight European countries (N=991) indicated that younger age was a significant and key risk factor for CINV across different chemotherapy cycles (Molassiotis, Aapro et al., 2014). That study also identified a number of new predictors for CINV that were seldom mentioned in previous literature, including the use of antiemetic medications that failed to follow the international antiemetic guidelines/recommendations, the absence of appropriate antiemetic treatment with regard to delayed nausea and vomiting, and unsatisfactory control of emesis during the previous cycles of chemotherapy (Molassiotis, Aapro et al., 2014). Recent reanalysis of the study data above further revealed several predictors for anticipatory CINV, including anxiety and nausea before the administration of chemotherapy and experience of nausea and emesis during the previous cycles of cancer treatment (Molassiotis et al., 2016). Similarly, another longitudinal study across six Asia-Pacific countries showed that anticipatory CINV in the subsequent chemotherapy cycles were closely associated with CINV experiences during the previous chemotherapy cycles (Chan et al., 2015).

Psychological problems such as anxiety and depression have been suggested as suspicious factors for introducing CINV (American Cancer Society, 2016; Chan et al., 2015; Lohr, 2008; Molassiotis, et al., 2016). Both longitudinal studies conducted by Chan et al. (2015) and Molassiotis et al. (2016) identified that the experience of anxiety in previous chemotherapy was

more likely to contribute to anticipatory CINV in the subsequent cycles of antineoplastic treatment. **Figure 2.6** below summarizes the commonly indentified treatment- and patient-related risk factors for CINV:

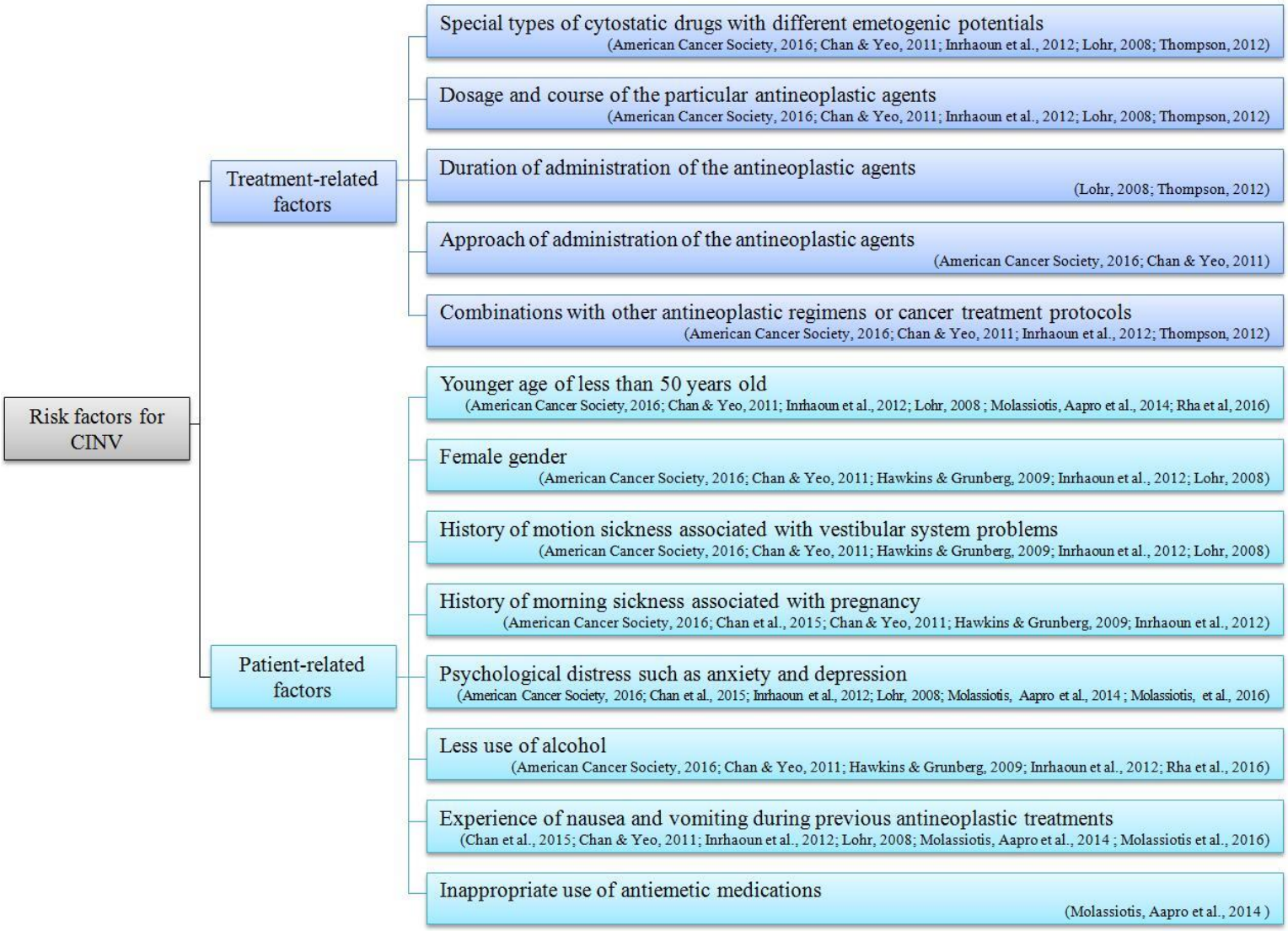


Figure 2.6 Treatment- and patient-related risk factors for CINV

2.6 Incidence of CINV

The incidence of CINV among cancer patients is generally influenced by different treatment- and patient-related factors, as described in Section 2.5. As highlighted in the study reported by Gralla et al. in the 1980s (as cited in Hawkins & Grunberg, 2009), in the early years when there was a lack of appropriate antiemetic treatments for cancer patients undergoing chemotherapy, patients who received chemotherapeutic drugs with highly emetogenic risk (e.g., cisplatin) could vomit up to 25 times during the first day of treatment (acute CINV phase). The introduction of effective antiemetics such as 5-HT_3 and NK_1 receptor antagonists in the past few decades has offered great assistance in the alleviation of CINV (Hawkins & Grunberg, 2009; Lohr, 2008; Olver, 2015; Thompson, 2012). However, complete control of CINV symptoms is still problematic in current practice and research; as stated by the American Cancer Society, "no one drug can prevent or control chemo-related nausea and vomiting 100% of the time" (American Cancer Society, 2016, p. 5).

A number of the latest prospective observational studies (sample size ranged from 240 to 991) revealed that in cancer patients undergoing chemotherapy with moderately to highly emetogenic potential, the incidence of acute vomiting ranged from 8.3% to 24.5% and the incidence of delayed vomiting was reported to be 16.5% to 29.5% (Escobar et al., 2015; Hsieh et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Rha et al., 2016). For nausea during chemotherapy, the incidence of acute nausea ranged from 23.3% to 46.0%, while it was 35.0% to 82.7% for delayed nausea (Escobar et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Rha et al., 2016). Delayed nausea and vomiting were more frequently reported than acute symptoms, and it is evident that nausea is much more difficult to control with current antiemetic therapies than vomiting, as the incidence of nausea was found to be twice that of vomiting during either the acute phase or the delayed phase of CINV (Escobar et al., 2015; Hsieh et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Olver, 2015; Rha et al., 2016). With regard to anticipatory CINV, a recent observational study conducted by Chan et al. (2015) (N=598) reported fewer cases of anticipatory vomiting among cancer patients undergoing moderately to highly emetogenic chemotherapy, with the incidence of 1.5% prior to the second chemotherapy cycle and 2.3% prior to the third cycle, while the incidence of anticipatory nausea was relatively higher, as it increased from 9.1% prior to chemotherapy cycle 1 to 17.6% prior to

cycle 3. Similar findings were also reported by Molassiotis et al. (2016) (N=991), and the incidence of anticipatory nausea was 8.3% before chemotherapy cycle 1, and then increased to 10.1% before cycle 2 and 13.8% before cycle 3.

2.7 Impact of CINV

Uncontrolled nausea and vomiting during chemotherapy can produce considerable negative impacts on cancer patients' physical and psychosocial well-being, increase their economic burden, and impede their QoL (Hawkins & Grunberg, 2009).

The most direct negative impacts of CINV on patients' physical functions might be medical complications and secondary health problems induced by uncontrolled gastrointestinal symptoms during chemotherapy. Previous literature has clearly shown that inadequate CINV management can lead to a variety of health disorders, including anorexia, malnutrition, dehydration, Mallory-Weiss tears of the esophagus, gastrointestinal hemorrhage, sleep disturbance, electrolyte and acid-based disorders, dehisced wounds, breathlessness, fatigue, aspiration pneumonia, physical deterioration, etc. (Hamadani et al., 2007; Lohr, 2008; Osoba et al., 1997; Schnell, 2003). These CINV-associated health problems may prolong patients' length of stay in the hospital, lay heavy burdens on healthcare utilization, and significantly increase healthcare costs (Schnell, 2003). As reported by Shin, Xu, and Elting (2007) (also cited in Hawkins & Grunberg, 2009), healthcare costs related to the management of uncontrolled post-chemotherapy nausea and emesis were estimated at around 1,300 USD per month, which places a great economic burden on cancer patients undergoing chemotherapy. For working-age cancer patients, their work abilities can also be seriously affected by CINV (Hawkins & Grunberg, 2009), which may partially be attributed to the physical distress caused by inadequately controlled CINV. According to Shin et al. (2007) (also cited in Hawkins & Grunberg, 2009), the average days in a month for work loss was 6.23 for cancer patients with unsatisfactorily controlled CINV, which is nearly twice as high as that for patients with well-managed nausea and vomiting (3.61 days). Poorly controlled CINV may also create some negative effects on patients' psychological well-being (Farrell, Brearley, Pilling, & Molassiotis, 2013; Lohr, 2008). A prospective observational study (N=104) indicated that patients' depressed moods became worse across multiple chemotherapy cycles, with the incidence

of clinical depression increasing from 1.9% at the baseline to 7.3% after the first treatment cycle, and 14.1% after the second treatment cycle (Farrell et al., 2013).

CINV and its associated physical distress can further generate considerable negative impacts on patients' QoL, which impede patients' maintenance of daily physical activities and functions, including enjoying leisure time (e.g., travelling and having meals) with friends/family members, personal care (e.g., dressing and washing), cleaning and housework, going to work, etc. (Lindley et al., 1992; Lohr, 2008). Prospective observational studies (Cohen et al., 2007; Farrell et al., 2013) have shown that CINV can deteriorate cancer patients' QoL as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) or the Functional Living Index-Emesis (FLIE), and these findings were further verified by the most recent systematic review in terms of the impacts of CINV on QoL and healthcare utilization (Sommariva, Pongiglione, & Tarricone, 2016). There is evidence that the experience of nausea and emesis in previous cycles of chemotherapy can further deteriorate patients' QoL in the following treatment cycles (Cohen et al., 2007). Another multicenter prospective observational study (N=160) demonstrated that the duration of nausea and vomiting during chemotherapy was closely associated with patients' QoL, with longer experience of CINV contributing to more severe effects on QoL (as measured by the FLIE) (Fernandez-Ortega et al., 2012). The study reported by Fernandez-Ortega et al. (2012), together with another multicenter and multinational observational study (N=298) (Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006), also indicated a more profound impact of nausea on QoL compared with vomiting. In addition, antineoplastic agents with different emetogenic potentials may contribute to different levels of QoL impairment among cancer patients, as reported by Bloechl-Daum et al. (2006). Patients receiving cytostatic drugs with highly emetogenic potential suffered more from an adverse impact on their daily functions than those receiving moderately emetogenic chemotherapy (Bloechl-Daum et al., 2006). As emphasized by Doherty (1999), Hesketh (2000) and the Italian Multicenter Study Group (1999) (cited in Schnell, 2003), because of the physical and psychosocial distress and the deterioration of QoL resulting from uncontrolled gastrointestinal disorders during chemotherapy, some cancer patients may even give up further antineoplastic treatment, which significantly reduces their chance of recovery.

2.8 Current treatment for CINV

2.8.1 Pharmacological approaches to CINV management

The use of antiemetic medications following international antiemetic guidelines is currently the most effective approach to CINV prophylaxis and management (Aapro et al., 2016; NCCN, 2015; Tipton et al., 2007). The most recommended antiemetic agents for controlling nausea and emesis at present include 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and corticosteroids (Aapro et al., 2016; Chan & Yeo, 2011; NCCN, 2015). In addition, some other types of antiemetic agents have also been used in combination with the above medications, including dopamine receptor antagonists and cannabinoids (Chan & Yeo, 2011; Hawkins & Grunberg, 2009; NCCN, 2015).

2.8.1.1 5-HT_3 receptor antagonists

The most effective antiemetic medications used for the management of acute CINV are 5-HT_3 receptor antagonists (Aapro et al., 2016; Jordan, Gralla, Jahn, & Molassiotis, 2014; NCCN, 2015). Several types of 5-HT_3 receptor antagonists are currently available on the market, which include ondansetron, granisetron, dolasetron, tropisetron, and palonosetron (Aapro et al., 2016; Jordan et al., 2014; NCCN, 2015). The efficacy of the first four 5-HT_3 receptor antagonists for CINV management was investigated in a meta-analysis, and they were found to be generally equivalent, with the only exception that granisetron was somewhat superior to tropisetron (Jordan et al., 2007). Palonosetron is a newly-introduced 5-HT_3 receptor antagonist in recent years, which has a relatively longer half-life ($t_{1/2}$) period (approximately 40 hours) than other 5-HT_3 receptor antagonists (around three to nine hours), and it has also been found to be effective in delayed nausea and emesis (Lohr, 2008; NCCN, 2015). Several rigorously-designed RCTs have proved that palonosetron is more effective in the prophylaxis of vomiting (particularly delayed symptoms) among cancer patients undergoing moderately to highly emetogenic chemotherapy (NCCN, 2015). Either oral or intravenous therapy could be considered when administrating 5-HT_3 receptor antagonists given the equivalent treatment effects of the two routes (Lohr, 2008; NCCN, 2015). However, the intravenous approach should be considered first if the cancer patient was exposed to a high risk of nausea and vomiting or had some difficulties in taking in or digesting the prescribed medications (NCCN, 2015). 5-HT_3 receptor antagonists are usually tolerated well and

headache is the frequently identified side effect (Lohr, 2008; NCCN, 2015; Wickham, 2012). Other commonly reported side effects associated with 5-HT_3 receptor antagonists include constipation, fatigue, fever, diarrhea, and taste changes (Lohr, 2008; Wickham, 2012).

2.8.1.2 NK_1 receptor antagonists

Aprepitant (the intravenous formulation is fosaprepitant) is currently the most commonly used NK_1 receptor antagonist for dealing with both acute and delayed nausea and emesis (Jordan et al., 2014; Lohr, 2008). The mechanism of aprepitant for CINV management selectively inhibits the emetic-center-related substance P-NK_1 (SP-NK_1) receptor system (Jordan et al., 2014; Lohr, 2008; NCCN, 2015). The antiemetic effects of aprepitant on nausea and emesis in patients with moderately to highly emetogenic antineoplastic agents were strongly supported by several rigorously-designed large-scale RCTs, and the antiemetic effects were found to be larger when aprepitant was used in combination with other standard antiemetics (5-HT_3 receptor antagonists plus dexamethasone) (Hesketh et al., 2003; NCCN, 2015; Poli-Bigelli et al., 2003; Warr et al., 2005). The safety of aprepitant was also well documented in the RCTs above, with some minor side effects reported, including hiccups, dyspepsia, and asthenia/fatigue (Hesketh et al., 2003; Poli-Bigelli et al., 2003; Schmoll et al., 2006; Warr et al., 2005). In addition to aprepitant, other types of NK_1 receptor antagonists, including rolapitant and netupitant, have also been introduced for use in CINV management according to the evidence of several of the latest RCTs and comprehensive reviews (Aapro et al., 2014; Chasen & Rapoport, 2016; Hesketh et al., 2014; Rapoport et al., 2016).

2.8.1.3 Corticosteroids

Corticosteroids also have some antiemetic effects, and dexamethasone is the most frequently adopted agent for CINV management (Chan & Yeo, 2011). Although not a formal type of antiemetic medication, dexamethasone is usually used in combination with other antiemetic agents (e.g., 5-HT_3 receptor antagonists and NK_1 receptor antagonists) to control CINV symptoms at both acute and delayed phases, and the underpinning antiemetic mechanism may be partially attributed to its anti-inflammatory potential (Chan & Yeo, 2011; Jordan et al., 2014; Lohr, 2008). Dexamethasone has been recognized by a number of international antiemetic guidelines for its efficacy in managing acute CINV following chemotherapy with low, moderately,

and highly emetogenic potential, and it can also be considered for delayed CINV management in some moderately to highly emetogenic chemotherapies (Aapro et al., 2016; Jordan et al., 2014; NCCN, 2015). The short-term application of corticosteroids in antiemetic treatment is well tolerated, and some commonly reported adverse events associated with corticosteroids are sleep disturbance, jitteriness, agitation, indigestion, and increased appetite (Lohr, 2008; Wickham, 2012).

2.8.1.4 Dopamine receptor antagonists and cannabinoids

Dopamine receptor antagonists had been widely utilized as an antiemetic treatment prior to the application of 5-HT_3 receptor antagonists, and their antiemetic mechanism is via blocking the dopamine receptors (Jordan et al., 2014; Lohr, 2008). Currently, they are used in practice for managing breakthrough/refractory nausea and emesis, and the frequently adopted agents include phenothiazines, metoclopramide, and butyrophenones (Lohr, 2008). Adverse events associated with dopamine receptor antagonists include drowsiness, jaundice, dizziness, and extrapyramidal reactions (Lohr, 2008). Cannabinoids have also been used to control nausea and vomiting, and currently there are two types of agents used for antiemetic therapy, including dronabinol and nabilone (Lohr, 2008). However, a number of reported adverse events associated with cannabinoids, including dizziness, dysphoria, and xerostomia, have limited their use in clinical practice (Lohr, 2008).

2.8.1.5 Guidelines for the use of pharmacological approaches to CINV management

In practice, the use of antiemetic therapies should comprehensively consider the emetogenic potential of the administered antineoplastic regimens, types of CINV, and patients' characteristics (Inrhaoun et al., 2012). Several international antiemetic guidelines are currently available to standardize the use of antiemetic agents for the prophylaxis and treatment of nausea and emesis, including the *MASCC/ESMO Antiemetic Guideline 2016* (Aapro et al., 2016), the *NCCN Clinical Practice Guideline in Oncology-Antiemesis* (NCCN, 2015), and the *American Society of Clinical Oncology (ASCO) Guideline for Antiemetics in Oncology* (Basch et al., 2011; Hesketh et al., 2016) (note: the status of the latest ASCO antiemetic guideline is still a review in progress and has not been released yet). According to the guidelines above, for chemotherapy with a high emetogenic risk, a combination of 5-HT_3 receptor antagonists, dexamethasone, and NK_1 receptor

antagonists is generally recommended for controlling acute CINV, and single-agent dexamethasone or NK_1 receptor antagonists, or a combination of both agents, is suggested for controlling delayed CINV (Aapro et al., 2016; Basch et al., 2011; Jordan et al., 2014; NCCN, 2015). In terms of chemotherapy with a moderate emetogenic potential, the guidelines above generally suggest a combination of dexamethasone and 5-HT_3 receptor antagonists for controlling acute CINV (except for carboplatin mentioned in the MASCC/ASCO guideline, which follows the antiemetic treatment for highly emetogenic chemotherapy), while for delayed CINV, dexamethasone is usually the preferred option for some chemotherapy protocols, but other options include 5-HT_3 receptor antagonists, NK_1 receptor antagonists, or no formal prophylaxis based on chemotherapeutic agents, antiemetic regimens used for acute CINV, and patients' conditions (Aapro et al., 2016; Basch et al., 2011; Jordan et al., 2014; NCCN, 2015). A single agent of dexamethasone (or 5-HT_3 receptor antagonists or dopamine receptor antagonists) before chemotherapy may be considered for low emetogenic chemotherapy, and no routine antiemetic therapy is suggested for chemotherapy with minimal emetogenic potential (Aapro et al., 2016; Basch et al., 2011; Jordan et al., 2014; NCCN, 2015). **Figures 2.7** and **2.8** below present the antiemetic options for acute and delayed nausea and vomiting as recommend by the *MASCC/ESMO Antiemetic Guideline 2016* (Aapro et al., 2016):

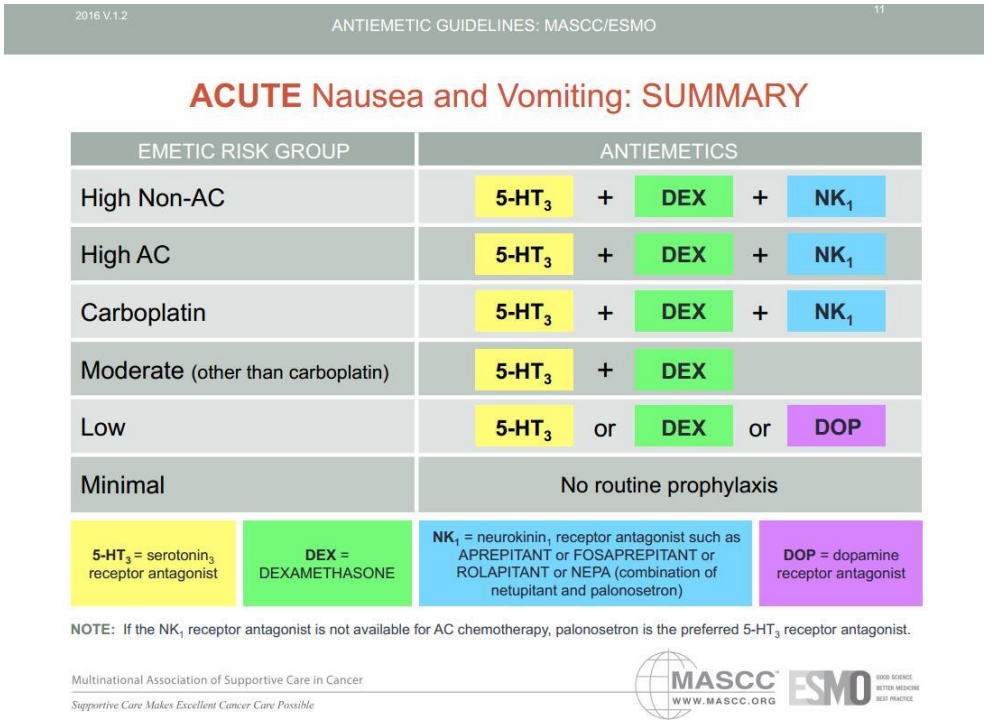


Figure 2.7 Antiemetic options for acute nausea and vomiting

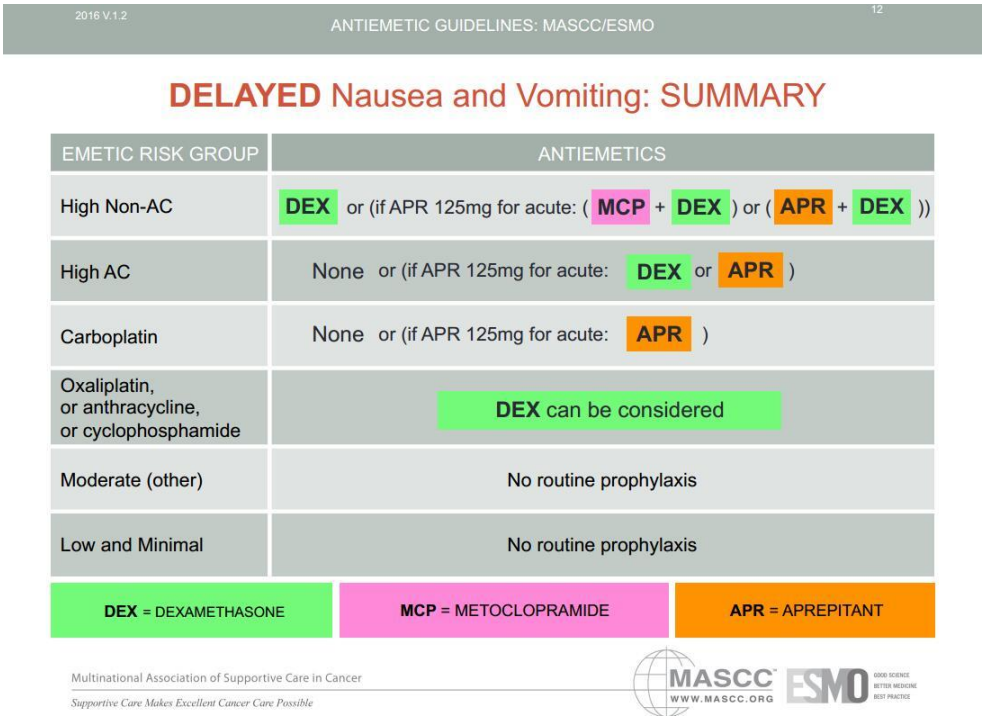


Figure 2.8 Antiemetic options for delayed nausea and vomiting

Note: Figures 2.7 to 2.8 reproduced with the permission of the Multinational Association of Supportive Care in Cancer (MASCC). Source: Aapro, M., Gralla, R. J., Herrstedt, J., Molassiotis, A., & Roila, F. (2016). MASCC/ESMO Antiemetic Guideline 2016. MASCC. Retrieved from http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_2016_v.1.2.pdf. Copyright MASCC.

2.8.1.6 Limitations of current pharmacological approaches to CINV management

Antiemetic medications have made great contributions to the prophylaxis and treatment of CINV in cancer patients, especially for the management of vomiting. However, as mentioned earlier, complete control of nausea and vomiting is impossible using current antiemetic medications (American Cancer Society, 2016). A number of large-scale prospective observational studies revealed that management of nausea is still problematic in current clinical practice, with the incidences of acute nausea and delayed nausea ranging from 23.3% to 46.0%, and from 35.0% to 82.7%, respectively, in patients receiving moderately to highly emetogenic chemotherapies (Escobar et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Rha et al., 2016). Delayed CINV symptoms are also more difficult to control than acute episodes. Taking into account that current antiemetic medications cannot completely control nausea and emesis during cancer chemotherapy, a number of non-pharmacological interventions have therefore been introduced as adjuvant approaches to antiemetic medications for the comprehensive management of CINV.

2.8.2 Non-pharmacological approaches to CINV management

Non-pharmacological techniques, including complementary health approaches (CHAs) and psychosocial interventions, have been used in combination with antiemetic agents to deal with CINV. The most frequently adopted non-pharmacological approaches include acupuncture, acupressure, relaxation, music therapy, guided imagery, massage, ginger, exercise, and hypnosis. A number of clinical trials have been conducted to explore the value of these interventions in CINV management, with different levels of research evidence. Guidelines or recommendations on the use of non-pharmacological approaches to CINV management are rare. The *MASCC/ESMO Antiemetic Guideline 2016* has recommended relaxation techniques, hypnosis, and systematic desensitization as non-pharmacological interventions for anticipatory CINV, but evidence and recommendations regarding other non-pharmacological therapies have not been addressed (Aapro et al., 2016). At present, the only available comprehensive recommendation of non-pharmacological approaches to CINV management is the *Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy-Induced Nausea and Vomiting* developed by the ONS's "Putting Evidence into Practice (PEP)" project, which was first developed in 2006 (Tipton et al., 2007) and updated in early 2017 (ONS, 2017). Commonly used pharmacological

and non-pharmacological interventions for CINV management can be categorized into six levels based on research evidence and strength of recommendation, including "recommended for practice," "likely to be effective," "benefits balanced with harm," "effectiveness not established," "effectiveness unlikely," and "expert opinion" (ONS, 2017; Tipton et al., 2007). Among these interventions, only antiemetic agents (e.g., 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and corticosteroids) were selected as "recommended for practice," while other non-pharmacological interventions mentioned above were mostly categorized as "likely to be effective" or "effectiveness not established" for reasons such as the research evidence for these interventions was mostly based on some small-scale clinical studies with different degrees of methodological flows or conflicting research findings in terms of their effectiveness in controlling CINV (ONS, 2017; Tipton et al., 2007).

2.8.2.1 Acupuncture and acupressure

Extensive attention has been given to acupuncture and acupressure for their therapeutic potential for nausea and emesis induced by antineoplastic treatment. According to Ng (1997), acupuncture can be defined as "the insertion of needles through the skin into underlying tissues at different depths and at strategic points on the body to produce a desired therapeutic effect" (p. 19). When the stimulation of acupuncture points is achieved by adding non-invasive pressure via fingers or other approaches instead of using invasive needles, it is called acupressure (Molassiotis, Helin, Dabbour, & Hummerston, 2007). The acupuncture point "*Neiguan*" (pericardium-6) is the most important and frequently adopted acupoint for controlling nausea and emesis (Streitberger, Ezzo, & Schneider, 2006). However, based on the most recent ONS recommendations, acupuncture and acupressure were categorized as "effectiveness not established" due to unsatisfactory methodological quality and conflicting study findings identified among current acupuncture/acupressure studies (ONS, 2017).

The latest RCT (N=56) indicated that gastric cancer patients in an acupuncture group reported better CINV outcomes than those in the control group without acupuncture (Zhou et al., 2017). A recent RCT with a cross-over design (N=70) explored the efficacy of acupuncture for the prophylaxis of delayed CINV in gynecologic cancer patients, and the study found a favorable effect of acupuncture on controlling delayed CINV compared with those in the control group with

antiemetics only (Rithirangsriroj et al., 2015). Another single-group study with a pre-post design (N=45) and a pilot RCT (N=11) also supported the treatment effects of acupuncture for CINV among cancer patients (Reindl et al., 2006; Tas et al., 2014). However, when acupuncture (combined with acupressure) was compared with a sham intervention (placebo comparison) (N=28), no difference could be found between the true and sham interventions for the alleviation of CINV (Melchart, Ihbe-Heffinger, Leps, von Schilling, & Linde, 2006). The majority of the studies above indicated a promising role of acupuncture in CINV management; however, their methodological flaws, to some degree, made their results unreliable and unconvincing. For instance, all of the studies had a very limited sample size, which may have decreased the power of statistical analysis (Melchart et al., 2006; Reindl et al., 2006; Rithirangsriroj et al., 2015; Tas et al., 2014; Zhou et al., 2017), some failed to provide detailed information regarding randomization or allocation concealment (Rithirangsriroj et al., 2015; Zhou et al., 2017), and one study failed to include a comparison group, which made the correct cause-and-effect relationship difficult to investigate given the significant confounding effects during the pre- and post-assessment within the one study group design (Tas et al., 2014). It should also be noted that the sham acupuncture design was seldom adopted, which made it impossible to distinguish the specific therapeutic effects of acupuncture from its non-specific (placebo) therapeutic effects.

The role of acupressure in CINV symptom management has also been examined by a number of clinical studies (Dibble et al., 2007; Genç & Tan, 2015; Molassiotis, Helin et al., 2007; Molassiotis, Russell et al., 2014; Suh, 2012). The quasi-experimental study conducted by Genç & Tan (2015) (N=64) supported the beneficial effects of acupressure on controlling CINV in breast cancer patients, and similar findings were also reported by a small-scale RCT (N=36) (Molassiotis, Helin et al., 2007). For studies involving a sham acupressure comparison, an RCT conducted by Dibble et al. (2007) (N=160) showed that breast cancer patients receiving true acupressure reported significantly less delayed CINV than those receiving sham acupressure and usual care; Suh's study (2012) (RCT, N=120) also indicated significantly better management of acute and delayed vomiting in breast cancer patients with true acupressure compared with those receiving the sham intervention. However, in a large-scale multicenter RCT conducted by Molassiotis, Russell et al. (2014) (N=500), there was no statistically significant difference in nausea and vomiting scores between the three study groups with true acupressure, sham acupressure, and no additional treatment, respectively.

The conflicting results reported in these studies made the evidence regarding the effectiveness of acupressure in CINV management inconclusive. In addition, methodological flaws were also identified in the acupressure trials, such as the relatively small sample size (Genç & Tan, 2015; Molassiotis, Helin et al., 2007), the lack of a (or unclear) blinding design (Suh, 2012) and sham comparisons (Genç & Tan, 2015; Molassiotis, Helin et al., 2007), and the failure to conduct intention-to-treat (ITT) analysis for all the randomized patients (Suh, 2012).

2.8.2.2 Relaxation techniques

As a popular non-pharmacological technique, relaxation has also been commonly used to manage nausea and vomiting in cancer patients undergoing chemotherapy. It has been viewed as a promising strategy for cancer patients to cope with physical and psychological distress during anti-cancer therapies (Lyles, Burish, Krozely, & Oldham, 1982). An RCT conducted in Hong Kong (Molassiotis, Yung, Yam, Chan, & Mok, 2002) examined the antiemetic effects of progressive muscle relaxation training (PMRT) on CINV in Chinese breast cancer patients (N=71), and the results indicated that PMRT can be an effective complementary approach used in combination with antiemetics to alleviate patients' nausea and emesis during chemotherapy. Similar findings were also reported in another RCT conducted in Japan (Arakawa, 1997) (N=60). However, study findings from these two RCTs should be prudently interpreted, taking into account the small sample size and the lack of clear descriptions of the randomization procedure (Arakawa, 1997) and allocation concealment (Arakawa, 1997; Molassiotis et al., 2002). Meanwhile, it should be noted that conflicting results regarding the effectiveness of relaxation training on CINV were also located in two studies from Finland (Holli, 1993) (RCT, N=67) and South Korea (Kim & Seo, 2010) (quasi-experimental design, N=74), respectively, which showed the ineffectiveness of relaxation in the reduction of nausea and/or emesis associated with chemotherapy.

A meta-analysis of 15 trials supported the effectiveness of relaxation techniques in relieving cancer-treatment-related nausea (Luebbert, Dahme, & Hasenbring, 2001). However, as most of the relaxation interventions were used in combination with guided imagery, the definite effects of relaxation on CINV management were therefore uncertain (Luebbert et al., 2001). The studies above revealed inconclusive research evidence in terms of using relaxation techniques to manage CINV. Moreover, relaxation techniques are time-consuming for healthcare professionals

and cancer patients, as healthcare professionals sometimes need to receive extensive training on relaxation skills before introducing them to patients, and patients are usually required to practice these techniques on a daily basis consecutively for several days, which can potentially increase their physical burden, especially for patients who have already suffered from considerable physical and mental distress (e.g., CINV, fatigue, and anxiety) and deteriorated QoL during cancer treatment.

2.8.2.3 Music therapy and guided imagery

Music therapy is a promising approach to improving patients' physical and psychosocial well-being (Stanczyk, 2011). The improvement of patients' emotional conditions is often the primary focus of music therapy, which may subsequently alter patients' attitudes toward cancer (and related treatment) and enhance their coping capacity for physical and psychosocial distress associated with cancer treatment (Stanczyk, 2011). Several clinical trials have examined the role of music therapy in CINV management and all supported the effectiveness of music therapy in cancer patients' nausea and vomiting associated with chemotherapy (Liu, Chen, Chen, Wu, & Zhang, 2012; Standley, 1992; Wang & Guo, 2011). However, it should be noted that the research evidence generated from these trials was very low as all of them had a very small sample size (ranging from 15 to 84), had no clear information regarding the procedures of randomization and allocation concealment, and failed to utilize valid instruments with adequate psychometric properties to measure CINV symptoms (Liu et al., 2012; Standley, 1992; Wang & Guo, 2011).

Guided imagery is an approach that "involves the generation (either by oneself or guided by a practitioner) of different mental images," and it generally aims at achieving "a psychophysiological state of relaxation" (Astin, Shapiro, Eisenberg, & Forys, 2003, p. 132). The effectiveness of guided imagery has also been explored in two clinical trials (Hosseini, Tirgari, Forouzi, & Jahani, 2016; Troesch, Rodehaver, Delaney, & Yanes, 1993). The most recent one was a quasi-experimental study with pre- and post-assessment of CINV (Hosseini et al., 2016) (N=55), and a single group of breast cancer patients reported significantly less nausea and vomiting after receiving two sessions of guided imagery. However, the other non-RCT (N=28) did not reveal any significant differences in nausea and vomiting scores between the intervention group with guided imagery plus antiemetics and the control group with antiemetics only (Troesch et al., 1993). In addition, there was one quasi-experimental study that combined both music therapy and guided visual imagery for

CINV management (N=40), and pre- and post-analysis of a single group of cancer patients indicated a positive effect of the combined intervention for CINV (Karagozoglu, Tekyasar, & Yilmaz, 2013). Considering the unsatisfactory quality and quantity of the clinical trials on music and guided imagery, as well as some conflicting study findings identified in current literature, there is no clear evidence to recommend the use of music therapy and guided imagery for CINV management. The ONS currently rates guided imagery as "effectiveness not established," and it has no recommendation for music therapy (ONS, 2017).

2.8.2.4 Massage

As a popular complementary health technique, massage has been widely applied for pain and stress management via the possible mechanisms of promoting blood circulation and facilitating muscle relaxation (Ahles et al., 1999). It has also been utilized for the prophylaxis and treatment of CINV. A Cochrane systematic review conducted by Fellowes, Barnes, and Wilkinson (2004) included two RCTs using massage to deal with cancer-treatment-related nausea (Ahles et al., 1999; Grealish, Lomasney, & Whiteman, 2000). Both trials concluded that massage is effective in controlling nausea during cancer treatment, but the findings should be prudently interpreted because of the very small sample size in one study (Ahles et al., 1999) (N=34) and unclear information in terms of randomization and allocation concealment in both studies (Ahles et al., 1999; Grealish et al., 2000). Blinded outcome assessment is also possible for massage trials, but neither of the two trials utilized such a design.

Several relevant trials were also published after the 2004 Cochrane review to provide new research evidence on the use of massage for CINV management (Billhult, Bergbom, & Stener-Victorin, 2007; Gong, 2014; Mazlum, Chaharsoughi, Banihashem, & Vashani, 2013; H. Zhao, 2015). Of these trials, three were RCT designs and all supported the antiemetic role of massage in cancer patients (Billhult et al., 2007; Gong, 2014; Mazlum et al., 2013). Unfortunately, a number of methodological flaws identified in those studies significantly downgraded their level of evidence, including the small sample size (Billhult et al., 2007) (N=39), absence of details regarding randomization and allocation concealment (Gong, 2014; Mazlum et al., 2013), failure to perform ITT analysis for all the randomized participants (Mazlum et al., 2013), and unreliable measurements (instruments without evidence of satisfactory psychometric properties) to assess nausea and vomiting

(Gong, 2014). A recent non-randomized clinical trial (H. Zhao, 2015) (N=120) also showed that a combination of massage and conventional care had significantly better effects on controlling CINV than using conventional care alone; however, this study only employed the "effective rate" to indicate the antiemetic effects of massage without describing the detailed judgment criteria, and there was no other valid scale used for CINV assessment. No sufficient evidence is available at present to support the use of massage to manage CINV, and the latest ONS guideline categorizes massage at the level of "effectiveness not established" (ONS, 2017).

2.8.2.5 Ginger

As a traditional medicinal approach, ginger has been used for years to deal with various types of emesis and pain, and its antiemetic mechanism may be partially related to its potential to facilitate gastric motility (Ansari et al., 2016; Giacosa et al., 2015; Manusirivithaya et al., 2004; Ryan et al., 2012). The role of ginger in CINV management has been investigated in several well-designed RCTs, with conflicting findings reported (Ansari et al., 2016; Manusirivithaya et al., 2004; Ryan et al., 2012; Thamlikitkul et al., 2017; Zick et al., 2009). In a small-scale, double-blinded, placebo-controlled, crossover RCT (Manusirivithaya et al., 2004) (N=48), ginger plus standard antiemetics were used in the intervention group to manage CINV, and the comparison was a placebo combined with metoclopramide and standard antiemetics. It was found that there was no statistically significant difference in the reduction of nausea and vomiting between the groups. Similar results were also reported in three other RCTs (sample size ranged from 34 to 162), that ginger plus standard antiemetics did not demonstrate significantly better outcomes in controlling CINV compared with a placebo plus standard antiemetics (Ansari et al., 2016; Thamlikitkul et al., 2017; Zick et al., 2009). However, in a large-scale, double-blinded, placebo-controlled RCT (Ryan et al., 2012) (N=744), cancer patients given different doses of ginger all reported significantly better control of chemotherapy-induced acute nausea than those who received a placebo. Evidence in terms of the effectiveness of ginger in CINV management was inconclusive due to the contradictory research findings identified in current literature. At present, the ONS lists ginger as "effectiveness not established" in the guideline for CINV management (ONS, 2017).

2.8.2.6 Exercise and hypnosis

It has been proven that increased physical activity is associated with better health outcomes among cancer populations (Jensen et al., 2014). However, clinical studies that have focused on the use of exercise for CINV management in cancer patients have been rare. A pilot RCT (N=26) conducted among advanced gastrointestinal cancer patients receiving chemotherapy investigated the effectiveness of two types of exercise training (aerobic exercise training vs. resistance training) in CINV management, but the findings failed to show a significant change in nausea/vomiting scores before and after the intervention in each study group (Jensen et al., 2014). Similar findings were also reported in a small-scale quasi-experimental study (Andersen et al., 2006) (N=54), where a single group of cancer patients underwent a six-week multidimensional exercise training regimen but not demonstrate a reduction in the combined score of chemotherapy-related nausea, emesis, and loss of appetite across the intervention period. However, in another small-scale RCT (N=42), the use of supervised aerobic exercise (intervention) was found to be more effective in controlling nausea than the use of conventional exercise (placebo) and no treatment (control) among breast cancer patients undergoing chemotherapy (Winningham & MacVicar, 1988).

Hypnosis is one type of psychotherapeutic approach that is believed to be a favorable intervention for managing anticipatory nausea and vomiting in cancer care (Kravits, 2015; Montgomery, Schnur, & Kravits, 2013), but no RCT has explored its value in CINV management. Hypnosis combined with relaxation was utilized in a small-scale quasi-experimental study (N=16), and a single group of cancer patients reported a significant reduction in anticipatory nausea and vomiting after receiving the intervention (Marchioro et al., 2000). A recent case report also supported the benefits of using hypnosis to manage anticipatory CINV (Kravits, 2015).

Current research evidence is insufficient to support the recommendation of exercise and hypnosis for CINV management, and it should be noted that some exercise programs have very high requirements of specific knowledge for both healthcare professionals and patients, which are time- and energy-consuming (ONS, 2017). The generalizability of these interventions also failed to take into account the requirements of additional training for healthcare professionals and patients, and sometimes even caregivers.

2.8.2.7 Limitations of current non-pharmacological approaches to CINV management and implications for future research

A wide range of non-pharmacological interventions have been utilized for the prophylaxis and treatment of CINV, with different levels of research evidence and recommendations. However, definite effects of these non-pharmacological interventions for CINV management remain uncertain due to the conflicting study findings for some approaches (e.g., acupressure, relaxation, guided imagery, ginger, and exercise) and various methodological flaws identified in most of the current literature. For instance, some studies failed to provide clear information regarding the procedures of randomization and allocation concealment, which may have led to potential selection bias during subject recruitment; some trials did not include all randomized subjects in the final statistical analysis, which may have produced some attrition bias that subsequently affected the correct cause-and-effect analysis; a blinded design for outcome assessment was seldom used in the interventional studies above, which may have increased the risk of detection bias during the outcome data collection; and for some interventions (e.g., acupuncture and acupressure) in which a placebo control was necessary for the study design to distinguish the true treatment effects of the interventions from the non-specific treatment (placebo) effects, sham comparisons were not included in many of the clinical trials.

Meanwhile, for most of the commonly used non-pharmacological interventions for CINV management (e.g., relaxation techniques, guided imagery, exercise, and hypnosis), patients, healthcare professionals, and/or caregivers need additional training to ensure that they have been well equipped with these skills before formally using them in research and practice. Some approaches, including acupuncture, relaxation, guided imagery, and hypnosis, may also need specific settings and/or equipment to administer such interventions. All of these non-pharmacological interventions are theoretically acceptable in research designs but they could be very time- and energy-consuming and could place significant burden on patients and their caregivers, as well as healthcare professionals and resources, in real clinical settings. In addition to the therapeutic benefits of alleviating nausea and vomiting symptoms, some procedures may also be associated with different side effects or potential risks, but relevant safety assessments were not addressed in many of the clinical trials.

Given the above concerns of current non-pharmacological interventions for CINV management, more rigorously-designed large-scale studies are warranted in the future to generate more reliable evidence to support the use of these non-pharmacological interventions for CINV management. Meanwhile, it is also necessary for future research to explore the roles of other non-pharmacological approaches to controlling nausea and emesis in cancer treatment. Promising candidates could be interventions with desirable therapeutic effects in theory; less burden on patients, healthcare professionals, and care providers; and less harm for patients. Among these possible interventions, AT could be an optimal option for the prophylaxis and management of CINV, as it is a popular form of non-pharmacological therapy that is widely used to prevent and treat different types of health disorders, and it has the features of convenience of use, low cost, and relatively risk-free. For some AT modalities such as auricular acupressure with plant seeds or metal pellets, patients can even perform self-treatment at home after receiving short-term training from AT practitioners, thereby avoiding frequent hospital visits for symptom management (Yeh et al., 2013). AT is theoretically believed to create some positive effects in relieving various types of nausea and emesis, but relevant research evidence in terms of AT for CINV management is rare at present. As such, the role of AT in cancer symptom management is worthy of exploration.

2.9 Summary of the chapter

This chapter has provided a comprehensive literature review of CINV, a distressing symptom during antineoplastic treatment that can be widely classified as acute, delayed, and anticipatory based on different time points of symptom onset. The mechanism of CINV is not fully conclusive to date, but current research has suggested that the emetic center and neurotransmitters play important roles in the development of CINV, the symptoms of which vary among cancer patients undergoing different chemotherapy protocols. The emetogenic potential of particular chemotherapeutic agents and cancer patients' own characteristics are two major factors for different CINV experiences. Despite the use of standard antiemetic agents, the incidence of CINV is still high among cancer patients with moderately to highly emetogenic anti-cancer treatments. The use of standard antiemetics has shown better outcomes in controlling vomiting rather than nausea, and delayed CINV symptoms have also been found to be more difficult to manage than acute symptoms. Uncontrolled CINV can deteriorate cancer patients' physical and psychosocial well-being and place a considerable negative impact on their QoL.

The use of antiemetic medications following international antiemetic guidelines has been recommended as the most effective approach to the prophylaxis and treatment of CINV, and a number of non-pharmacological interventions have also been utilized as adjuvant approaches to antiemetic medications for CINV management. However, evidence regarding the antiemetic effects of current non-pharmacological interventions has been inconclusive due to unsatisfactory study quality and conflicting results identified in current literature. Rigorously-designed studies are necessary in the future to provide more reliable evidence for the use of non-pharmacological approaches to antiemetic treatment in cancer patients, and the roles of other non-pharmacological therapies with promising antiemetic effects in theory, with less burden on patients, healthcare professionals, and caregivers, are also worthy of further exploration. AT is a good candidate for CINV management but relevant research evidence has been scanty so far. The next chapter will present a comprehensive literature review of the role of AT in CINV management, which will include the definition and underpinning theories of AT, the clinical applications and medical indications of AT, and the theoretical rationale for using AT to alleviate nausea and vomiting during cancer chemotherapy.

CHAPTER THREE: LITERATURE REVIEW: AURICULAR THERAPY (AT)

3.1 Introduction

This chapter will present a comprehensive literature review of AT. The definition and underpinning theories of AT will be introduced first in Sections 3.2 and 3.3, respectively. Section 3.4 will introduce the commonly used AT modalities in clinical practice, and Section 3.5 will summarize the commonly recognized standards in terms of the nomenclature and location of auricular acupoints. Current research evidence regarding the effectiveness of AT in managing different health problems will be presented in Section 3.6, while potential adverse events associated with AT will be summarized in Section 3.7. Section 3.8 will present the theoretical rationales for using AT to control nausea and vomiting during cancer chemotherapy, and Section 3.9 will provide a summary of this chapter.

3.2 Definition of AT

As a popular CHA, AT can generally be defined as "a health care modality whereby the external surface of the ear, or auricle, is stimulated to alleviate pathological conditions in other parts of the body" (Oleson, 2014, p. 1). The use of AT as a preventative and therapeutic approach can be traced back to ancient China two thousand years ago, while the modern application of AT was established and promoted by Paul Nogier, a French physician and neurologist, in the late 1950s (L. Huang, 2001; Oleson, 2014). AT has been recognized by the WHO as a micro-acupuncture system within the ear that can generate beneficial effects in regulating and maintaining normal functions of the human body system (WHO, 1990).

3.3 Underpinning theories of AT

Potential mechanisms of AT have yet to be fully clarified. Several underpinning theories have been proposed by a number of AT practitioners and researchers to explain the preventive, therapeutic, and diagnostic role of AT in various health problems. Among these underpinning theories, the most widely accepted are the homuncular reflex theory, the neurohumor theory, and the Chinese *zang-fu* organs and meridians theory.

3.3.1 Homuncular reflex theory

Through a potential homuncular reflex pathway, the homuncular reflex theory highlights a close somatotopic connection between particular areas or acupoints in the outer auricles and certain parts/regions of the body or internal organs (Bai, 1994; Suen et al., 2001). A group of neurons are centrally clustered in the brain stem, which is regarded as the management center of the homuncular reflex pathway, and this center is mainly responsible for connecting and coordinating two different afferent projections, with one from a particular region (e.g., fingers, shoulder, wrist, and hip) or internal organ (e.g., liver, stomach, spleen, and small intestine) and the other from related areas or acupoints located in the ear (Bai, 1994, pp. 11-13; Shan, 1996, pp. 5-6; Suen et al., 2001). The message exchange between the ear acupoints/areas and the related internal organs or body regions via the center for the homuncular reflex pathway is bidirectional (Bai, 1994, pp. 11-13; Shan, 1996, pp. 5-6; Suen et al., 2001). The homuncular reflex theory serves as the theoretical basis of the modern AT practice developed by Paul Nogier (Abbate, 2004; Bai, 1994; Oleson, 2014). In his modern auricular medicine system, Nogier pointed out that the outer auricle of the human ear has a somatotopic arrangement similar to that of an inverted fetus within the uterus (Abbate, 2004; Bai, 1994; Oleson, 2014), "with the head towards the lower lobule, the feet towards the upper rim of ear, and the body in-between" (Abbate, 2004, p. 2) (see **Figure 3.1**), and each particular region of the human body or internal organ is closely linked with a corresponding ear acupoint or area (Abbate, 2004, p. 2; Bai, 1994, pp. 11-12; Shan, 1996, pp. 5-6).

Nogier's homuncular reflex theory regarding AT has been well supported by many clinical observational studies throughout the years, and it has been identified that pathological conditions in a certain internal organ or part of the body can be reflected in the corresponding ear acupoints/areas with some physical changes of the ear skin, such as increased tenderness and pain around the ear acupoints/areas when adding manual acupressure and decreased electrical resistance of the local ear skin (Bai, 1994, p. 12). In some cases, more visible alterations of the corresponding ear acupoints/areas can be detected, such as white flaky skin and local redness (Bai, 1994, p. 12). By using a particular AT approach, such as auricular acupressure, auricular acupuncture, or auricular laser therapy at the affected ear acupoints or areas, a therapeutic effect can be generated, possibly via the homuncular reflex pathway, to alleviate the symptoms or fix the dysfunctions of the associated body parts and/or internal organs (Bai, 1994, p. 12; Shan, 1996,

p. 6). The homuncular reflex theory in Nogier's auricular medicine system is currently the most widely accepted AT theory.

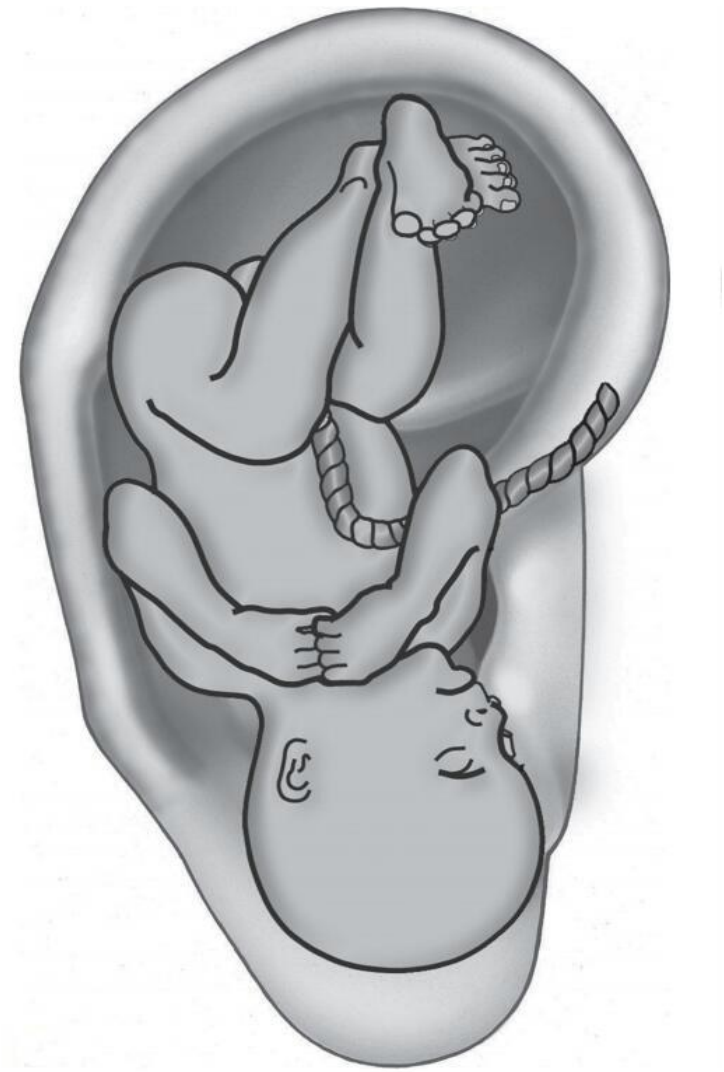


Figure 3.1 Somatotopic map of the outer auricle (developed by Dr. Terry Oleson)

Note: Reprinted from the Auriculotherapy Manual: Chinese and Western Systems of Ear Acupuncture, 4th ed., Terry Oleson, Overview and History of Auriculotherapy, pp. 1-24, Copyright (2014), with permission from Elsevier. (License Number: 4094020195030. Source: Oleson, T. [2014]. *Auriculotherapy manual: Chinese and Western systems of ear acupuncture* (4th ed.). Edinburgh, SCT: Churchill Livingstone, Elsevier. [p. 14, "figure 1.4: Images of the somatotopic pattern on the external ear developed by Dr. Terry Oleson, showing an inverted fetus perspective (A) and an actual orientation of the somatotopic body (B)"]).

3.3.2 Neurohumor theory

The neurohumor theory posits that the human ear has a high sensitivity to a wide range of external stimuli because many nerve terminals and neurotransmitter receptors are concentrated in every part of the outer auricle (Shan, 1996, p. 4; Xiao & Wei, 1996, pp. 6-7). According to the neurohumor theory, pathological changes in certain body regions or internal organs can evoke related nerve impulses, which subsequently change the sensory threshold of the neurons that are concentrated around the related ear acupoints or areas, and further contribute to a significant increase of auricular sensitivity (Shan, 1996, p. 4). The use of AT can potentially block the pathological cycle between body parts and the corresponding ear acupoints or areas via two different mechanisms: **(1)** therapeutic procedure-induced sensory stimulation reduces the disease-related nervous impulses by generating a biological inhibition to the involved neurons; and **(2)** sensory stimulation directly creates a much stronger nerve excitability to suppress the pathological one (Shan, 1996, p. 4). The neurohumoral mechanism is crucial in maintaining normal body functions, and this mechanism is believed to partially contribute to the therapeutic effects of AT, whose treatment stimulation at certain auricular acupoints can activate the neurohumoral system and subsequently generate some positive responses to alleviate dysfunctions in other parts of the body (Shan, 1996, p. 4).

3.3.3 Chinese *zang-fu* organs and meridians theory

Another widely accepted AT theory is the Chinese *zang-fu* organs and meridians theory. As early as 500 to 300 B.C., an ancient Chinese classic, *Yellow Emperor's Inner Canon* (*Huang Di Nei Jing*), illustrated a close relationship between the human ear with its "five viscera" (five *zang* organs: heart, liver, spleen, liver, and kidney) and "six bowels" (six *fu* organs: stomach, small intestine, large intestine, gallbladder, bladder, and *san jiao*) (Abbate, 2004, p. 2; Shan, 1996, pp. 1-3; Suen et al., 2001), and this book also indicated that "all meridians converge at the ear" (Bai, 1994, p. 15). The Chinese *zang-fu* organs and meridians theory hypothesizes that there are direct and indirect connections between the ear and the regular meridians of the human body, which include the six *yang* meridians (the hand *tai yang* small intestine meridian, the hand *shao yang san jiao* meridian, the foot *shao yang* gallbladder meridian, the hand *yang ming* large intestine meridian, the foot *yang ming* stomach meridian, and the foot *tai yang* bladder meridian),

and the six *yin* meridians (the hand *tai yin* lung meridian, the foot *tai yin* spleen meridian, the hand *shao yin* heart meridian, the foot *shao yin* kidney meridian, the hand *jue yin* pericardium meridian, and the foot *jue yin* liver meridian) (Shan, 1996, pp. 1-2; Suen et al., 2001; Xiao & Wei, 1996, p. 5).

Associations or auricular acupoints with the meridians have been investigated and approved via a series of clinical observational studies that found that the stimulation of particular ear acupoints/areas generated some "meridian transmission" (note: in some books, "meridian transmission" is also called "channel transmission") reactions in corresponding body parts or internal organs (Bai, 1994, p. 15; Shan, 1996, pp. 2-3; Xiao & Wei, 1996, pp. 5-6). For instance, different skin sensations were identified along the stomach-related meridian once the auricular acupoint "stomach" was accurately and appropriately stimulated by AT approaches such as auricular acupressure or auricular acupuncture (Bai, 1994, p. 15). Nogier once stated that particular "energy pathways" may exist between the ear and other body parts or internal organs that contribute to the therapeutic potential of AT, which do not belong to the circulation system or the nervous system, and this explanation is in accordance with the Chinese *zang-fu* organs and meridians theory (Bai, 1994, pp. 15-16).

The connections between auricular acupoints and *zang-fu* organs were also identified in many ancient Chinese classics and supported by a series of clinical studies (Shan, 1996, p. 3; Xiao & Wei, 1996, p. 6). For instance, dysfunctions that occur in particular *zang-fu* organs can be reflected in their related auricular acupoints by some pathological changes in ear tenderness and electrical resistance (Shan, 1996, p. 3), which is very similar to that described above in the homuncular reflex theory (Bai, 1994, p. 12). The Chinese *zang-fu* organs and meridians theory recognizes that *zang-fu* organs are not isolated but instead are closely connected with each other (Bai, 1994, p. 16). Therefore, apart from using AT to treat certain body disorders that directly correspond to specific auricular acupoints, the use of AT on a certain ear acupoint can also help relieve dysfunctions that occur in other *zang-fu* organs that are "internally and externally" linked with their corresponding *zang-fu* organ (Bai, 1994, p. 16). For instance, auricular acupoint "lung" can be stimulated to alleviate large-intestine-associated gastrointestinal disorders because the *zang* organ "lung" and the *fu* organ "large intestine" are closely connected via related meridians

(Bai, 1994, p. 16). The Chinese *zang-fu* organs and meridians theory shares many similarities with the homuncular reflex theory, and both theories have been commonly referred to as theoretical backgrounds for the development of AT treatment protocols for different types of health problems in current clinical practice and research.

3.4 Modalities of AT

Different AT modalities have been used in practice, including auricular acupressure, auricular acupuncture, auricular laser stimulation, auricular electrostimulation, auricular injection, auricular moxibustion, and auricular bloodletting therapy (Guan, Guan, Jiang, & Tang, 2002, pp. 113-142; Tan et al., 2014a). Among these AT modalities, auricular acupressure and auricular acupuncture are the two most frequently adopted AT approaches.

3.4.1 Auricular acupressure

Auricular acupressure (also referred to as "auricular pressing/taping therapy") is a non-invasive AT modality in which the auricular acupoints are stimulated by small-sized, round, hard objects (e.g., vaccaria seeds, magnet pellets, or metal pellets) via manual acupressure (Guan et al., 2002, pp. 113-114; Suen et al., 2001). Its non-invasive nature makes auricular acupressure one of the most widely accepted AT techniques because it is a convenient treatment approach with less expense and a relatively safe method with less and minor side reactions (Guan et al., 2002, p. 113). Regarding the objects used to produce acupoint stimulation in ear acupressure, vaccaria seeds (*wang bu liu xing zi*) are currently the most popular option since "they are plentiful, inexpensive and of appropriate size and density to deliver a strong stimulus when pressed" (Abbate, 2004, p. 99). In current clinical practice, well-sterilized vaccaria seeds are usually attached to desensitization tape to form auricular plasters, which are available in the medical marketplace (Abbate, 2004, p. 99). An auricular plaster can be attached to a certain ear acupoint to create constant acupoint stimulation and maintain a satisfactory AT treatment effect (Abbate, 2004, p. 99). It should be noted that the use of vaccaria seeds in auricular acupressure is not because of its potential pharmacological effects but because of its texture and size, which make it an optimal choice for acupoint stimulation (Guan et al., 2002, p. 114). Other objects with features similar to vaccaria seeds, such as metal pellets and magnet pellets, can also be used for

auricular acupoint stimulation (Abbate, 2004, pp. 101-102; Guan et al., 2002, pp. 113-114; Suen et al., 2001). Metal pellets used for AT are usually made of gold, copper, silver, or stainless steel (Abbate, 2004, p. 101). The use of magnet pellets in AT serves a dual purpose: physical properties for acupressure and magnetic treatment effect for targeted health problems (Suen, Wong, Leung, & Ip, 2003).

The taped seeds or pellets can be kept in the auricle for about three to five days and sometimes up to one week based on the patients' condition as well as the nature of their health disorders (Abbate, 2004, p. 100; Yeh, Chien, Chiang, & Huang, 2012). During the AT treatment period, patients are usually required to add manual acupressure to the taped seeds or pellets about three to five times a day to achieve satisfactory treatment effects (Abbate, 2004, p. 100). In AT treatment, successful achievement of AT therapeutic effects is determined by a sensation of "*de qi*," which is a TCM term used to describe a local sensation at the sites of acupoint stimulation, including soreness, tingling, minor aching, heaviness, or heat (Guan et al., 2002, p. 116; MacPherson & Asghar, 2006). Patients receiving auricular acupressure are also required to well protect the taped seeds or pellets by not dropping or wetting them during showering or washing their hair (Abbate, 2004, p. 100). The use of auricular acupressure is very convenient for patients (Guan et al., 2002, pp. 113-114; Yeh et al., 2013). Once the auricular tapes have been placed on the ear acupoints by the AT practitioner, patients can follow the practitioner's instructions for self-acupressure at home to avoid frequent visits to healthcare services (Yeh et al., 2013).

3.4.2 Auricular acupuncture

Auricular acupuncture can be defined as "a form of acupuncture in which needles are placed in various positions of the ear to affect the person" (He & Tong, 2012, p. 168). Apart from auricular acupressure, auricular acupuncture is currently one of the most commonly adopted AT techniques in Eastern countries. Regarding the types of needles for auricular acupuncture, regular one-inch (25 mm) and half-inch (13 mm) acupuncture needles, press tack needles, and short intradermal needles are widely used (Guan et al., 2002, pp. 118-125; Suen et al., 2001). Regular ear acupuncture needles come in different thicknesses, including diameters of 0.45 mm (#26 gauge), 0.38 mm (#28 gauge), 0.32 mm (#30 gauge), 0.26 mm (#32 gauge), and 0.22 mm (#34 gauge) (Guan et al., 2002, p. 119). Some ear acupuncture needles smaller than the regular

half-inch size are also used in practice (Guan et al., 2002, p. 119). Press tack needles and short intradermal needles are two types of small needles that are particularly designed for auricular acupuncture, as they can be taped (similar to ear acupressure) and imbedded into certain ear areas to generate constant acupoint stimulation (Guan et al., 2002, p. 124; Suen et al., 2001).

As an invasive approach, auricular acupuncture should be used with caution and should be administered only by trained AT/acupuncture practitioners. Routine disinfection of the local ear skin and the use of disposable ear needles are essential in preventing serious adverse events such as infections and hepatitis (Guan et al., 2002, pp. 119-125). Once the ear needle has been placed at the correct auricular acupoint, manual acupressure and rotation of the needle is often needed to achieve the *de qi* (therapeutic) sensation, and minor adjustment of the angle of the inserted needle is also required when the *de qi* sensation cannot be detected (Abbate, 2004, p. 98). For auricular acupuncture using regular needles, the recommended duration of needle retention is generally 15 to 20 minutes and no more than 30 minutes (Abbate, 2004, p. 98; Guan et al., 2002, p. 123). For the use of imbedded needles (i.e., press tack needles and short intradermal needles), the selection of two to five ear acupoints is appropriate and the imbedded needles can be kept in place for more than two days (Guan et al., 2002, p.125). However, imbedded ear needles should be used carefully because this invasive intradermal approach is highly likely to induce some local infections (Abbate, 2004, p. 102; Guan et al., 2002, p. 125).

3.4.3 Other AT approaches

In addition to auricular acupressure and acupuncture, other AT techniques have also been utilized in routine practice, including auricular electrostimulation, auricular laser therapy, auricular moxibustion, auricular injection, and auricular bloodletting therapy (Guan et al., 2002, pp. 113-142; Tan et al., 2014a).

Auricular electrostimulation can be used in combination with or without regular auricular acupuncture needles (Guan et al., 2002, pp. 126-128). When combined with ear acupuncture needles, the auricular electrostimulation approach is called auricular electroacupuncture (Guan et al., 2002, pp. 126-128). The procedures for administering auricular electroacupuncture usually follow standard ear acupuncture practices, placing the acupuncture needles on the targeted acupoints first,

and then connecting the needles to electrical devices to transfer impulse currents to the targeted auricular acupoints (Guan et al., 2002, pp. 126-128). Another approach, without using ear acupuncture needles, is to attach the electrodes directly to both the inner and outer sides of the auricular acupoints to generate electrical stimulation (Guan et al., 2002, pp. 126-128).

Auricular laser therapy is one type of light therapy that follows AT theories to manage a variety of health problems (Abbate, 2004, p. 109). The use of auricular laser therapy has been increasing in recent years, accounting for its non-invasive and risk-free feature of not penetrating the ear skin, and reported side reactions are rare (Abbate, 2004, p. 109). Given the potential harm of lasers to the eyes, protective eyewear may be necessary for both AT practitioners and patients (Guan et al., 2002, p. 142).

Guided by the Chinese *zang-fu* organs and meridians theory, auricular moxibustion uses heat to accelerate the *qi*-blood (*qi xue*) circulation of the ear, which can subsequently generate some meridian-warming and cold-dispersing (*wen jin san han*) treatment effects for a number of chronic conditions (Abbate, 2004, p. 108; Guan et al., 2002, p. 136). Ear moxibustion should be used prudently in practice given its potential adverse events, such as burns to the ear skin (Guan et al., 2002, p. 137).

Auricular injection and auricular bloodletting therapy are two types of traditional Chinese AT techniques that are no longer commonly used at present. During ear injection, pharmacological agents are injected into certain auricular acupoints to relieve health disorders occurring in particular internal organs or body parts, and this approach combines both ear acupoint-stimulation effects and pharmacological effects of the injected agents (Abbate, 2004, pp. 108-109; Guan et al., 2002, p. 128). Local pain at the ear injection site is one of the most cited adverse reactions associated with auricular injection (Abbate, 2004, p. 109). Ear bloodletting therapy is a treatment method that releases blood at certain ear acupoints by needles to remove the heat toxin (*re du*) and fire toxin (*huo du*), accelerate *qi*-blood circulation, and alleviate *qi* stagnation and blood stasis (*qi xue yu zhi*) in certain body regions or internal organs (Abbate, 2004, p. 107; Guan et al., 2002, p. 134). Local disinfection is required during the ear bloodletting procedure to avoid ear infections,

and it must be noted that this technique is not appropriate for use in patients who have hemorrhagic diseases (Abbate, 2004, p. 107; Guan et al., 2002, p. 136).

3.5 Standard nomenclature and location of auricular acupoints

Prior to the early 1950s, there were only 10 auricular acupoints that were commonly used in clinical practice in China (Guan et al., 2002, p. 25). With the development of the modern auricular medicine system proposed by Nogier, and the further investigation of AT practices based on the Chinese *zang-fu* organs and meridians theory, more and more auricular acupoints have been identified and recorded. In the early 1970s, 154 auricular acupoints were systematically recorded in the book *Science of Acupuncture and Moxibustion* compiled by the Shanghai College of Traditional Chinese Medicine (L. Huang, 1991, p. 9). In a book compiled by the Jiangsu New Medical College and its affiliated hospital in 1972, 284 auricular acupoints were recorded (L. Huang, 1991, p. 9). However, there were no commonly accepted standards for naming and locating auricular acupoints until the early 1980s, and some acupoints even had several different names when used in practice, which significantly affected the development of the modern auricular medicine system (L. Huang, 1991, p. 9; Suen et al., 2001).

Therefore, in December 1982, the WHO delegated the Chinese Association of Acupuncture-Moxibustion (CAAM) to draft standards for locating and naming auricular acupoints (Bai, 1994, p. xiv; Guan et al., 2002, p. 25; L. Huang, 1991, p. 10; Suen et al., 2001). In October 1992, the China State Bureau of Technical Supervision (CSBTS) released a Chinese standard ear acupoints chart (*Nomenclature and Location of Auricular Points*, GB/T-13734-1992), which has been widely accepted for use in AT clinical practice and research (Guan et al., 2002, p. 25). The latest updated version (GB/T-13734-2008) of the 1992 standard was released in 2008 by the National Standard Information Sharing Infrastructure (2008), and it has since been adopted in other countries as one of the most important practice standards in terms of the nomenclature and location of auricular acupoints.

3.6 Effectiveness of AT in clinical practice

AT has been recommended as a promising CHA for regulating and maintaining normal body functions (WHO, 1990). Many RCTs, meta-analyses, and systematic reviews have been conducted in the past few decades to test the effectiveness of AT on a variety of health problems, and the research findings have supported the effectiveness of AT in producing some favorable effects on relieving different types of pain, sleep problems, constipation, anxiety, and depression, although future research is still needed to generate more reliable research evidence. The role of AT in smoking cessation has also been investigated, with contradictory research evidence located in current literature.

A systematic review and meta-analysis of 22 RCTs on AT for pain management indicated that AT, including both auricular acupressure and auricular acupuncture, is superior to sham AT comparisons in terms of pain management (Yeh, Chiang et al., 2014). The evidence from this systematic review was relatively reliable given that the majority of the analyzed RCTs were judged as possessing good methodological quality (Yeh, Chiang et al., 2014). The latest systematic review and meta-analysis included 10 RCTs with fair to excellent study quality for analysis, and it concluded that auricular acupuncture plays a promising role in immediate pain relief (Murakami et al., 2017). Another systematic review published in 2015 (Zhao, Tan, Wang, & Jin, 2015) included 15 RCTs on AT for chronic pain management, and both the quantitative synthesis and the descriptive analysis of the included studies supported that AT is effective in managing chronic pain, especially chronic tension-type headaches and chronic lower back pain, compared with sham AT or other active comparisons.

For sleep problems, two systematic reviews (Chen, 2007; Lee et al., 2008) found that auricular acupuncture could be an effective approach to managing insomnia, although the review authors also pointed out that the evidence regarding the use of AT for insomnia management was not fully reliable given the poor methodological quality among the included trials. In the most recent systematic review (Lan et al., 2015), AT using plant seeds or pellets was found to be more effective in dealing with primary insomnia compared with sham AT approaches or other active comparisons, but the authors also pointed out that more high-quality trials are needed to conclude the definite effects of AT on sleep problems.

In terms of the role of AT in constipation management, the results from two well-designed RCTs showed that AT was more effective in reducing constipation symptoms than sham AT and routine methods of care (Li et al., 2014; Shin & Park, 2016). Two other RCTs focused on AT for anxiety management, and the findings indicated that true auricular acupuncture was superior to sham auricular acupuncture and/or the no-intervention control in reducing state anxiety (Gagliardi et al., 2014; Michalek-Sauberer et al., 2012). In addition, a recent systematic review showed that auricular acupressure and auricular electrostimulation can effectively reduce depressive symptoms (Zhang et al., 2016). Given the limited number of studies identified in current literature, more research is needed to provide more conclusive evidence for AT in the management of constipation and emotional distress.

AT is also considered a promising treatment approach to smoking cessation, but the research evidence is still inconclusive and even conflicting between different studies. An RCT conducted by Bier, Wilson, Studt, and Shakleton (2002) showed that the participants receiving true auricular acupuncture plus education reported a significantly higher rate of successful smoking cessation compared with those receiving sham auricular acupuncture plus education and those receiving education alone. Another RCT compared the differences in smoking cessation between true and sham ear acupressure groups, and the study findings indicated a statistically significant within-group difference in the self-efficacy of smoking cessation between the true AT group and the sham AT group at post-intervention assessment, and the change in scores for self-efficacy in smoking cessation was found to be significantly better in the true AT group than in the sham AT group (between-group difference) (Lee & Park, 2017). However, two other RCTs reported conflicting study results, in that true AT (auricular acupuncture or auricular acupressure) did not statistically differ from sham AT comparisons in smoking cessation (Wing et al., 2010; Wu, Chen, Liu, Lin, & Hwang, 2007). A Cochrane systematic review included seven low-quality RCTs that focused on auricular acupuncture for the reduction of cocaine dependence, and the data analysis revealed no difference between true auricular acupuncture and sham auricular acupuncture, and between true auricular acupuncture and no acupuncture (Gates, Smith, & Foxcroft, 2006). No reliable evidence can be summarized to support the use of auricular acupuncture for cocaine dependence (Gates et al., 2006). Considering the conflicting study findings identified in current literature regarding the effectiveness of AT in smoking cessation, more

rigorously-designed studies are warranted in the future to generate more convincing research evidence.

3.7 Safety of AT

AT is now one of the most frequently utilized CHAs in clinical practice, but issues related to its safety also deserve attention (Tan, Molassiotis, Wang, & Suen, 2014b). Apart from its promising treatment effects in dealing with a number of health problems, another important reason for the popularity of AT is because of its "convenience and safety" (Tan et al., 2014b, p. 1), particularly in non-invasive AT modalities such as auricular acupressure and auricular laser intervention. Moreover, it has been identified that adverse reactions associated with AT are fewer and milder than other commonly used complementary health approaches, including body acupuncture, traditional cupping therapy, and moxibustion (Tan et al., 2014b). However, it should be noted that a large number of capillaries are concentrated in the very small ear area, so a series of harm to the ear skin (e.g., local infections and skin irritation) might occur during AT procedures (Abbate, 2004, pp. 83-88; Tan et al., 2014b).

A systematic review conducted by the doctoral researcher in 2014 comprehensively analyzed current literature to identify potential adverse events associated with different AT modalities, including auricular acupuncture, auricular acupressure, auricular electrostimulation, and auricular bloodletting therapy (Tan et al., 2014b). Thirteen English and Chinese online databases were searched and several Chinese journals were also manually checked to locate eligible articles that reported potential adverse events associated with different AT approaches (Tan et al., 2014b). This systematic review also utilized the *WHO-Uppsala Monitoring Centre (UMC) System for Standardized Case Causality Assessment* to evaluate the causality between the identified side effects and the AT approaches used (Tan et al., 2014b). Thirty-two RCTs, five uncontrolled clinical studies, two non-randomized clinical studies, and four case studies were finally included for descriptive analysis, and the total number of patients involved in AT treatment in this review was 3,396 (Tan et al., 2014b). The most commonly reported adverse reactions associated with ear acupuncture were pain or tenderness at the AT site, dizziness, local bleeding and discomfort at the AT site, nausea, local pain around the head or neck, and local inflammation at the needling site (Tan et al., 2014b). The most frequently reported side effects of auricular

acupressure in the analyzed literature included irritation of the local ear skin, discomfort around the AT site, pain or tenderness at the AT site, and dizziness (Tan et al., 2014b). Reported adverse reactions associated with ear electrostimulation included local irritation of the ear skin and local pain or discomfort around the AT site (Tan et al., 2014b). Minor infections of the ear were reported in the only study that utilized ear bloodletting therapy (Tan et al., 2014b). The majority of the AT-related side effects identified in this systematic review were deemed transient, mild, and well tolerated, and no serious adverse reactions associated with AT (e.g., disability and hospitalization) were located (Tan et al., 2014b).

The systematic review above suggests that AT can be used as a safe and convenient treatment approach in clinical practice (Tan et al., 2014b). Moreover, the review findings clearly indicated that non-invasive AT modalities, particularly auricular acupressure, are superior to invasive auricular treatment techniques (e.g., ear acupuncture and bloodletting therapy) regarding the safety issue (Tan et al., 2014b). Adverse reactions, including local inflammation and bleeding at the AT sites, which were frequently identified in patients with invasive AT modalities, were seldom reported in those receiving auricular acupressure (Tan et al., 2014b). However, it should be pointed out that the most commonly reported side effects associated with ear acupressure, including local irritation and discomfort of the ear skin, can easily be minimized using desensitization materials for acupressure seed attachment (Tan et al., 2014b).

Some precautions must be emphasized when AT is used in some special populations, including older people, patients with significant weakness, pregnant women, patients with hemorrhagic diseases, patients with immunodeficiency, and pediatric patients (Abbate, 2004, pp. 83-88; Tan et al., 2014b). For example, for older adults and patients with significant weakness, hemorrhagic diseases, or immunodeficiency, invasive AT modalities such as auricular acupuncture should be adopted prudently given that these patients are highly likely to suffer from infections or persistent bleeding during the AT treatment procedures (Abbate, 2004, p. 84; Tan et al., 2014b). For older people receiving AT treatment, a semi-reclining position during the treatment and short-term rest after the treatment are highly recommended to prevent accidental falls caused by the adverse event of dizziness (Tan et al., 2014b). For pregnant women, the use of auricular acupuncture is usually not allowed because a miscarriage could be induced by the strong auricular acupoint stimulation

(Abbate, 2004, p. 83). AT treatments are generally not recommended for use on pediatric patients, as children may swallow the taped auricular seeds or pellets (Abbate, 2004, p. 84). The use of AT for pediatric patients who are less than seven years old is also not recommended, as the treatment may hinder the normal growth and development of their bodies (Abbate, 2004, p. 84). In terms of patients with significant mental health disorders, AT must be used with caution, as these patients sometimes find it difficult to follow AT practitioners' instructions and some are not able to give proper responses for the achievement of its therapeutic effects (*de qi* sensation) (Abbate, 2004, p. 84). Based on the information provided by Abbate (2004, pp. 83-88) and Tan et al. (2014b), **Figure 3.2** below summarizes the commonly reported adverse events associated with AT treatments and precautions in the use of AT in special populations:

Figure 3.2 Commonly reported AT-related adverse events and precautions for the use of AT in special populations

3.8 Theoretical rationales for adopting AT for CINV management

According to the TCM theory, disharmony and imbalance of *qi* circulation is believed to be the primary source of different types of health disorders (Huang & Huang, 2007, p. 310). *Qi* is also regarded as one of the most vital substances in constructing all human body functions, and *qi* circulates into different parts of the body and *zang-fu* organs to facilitate body movements and energy transformations (Huang & Huang, 2007, p. 310; Oleson, 2014, p. 46).

Based on the Chinese *zang-fu* organs and meridians theory, the normal activities of the gastrointestinal system are coordinated by two major *zang-fu* organs, the spleen (*pi*) and the stomach (*wei*), which are traditionally believed to be the "roof of the later heaven (*hou tian zhi ben*)" and the "source of the formation of *qi* and blood (*qi xue sheng hua zhi yuan*)" (L. Li, 2014; Liu & Yang, 2006; M. Wang, 2010; X. Wang, 2006, p. 483). The stomach governs the intake of both liquids and food (*wei zhu shou na*) and the flow of stomach *qi* is particularly downward (Ling, Yang, & Shao, 2012; X. Wang, 2006, pp. 482-483; R. Zhao, 2007), while the spleen is closely linked with the stomach from the TCM perspective and the movement of spleen *qi* is typically upward; it is particularly responsible for the movement of food and liquids, subsequently helping to transform them into the essences that support normal body functions (*pi zhu yun hua*) (Bai, 1994, p. 88; Ling et al., 2012; X. Wang, 2006, pp. 482-483; R. Zhao, 2007). The stomach and spleen are functionally paired with each other to coordinate the normal functions of the gastrointestinal system (Liu & Yang, 2006; X. Wang, 2006, pp. 482-483; R. Zhao, 2007).

In addition to the stomach and spleen, the liver (*gan*) also contributes to the regulation of the normal functions of the gastrointestinal system (Ling et al., 2012; R. Zhao, 2007). As an important organ that supports the functions of the stomach and spleen, the liver is mainly responsible for governing free coursing (*gan zhu shu xie*), which can either assist the stomach with food and liquid intake and the descending of stomach *qi*, or facilitate the movement and transformation functions of the spleen and the ascending of spleen *qi* (R. Zhao, 2007). In turn, a good functional status of the stomach and spleen can also enrich and nourish the liver function (L. Li, 2014). The normal functions of the stomach, spleen, and liver are the bases for supporting and regulating gastrointestinal functions (see **Figure 3.3** below).

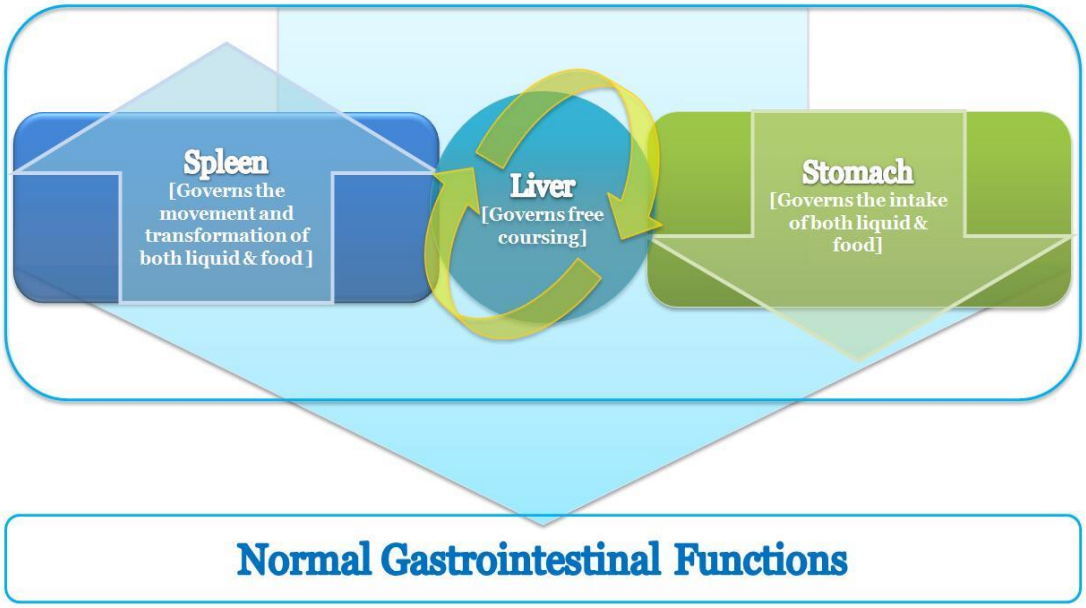


Figure 3.3 Normal gastrointestinal functions maintained by the stomach, spleen, and liver

Given the close associations among the stomach, spleen, and liver, dysfunctions in one organ can impede the other organs' functions; for instance, the dysfunction of the spleen in transporting essences and chaotic flow of spleen *qi* can significantly affect normal stomach functions, and vice versa (Ling et al., 2012). Disharmony of the liver in free coursing can also result in an abnormal movement of stomach *qi* and dysfunctions in taking in food and liquids, which subsequently impede spleen functions (L. Li, 2014; Ling et al., 2012; R. Zhao, 2007). Under pathological conditions, the movement of *qi* among the stomach, spleen, and liver can be significantly disrupted, which can further lead to a series of gastrointestinal disorders (Ling et al., 2012). For the pathogenesis of CINV, based on the Chinese *zang-fu* organs and meridians theory, two principles are involved: "dysfunction of spleen in movement and transportation (*pi shi jian yun*)" and "dysfunction of stomach in turbidity elimination (*wei bu jiang zhuo*)" (X. Wang, 2006, p. 483; Zhu et al., 1996). The direct cause of emesis is "the loss of gastric homeostasis and the ascending *qi* flow" (Ling et al., 2012, p. 143). According to the TCM medicinal principles, chemotherapeutic regiments can be viewed as fire toxins (*huo du zhi xie*), which can help fight against tumors but can also act as one type of external evil, fire evil, that can impede and deteriorate the functions and *qi* movements of the stomach and spleen ("*qi* deficiency of the spleen

and stomach [*pi wei qi xu*]" and "upward movement of the stomach *qi* [*wei qi shang ni*]") (C. Li, 2009; L. Li, 2014; Liu & Yang, 2006; X. Wang, 2006, p. 483; Zhu et al., 1996). Given the close relationship of the liver with both the stomach and the spleen, the chaotic movement of stomach-spleen *qi* can further hinder the liver's role of free coursing (L. Li, 2014), all of which can contribute to dysfunctions of the gastrointestinal system and lead to a series of symptoms, including vomiting, emesis, and abdominal distension (Ling et al., 2012; Zhu et al., 1996). As the most direct result, the upward movement of stomach *qi* (the primary cause of emesis) will directly bring up gastric contents (Ling et al., 2012), which can lead to the symptom of emesis during chemotherapy. **Figure 3.4** below shows the dysfunctions of the stomach, spleen, and liver in the development of nausea and emesis during cancer chemotherapy:

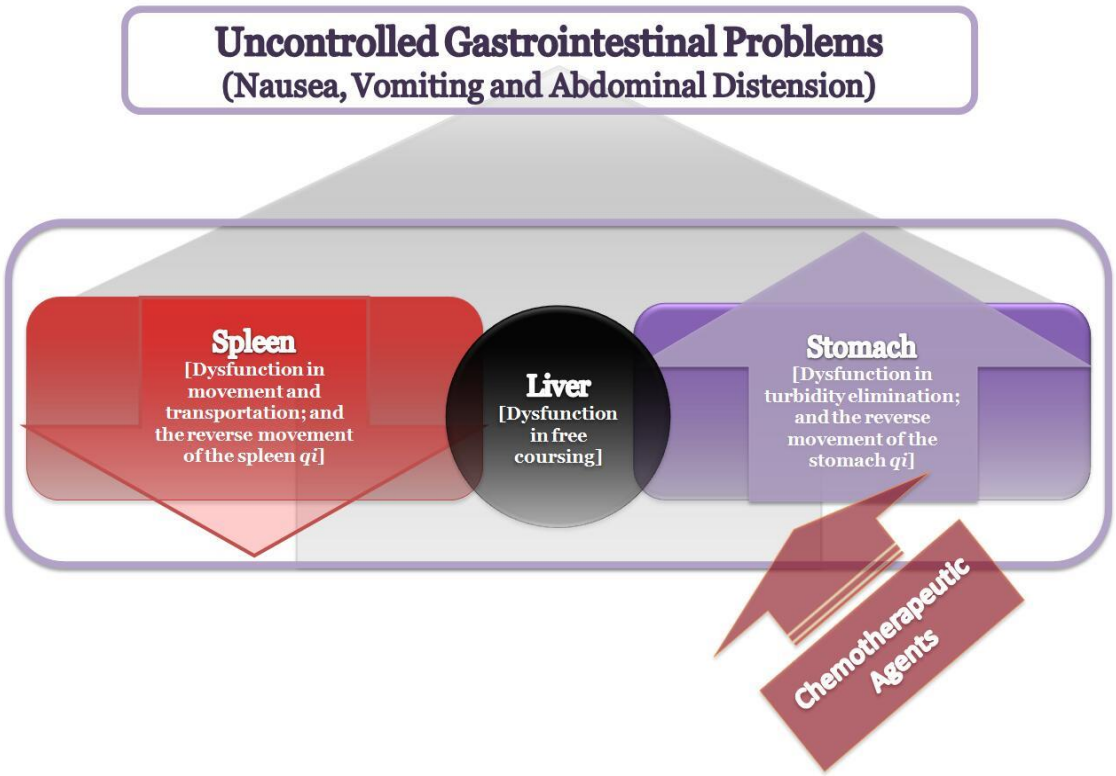


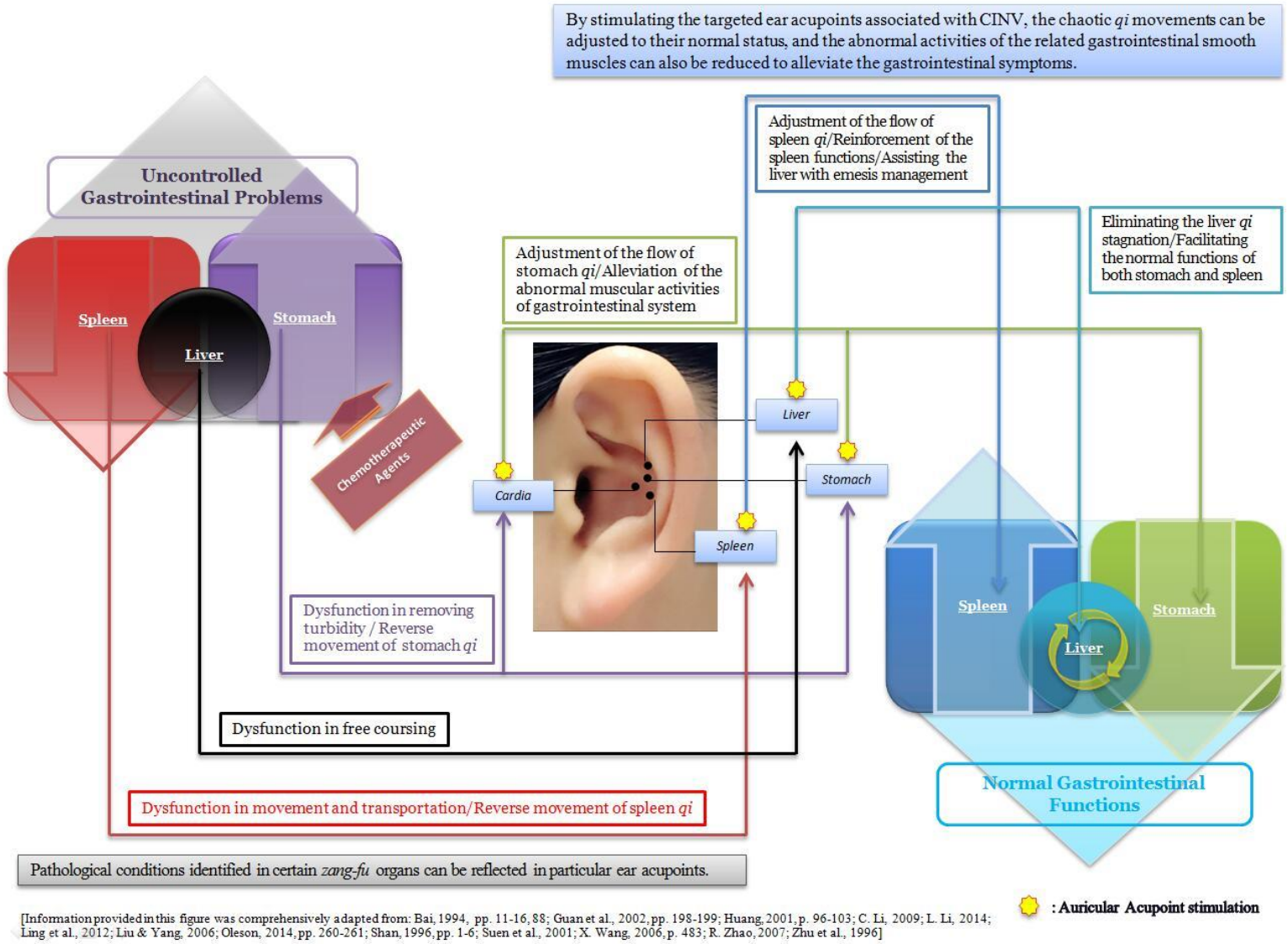
Figure 3.4 Dysfunctions of the stomach, spleen, and liver in the development of CINV

The chaotic and abnormal movements of *qi* among the stomach, spleen, and liver should be reversed to their normal circulations to alleviate nausea and vomiting symptoms and maintain normal gastrointestinal functions. Based on the homuncular reflex theory and the Chinese *zang-fu* organs and meridians theory of auricular medicine, dysfunctions identified in certain *zang-fu* organs or parts of the body can be reflected in particular auricular acupoints (Bai, 1994, pp. 11-16; Shan, 1996, pp. 1-6; Suen et al., 2001). In patients with CINV, the involved *zang-fu* organs also have certain corresponding ear acupoints. For instance, the stomach (including the cardia) corresponds to the auricular acupoints "stomach (CO_4)" and "cardia (CO_3)," the spleen corresponds to the auricular acupoint "spleen (CO_{13})," and the liver is linked with the auricular acupoint "liver (CO_{12})."

"Cardia" and "stomach" are the two most important auricular acupoints for the management of nausea and vomiting, as they directly correspond to the affected organ (stomach) and can be stimulated to remove fire evil (*huo xie*), readjust the flow of stomach *qi* to the normal downward movement, and relieve the activities of related gastrointestinal smooth muscles to reduce emesis reactions (Bai, 1994, p. 88; Guan et al., 2002, pp. 198-199; Oleson, 2014, pp. 260-261). As the spleen is theoretically believed to be closely associated with stomach functions, the auricular acupoint "spleen" can also be stimulated to produce some favorable effects in strengthening the functions of the spleen and assisting the liver with emesis management (Bai, 1994, p. 88; Guan et al., 2002, pp. 198-199; L. Huang, 2001, p. 103). The auricular acupoint "liver" also plays a crucial role in managing gastrointestinal dysfunctions, and stimulation of the "liver" acupoint can eliminate liver *qi* stagnation (*qi zhi*) and facilitate normal functions of both the stomach and the spleen (Bai, 1994, p. 88; L. Huang, 2001, p. 96; Oleson, 2014, p. 260).

The auricular acupoints mentioned above are frequently adopted in practice to manage nausea and vomiting (Bai, 1994, p. 88; Guan et al., 2002, pp. 198-199; L. Huang, 1991, p. 136). By stimulating the targeted auricular acupoints associated with the affected *zang-fu* organs during CINV, chaotic *qi* movements among those organs can be readjusted to their normal status, and the abnormal activities of related gastrointestinal smooth muscles can also be reduced to alleviate gastrointestinal symptoms. In addition to the previous underpinning mechanisms of using AT for CINV management, Abbate (2003) pointed out that the role of the stomach and spleen in blood

formation (*sheng xue*) can be disturbed by antineoplastic regiments, and stimulation of ear acupoints "stomach" and "spleen" may facilitate blood formation (p. 157), which may also contribute to CINV symptom relief during AT treatment. **Figure 3.5** below comprehensively presents the development process of CINV induced by the dysfunctions of *zang-fu* organs associated with the regulation of normal gastrointestinal functions, and the potential roles of the auricular acupoints "stomach," "cardia," "spleen," and "liver" in AT treatment for CINV:



[Information provided in this figure was comprehensively adapted from: Bai, 1994, pp. 11-16, 88; Guan et al., 2002, pp. 198-199; Huang, 2001, p. 96-103; C. Li, 2009; L. Li, 2014; Ling et al., 2012; Liu & Yang, 2006; Oleson, 2014, pp. 260-261; Shan, 1996, pp. 1-6; Suen et al., 2001; X. Wang, 2006, p. 483; R. Zhao, 2007; Zhu et al., 1996]

Figure 3.5 Theoretical rationales for adopting AT for CINV management

AT is theoretically believed to be a promising approach to managing nausea and emesis in cancer patients receiving chemotherapy. Given that AT is also a convenient and relatively safe method, the role of AT in cancer symptom management is worthy of exploration. Unfortunately, current clinical research evidence regarding the effectiveness of AT in CINV has been scanty. During the past few decades, several small-scale clinical studies that have examined the role of AT in alleviating CINV have been published; however, their study findings and methodological quality issues have not been systematically analyzed yet. Therefore, a systematic review was conducted by the doctoral researcher to comprehensively explore the current research evidence on AT for CINV management in cancer patients (Tan et al., 2014a). Available RCTs focusing on AT to control CINV were retrieved through different resources, and the methodological quality of all the included trials, details of the AT treatment protocols (e.g., AT modalities employed for acupoint stimulation and the commonly selected auricular acupoints for alleviating CINV), the frequently utilized outcome measures for assessing nausea and vomiting, and the clinical efficacy of using AT to manage CINV were comprehensively summarized and analyzed (Tan et al., 2014a). This systematic review confirmed a number of methodological limitations that deserve further improvement, and it concluded some implications for future research and practice (Tan et al., 2014a). The limitations identified in this systematic review clearly demonstrated the current research gaps in terms of using AT to control nausea and emesis during cancer chemotherapy. The study procedures and findings of this systematic review will be presented in the next chapter.

3.9 Summary of the chapter

This chapter presented a comprehensive literature review of AT. The use of AT has a history of nearly two thousand years, and the modern system of auricular medicine was developed in the late 1950s. There are several underpinning theories that are commonly utilized to clarify the potential mechanisms of AT, and they all recognize that the internal organs and different body regions have their own typical correspondences to particular auricular acupoints/areas located at the outer auricle. Pathological conditions occurring in certain internal organs or body regions can be reflected in their corresponding auricular acupoints, and appropriate stimulations of particular ear acupoints are believed to create some potential therapeutic effects for certain dysfunctions in corresponding body areas. Several AT modalities used in clinical practice include auricular acupressure, auricular acupuncture, auricular laser stimulation, and auricular

electrostimulation. Among these AT techniques, auricular acupuncture and auricular acupressure are the most popular techniques used to alleviate various types of health disorders. Much research has been undertaken to explore the role of AT in the management of different health problems, and findings have indicated that AT can be utilized as a promising CHA to deal with different types of pain, sleep disturbance, constipation, and emotional distress, such as anxiety and depression. The role of AT in smoking cessation has also been supported by some research findings, but more studies are needed to conclude reliable evidence. In terms of the safety issue of AT, current literature has well documented the safety of AT, with only mild and transient adverse reactions. Theoretically, AT can also be used as a favorable approach to managing CINV, but relevant research evidence has been scarce. Several small-scale RCTs that examined the role of AT in controlling CINV have been published, but their study findings and methodological quality issues have not been systematically analyzed yet. The next chapter will present a systematic review conducted by the doctoral researcher that will comprehensively conclude the current evidence on the use of AT for CINV management. The limitations of current AT research drawn from this systematic review will be summarized and will serve as potential research gaps in this doctoral research project.

CHAPTER FOUR: SYSTEMATIC REVIEW: IDENTIFICATION OF THE RESEARCH GAPS

4.1 Introduction

The limitations of current research in terms of the use of AT for CINV management were identified via a systematic review of RCTs. The study limitations retrieved from the current RCTs, which focused on the effectiveness of AT in CINV management, will serve as potential research gaps in this doctoral research project. In addition, based on the critical analysis of all the included RCTs in this systematic review, some implications for future research and practice were concluded and adapted for the development of the AT intervention protocols used in this doctoral research project. This chapter will present a systematic review of the current research evidence on AT for CINV management in cancer patients. Four sections will be presented: this first section (4.1) will offer a general introduction of this chapter; Section 4.2 will describe the whole systematic review, including the study aim and objectives, study methods, review findings, discussion of the study results, and study limitations and implications for future research and practice; research gaps identified in this systematic review will be listed in Section 4.3; and a summary of the chapter will be presented in Section 4.4. It should be noted that the following systematic review has already been published in an international peer-reviewed journal (Tan et al., 2014a). According to the publisher, the published systematic review is "an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited" (Source: https://www.hindawi.com/journals/ecam/2014/430796/). In this doctoral thesis, the major contents and styles of text citations and reference list of the published systematic review have been slightly modified to fit the structure and organization of this doctoral thesis.

4.2 Systematic review of current evidence on AT for CINV management in cancer patients

4.2.1 Study aim and objectives

The overall aim of this systematic review was to conclude the current evidence on AT for CINV management. Accordingly, the objectives of the review were: **(1)** to explore the therapeutic outcomes of AT in controlling CINV; **(2)** to evaluate the methodological quality of the analyzed studies; **(3)** to summarize the AT protocols used in current clinical practices for CINV management; **(4)** to review the commonly utilized CINV outcome measures reported in the AT trials; **(5)** to identify the limitations in the current AT trials for managing CINV and the research

gaps that need to be further addressed in future studies; and **(6)** to conclude the implications for future research and clinical practice.

4.2.2 Methods

4.2.2.1 Data sources and search strategies

A study protocol accompanied by a data extraction form was formulated and was critically reviewed by two experts prior to the initiation of this study. Relevant studies were mainly searched and retrieved from electronic databases, and a total of 12 databases (from inception to May 27, 2014) were accessed, including PubMed, EMBase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), AMED, PsycINFO, Thomson Reuters Web of Science, Science Direct, China National Knowledge Infrastructure (CNKI), WanFang Data, Chinese Scientific Journal Database (VIP), and Chinese Biomedical Literature Database (CBMdisc). No language restrictions were applied in the electronic searches. Meanwhile, a manual search was conducted in Chinese journals of complementary and alternative medicine published within the last five years, and the reference lists of the final included studies were also checked to identify any possibly eligible studies. Two reviewers (Tan, J. Y. and Wang, T.) independently searched the literature according to the study protocol. Mesh terms, key words, and free words such as "auriculotherapy," "acupuncture, ear," "auricular therap*," "ear acupunctur*," "nausea," "vomiting," "antiemetic*," "chemotherapy," "antineoplastic agent*," and "neoplasms" were used in the search strategies. **Table 4.1** presents two representative search strategies for this systematic review.

4.2.2.2 Inclusion and exclusion criteria

The inclusion criteria for this systematic review were: **(1)** RCTs; **(2)** cancer patients with acute or delayed nausea and vomiting after receiving chemotherapy; and **(3)** trials comparing AT with or without antiemetic medications to one or more of the following: sham AT control, concomitant antiemetic medications, usual care, waiting-list control, or no treatment. The types of AT could be auricular acupressure, auricular manual/electronic/laser acupuncture, auricular moxibustion,

auricular injection, or auricular bloodletting therapy. Clinical case reports and case series, non-randomized controlled trials, and other uncontrolled clinical trials were excluded.

4.2.2.3 Study selection

The study characteristics and outcome data of each included RCT were extracted using a pre-defined data extraction form, which included: **(1)** first author, year of publication, study design, and setting; **(2)** patient and disease characteristics (age, gender, types of cancer, chemotherapeutic agents, and antiemetics used); **(3)** intervention protocols (types of AT, selected auricular acupoints, approaches to acupoint detection, manual pressing instruction, and treatment duration) and types of control; **(4)** outcome measures and the therapeutic effects of AT on CINV; and **(5)** possible adverse events associated with AT. The study selection and data extraction were also conducted by two reviewers (Tan, J. Y. and Wang, T.) independently. Any disagreement about the studies between the reviewers was resolved by further assessment of the study with another reviewer (Molassiotis, A. or Suen, L. K. P.), reaching consensus.

Table 4.1 Selected search strategies for the systematic review

ID	Search Strategies
PubMed	
#1	"auriculotherapy"[MeSH Terms] OR "acupuncture, ear"[MeSH Terms]
#2	((((((((((((((((auriculotherap*[Title/Abstract]) OR (acupunctur*[Title/Abstract] AND ear*[Title/Abstract])) OR (acupunctur*[Title/Abstract] AND auricu*[Title/Abstract])) OR (acupressur*[Title/Abstract] AND ear*[Title/Abstract])) OR (acupressur*[Title/Abstract] AND auricu*[Title/Abstract])) OR (auricu*[Title/Abstract] AND poin*[Title/Abstract])) OR (ear[Title/Abstract] AND poin*[Title/Abstract])) OR (ear[Title/Abstract] AND acupoin*[Title/Abstract])) OR (auricu*[Title/Abstract] AND plaster*[Title/Abstract])) OR (massag*[Title/Abstract] AND ear*[Title/Abstract])) OR (ear[Title/Abstract] AND plaster*[Title/Abstract])) OR (massag*[Title/Abstract] AND auricu*[Title/Abstract])) OR (magne*[Title/Abstract] AND ear*[Title/Abstract])) OR (magne*[Title/Abstract] AND auricu*[Title/Abstract])) OR otopoin*[Title/Abstract]) OR (ear[Title/Abstract] AND hol*[Title/Abstract])) OR vaccaria*[Title/Abstract]) OR seed*[Title/Abstract]) OR erxue[Title/Abstract]
#3	#1 OR #2
#4	((“nausea” [MeSH Terms] OR “vomiting” [MeSH Terms]) OR “drug related side effects and adverse reactions” [MeSH Terms]) OR “antiemetics” [MeSH Terms]
#5	((((((((((((nausea[Title/Abstract]) OR vomiting[Title/Abstract]) OR emesis[Title/Abstract]) OR antiemetic*[Title/Abstract]) OR anti-emetic*[Title/Abstract]) OR (anti[Title/Abstract] AND emetic*[Title/Abstract])) OR puke*[Title/Abstract]) OR (gastrointest*[Title/Abstract] AND toxicit*[Title/Abstract])) OR (gastrointest*[Title/Abstract] AND reactio*[Title/Abstract])) OR (intest*[Title/Abstract] AND toxicit*[Title/Abstract])) OR (intest*[Title/Abstract] AND reactio*[Title/Abstract])) OR (drug[Title/Abstract] AND toxicit*[Title/Abstract])) OR (adverse[Title/Abstract] AND reactio*[Title/Abstract] AND drug[Title/Abstract])) OR (adverse[Title/Abstract] AND event*[Title/Abstract] AND drug[Title/Abstract])
#6	#4 OR #5
#7	((“neoplasms” [MeSH Terms] OR “drug therapy” [MeSH Terms]) OR “antineoplastic agents” [MeSH Terms]) OR “antineoplastic combined chemotherapy protocols” [MeSH Terms]
#8	((((((((((neoplasm*[Title/Abstract]) OR tumo*[Title/Abstract]) OR tumou*[Title/Abstract]) OR neoplasia[Title/Abstract]) OR cance*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR drug therap*[Title/Abstract]) OR chemo*[Title/Abstract]) OR antineoplasti*[Title/Abstract]) OR cytotoxic*[Title/Abstract]) OR malignant[Title/Abstract]) OR Oncolog*[Title/Abstract]
#9	#7 OR #8
#10	#3 AND #6 AND #9
#11	(((((((“randomized controlled trial” [Publication Type]) OR “controlled clinical trial” [Publication Type]) OR “ramdomized” [Title/Abstract]) OR “ramdomised” [Title/Abstract]) OR “placebo” [Title/Abstract]) OR “sham” [Title/Abstract]) OR “randomly” [Title/Abstract]) OR “trial” [Title/Abstract]) OR “groups” [Title/Abstract]
#12	(animals [MeSH Terms] NOT (humans [MeSH Terms] AND animals [MeSH Terms]))
#13	#11 NOT #12
#14	#10 AND #13
EMBase	
#1	‘acupuncture’/exp
#2	auriculotherap*:ab,ti OR (ear NEAR/3 acupuncture*):ab,ti OR (auricu* NEAR/3 acupunctur*):ab,ti OR (ear NEAR/3 acupressur*):ab,ti OR (auricu*NEAR/3 acupressur*):ab,ti OR (auricu* NEAR/3 poin*):ab,ti OR ‘auricular plaster’:ab,ti OR (ear NEAR/3 plaster*):ab,ti OR (ear NEAR/3 poin*):ab,ti OR (ear NEAR/3 acupoint*):ab,ti OR otopoin*:ab,ti OR earhole*:ab,ti OR

	(vaccaria* NEAR/15 ear*):ab,ti OR (vaccaria* NEAR/15 auricu*):ab,ti OR (massag* NEAR/3 auricu*):ab,ti OR (massag* NEAR/3 ear*):ab,ti OR (cowherb NEAR/15 ear*):ab,ti OR (cowherb NEAR/15 auricu*):ab,ti OR (seed*NEAR/15 auricu*):ab,ti OR (seed* NEAR/15 ear):ab,ti OR (magne* NEAR/15 ear*):ab,ti OR (magne* NEAR/15 auricu*):ab,ti OR erxue*:ab,ti
#3	#1 OR #2
#4	'chemotherapy induced nausea and vomiting'/exp
#5	'antiemetic agent'/exp
#6	'adverse drug reaction'/exp
#7	'chemotherapy induced emesis'/exp
#8	'gastrointestinal toxicity'/exp
#9	'chemotherapy induced nausea and vomiting':ab,ti OR nausea:ab,ti OR vomiting:ab,ti OR emesis:ab,ti OR (anti NEAR/3 emetic*):ab,ti OR puck*:ab,ti OR (gastrointest* NEAR/5 toxicit*):ab,ti OR (gastrointest* NEAR/5 reactio*):ab,ti OR (intest* NEAR/5 toxicit*):ab,ti OR (intest* NEAR/5reactio*):ab,ti OR (drug NEAR/10 toxicit*):ab,ti OR (adverse NEAR/5 reactio*):ab,ti OR (adverse NEAR/5 event*):ab,ti
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	'neoplasm'/exp
#12	'chemotherapy'/exp
#13	'antineoplastic agent'/exp
#14	neoplasm*:ab,ti OR tumo*:ab,ti OR tumou*:ab,ti OR neoplasia:ab,ti OR cance*:ab,ti OR carcinom*:ab,ti OR chemo*:ab,ti OR antineoplasti*:ab,ti OR cytotoxic*:ab,ti OR malignant:ab,ti OR Oncolog*:ab,ti
#15	#11 OR #12 OR #13 OR #14
#16	#3 AND #10 AND #15
#17	'controlled clinical trial'/exp OR 'single blind procedure'/exp OR 'double-blind procedure'/exp OR 'crossover procedure'/exp
#18	random*:ab,ti OR crossover*:ab,ti OR (cross NEAR/3 over*):ab,ti OR placebo:ab,ti OR (doubl* NEAR/3 blind*):ab,ti OR (doubl* NEAR/3 mask*):ab,ti OR (singl* NEAR/3 blind*):ab,ti OR (singl* NEAR/3 mask*):ab,ti OR (trebl* NEAR/3 blind*):ab,ti OR (trebl* NEAR/3 mask*):ab,ti OR (tripl* NEAR/3 blind*):ab,ti OR (tripl* NEAR/3 mask*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti
#19	#17 OR #18
#20	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#21	'human'/exp
#22	#20 AND #21
#23	#20 NOT 22
#24	#19 NOT #23
#25	#16 AND #24

4.2.2.4 Methodological quality assessment

The Cochrane collaboration's tool for risk of bias was utilized to evaluate the methodological quality of each trial (Higgins & Green, 2011). The tool consists of seven specific domains: "random sequence generation," "allocation concealment," "blinding of participants and personnel," "blinding of outcome assessment," "incomplete outcome data," "selective outcome reporting," and "other bias" (Higgins & Green, 2011). In this review, "other bias" was further clarified into several categories to assess whether the author reported sample size calculation, baseline assessment, diagnostics, inclusion and exclusion criteria, evaluation of therapeutic effects, adverse events, and the method of data analysis in the article. Each item was rated as "low risk of bias," "unclear risk of bias," or "high risk of bias" (Higgins & Green, 2011). Disagreement between reviewers was resolved through discussion.

4.2.2.5 Data analysis

Incidence and severity of CINV was the primary outcome of this systematic review, and type and frequency of AT-related adverse events, patients' physical performance status, and emotional conditions (anxiety and depression symptoms) were set as secondary outcomes. A meta-analysis using Review Manager 5.2 was originally planned. However, because of the significant methodological flaws identified in the analyzed literature, as well as the clinical heterogeneity of the types of cancer, intervention protocols, and control methods used among the studies, meta-analysis was deemed inappropriate and a descriptive analysis was employed instead to summarize the therapeutic effects of AT for both the primary and secondary outcomes.

4.2.3 Results

4.2.3.1 Characteristics of the included studies

Electronic and manual searches yielded 1,056 records, of which 166 duplicated items were deleted and another 809 items were further excluded after browsing the title and abstract. Full-text articles of the remaining 81 records were retrieved for the evaluation of their eligibility for final inclusion, of which 60 articles were excluded because they were not a randomized design (n=21), were clinical case reports (n=10) or narrative reviews (n=1), and the participants (n=3) and intervention (n=25) did not meet the inclusion criteria of the systematic review. Therefore,

21 studies (Bi, 2011; Fang, 2013; Y. Huang, 2011; Huang, Hu, Guo, & Feng, 2012; Jiang, 2012; Jing, 2007; D. Li, 2013; Lin et al., 2012; Liu & Chen, 2011; Lu, 2012; Luo, 2011; Qian, Fan, Yang, Qian, & Zong, 2006; Sun, 2003; Y. Wang, 2012; Yang & Liang, 2013; Ye et al., 2011; Yeh, Chien, Chiang, Lin et al., 2012; Zhang et al., 2003; Zhang, Chen, Gao, & Tian, 2012; Zhang, Ji, Sun, & Jin, 2013; Zhong et al., 2012) were identified for analysis. The flowchart of the study selection is presented in **Figure 4.1** below:

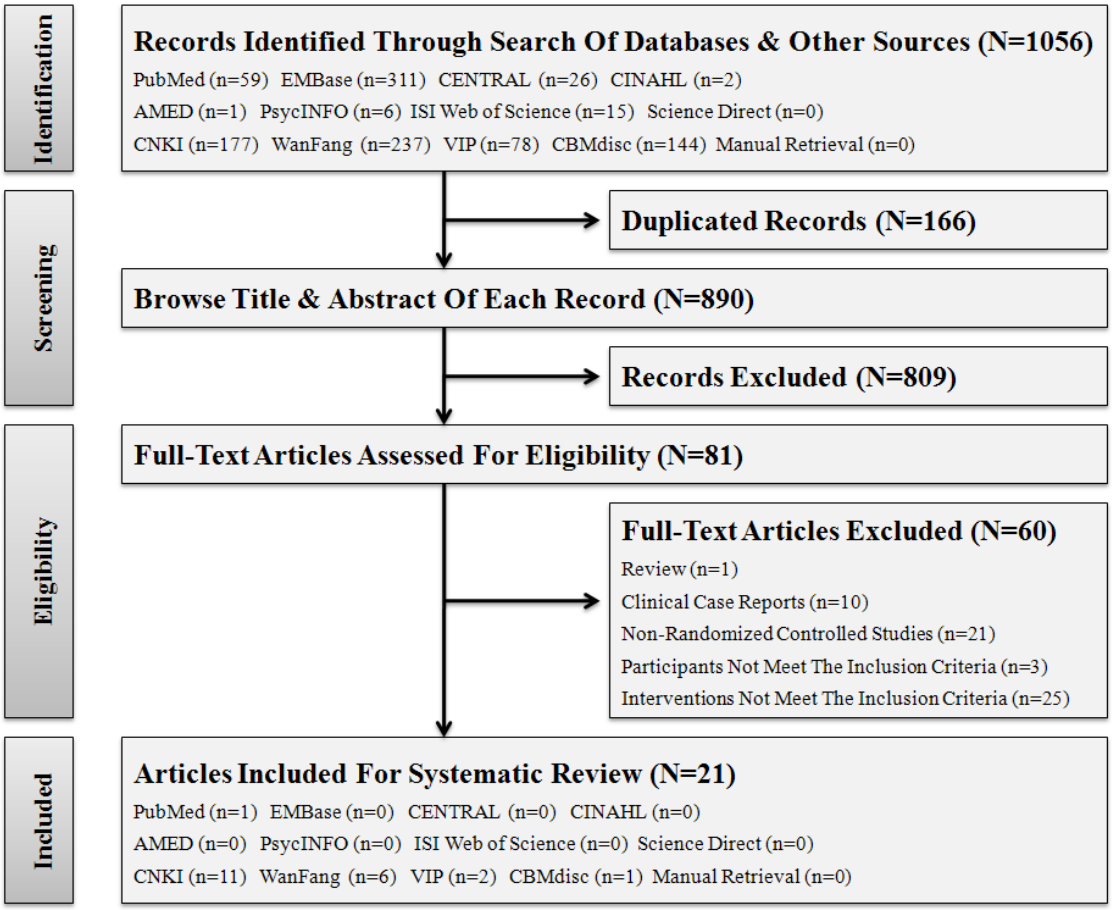


Figure 4.1 Flowchart of study selection for the systematic review

The included studies (20 journal articles and one master's thesis) were published between 2003 and 2013, with two English articles and 19 Chinese articles. One trial was conducted in Taiwan, and the other 20 were carried out in different provinces of Mainland China. The studies focused on different types of malignancies, including breast cancer in five studies, lung cancer in two studies, leukemia in two studies, gastrointestinal cancer in one study, and pediatric cancer in one

study. Seven studies included more than two types of cancer, while the other three studies did not specify what kind of cancer patients they included. A total of 1,713 participants were identified in the included trials, with their ages ranging from 6 to 80 years old. All participants were recruited from outpatient clinics or inpatient departments. The average sample size was 81 (range=10 to 173), and only eight studies had a sample size of more than 100 subjects.

All participants in the intervention groups received AT before and after chemotherapy, of which 20 studies applied auricular acupressure, while another one (Zhang et al., 2013) chose auricular acupuncture. Of the 20 studies that used auricular acupressure as the intervention approach, 15 investigated the therapeutic effects of auricular acupressure by comparing auricular acupressure plus antiemetic drugs with antiemetic drugs alone, and two (Ye et al., 2011; Yeh, Chien, Chiang, Lin et al., 2012) incorporated a sham acupressure control group and compared data from that group with data from the intervention group using the same antiemetics. Furthermore, the intervention groups in two studies (Sun, 2003; Zhang et al., 2003) received only auricular acupressure while the control groups were treated with antiemetic drugs, and one study (Fang, 2013) used "usual care" to describe the conventional medical care received in both groups but failed to specify whether they included any antiemetic treatment.

The primary outcome was the incidence and severity of CINV in 20 studies, and only one study (Bi, 2011) used different dosages of the antiemetic drugs received between the groups to evaluate the therapeutic effects of AT. The secondary outcomes in the analyzed trials included physical performance status, adverse events associated with AT or antiemetics, incidence of constipation and abdominal bloating, anxiety, and depression symptoms. Although report of adverse events is an important issue in evaluating the safety of AT, there were only three studies (Jiang, 2012; Luo, 2011; Yeh, Chien, Chiang, Lin et al., 2012) that stated such events. The characteristics of the analyzed studies are presented in **Table 4.2** below:

Table 4.2 Characteristics of the included trials

Study & Setting	Types of Cancer	Participants	Chemotherapy Agents	Intervention	Control	Outcomes
S[a]1: You et al., 2013 RCT, Zhejiang Cancer Hospital, Hangzhou, China	Non-small-cell lung cancer	**Randomized**=120 **Completed**=120 **Intervention group**: 60 **Control group**: 60	Etoposide + cisplatin	Auricular acupressure + antiemetic medications (not specified)	Antiemetic medications (not specified)	- CINV - Abdominal bloating - Abdominal pain - Blood glucose & insulin - Anxiety - Depression - Pain intensity
S2: Yang & Liang, 2013 RCT, The Second Affiliated Hospital of SUCM, Xianyang, China	Leukemia	**Randomized**=58 **Completed**=58 M/F=23/35, age(yr)=20-67 **Intervention group**: 38 **Control group**: 20	Cytarabine, homoharringtonine, daunorubicin, cyclophosphamide, mitoxantrone	Auricular acupressure + antiemetic medication (granisetron, 3mg, iv, qd)	Antiemetic medication (granisetron, 3mg, iv, qd)	- CINV
S3: Li, 2013 RCT, The first Affiliated Hospital of Soochow University, Suzhou, China	Lung cancer Breast cancer Ovarian cancer Cervical cancer Esophagus cancer Nasopharynx cancer	**Randomized**=32 **Completed**=32 **Intervention group**: 16, M/F=5/11, age(yr)=37-65 **Control group**: 16, M/F=4/12, age(yr)=36-67	Combined chemotherapy based on cisplatin or pharmorubicin	Auricular acupressure + antiemetic medications (azasetron, 10mg, iv, qd + dexamethasone, 10mg, iv, qd)	Antiemetic medications (azasetron, 10mg, iv, qd + dexamethasone, 10mg, iv, qd)	- CINV
S4: Fang, 2013 RCT, Jiangyan TCM Hospital, Taizhou, China	Lung cancer Liver cancer Breast cancer Colon cancer Esophagus cancer Nasopharynx cancer	**Randomized**=100 **Completed**=100 M/F=42/58, age(yr)=35-75 **Intervention group**: 50 **Control group**: 50	Not reported	Auricular acupressure + usual care	Usual care	- CINV
S5: Zhang et al., 2013 RCT, Hangzhou TCM Hospital, Hangzhou, China	Breast cancer	**Randomized**=80 **Completed**=80 **Intervention group**: 40, age(yr)=29-65 (mean: 47) **Control group**: 40, age(yr)=32-67 (mean: 48)	Not Reported	Auricular acupuncture + antiemetic medications (tropisetron, 5mg, iv, qd)	Antiemetic medications (tropisetron, 5mg, iv, qd)	- CINV

S6: Yeh et al., 2012b RCT (crossover design), a large children's hospital, Taiwan	Pediatric cancers	**Randomized**=10 **Completed**=10 M/F=6/4, age(yr)=13.29±3.31 (range from 6 to 18) **Intervention group**: NR **Control group**: NR (crossover after first treatment)	Cyclophosphamide	Auricular acupressure + antiemetic medications (ondansetron or granisetron + dexamethasone)	Auricular acupressure using sham acupoints + Antiemetic medications (ondansetron or granisetron + dexamethasone)	- CINV - Adverse events - Booklet used to record intensity and duration of acupressure technique
S7: Zhang et al., 2012 RCT, The First Affiliated Hospital of GUCM, Guangzhou, China	Acute leukemia	**Randomized**=100 **Completed**=100 **Intervention group**: 50, M/F=24/26, age(yr)=45±14.8 (range from 17 to 64) **Control group**: 50, M/F=23/27, age(yr)=44±15.2 (range from 14 to 62)	DA combination (daunorubicin + cytarabine) or VP combination (vincristine + prednisone)	Auricular acupressure + antiemetic medications (ondansetron, 8mg, iv, qd)	Antiemetic medications (ondansetron, 8mg, iv, qd)	- CINV - Food intake
S8: Jiang, 2012 RCT, Zhejiang Cancer Hospital, Hangzhou, China	Not specified	**Randomized**=85 **Completed**=85 **Intervention group**: 43, M/F=27/16, age(yr)=36 to 75 **Control group**: 42, M/F=25/17, age(yr)=33 to 72	Combined chemotherapy based on cisplatin or adriamycin	Auricular acupressure + antiemetic medication (granisetron, 8mg, iv, qd)	Antiemetic medication (granisetron, 8mg, iv, qd)	- CINV - Adverse events
S9: Zhong et al., 2012 RCT (crossover design), The First Hospital of Wuhan, Wuhan, China	Lung cancer Breast cancer Gastric cancer Colon cancer Ovarian cancer Cervical cancer Tongue cancer Endometrial cancer Nasopharynx cancer	**Randomized**=100 **Completed**=94, M/F=58/42, age(yr)=17-70 (mean: 52.3) **Intervention group**: NR **Control group**: NR (crossover after first treatment)	GP combination (gemcitabine + cisplatin) or TP combination (docetaxel + cisplatin) or ac combination (adriamycin + cyclophosphamide) or DF combination (cisplatin + fluorouracil), etc.	Auricular acupressure + antiemetic medications (tropisetron, qd + diphenhydramine, qd + dexamethasone, qd)	Antiemetic medications (tropisetron, qd + diphenhydramine, qd + dexamethasone, qd)	- CINV - Constipation

S10: Lu, 2012 RCT, Ningbo TCM Hospital of Zhejiang Province, Ningbo, China	Breast cancer	**Randomized**=128 **Completed**=128 **Intervention group**: 64, age(yr)=45.10±10.42, **Control group**: 64, age(yr)=52.96±6.11	CAF combination (cyclophosphamide + adriamycin + fluorouracil) or CMF combination (cyclophosphamide + methotrexate + fluorouracil)	Auricular acupressure + antiemetic medication (granisetron, 3mg, iv, qd)	Antiemetic medication (granisetron, 3mg, iv, qd)	- CINV
S11: Huang et al., 2012 RCT, The First Hospital of Wuhan, Wuhan, China	Breast cancer	**Randomized**=80 **Completed**=80, age(yr)=28-65 (mean: 46.5) **Intervention group**: 40 **Control group**: 40	Anthracycline-based combination	Auricular acupressure + antiemetic medications (tropisetron, 4mg, iv, bid)	Antiemetic medications (tropisetron, 4mg, iv, bid)	- CINV - Constipation
S12: Wang, 2012 RCT, Xuzhou TCM Hospital of Jiangsu Province, Xuzhou, China	Breast cancer	**Randomized**=52 **Completed**=52, age(yr)=47.4 (mean) **Intervention group**: 26, **Control group**: 26	Cyclophosphamide or fluorouracil or adriamycin or taxol or doxorubicin or navelbine	Auricular acupressure + antiemetic medications (azasetron, 10mg, iv + omeprazole, 40mg, iv)	Antiemetic medications (azasetron, 10mg, iv + omeprazole, 40mg, iv)	- CINV - Constipation - Abdominal bloating - Abdominal pain - Headache
S13: Huang, 2011 RCT, The First Hospital of Shangqiu City, Shangqiu, China	Lung cancer Gastric cancer Colon cancer Breast cancer	**Randomized**=120 **Completed**=120 M/F=70/50, age(yr)=30-76 **Intervention group**: 60 **Control group**: 60	Not reported	Auricular acupressure + antiemetic medications (azasetron)	Antiemetic medications (azasetron)	- CINV - Physical performance status
S14: Liu & Chen, 2001 RCT, The First Affiliated Hospital of GUCM, Guangzhou, China	Lung cancer	**Randomized**=127 **Completed**=127 **Intervention group**: 85, M/F=53/32, age(yr)=56±11.4 (range from 31 to 75) **Control group**: 42, M/F=23/19, age(yr)=51±10.9 (range from 35 to 75)	Platinum-based chemotherapy	Auricular acupressure + antiemetic medications (granisetron, 3mg, iv, bid or ondansetron, 8mg, iv, bid)	Antiemetic medications (granisetron, 3mg, iv, bid or ondansetron, 8mg, iv, bid)	- CINV - Physical performance status

S15: Ye et al., 2011 RCT, The General Hospital of Chinese People's Liberation Army, Beijing, China	Not specified	**Randomized**=47 **Completed**=47 **Intervention group**: 27, M/F=15/12, age(yr)=58±12 (range from 33 to 76), **Control group**: 20, M/F=11/9, age(yr)=57±11 (range from 40 to 78)	Not reported	Auricular acupressure + antiemetic medications (tropisetron, 4mg, iv, bid)	Auricular acupressure using sham acupoints + Antiemetic medications (tropisetron, 4mg, iv, bid)	- CINV - Constipation
S16: Bi, 2011 RCT, LongHua Hospital Affiliated to SUTCM, Shanghai, China	Gastrointestinal cancer	**Randomized**=50 **Completed**=50, M/F=23/27, age(yr)=45.27 **Intervention group**: 25 **Control group**: 25	Cisplatin + fluorouracil	Auricular acupressure + antiemetic medications (ondansetron, basic dose: 8mg, iv, qd)	Antiemetic medications (ondansetron, basic dose: 8mg, iv, qd)	- Use of antiemetic medications
S17: Luo, 2011 RCT, The First Affiliated Hospital of GUCM, Guangzhou, China	Lung cancer Colon cancer Breast cancer Gastric cancer Ovarian cancer Nasopharynx cancer	**Randomized**=50 **Completed**=50 age(yr)=20 to 80 (mean:52.24±10.75) I**ntervention group**: 26, M/F=12/14, **Control group**: 24, M/F=9/15	Platinum-based chemotherapy	Auricular acupressure + antiemetic medications (granisetron, 3 mg, iv, bid)	Antiemetic medications (granisetron, 3 mg, iv, bid)	- CINV - Adverse events - Clinical symptoms - Physical performance status
S18: Jing, 2007 RCT, Jiangsu Province Hospital of TCM, Nanjing, China	Not specified	**Randomized**=54 **Completed**=54 **Intervention group**: 30, M/F=20/10, age(yr)=47.65 **Control group**: 24, M/F=16/8, age(yr)=47.59	Platinum-based chemotherapy	Auricular acupressure + antiemetic medications (ondansetron, 8mg, iv, qd)	Antiemetic medications (ondansetron, 8mg, iv, qd)	- CINV
S19: Qian et al., 2006 RCT, LongHua Hospital Affiliated to SUTCM, Shanghai, China	Lung cancer Breast cancer Gastrointestinal cancer	**Randomized**=67 **Completed**=67, M/F=35/32, age(yr)=39-77 **Intervention group**: 36 **Control group**: 31	Combined chemotherapy based on cisplatin or fluorouracil	Auricular acupressure + antiemetic medications (ondansetron, 8mg, iv, qd)	Antiemetic medications (ondansetron, 8mg, iv, qd)	- CINV

S20: Zhang et al., 2003 RCT, LongHua Hospital Affiliated to SUTCM, Shanghai, China	Respiratory cancer Gastrointestinal cancer	**Randomized**=173 **Completed**=173 **Intervention group**: 70, M/F=28/42, age(yr)=25-78 **Control group**: **1**: 50, M/F=19/31, age(yr)=24-77 **Control group 2**: 53, M/F=23/30, age(yr)=26-76	MVP combination (mitomycin + vindesine + cisplatin) or NP combination (navelbine + cisplatin) or FAM combination (fluorouracil + adriamycin + mitomycin), etc.	Auricular acupressure	Control group 1: Antiemetic medications (ondansetron, 8mg, iv, qd) Control group 2: Antiemetic medications (metoclopramide, 20mg, im, qd)	- CINV
S21: Sun, 2003 RCT, The Affiliated Hospital of SDUTCM, Jinan, China	Breast cancer	**Randomized**=80 **Completed**=80, **Intervention group**: 40, age(yr)=41.5, **Control group**: 40, age(yr)=42.3	Not reported	Auricular acupressure	Antiemetic medications (metoclopramide, 30mg, iv)	- CINV

Note: a=study; RCT=randomized controlled trial; CINV=chemotherapy-induced nausea and vomiting; SUCM=Shanxi University of Chinese Medicine; iv=intravenous; qd=once a day; TCM=Traditional Chinese Medicine; NR=not reported; GUCM=Guangzhou University of Chinese Medicine; bid=twice a day; SUTCM=Shanghai University of Traditional Chinese Medicine; SDUTCM=Shandong University of Traditional Chinese Medicine

4.2.3.2 Description of AT protocols

A summary of the AT protocols utilized in the included studies is presented in **Table 4.3**. All of the studies briefly described their AT protocols, which included the selection and identification of targeted auricular acupoints, instructions on manual pressing, and duration of treatment. Of the studies that employed auricular acupressure as the therapeutic approach, vaccaria seeds were the most commonly applied pellets (16 studies), while magnet pellets (one study) and radish seeds (one study) were also used for acupressure. The number of selected acupoints ranged from three to 11, with three to seven main acupoints and two to four adjunct points. Among these acupoints, "s*henmen*" (21 studies) and "stomach" (21 studies) were the most commonly selected main acupoints, followed by "sympathetic" (14 studies), "spleen" (12 studies), "liver" (10 studies), "subcortex" (eight studies), and "cardia" (six studies), which were applied as additional main or adjunct ear acupoints.

Fourteen studies described the methods used for acupoint identification—and an acupoint detector (an electronic finder) was used in 10 studies and cotton swabs or needles were used in four studies—whereas the other seven studies did not specify their method for acupoint identification. The instructions on manual acupressure of taped pellets varied. The frequencies of manual acupressure ranged from three to eight times a day, and the duration of acupressure for each acupoint was quite inconsistent among the studies. Pressing each acupoint for no more than two minutes was mentioned in six studies (D. Li, 2013; Liu & Chen, 2011; Luo, 2011; Sun, 2003; Y. Wang, 2012; Zhang et al., 2012); however, four studies (Jiang, 2012; Qian et al., 2006; Ye et al., 2011; Zhang et al., 2003) required the participants to press each acupoint for three to five minutes each time. A sensation of *de qi* was described in the majority of the included studies to indicate a sign of therapeutic efficacy. *De qi*, as mentioned, is a TCM terminology that illustrates a subjective feeling of numbness, pressure sensation, soreness, or distension induced by acupoint stimulation such as acupuncture or acupressure, which is viewed as an immediate indicator of accurate acupoint location and treatment efficacy (Luo, 2011). Some studies informed the participants to press the acupoints before meals and/or before and after chemotherapy, and in addition to the regular manual acupressure, three studies (Liu & Chen, 2011; Yeh, Chien, Chiang, Lin et al., 2012; Zhang et al., 2013) also required the participants to press the seeds as soon as they had a feeling of nausea and vomiting.

The treatment duration varied significantly among the studies. One study (Zhang et al., 2013) used a one-day-only AT, one study (Ye et al., 2011) conducted a two-day treatment, one study (Fang, 2013) utilized AT for three days, and five studies (Jiang, 2012; Luo, 2011; Y. Wang, 2012; Yeh, Chien, Chiang, Lin et al., 2012; Zhang et al., 2012) applied the intervention for seven days, while nearly half of the included trials provided AT during the whole chemotherapy cycle. Unfortunately, those studies that designed an AT treatment for a complete chemotherapy cycle failed to specify the specific length of each treatment. Apart from these treatment durations, the longest treatment course was found in one study (Zhong et al., 2012), which was 27 days for one AT treatment over two treatments in total.

Table 4.3 AT treatment protocols used in the included trials

Study	Types of Auricular Therapy	Selected Auricular Acupoints (No.) Main Acupoints (M), Adjunct Acupoints (A)	Acupoints Detection	Instructions of Manual Acupressure	Duration of Treatment
S[a]1	Auricular acupressure using vaccaria seeds	**4**: Stomach, Liver, Spleen, *Shenmen*	Not reported	3-5 times/day for 1-2 minutes/time until *de qi* [b]	Not reported
S2	Auricular acupressure using vaccaria seeds	**6**: Spleen, Stomach, Liver, *Shenmen*, Sympathetic, *Sanjiao*	Acupoint detector	5-6 times/day for 2-3 minutes/acupoint/time until *de qi*	A complete chemotherapy cycle
S3	Auricular acupressure using magnet pellets	**M (7)**: Stomach, Cardia, Esophagus, Sympathetic, *Shenmen*, Spleen, Liver **A (4)**: Lung, Pancreas, Gallbladder, Adrenal Gland	Acupoint detector	Several times/day for 1-2 minutes/acupoint/time until *de qi*	Not reported
S4	Auricular acupressure using plant seeds	**4**: Stomach, *Shenmen*, Sympathetic, Adrenal Gland	Not reported	3-4 times/day for 3 minutes/time	3 days
S5	Auricular acupuncture	**M (3)**: Stomach, *Shenmen*, Sympathetic **A (2)**: Liver, Spleen	Acupoint detector	4-5 times/day for 1 minute/time, press when feeling nausea or vomiting	1 day
S6	Auricular acupressure using plant seeds	**5**: *Shenmen*, Sympathetic, Cardia, Stomach, Digestive Subcortex	Acupoint detector	At least 3 times/day for at least 3 periods of 3-minute duration, and press as soon as feeling the symptom of nausea	7 days
S7	Auricular acupressure using vaccaria seeds	**M (3)**: Stomach, Sympathetic, *Shenmen* **A (4)**: Liver, Spleen, Cardia, Esophagus	Not reported	5-6 times/day for 2 minutes/acupoint/time until *de qi*	7 days
S8	Auricular acupressure using radish seeds	**5**: *Shenmen*, Stomach, Sympathetic, Spleen, Large Intestine	Acupoint detector	4 times/day for 5 minutes/acupoint/time until *de qi*	7 days
S9	Auricular acupressure using vaccaria seeds	**7**: Stomach, Liver, Spleen, Cardia, *Shenmen*, Sympathetic, Subcortex	Not reported	3 times (morning, noon, night)/day for 5 minutes/time until *de qi*	27 days for one treatment, 2 treatments in total (crossover after the first intervention)
S10	Auricular acupressure using vaccaria seeds	**4**: Stomach, *Shenmen*, Sympathetic, Endocrine	Acupoint detector	Regularly press until *de qi*	Not reported
S11	Auricular acupressure using vaccaria seeds	**M (3)**: Stomach, Sympathetic, *Shenmen* **A (3)**: Liver, Spleen, Large Intestine	Not reported	3-4 times/day for 2 minutes/time until *de qi*	A complete chemotherapy cycle

S12	Auricular acupressure using vaccaria seeds	**7**: Endocrine, *Shenmen*, Sympathetic, Stomach, Cardia, Spleen, *Sanjiao*	Acupoint detector	8 times (before and after three meals and chemotherapy)/day for 1 minute/acupoint/time until *de qi*	7 days
S13	Auricular acupressure using vaccaria seeds	**M (5)**: Stomach, Cardia, Esophagus, *Shenmen*, Small Intestine **A (2)**: Large Intestine, Rectum	Acupoint detector	4-6 times/day for 60-150 seconds/acupoint/time until *de qi*	A complete chemotherapy cycle
S14	Auricular acupressure using vaccaria seeds	**7**: Lung, Spleen, Stomach, Center of Ear, Large Intestine, *Shenmen*, Subcortex	Not reported	3 times/day for 1-2 minutes/acupoint/time until *de qi*, press when feeling the symptom of nausea or vomiting	A complete chemotherapy cycle
S15	Auricular acupressure using vaccaria seeds	**M (4)**: Stomach, *Shenmen*, Liver, Subcortex **A (4)**: Spleen, Lung, Kidney, Heart	Not reported	5-6 times/day for 3-5 minutes/acupoint/time until *de qi*	2 days
S16	Auricular acupressure using vaccaria seeds	**3**: Stomach, *Shenmen*, Subcortex	Acupoint detector	4-5 times/day for 10-15 minutes/time until *de qi*	A complete chemotherapy cycle
S17	Auricular acupressure using vaccaria seeds	**6**: *Shenmen*, Stomach, Sympathetic, Subcortex, Center of Ear, Spleen	Cotton swab	3-5 times/day for 30-60 seconds/acupoint/time until *de qi*	7 days
S18	Auricular acupressure using vaccaria seeds	**3**: Stomach, *Shenmen*, Subcortex	Acupoint detector	4-5 times/day for 10-15 minutes/time until *de qi*	From the day prior to current chemotherapy cycle to two days after the completion of the current cycle
S19	Auricular acupressure using vaccaria seeds	**3**: Stomach, *Shenmen*, Sympathetic	Needle	5-6 times/day for 3-5 minutes/acupoint/time until *de qi*	A complete chemotherapy cycle
S20	Auricular acupressure using vaccaria seeds	**M (3)**: Stomach, *Shenmen*, Sympathetic **A (2)**: Liver, Subcortex	Needle	5-6 times/day for 3-5 minutes/acupoint/time until *de qi*	A complete chemotherapy cycle
S21	Auricular acupressure using vaccaria seeds	**M (4)**: Stomach, *Shenmen*, Subcortex, Center of Ear **A (2)**: Liver, Occiput	Cotton swab	3-5 times/day for 1-2 minutes/acupoint/time until *de qi*	A complete chemotherapy cycle

Note: a=study; b=*de qi*: a subjective feeling of numbness, pressure sensation, heaviness, soreness, or distension (Luo, 2011)

4.2.3.3 Methodological quality and risk of bias of the included studies

Table 4.4 shows the methodological assessment of the included trials. Significant methodological flaws were identified. Randomization was mentioned in all of the studies, but only three described the details of generating the random sequence by a random number table or computer-based randomization. One study did not have blinding for participants, and for all the other studies, there was no sufficient information to judge whether they applied adequate blinding or not. All of the 21 studies failed to specify whether they conducted allocation concealment. One study reported the dropout rate of subjects but failed to perform an ITT analysis to handle missing data, and two studies selectively reported the study outcomes. In terms of "other bias," no studies claimed that they had calculated the sample size to determine how many subjects were appropriate for their study, except for one pilot study that had estimated the effect size of the primary outcome for sample size calculation in a future main trial; baseline assessment was reported in the majority of the analyzed studies; more than half of the studies clearly described the diagnostics and the inclusion and exclusion criteria for study participants; all of the studies described the therapeutic evaluation criteria for the primary or secondary outcomes; only three studies included adverse events as a secondary outcome; and 18 studies clearly described the statistical methods used for data analysis.

Table 4.4 Methodological quality assessment of the included trials

Criteria	S[a]1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	S21
Random sequence generation	√	?	?	?	?	√	√	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Allocation concealment	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Blinding of participants and personnel	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	×	?	?	?	?
Blinding of outcome assessment	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Incomplete outcome data	?	?	?	?	?	?	?	?	×	?	?	?	?	?	?	?	?	?	?	?	?
Selective outcome reporting	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	√	√	√	√	√	√
Other bias	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
- Sample size calculation	×	×	×	×	×	NA[b]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
- Baseline assessment	√	√	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√
- Diagnostic criteria	√	√	√	√	×	×	√	√	√	√	×	×	√	√	√	×	√	×	√	√	×
- Inclusion criteria	√	√	√	√	√	√	√	√	√	×	×	×	×	√	√	×	√	×	×	√	×
- Exclusion criteria	×	√	√	√	√	×	√	×	√	√	×	×	√	×	√	×	√	×	×	×	√
- Evaluation of therapeutic effect	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
- Report of adverse events	×	×	×	×	×	√	×	√	×	×	×	×	×	×	×	×	√	×	×	×	×
- Method of data analysis	√	√	×	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×

Note: Based on the *Cochrane Handbook for Systematic Reviews of Intervention* (Part 2: 8.5.); a=study; √=low risk of bias; ×=high risk of bias; ?=unclear risk of bias; b=NA: not applicable due to the design of the pilot study

4.2.3.4 Therapeutic effects of AT

Table 4.5 summarizes the therapeutic effects of AT on CINV. Twenty studies specified the criteria used to evaluate the therapeutic effect of AT on managing nausea and emesis. The most common tool utilized was the WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (17 studies). One study (Yeh, Chien, Chiang, Lin et al., 2012) employed the Morrow Assessment of Nausea and Emesis (MANE) Scale, one (Luo, 2011) used the National Cancer Institute (NCI) Common Toxicity Criteria, and one (Bi, 2011) used different dosages of antiemetic medications received between the groups to evaluate the therapeutic effects of AT. For studies that employed the WHO or the NCI Criteria, the therapeutic effects were normally classified into three categories, including "markedly effective," "effective," and "not effective." However, the cutoff point for each category was inconsistent among the studies, and more than half used the grades 0 to 2 to represent "markedly effective" and "effective," which means no nausea and vomiting or experienced only transient vomiting, and a grade of 3 and above indicated "not effective," which means uncontrolled or intractable vomiting requiring additional therapy.

Due to the significant methodological flaws and clinical heterogeneity identified in the included trials, meta-analysis was not conducted and a descriptive analysis was employed instead to summarize the therapeutic effects of AT for both the primary and secondary outcomes. Among all the analyzed trials, the effective rate of the management of acute CINV ranged from 44.44% to 93.33% in the intervention groups and 15% to 91.67% in the control groups. For delayed CINV, the rates were 62.96% to 100% and 25% to 100%, respectively.

Of the 15 studies that compared auricular acupressure plus antiemetic medications with antiemetic medications alone, the combination of AT and medications was found to be more effective in controlling CINV than using antiemetic drugs alone, with the effectiveness rate ranging from 84.62% to 100% in the intervention groups and 34.38% to 100% in the control groups. However, only four studies (Jiang, 2012; Jing, 2007; Luo, 2011; Zhang et al., 2012) separately investigated the therapeutic effects of auricular acupressure for either acute or delayed CINV, of which one study (Jiang, 2012) reported significantly better outcomes for both acute and delayed CINV in the intervention groups compared with those in the control groups, and

one (Jing, 2007) detected a slightly positive trend of AT in managing acute CINV and a significantly better effect for controlling delayed nausea and vomiting. One study (Zhang et al., 2012) found no difference between groups for the management of acute CINV (effectiveness rate was 88% in both groups), and a positive effect of AT was detected only for delayed nausea and vomiting, where the effectiveness rate ranged from 90% to 94% in the intervention group and 70% to 78% in the control group from day 2 to day 7 of the chemotherapy cycle. One study (Luo, 2011) showed that AT plus antiemetic drugs was only slightly more effective in relieving acute vomiting compared with using antiemetic drugs alone.

There was only one study that employed auricular acupuncture as an adjunct to conventional antiemetic medications, and CINV was also evaluated according to the WHO Recommendations (Zhang et al., 2013). Auricular acupuncture combined with antiemetic agents was reported to be more effective than using antiemetic agents alone, with the effectiveness rate at 87.50% in the intervention group and 45% in the control group. However, conflicting results were reported for both comparisons of "auricular acupressure versus sham acupressure" (Ye et al., 2011; Yeh, Chien, Chiang, Lin et al., 2012) and "auricular acupressure alone versus antiemetic drugs alone" (Sun, 2003; Zhang et al., 2003), where significant differences between groups were stated in two studies (Sun, 2003; Ye et al., 2011), while the other two (Yeh, Chien, Chiang, Lin et al., 2012; Zhang et al., 2003) reported no significant differences.

In addition to the primary outcome, some studies also focused on the effects of AT on physical performance status and emotional conditions among cancer patients undergoing chemotherapy. Three studies (Y. Huang, 2011; Liu & Chen, 2011; Luo, 2011) employed physical performance status as the secondary outcome, which showed a favorable effect (as measured by the Karnofsky Performance Scale Index) in the intervention groups compared with the control groups. One study (You et al., 2013) evaluated patients' emotional conditions (as measured by the Hamilton Anxiety/Depression Scale) and reported positive effects of AT on relieving patients' anxiety and depression symptoms. Regarding the adverse events identified in the analyzed literature, one study (Yeh, Chien, Chiang, Lin et al., 2012) reported adverse events caused by pellet tapes, which was itching in three cases. In another study (Jiang, 2012), the reported adverse events were adverse drug reactions caused by antiemetic medications, such as

constipation, headache, and fatigue, and the author compared the incidence of these events between groups and stated that AT could also relieve adverse drug reactions.

Table 4.5 Therapeutic effects of AT on CINV and reports of adverse events in the included trials

Study	Evaluation of Therapeutic Effects	Therapeutic Effects			Effectiveness Rates	Adverse Eevents
		Markedly Effective (No.)	Effective (No.)	Not Effective (No.)		
Sª 1	Not reported	Not reported	Nausea: I=53 (88.33%), C=47 (78.33%) Vomiting: I=55 (91.67%), C=48 (80.00%)	Nausea: I=7 (11.67%), C=13 (21.67%) Vomiting: I=5 (8.33%), C=12 (20.00%)	Nausea: I=88.33%, C=78.33% Vomiting: I=91.67%, C=80.00%	Not reported
S 2	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0 I=3 (7.89%), C=1(5.00%)	Grade 1 I=34 (89.47%), C=15 (75.00%)	Grade 2-4 I=1 (2.63%), C=4 (20.00%)	I=97.37%, C=80.00%	Not reported
S 3	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=11 (68.75%), C=7 (43.75%)	Grade 2 1=5 (31.25%), C=6 (37.50%)	Grade 3-4 I=0 (0.00%), C=3 (18.75%)	I=100.00%, C=81.25%	Not reported
S 4	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=38 (76.00%), C=12 (24.00%)	Grade 2-3 I=7 (14.00%), C=18 (36.00%)	Grade 4 I=5 (10.00%), C=20 (40.00%)	I=90.00%, C=60.00%	Not reported
S 5	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0 I=13 (32.50%), C=7 (17.50%)	Grade 1-2 I=22 (55.00%), C=11 (27.50%)	Grade 3-4 I=5 (12.50%), C=22 (55.00%)	I=87.50%, C=45.00%	Not reported
S 6	Morrow Assessment of Nausea and Emetics	True auricular acupressure group showed it had a better impact on managing CINV compared with the usual care group (p<0.05); no difference in CINV was found between the true auricular acupressure group and the sham auricular acupressure group.			Not applicable	Itching of tapes (n=3)

S 7	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4), Diagnostic Standard for TCM Differentiation of Symptoms and Signs	Grade 0-1 **Day 1: Acute CINV** I=12 (24.00%), C=12(24.00%) **Day 2-7: Delayed CINV** Day 2: I=12 (24.00%), C=8 (16.00%) Day 3: I=13 (26.00%), C=10 (20.00%) Day 4: I=13 (26.00%), C=10 (20.00%) Day 5: I=12 (24.00%), C=8 (16.00%) Day 6: I=13 (26.00%), C=10 (20.00%) Day 7: I=13 (26.00%), C=10 (20.00%)	Grade 2 **Day 1: Acute CINV** I=32 (64.00%), C=32 (64.00%) **Day 2-7: Delayed CINV** Day 2: I=34 (68.00%), C=30 (60.00%) Day 3: I=33 (66.00%), C=29 (58.00%) Day 4: I=33 (66.00%), C=29 (58.00%) Day 5: I=33 (66.00%), C=28 (56.00%) Day 6: I=34 (68.00%), C=25 (50.00%) Day 7: I=34 (68.00%), C=26 (52.00%)	Grade 3-4 **Day 1: Acute CINV** I=6 (12.00%), C=6 (12.00%) **Day 2-7: Delayed CINV** Day 2: I=4 (8.00%), C=12 (24.00%) Day 3: I=4 (8.00%), C=11 (22.00%) Day 4: I=4 (8.00%), C=11 (22.00%) Day 5: I=5 (10.00%), C=14 (28.00%) Day 6: I=3 (6.00%), C=15 (30.00%) Day 7: I=3 (6.00%), C=14 (28.00%)	**Day 1: Acute CINV** I=88.00%, C=88.00% **Day 2-7: Delayed CINV** Day 2: I=92.00%, C=76.00% Day 3: I=92.00%, C=78.00% Day 4: I=92.00%, C=78.00% Day 5: I=90.00%, C=72.00% Day 6: I=94.00%, C=70.00% Day 7: I=94.00%, C=72.00%	Not reported
S 8	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0 **Day 1: Acute CINV** I=0 (00.00%), C=0 (00.00%) **Day 2-7: Delayed CINV** I=0 (00.00%), C=0 (00.00%)	Grade 1-2 **Day 1: Acute CINV** I=39 (90.70%), C=29 (69.05%) **Day 2-7: Delayed CINV** I=43 (100.00%), C=36 (85.71%)	Grade 3-4 **Day 1: Acute CINV** I=4 (9.30%), C=13 (30.95%) **Day 2-7: Delayed CINV** I=0 (00.00%), C=6 (14.29%)	**Day 1: Acute CINV** I=90.70%, C=69.05% **Day 2-7: Delayed CINV** I=100.00%, C=85.71%	I: Fatigue (n=1), Constipation (n=11) C: Headache (n=2), Constipation (n=20), Fatigue (n=5)
S 9	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0 I=44 (46.81%), C=23 (24.47%)	Grade 1-2 I=45 (47.87%), C=58 (61.70%)	Grade 3-4 I=5 (5.32%), C=13 (13.83%)	I=94.68%, C=86.17%	Not reported
S 10	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Complete relief (Grade 0) I=28 (43.75%), C=4 (6.25%)	Partial relief (Grade 1-2) I=32 (50.00%), C=18 (28.13%)	Minor relief + failure (Grade 3-4) I=4 (6.25%), C=42 (65.63%)	I=93.75%, C=34.38%	Not reported
S 11	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=28 (70.00%), C=23 (57.50%)	Grade 2 I=10 (25.00%), C=9 (22.50%)	Grade 3-4 I=2 (5.00%), C=8 (20.00%)	I=95.00%, C=80.00%	Not reported
S 12	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=19 (73.08%), C=12 (46.15%)	Grade 2 I=6 (23.08), C=9 (34.62%)	Grade 3-4 I=1 (3.85%), C=5 (19.23%)	I=96.15%, C=80.77%	Not reported

S 13	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=32 (53.33%), C=7 (11.67%)	Grade 2 I=20 (33.33%), C=24 (40.00%)	Grade 3-4 I=8 (13.33%), C=29 (48.33%)	I=86.67%, C=51.67%	Not reported
S 14	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0 I=16 (18.82), C=5 (11.90%)	Grade 1 I=62 (72.94%), C=27 (64.29%)	Grade 2-4 I=7 (8.24%), C=10 (23.81%)	I=91.76%, C=76.19%	Not reported
S 15	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 **Acute CINV** I=5 (18.52%), C=1 (5.00%) **Delayed CINV** I=11 (40.74%), C=1 (5.00%)	Grade 2 **Acute CINV** I=7 (25.93%), C=2 (10.00%) **Delayed CINV** I=6 (22.22%), C=4 (20.00%)	Grade 3-4 **Acute CINV** I=15 (55.56%), C=17 (85.00%) **Delayed CINV** I=10 (37.04%), C=15 (75.00%)	**Acute CINV** I=44.44%, C=15.00% **Delayed CINV** I=62.96%, C=25.00%	Not reported
S 16	Use of antiemetic medications (ondansetron), (categories: > 20mg/d, 10-20mg/d, and < 10mg/d)	Number of patients using ondansetron at a dose of > 20mg/d in the intervention group was significantly less than those in the control group; number of patients using ondansetron at a dose of < 10mg/d in the intervention group was significantly more than those in the control group; no statistical difference was found in the number of patients using ondansetron at a dose of 10-20mg/d between groups.				Not reported
S 17	National Cancer Institute (NCI)-Common Toxicity Criteria, Version 2.0 (Vomiting, Grade 0-4)	Complete Relief (Vomiting Grade 0) **Day 1: Acute Vomiting** I=18 (75.00%), C=16 (66.67%) **Day 2-7: Delayed Vomiting** Day 2: I=18 (69.23%), C=10 (41.67%) Day 3: I=17 (65.38%), C=9 (37.50%) Day 4: I=15 (57.69%), C=7 (29.17%) Day 5: I=16 (61.54%), C=8 (33.33%) Day 6: I=19 (73.08%), C=11 (45.83%) Day 7: I=25 (96.15%), C=18 (75.00%)	Partial Relief (Vomiting Grade 1) **Day 1: Acute Vomiting** I=3 (12.50%), C=4(16.67%) **Day 2-7: Delayed Vomiting** Day 2: I=5 (19.23%), C=8 (33.33%) Day 3: I=5 (19.23%), C=10 (41.67%) Day 4: I=8 (30.77%), C=15 (62.50%) Day 5: I=8 (30.77%), C=15 (62.50%) Day 6: I=6 (23.08%), C=13 (54.17%) Day 7: I=1 (3.85%), C=6 (25.00%)	Minor Relief + Failure (Vomiting Grade 2-4) **Day 1: Acute Vomiting** I=3 (12.50%), C=4(16.67%) **Day 2-7: Delayed Vomiting** Day 2: I=3 (11.54%), C=6 (25.00%) Day 3: I=4 (15.38%), C=5 (20.83%) Day 4: I=3 (11.54%), C=2 (8.33%) Day 5: I=2 (7.69%), C=1 (4.17%) Day 6: I=1 (3.85%), C=0 (00.00%) Day 7: I=0 (00.00%), C=0 (00.00%)	**Day 1: Acute Vomiting** I=87.50%, C=83.33% **Day 2-7: Delayed Vomiting** Day 2: I=88.46%, C=75.00% Day 3: I=84.62%, C=79.17% Day 4: I=88.46%, C=91.67% Day 5: I=92.31%, C=95.83% Day 6: I=96.15%, C=100.00% Day 7: I=100.00%, C=100.00%	No adverse events
S 18	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)[b]	Grade 0 **Acute CINV** I=19 (63.33%), C=14 (58.33%) **Delayed CINV** I=18 (60.00%), C=8 (33.33%)	Grade 1 **Acute CINV** I=9 (30.00%), C=8 (33.33%) **Delayed CINV** I=9 (30.00%), C=6 (25.00%)	Grade 2-4 (Minor Relief + No Effect) **Acute CINV** I=2 (6.67%), C=2 (8.33%) **Delayed CINV** I=3 (10.00%), C=10 (41.67%)	**Acute CINV** I=93.33%, C=91.67 **Delayed CINV** I=90.00%, C=58.33%	Not reported

S 19	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)	Grade 0-1 I=32 (88.89%), C=11 (35.48%)	Grade 2 I=3 (8.33%), C=12 (38.71%)	Grade 3-4 I=1 (2.78%), C=8 (25.81%)	I=97.22%, C=74.19%	Not reported
S 20	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)[c]	Grade 0-1 I=46 (65.71%), C1=33 (66.00%), C2=15 (28.30%)	Grade 2 I=14 (20.00%), C1=11 (22.00%), C2=18 (33.96%)	Grade 3 I=10 (14.29%), C1=6 (12.00%), C2=20 (37.74%)	I=85.71%, C1=88.00%, C2=62.26%	Not reported
S 21	WHO Recommendations for Grading of Acute and Sub-Acute Toxicity (Nausea/Vomiting, Grade 0-4)[c]	Grade 0-1 I=16 (40.00%), C=7 (17.50%)	Grade 2 I=18 (45.00%), C=10 (25.00%)	Grade 3 I=6 (15.00%), C=23 (57.50%)	I=85.00%, C=42.50%	Not reported

Note: a=study; I=intervention group; C=control group; WHO=World Health Organization; CINV=chemotherapy-induced nausea and vomiting; NA=not applicable; b=the study used the WHO recommendations to judge the incidence and severity of nausea and vomiting, but failed to specify the source of the criteria; c=the study only applied the first four grades (grade 0-3) to evaluate the incidence and severity of nausea and vomiting

4.2.4 Discussion of the study results and limitations and summary of evidence

Encouraging results of AT for CINV management were reported in the analyzed studies. However, because the methodological quality of the included trials was generally poor, a definite effect is uncertain and the strength of evidence on AT in alleviating CINV is limited and not convincing.

In the analyzed studies, "*shenmen*," "stomach," "sympathetic," "spleen," and "liver" were the most popular selected auricular acupoints for controlling CINV. According to the AT theories (which were mentioned in Chapter 3), "*shenmen*," located in the apex of the triangular fossa, is the most commonly referred main acupoint for controlling nausea and vomiting, with the role of tranquilizing the mind, promoting serenity, and soothing the nerves (Bai, 1994, pp. xiii-88; Guan et al., 2002, pp.33-199). "Stomach," which can be found on the medial concha ridge, is another main acupoint for treating gastrointestinal disorders and it has the potential of harmonizing the stomach and rectifying *qi* (Guan et al., 2002, pp. 33-199). "Sympathetic" is also widely used for managing nausea and emesis by reducing hyper-responsiveness of the sympathetic nervous system and alleviating spasms in gastrointestinal smooth muscles (Bai, 1994, pp. xiii-88; Guan et al., 2002, pp. 33-199). "Spleen" is believed to be internally and externally linked with the stomach and it is involved in all muscular movements, whereas "liver" is mainly responsible for facilitating the free flow of *qi*. When dealing with CINV, "spleen" and "liver" are chosen for strengthening the stomach functions and relieving muscle tension and spasms (Bai, 1994, pp. xiii-88; Guan et al., 2002, pp.33-199).

All of the studies described their AT treatment protocols. Reference to identifying auricular acupoints was seldom mentioned in these studies, except for two that used Huang's ear reflex theory (Yeh, Chien, Chiang, Lin et al., 2012) and the Chinese standard ear acupoints chart (Luo, 2011). It is suggested that future studies use the Chinese standard ear acupoints chart as a guide for locating and identifying auricular acupoints, which could improve international recognition of AT. Meanwhile, the former widely used Chinese standard ear acupoints chart, which was recommended by the WHO in 1992, was updated in 2008, which is now the Chinese standard ear acupoints chart—*Nomenclature and Location of Auricular Points* (GB/T-13734-2008) (National Standard Information Sharing Infrastructure, 2008). For the frequency of manual

acupressure, it was pointed out that manual acupressure frequencies are closely related to the therapeutic effects of AT (Guan et al., 2002, pp. 33-199). However, significant inconsistencies regarding acupressure instructions were found among the trials. The length of pressing each acupoint ranged from 30 seconds to five minutes, while some authors also instructed participants to use the *de qi* sensation as an indicator for stopping the acupressure. This contradictory statement could confuse participants, and it should be noted that continuous acupressure with inappropriate intensity may induce some side effects to the ear skin, such as skin breakdown and subsequent infection.

Compliance with treatment is of significant importance, as appropriate compliance could be linked to a more desired outcome and more credible study results (Jin, Sklar, Oh, & Li, 2008). However, 20 of the included studies failed to monitor the patients' compliance with AT, and incomplete or non-compliance could have produced detrimental effects on the outcome assessment and subsequently could have led to type II errors in the statistical analysis (Jin et al., 2008; Sidani, 1998). Because various types of cancers were included, the treatment duration varied significantly among the studies. More than half stated that the AT covered the present chemotherapy cycle, but this ambiguous description made unclear the exact length (days) of each treatment course. Meanwhile, some trials utilized only one or two days of intervention, which seems quite insufficient for investigating the effects of AT on delayed CINV, as the delayed phase typically lasts five days or more after chemotherapy.

The majority of the included studies reported positive CINV outcomes through the use of AT. However, it is worth noting that there were only six studies (Jiang, 2012; Jing, 2007; Luo, 2011; Ye et al., 2011; Yeh, Chien, Chiang, Lin et al., 2012; Zhang et al., 2012) that separately investigated the effects of AT on either acute or delayed CINV, and the outcomes were seldom reported for nausea and vomiting separately. The overall impact as well as the particular impact of AT on both acute and delayed CINV symptoms should be investigated further, particularly with regard to delayed CINV, which is more difficult to manage with current antiemetics. Moreover, the instrument used for outcome evaluation in most of the included studies was the WHO Recommendations for Grading of Acute and Sub-Acute Toxicity. The scale was developed in the late 1970s and the assessment criteria were mainly based on healthcare

providers' observations (Miller, Hoogstraten, Staquet, & Winkler, 1981). A lack of a clear description of the severity and incidence of nausea or vomiting for each grade has limited the applicability and reliability of the tool used in clinical practice, and detection bias may also be unavoidable as the evaluation mainly depends on researchers' subjective observations.

One of the advantages of CHAs may be that they are relatively free of risks, which means less adverse events. Reporting adverse events is an important issue in clinical studies; however, only two studies (Luo, 2011; Yeh, Chien, Chiang, Lin et al., 2012) included "adverse events associated with AT" as an outcome measure, and this review cannot prove the safety of AT because the sample size included in the studies that reported adverse events was too small.

Although encouraging results of AT for CINV management were reported, the strength of the research evidence was still rated as low because of the significant methodological flaws identified in the analyzed studies. Studies with unsatisfactory methodological quality are more inclined to overestimate the effect size (Kunz, Vist, & Oxman, 2007). The description of random sequence generation was absent in most of the included studies, and the blinding design was unclear in all of the studies. Even if it is difficult to conduct blinding for participants and healthcare providers in studies that compare AT with antiemetic medications, a blinding design of the outcome assessment and data analysis is possible, and it has been pointed out that incomplete blinding in RCTs can exaggerate the observed effect size (Wood et al., 2008). All of these methodological flaws could have affected the study results, making the current evidence on AT for CINV management low in quality and of limited value.

4.2.5 Implications for future research and practice

Some implications from this systematic review were revealed. First, a detailed AT protocol should be formulated that clearly describes the identification of the main and/or adjunct ear acupoints, the instructions for manual acupressure, and the length of treatment. Second, more reliable and valid instruments for CINV assessment, such as the MAT, FLIE, MANE, or INVR, should be considered in future studies (Brearley, Clements, & Molassiotis, 2008). Third, the treatment duration should be sufficient enough to detect the effects of AT on both acute and delayed CINV, and patients' compliance with AT should be monitored to give indications of the

data quality and to optimize the treatment effect. In addition to emphasizing the therapeutic effects of AT on gastrointestinal symptoms, patients' social and psychological well-being also needs attention, and a follow-up approach should be used to monitor the impact of AT on patients' QoL. Moreover, adverse events associated with AT and the likelihood of causality should be recorded and analyzed. Lastly and perhaps most importantly, the methodological quality of future studies needs to be improved, with more clear descriptions of the generation of random sequence and allocation concealment, a reasonable blinding design, and an appropriate method for sample size calculation and effect size estimation. Following the CONSORT (Consolidated Standards of Reporting Trials) statement (Schulz, Altman, & Moher, 2010) and the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) guidelines (MacPherson et al., 2010) to report acupuncture trials should be used for the design, description, and reporting of the study methodology.

4.3 Research gaps

Several research gaps were identified in a number of the current RCTs using AT for CINV management through this systematic review, including poor methodological quality, non-standardized AT treatment protocols, the lack of sham AT comparisons, and unsatisfactory outcome measures for nausea and vomiting.

4.3.1 Poor methodological quality

The methodological quality of the current AT trials on CINV was extremely poor, with many methodological flaws. Although stating themselves as "randomized" trials, the majority of the analyzed studies failed to report the process of generating the random sequence and the procedure of performing allocation concealment; the blinding design for the study participants, healthcare providers, or outcome assessors was not mentioned in any of the analyzed trials; none of the included studies had conducted sample size estimation; and no detailed information was given regarding the baseline assessment in the majority of the included trials. Most importantly, none of the studies had stated that they followed the CONSORT statement or the STRICTA guidelines for designing and reporting the study.

4.3.2 Non-standardized AT intervention protocols

It is reasonable that the AT treatment protocol should be tailored according to the specific type of cancer and chemotherapeutic regimens as well as patients' characteristics. The AT treatment protocols employed in the majority of the analyzed RCTs were still scientifically inadequate in a number of aspects. For instance, the standards or guidelines used for selecting, identifying, and locating auricular acupoints were omitted in most of the studies; the rationale for selecting particular ear acupoints for CINV management was not elaborated; and the approaches used for accurately locating the auricular acupoints were not reported. The procedures for manual acupressure of the taped AT seeds or imbedded AT needles were not clearly described and a "return demonstration" to ensure that patients had well performed the AT acupressure was not reported in the majority of the analyzed RCTs. Some studies also employed insufficient AT treatment durations that were much shorter than the normal length of delayed nausea and vomiting symptoms after receiving chemotherapy. All of these inadequacies indicate a lack of scientific processes regarding the development of an AT treatment protocol for CINV management in current research.

4.3.3 Lack of sham AT comparisons

A placebo or a sham comparison is of great importance in clinical trials to help distinguish the specific treatment (true) effects of an intervention from the non-specific treatment (placebo) effects (Dincer & Linde, 2003). For acupoint stimulation, the placebo effects have been found to be considerable, and adequate sham approaches for acupoint stimulation have therefore been recommended to better explore the true treatment effects of acupoint stimulation (Dincer & Linde, 2003; Tan, Suen, Wang, & Molassiotis, 2015). A similar concern has also been raised for clinical studies using AT (Zhang, Yang, Zhang, May, & Xue, 2014). However, of the analyzed trials in the systematic review, the majority failed to employ a sham AT procedure as the placebo comparison, which made it difficult to judge whether the positive impact of AT on relieving nausea and vomiting was induced by the specific treatment (true) effects of ear acupoint stimulation or just the non-specific physical and psychological treatment (placebo) effects.

4.3.4 Unsatisfactory outcome assessment

The instrument used to measure nausea and vomiting in most of the included studies was the WHO Recommendations for Grading of Acute and Sub-Acute Toxicity, which mainly depends on researchers' observations and subjective judgment. The most popular assessment tools with satisfactory psychometric properties, such as the MAT, INVR, MANE, or FLIE, were seldom utilized in the analyzed RCTs. Moreover, QoL was not evaluated in the majority of the included trials. In addition, the potential adverse reactions associated with the use of AT should be reported and well assessed in clinical practice and research; unfortunately, AT-related adverse events were not included as a safety outcome measurement in the majority of the included trials.

The inconclusive research evidence in terms of the use of AT for CINV management as well as the considerable limitations identified in the current AT studies on controlling CINV highlight the necessity of conducting more rigorously-designed research in this area. The research gaps located in this systematic review also provided valuable implications for future research. An evidence-based AT treatment protocol for CINV management should be developed and tested in cancer patients via well-designed clinical studies, and valid and reliable instruments should be utilized to measure the potential impacts of AT on patients' CINV symptoms and QoL. In addition, the non-specific treatment (placebo) effects of AT should be well distinguished from the specific treatment (true) effects via the inclusion of an adequate sham AT comparison.

This doctoral research project therefore proposed to address the research gaps described above. Following the *MRC Framework for Developing and Evaluating Complex Interventions* (Craig et al., 2008), an evidence-based AT treatment protocol (including both true and sham AT) for CINV management was developed first based on several recent systematic reviews, AT theories and standards, and the characteristics of cancer symptoms, and subsequently validated by a group of experts specialized in AT and TCM via a content validity study; a preliminary RCT with a pilot study design was then utilized to examine the feasibility of using the AT treatment protocol in cancer populations and to preliminarily explore the effects of AT on nausea, vomiting, and QoL among cancer patients receiving chemotherapy; in addition, the patients' experiences of participating in the preliminary RCT and receiving the AT treatment were also explored after the completion of the trial. The study findings of the doctoral research project can

be further used to refine the study protocol for a future multicenter large-scale RCT to investigate the definite effects of AT on CINV in cancer patients. The research aim, objectives, and hypotheses of this doctoral research project, as well as the research methodologies, will be described in detail in the following methodology chapter.

4.4 Summary of the chapter

This chapter presented a systematic review that summarized the current research evidence on AT for CINV management. Twenty-one available RCTs that focused on the use of auricular acupressure or auricular acupuncture to control CINV were included and comprehensively analyzed in this systematic review. The review findings support that AT could be a promising approach to alleviating CINV symptoms, but the current research evidence is deemed inconclusive given the significant methodological flaws located in the reviewed AT trials. This systematic review highlighted several research gaps, including an unclear process for the development of evidence-based AT treatment protocols for CINV management, the lack of a rigorously-designed study to examine the effects of AT on CINV and QoL in cancer patients, and the absence of sham AT comparisons in current AT research to distinguish the true treatment effects of AT from the placebo effects. The current doctoral research project was therefore designed to address the research gaps mentioned above. The next chapter will comprehensively present the research aim, objectives, and hypotheses as well as the detailed research methodology of this doctoral research project, which includes the development of an evidence-based AT treatment protocol, the design of the preliminary RCT to examine the feasibility and antiemetic role of the AT treatment protocol in cancer patients receiving chemotherapy, and the design of the semi-structured interview to explore the patients' experiences of participating in the trial and receiving the AT intervention.

CHAPTER FIVE: RESEARCH METHODOLOGY

5.1 Introduction

This chapter will present the research methodology of this doctoral research project, which includes eight major sections. Section 5.1 will provide a general introduction of this chapter, and Section 5.2 will present the research aim, objectives, questions, and hypotheses. Section 5.3 will introduce the *MRC Framework for Developing and Evaluating Complex Interventions*, and then present a summary of the study design following the MRC framework. The following three sections (Sections 5.4 to 5.6) will describe the doctoral research project's design based on each phase of the MRC framework, including the development of an evidence-based AT treatment protocol for CINV management (Section 5.4), the design of a pilot RCT to examine the feasibility of using the AT treatment protocol for cancer patients and to preliminarily explore the effects of AT on CINV and QoL (Section 5.5), and the design of semi-structured interviews to explore the patients' experiences of participating in the pilot trial and receiving the study intervention (Section 5.6). Section 5.7 will present the study team, the study's quality assurance, and the ethical considerations of the doctoral research project. A summary of the chapter will be presented in Section 5.8.

5.2 Research aim, objectives, questions, and hypotheses

This section will present the specific research aim, objectives, questions, and null hypotheses of the study, which was a pilot RCT design with three parallel arms (true AT arm, using true auricular acupressure plus standard antiemetic treatment and care; sham AT arm, using sham auricular acupressure plus standard antiemetic treatment and care; and standard care arm, using standard antiemetic treatment and care only). In terms of the research objectives of the pilot RCT, it is recommended that either the specific research objectives and hypotheses for the future main study (which were also preliminarily analyzed in the pilot trial) or the specific feasibility objectives should be included and clearly stated in the pilot RCT design (Thabane et al., 2010).

5.2.1 Research aim

The overall aim of this study was to evaluate the feasibility of an evidence-based standard AT treatment protocol for managing nausea and vomiting in female breast cancer patients undergoing

moderately to highly emetogenic chemotherapy, and to preliminarily examine the effects of AT on patients' CINV and QoL via a three-parallel-arm, sham-AT-controlled randomized pilot trial.

5.2.2 Research objectives

The objectives of this study were:

(1) to develop an evidence-based standard AT treatment protocol for CINV management;

(2) to pilot the methodological procedures of the RCT using the standard AT treatment protocol for controlling nausea and vomiting in female breast cancer patients undergoing chemotherapy;

(3) to determine the eligibility rate, recruitment rate, retention rate, and attrition rate during the pilot RCT subject recruitment and follow-up process;

(4) to determine the feasibility and acceptability of the study questionnaires and AT treatment protocol for the study participants;

(5) to identify potential adverse events associated with AT in female breast cancer patients;

(6) to preliminarily examine the effects of AT on acute, delayed, and anticipatory CINV as well as QoL status in female breast cancer patients;

(7) to explore the participants' experiences of participating in the pilot RCT and receiving the AT treatment; and

(8) to refine the study protocol for a future multicenter large-scale RCT to examine the definite effects of AT on CINV and QoL in female breast cancer patients.

5.2.3 Research questions

Specific research questions for the pilot RCT and semi-structured interview are as follows:

(1) What are the eligibility, recruitment, retention, and attrition rates during the pilot RCT subject recruitment and follow-up process?

(2) What are the completion rates of the study questionnaires (INVR, MAT, and FACT-B) administered to the study participants during the data collection period of the pilot RCT?

(3) What are the completion rates of the true and sham AT protocols used among the study participants during the intervention period of the pilot RCT?

(4) What are the potential adverse events associated with the AT treatment for female breast cancer patients?

(5) Are there any statistically significant differences in the complete response of CINV symptoms among the three study groups during the first cycle of chemotherapy?

(6) Are there any statistically significant differences in the occurrence, frequency, and severity of acute/delayed nausea and vomiting among the three study groups during the first cycle of chemotherapy?

(7) Are there any statistically significant differences in the MAT scores (acute and delayed CINV scores) among the three study groups during the first cycle of chemotherapy?

(8) Are there any statistically significant differences in the INVR scores (anticipatory CINV scores) among the three study groups prior to the second cycle of chemotherapy?

(9) Are there any statistically significant differences in the FACT-B total and domain scores (QoL scores) among the three study groups at the end of the first cycle of chemotherapy?

(10) What are the participants' experiences of participating in the pilot trial and receiving the AT treatment?

5.2.4 Null hypotheses

One of the study's objectives was to preliminarily examine the effects of AT on acute, delayed, and anticipatory nausea and vomiting as well as QoL status in female breast cancer patients undergoing chemotherapy, and hypothesis testing was utilized to address this objective. Therefore, the related null hypotheses are presented as follows:

(1) There will be no statistically significant differences in the complete response of CINV symptoms among the three study groups during the first cycle of chemotherapy.

(2) There will be no statistically significant differences in the occurrence, frequency, and severity of acute/delayed nausea and vomiting among the three study groups during the first cycle of chemotherapy.

(3) There will be no statistically significant differences in the MAT scores (acute and delayed CINV scores) among the three study groups during the first cycle of chemotherapy.

(4) There will be no statistically significant differences in the INVR scores (anticipatory CINV scores) among the three study groups prior to the second cycle of chemotherapy.

(5) There will be no statistically significant differences in the FACT-B total and domain scores (QoL scores) among the three study groups at the end of the first cycle of chemotherapy.

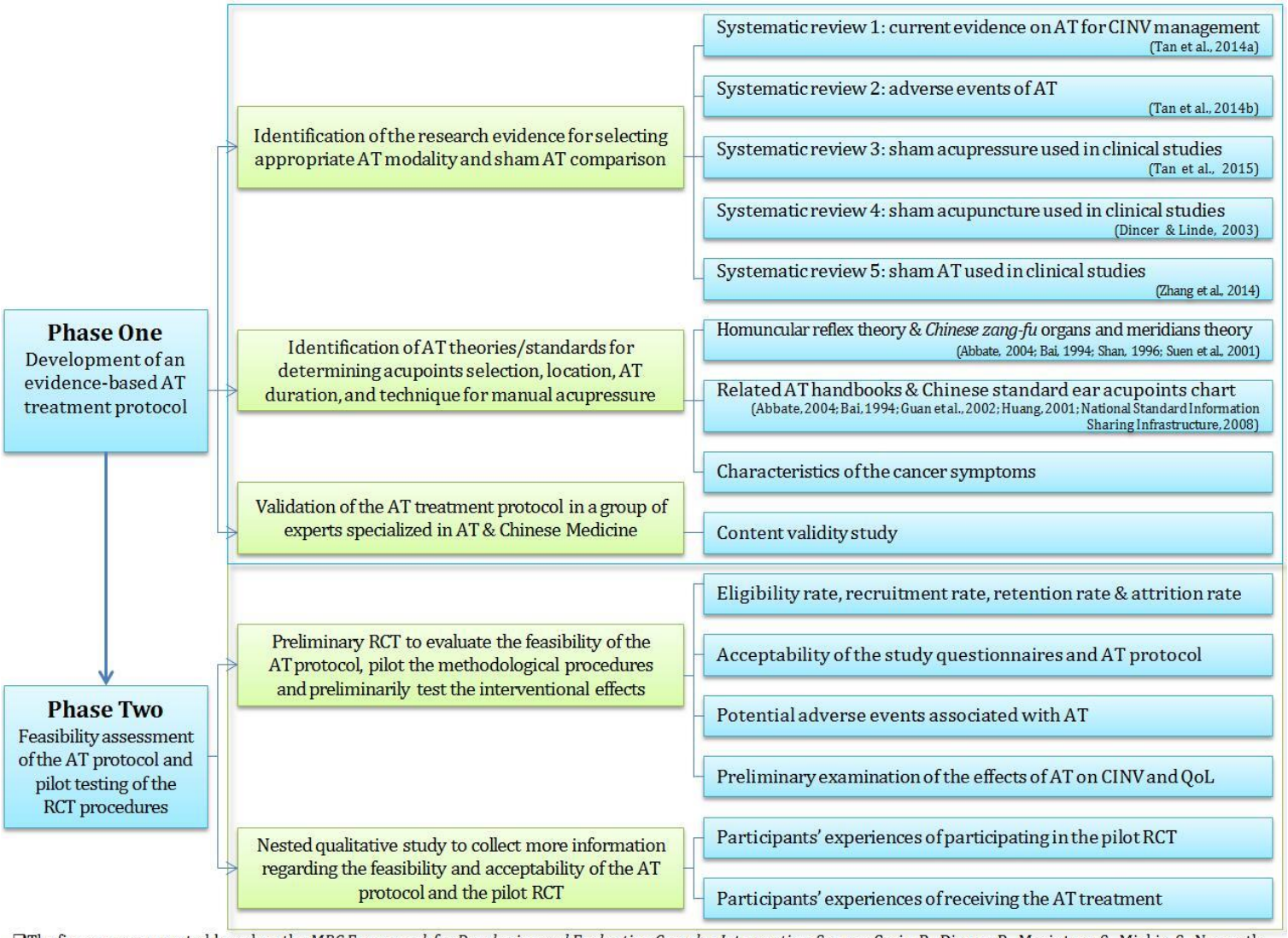
5.3 The MRC framework for developing and evaluating complex interventions

The *MRC Framework for Developing and Evaluating Complex Interventions* was utilized to guide the study design of this doctoral research project. The MRC framework emphasizes a general principle for designing and testing a complex intervention with multiple components, which is the "development-evaluation-implementation" process (Craig et al., 2008). There are usually four different stages in the process, including development of the complex intervention, assessment of the feasibility of the intervention and pilot testing of the research methodology, evaluation of the complex intervention, and final implementation of the intervention in real practice (Craig et al., 2008). It should be noted that the four stages included in the MRC framework sometimes do not follow a linear procedure but instead are part of a cyclical process, which can enhance mutual improvement between different stages (Craig et al., 2008).

In the development stage of a complex intervention, existing research evidence and appropriate underpinning theories should be systematically collected to serve as the evidence and theory bases for developing the complex intervention (Craig et al., 2008). Prior to the formal evaluation of the intervention, preliminary studies are also necessary to evaluate the feasibility and acceptability of the intervention, pilot the subject recruitment process, and perform adequate sample size estimation for the evaluation stage to examine the definite effects of the intervention, and a mixture of both quantitative and qualitative research approaches is often recommended at this stage to capture a complete picture of the potential pros and cons that could facilitate or hinder the future evaluation and implementation of the intervention (Craig et al., 2008). During the evaluation stage of the intervention, clinical effectiveness, change patterns, and cost-effectiveness should be addressed via a series of interventional studies, and reliable research evidence concluded at this stage could be used to further promote the implementation and dissemination of the intervention in clinical practice settings (Craig et al., 2008).

In the current doctoral research project, the MRC framework was followed to develop an evidence-based AT treatment protocol based on several recent systematic reviews, related AT theories and standards, and the characteristics of cancer symptoms. Before pilot testing the intervention protocol, the appropriateness of the intervention protocol for use in the cancer population was evaluated and confirmed by a group of experts specialized in AT and TCM. A

pilot study was designed in accordance with the second stage of the MRC framework to comprehensively evaluate the feasibility and acceptability of the intervention and the study's methodological procedures. As the pilot study was designed as a randomized placebo-controlled study, the clinical effectiveness of the auricular acupressure protocol in CINV and QoL was also preliminarily assessed at this stage. Meanwhile, semi-structured interviews were also included in this stage to collect more information in terms of the acceptability of the intervention and the patients' experiences of participating in the pilot RCT, which could provide valuable information for the further refinement of the study protocol used in a future main study. The current doctoral research project mainly focused on the first two stages of the MRC framework, namely, the development and evaluation of the AT treatment protocol for CINV management. Study implications retrieved from the doctoral research project will be utilized in a future main study for the formal evaluation and implementation of the AT treatment protocol. **Figure 5.1** below presents the process of the current study design following the *MRC Framework for Developing and Evaluating Complex Interventions*:



❑The figure was presented based on the *MRC Framework for Developing and Evaluating Complex Intervention*. Source: Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, 337, a1655.

Figure 5.1 Process of the study design following the *MRC Framework for Developing and Evaluating Complex Interventions*

5.4 Part one: Development of an evidence-based AT treatment protocol for CINV management

The first phase of the doctoral project design was the development of the AT treatment protocol for CINV management. To distinguish the specific treatment (true) effects of AT from the non-specific treatment (placebo) effects, a true AT protocol and a sham AT protocol were developed accordingly. The development of the AT protocol was based on several systematic reviews on AT and acupressure (Dincer & Linde, 2003; Tan et al., 2014a, 2014b, 2015; Zhang et al., 2014), related AT theories and standards (Abbate, 2004; Bai, 1994; Guan et al., 2002; Huang, 2001), and the characteristics of cancer symptoms. The AT treatment protocol was then validated by a group of experts specialized in AT and TCM. In the following sections, the development process for the true AT protocol (Section 5.4.1) and the sham AT protocol (Section 5.4.2) will be reported separately.

5.4.1 Development of the intervention protocol for true AT treatment

The development of the true AT treatment protocol was based on the following procedures: selection of appropriate AT modality; justifications for the selected auricular acupoints for alleviating nausea and emesis; location and identification of the selected acupoints; duration and courses of AT treatment; and intensity of and techniques for AT manual acupressure.

5.4.1.1 Selection of appropriate AT modality

The previous literature review chapters clearly presented that cancer patients undergoing antineoplastic therapies have already suffered from considerable physical and psychological distress and economic burden. Therefore, it is recommended that the proposed adjunctive non-pharmacological interventions used for cancer symptom management should not produce a significant burden on patients' healthcare costs or put them in a dangerous situation of exposing them to unwanted side effects associated with the intervention. In other words, the AT modality utilized in this study should be associated with less harm and healthcare costs and should take a less invasive approach. The selection of the AT modality was based on two systematic reviews (conducted by the doctoral researcher) that focused on the current evidence on AT for CINV management and the safety of AT used in research and clinical practice (Tan et al., 2014a, 2014b).

For the commonly used AT approaches, one of the most popular modalities is auricular acupuncture, which employs needle stimulation at particular auricular acupoints. However, auricular acupuncture might not be widely accepted by cancer patients with relatively weak functions in immune defenses given the invasive nature of the technique and potential harm associated with needle insertion, such as local infection, pain, and bleeding (Tan et al., 2014b). Auricular acupressure, a non-invasive AT method, may be an optimal option considering its superiority to invasive AT modalities in terms of convenience and safety. Auricular acupressure is deemed an effective treatment approach for different health disorders and is commonly used in clinical practice to deal with cancer-related symptoms (Tan et al., 2014a). Moreover, it can be quickly mastered by patients after receiving appropriate training by AT or acupuncture practitioners. Once trained by qualified practitioners, patients with auricular acupressure tapes can even perform self-acupressure at home, which would decrease the need for frequent visits to healthcare services (Yeh et al., 2013). Meanwhile, adverse events and risk-benefit balance related to auricular acupressure and auricular acupuncture were also assessed (Tan et al., 2014b). It was found that both approaches proved to be effective in preventing and treating various types of disorders, but the harm data were reported to be much less and minor for auricular acupressure than for auricular acupuncture, and the adverse reactions associated with auricular acupressure were generally identified to be transient, mild, and well-tolerated (Tan et al., 2014b).

Vaccaria seeds (*wang bu liu xing zi*) have been commonly used in auricular acupressure for CINV management (Tan et al., 2014a), and they were adopted as the medium for performing acupressure in this doctoral research project. Vaccaria seeds are the most frequently adopted objects for auricular acupressure and are now available in the healthcare marketplace (Abbate, 2004, p. 99). Vaccaria seeds are usually well-sterilized, and when used in clinical practice, the seeds are often taped to certain ear acupoints to produce constant stimulation (Abbate, 2004, p. 99). It should be emphasized again that the reason for adopting vaccaria seeds as the acupressure medium was not because of their pharmacological features but because of their physical properties (Guan et al., 2002, p. 114). The texture, density, and size of vaccaria seeds make them the most appropriate candidate for creating constant and strong stimulation of the acupoints to achieve adequate treatment effects (Abbate, 2004, p. 99).

Magnet pellets are also used for auricular acupressure, and this kind of AT approach combines the effects of magnetic therapy and acupoint stimulation. However, magnetic therapy can induce some side reactions such as nausea, emesis, drowsiness, and sleep disturbance (Guan et al., 2002, p. 132), making it not an optimal option for use in ear acupressure to manage CINV, as the side effects of magnetic therapy, especially nausea and emesis, could have significant confounding effects on the cause-and-effect analysis between AT and cancer-treatment-related nausea and emesis. Based on the evidence mentioned above, auricular acupressure with vaccaria seeds was utilized as the study intervention in this doctoral research project. Furthermore, given that local redness and discomfort may also be induced by the regular tapes used for acupressure seed attachment (Tan et al., 2014b), desensitization tapes were used in this study to minimize the potential side effects associated with auricular acupressure (see **Figure 5.2**).

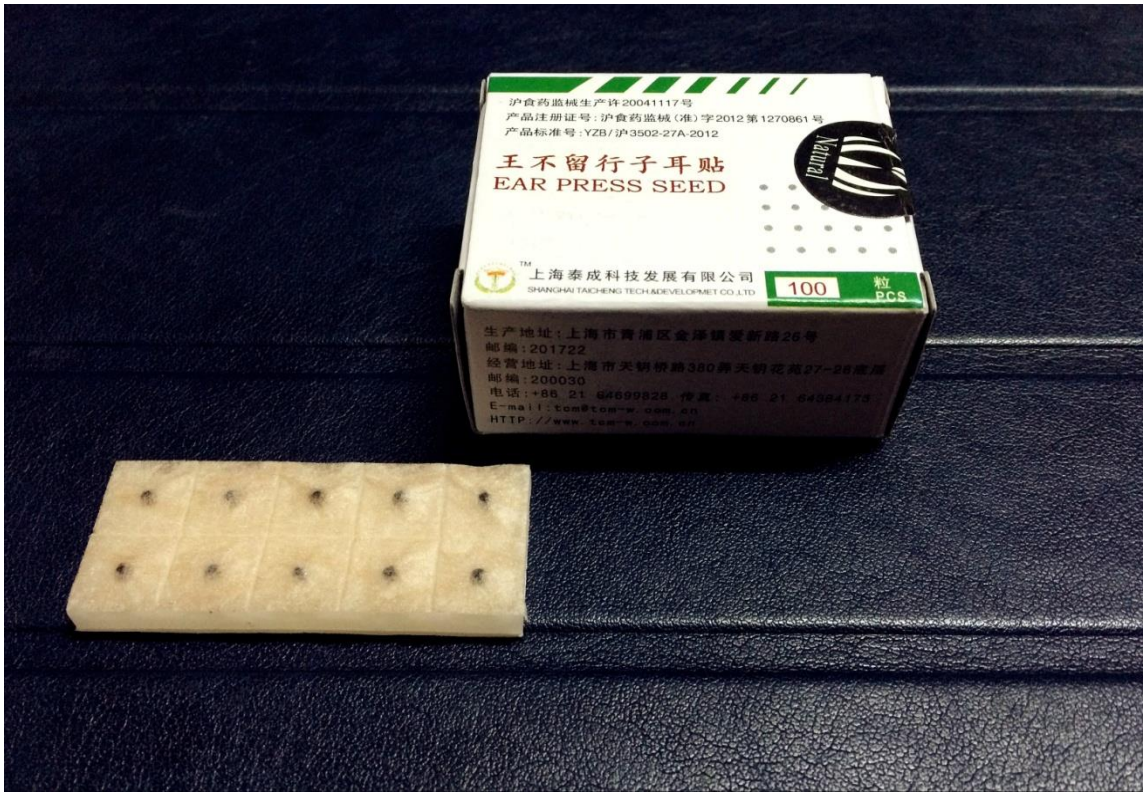


Figure 5.2 Auricular acupressure tapes (desensitization material) used for vaccaria seeds
(Brand: Tai Cheng; Approval Number: 滬食藥監械 (準) 字 2012 第 1270861 號)

5.4.1.2 Justifications for the selected auricular acupoints

The selection of the targeted auricular acupoints for CINV management in this study was based on two commonly referred to AT theories, namely, homuncular reflex theory and Chinese *zang-fu* organs and meridians theory, and two general principles for acupoint selection mentioned in the AT handbook written by Dr. Li-Chun Huang, "selection of auricular acupoints corresponding to the afflicted parts" and "selection of auricular acupoints according to the effects of acupoints" (L. Huang, 2001, pp. 265-272). The two AT theories share a common belief that dysfunctions that occur in particular *zang-fu* organs and body regions correspond to certain acupoints located in the outer auricle, which is also in accordance with the principle of "selection of auricular acupoints corresponding to the afflicted parts." The second principle, "selection of auricular acupoints according to the effects of acupoints," reflects another aspect of the AT theories above in that the stimulation of every auricular acupoint has typical treatment effects for health disorders that occur in the corresponding organ/body region and other organs/body regions that are internally and externally connected with the affected area; this principle also emphasizes that some ear acupoints may have some specific effects on alleviating various pathological conditions, which can be included in different AT treatment protocols targeting different health problems (L. Huang, 2001, p. 269).

As mentioned in the literature review chapter on AT (Chapter 3), dysfunctions in the stomach, cardia, spleen, and liver are commonly believed to be the primary causes of nausea and vomiting during cancer chemotherapy. Following the homuncular reflex theory and Chinese *zang-fu* organs and meridians theory, as well as the principle of "selection of auricular acupoints corresponding to the afflicted parts," the auricular acupoints "stomach (CO_4)," "cardia (CO_3)," "spleen (CO_{13})," and "liver (CO_{12})" were selected for the AT treatment protocol for controlling nausea and emesis. In accordance with the principle of "selection of auricular acupoints according to the effects of acupoints," three other ear acupoints that are commonly used for CINV management, including "*shenmen* (TF_4)," "sympathetic (AH_{6a})," and "subcortex (AT_4)" (Tan et al., 2014a), were also included in the AT treatment protocol. These acupoints were selected because of their potential roles in alleviating gastrointestinal dysfunctions (Bai, 1994, pp. 87-89; Guan et al., 2002, pp. 198-199; L. Huang, 2001, p. 153). As recommended by Abbate (2004), the AT protocol should usually start with ear acupoint "*shenmen*" unless there are some contraindications, as *shenmen* "quiets the Heart, calms the spirit, and puts the patient into a state of receptivity for treatment"

(p.153). “Sympathetic (AH_{6a})” and “subcortex (AT_4)” were chosen for their potential in regulating the neural activities associated with the sympathetic nervous system (SNS) and high-level central nervous system (CNS), which can further assist with the regulation of abnormal activities of the gastrointestinal smooth muscles (Bai, 1994, p. 88; Guan et al., 2002, p. 199).

Therefore, seven auricular acupoints were included in the AT treatment protocol for CINV management. The location of each acupoint was determined based on the latest Chinese standard ear acupoints chart (*Nomenclature and Location of Auricular Points*, GB/T-13734-2008) (National Standard Information Sharing Infrastructure, 2008). **Figure 5.3** below shows the selected auricular acupoints in this study, and **Table 5.1** following summarizes the anatomical location and potential effects of each selected auricular acupoint:

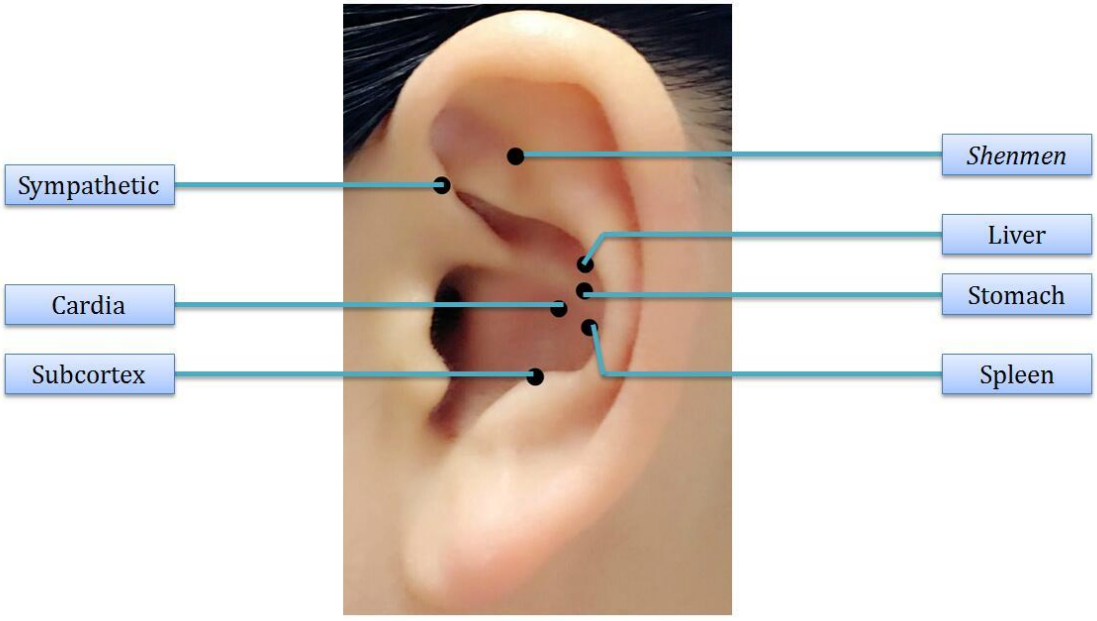


Figure 5.3 Selected auricular acupoints for CINV management

Table 5.1 Anatomical locations and potential effects of the selected auricular acupoints[a]

Cardia (CO_3)	
Location[b]	"outer (distal) 1/3 section inferior to the helix crus" (L. Huang, 2001, p. 42)
Effects	▪ One of the key auricular acupoints for alleviating nausea and emesis ▪ Directly corresponds to the affected organs related to nausea and emesis ▪ Assists with the adjustment of the movement of stomach *qi* (Bai, 1994, p. 88; L. Huang, 2001, pp. 107-108)
Stomach (CO_4)	
Location[b]	"area where the helix crus disappears" (L. Huang, 2001, p. 42)
Effects	▪ One of the key auricular acupoints for alleviating nausea and emesis ▪ Directly corresponds to the affected organs related to nausea and emesis ▪ Regulates abnormal activities of the gastrointestinal smooth muscles ▪ Maintains normal movement of stomach *qi*; can support normal spleen functions (Bai, 1994, p. 88; L. Huang, 2001, pp. 103-104; Oleson, 2014, p. 261)
Spleen (CO_{13})	
Location[b]	"midpoint of a line from stomach to the notch between antihelix and antitragus" (L. Huang, 2001, p. 47)
Effects	▪ Internally and externally linked with the acupoint stomach ▪ Regulates digestive functions ▪ Strengthens spleen functions and assists the stomach with the management of nausea and emesis ▪ Alleviates tension and spasms of the gastrointestinal smooth muscles (Bai, 1994, p. 88; L. Huang, 2001, p. 97; Oleson, 2014, p. 260)
Liver (CO_{12})	
Location[b]	The "lateral inferior area of cymba conchae" (L. Huang, 2001, p. 44)
Effects	▪ Adjusts the movement of liver *qi* ▪ Regulates the functions of both stomach and spleen for the management of nausea and emesis (Bai, 1994, p. 88; L. Huang, 2001, p. 96)
***Shenmen* (TF_4)**	
Location[b]	"superior and central to the tip of the triangular fossa, between the junction of the superior crus and the inferior crus of the antihelix" (Oleson, 2014, p. 227)
Effects	▪ The key auricular acupoint for tranquilizing the mind and spirit (Bai, 1994, p. 87; Guan et al., 2002, p. 199; Oleson, 2014, p. 227)
Sympathetic (AH_{6a})	
Location[b]	"end of the upper edge of the lower crus of the antihelix" (L. Huang, 2001, p. 36)
Effects	▪ Regulates the neural activities associated with the sympathetic nervous system (SNS) ▪ Regulates abnormal activities of the gastrointestinal smooth muscles (Bai, 1994, p. 88; Guan et al., 2002, p. 199)
Subcortex (AT_4)	
Location[b]	"anterior side of the interior wall of the antitragus" (L. Huang, 2001, p. 28)
Effects	▪ Regulates the neural activities associated with the high-level central nervous system (CNS) ▪ Alleviates gastrointestinal disorders, including nausea and vomiting (Bai, 1994, p. 88; Guan et al., 2002, p. 199; L. Huang, 2001, p. 77)

Note: a=the table contents were comprehensively adapted from Bai, 1994; Guan et al., 2002; L. Huang, 2001; National Standard Information Sharing Infrastructure, 2008; and Oleson, 2014; b=sentences and phrases in quotation marks were quoted from their original sources; to standardize the AT terms used in different AT books, some terms in quotation marks that were originally capitalized were all changed to lower case in this table

5.4.1.3 Location identification of the selected acupoints

An auricular acupoint detector was utilized to precisely locate the targeted auricular acupoints by measuring the electrical resistance of the local ear skin. The auricular acupoint detector is commercially available (Brand: SUKO, Quiescent Current: ≤ 10mA, Operating Current: ≤ 20mA, Registration certificate of medical equipment: 2003NO.2270426; Quality Guaranteeing: ISO-9001, Patent number: ZL98227652.4) and it has been commomly utilized in practice to help accurately locate the targeted acupoints (see **Figure 5.4**). The auricular acupoint "Ear Center" was utilized as the reference point (Oleson, 2014, p. 118). When pathological changes occur in particular internal organs or body regions, the electrical resistance of the ear skin at the corresponding acupoints decreases below that of normal ear skin, which can be detected by an auricular acupoint detector (Guan et al., 2002, pp. 96-98). When using the acupoint detector, the practitioner should first adjust the detector to the basic level of electrical resistance tailored for each patient. Once the targeted acupoints associated with nausea and vomiting have been accurately located in cancer patients, signals will be made by the detector, including an alert sound and a red light shown on the detector.

Figure 5.4 Auricular acupoint detector used to locate targeted ear acupoints associated with CINV
(Brand: SUKO, Product Registration Number: 蘇食藥監械生產許 2001-0105 號)

5.4.1.4 Duration of treatment

The length of AT is usually determined by the nature of the treated disease or health problems (Guan et al., 2002, p. 117). For chronic diseases, regular AT treatment courses are recommended, while for acute conditions, there are often no particular rules for AT treatment durations or courses, but AT can usually be administered until patients recover from their disorders (Guan et al., 2002, p. 117). The total AT treatment duration in the study was determined by the general extent of CINV symptoms experienced after undergoing the most recent chemotherapy. In cancer patients receiving chemotherapy, the delayed phase of CINV can usually be identified in 25 to 120 hours (day 2 to day 5) after receiving chemotherapeutic regimens (dos Santos, Souza, Brunetto, Sasse, & Lima, 2012; Wenzell et al., 2013). Therefore, the total AT treatment duration was scheduled for five days (day 1 to day 5) during the chemotherapy cycle. Bilateral ear acupoints are generally recommended for auricular acupressure unless the targeted healthcare disorders occur on only one side of the body (L. Huang, 2001, p. 225). For CINV, the involved *zang-fu* organs, including the stomach, cardia, liver, and spleen, do not fully belong to one particular side of the body; therefore, bilateral ear acupoints were treated at the same time in this study. One treatment course was deemed adequate as the auricular acupressure seeds can usually be kept on the ear for three to seven days if properly protected (L. Huang, 2001, p. 227).

5.4.1.5 Intensity and technique for auricular acupressure

The researchers responsible for AT implementation taped the vaccaria seeds on the targeted auricular acupoints using auricular tapes made with desensitization materials (one vaccaria seed on each tape). Manual acupressure of the taped seeds was conducted by the study participants themselves. The researchers first demonstrated the manual acupressure technique to the participants several times and the participants were then asked to do a return demonstration to the researchers to ensure that they could correctly perform the manual acupressure skill. The intensity of acupoint stimulation mainly depended on the individual condition of each participant, and the achievement of *de qi* sensation was utilized as an indication of appropriate intensity of the manual acupressure as well as a sign of achieving satisfactory treatment effects (L. Huang, 2001, p. 225). As mentioned in the previous literature review chapter on AT (Chapter 3), *de qi* is a TCM term used to illustrate a group of typical sensations at the acupoint stimulation site,

including minor aching, soreness, heaviness, heat, and tingling (Guan et al., 2002, p. 116; Kong et al., 2007; MacPherson & Asghar, 2006; Yang et al., 2013). The achievement of *de qi* at certain acupoints is a sign which indicates that the acupoint stimulation has successfully evoked positive flows of *qi* in the corresponding internal organs or body regions (Kong et al., 2007), and potential treatment effects have also been triggered to regulate the balance between *yin* and *yang* and alleviate particular body dysfunctions (Kong et al., 2007; Yang et al., 2013). *De qi* can be regarded as an immediate indicator of the achievement of acupoint stimulation treatment efficacy (Kong et al., 2007; Tan et al., 2014a; Yang et al., 2013).

AT treatment was scheduled three times daily (Guan et al., 2002, pp. 115-116; L. Huang, 2001, p. 227), with each time lasting about four to seven minutes, pressing all the targeted ear acupoints located on both ears. For self-acupressure of each of the selected auricular acupoints, the index finger and thumb should be placed at the interior and exterior of the auricle, respectively, where the targeted acupoint is located (Guan et al., 2002, pp. 115-116). Then, the participants pressed the taped seeds by gradually adding pressure until the occurrence of a feeling of heat, heaviness, pressure sensation, soreness, tingling, or distension (i.e., the achievement of *de qi* sensation) (Guan et al., 2002, pp. 115-116; Tan et al., 2014a). After reaching the *de qi* sensation, the participants had to move their fingers around the acupoint area slightly to identify the point with the most obvious distension, the so-called "sensitive point," and then continue to add pressure on the "sensitive point" for 20 to 30 seconds (Guan et al., 2002, pp. 115-116). Daily acupressure was conducted in the morning, afternoon, and evening (before sleep), respectively, during the five-day AT treatment period (day 1 to day 5 of the chemotherapy cycle), regardless of whether the participants had experienced CINV symptoms or not. Based on the research evidence summarized by the doctoral researcher (Tan, et al., 2014a), in addition to the regular three-times-daily ear acupressure, the participants were also instructed to add pressure to the taped AT seeds as soon as they had the feeling of the coming of nausea and emesis.

The researchers also instructed the participants on precautions in terms of the use of auricular acupressure tapes, explaining that the taped seeds should be kept dry during the entire AT treatment period (five days), and a shower cap or a towel should be used to cover the taped seeds when taking a shower or washing their hair (Abbate, 2004, p. 100). To avoid breakdown of the

local ear skin, the participants were also instructed not to roll the taped seeds when adding pressure to the ear acupoints (L. Huang, 2001, p. 228). The participants were asked to inform the researchers when they needed replacement ear acupressure seeds if the tapes fell off or got wet during the five-day AT treatment period, and for those who were discharged from the hospital during the five-day AT treatment, they were instructed to contact the researchers and go back to the hospital for AT seed replacement during working hours (9:00 a.m. to 6:00 p.m.). The participants were also informed that shifting tapes seldom got into the ear canal given that the size of the ear acupressure tapes was usually a standard measurement of "0.6 cm × 0.6 cm" or "0.8 cm × 0.8 cm" (Guan et al., 2002, p. 115). However, the participants were also instructed to return to the hospital immediately for medical assistance if the tapes got into the ear canal.

The participants were instructed to remove all the taped seeds by themselves once the five-day AT treatment was completed. If the tapes were found to be too sticky, the participants were instructed to add moisture to the local ear skin using warm water before removing them. Importantly, the participants were asked to count the auricular tapes, which should be 14 in total, to ensure that they had removed all the tapes, and it was suggested that they use a mirror to check for possible tapes left in the auricle. **Figure 5.5** below shows the procedure of auricular acupressure in this study:

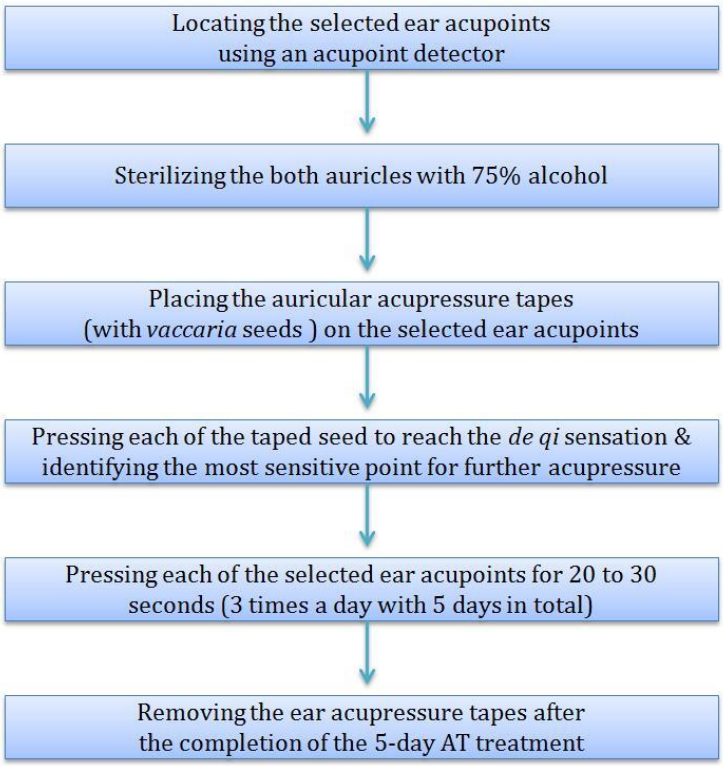


Figure 5.5 Procedure of auricular acupressure in this study

5.4.2 Development of the intervention protocol for sham AT treatment

The development of the intervention protocol used in the sham AT group was based on several systematic reviews on sham interventions in body/auricular acupoint stimulation (Dincer & Linde, 2003; Tan et al., 2015; Zhang et al., 2014). To maintain a successful blinding design among the participants from the true AT and sham AT groups, the selected ear acupoints for the sham AT intervention were exactly the same as those in the true AT treatment protocol. Meanwhile, to avoid any potential specific treatment effects generated from the acupoint stimulation, no manual acupressure was scheduled for the participants in the sham AT group, and the vaccaria seeds were replaced by Junci Medulla (*deng xin cao*), one type of herb that is soft in texture and that is unable to produce sufficient stimulation of the acupoints to evoke potential therapeutic effects.

5.4.2.1. Justifications for the selected sham acupoints

Three types of sham acupoints have been frequently utilized in acupuncture/acupressure trials, which include non-acupoints (faked/inactive points), irrelevant acupoints to the treated diseases, and

the same true acupoints as in the true treatment group without adequate acupoint stimulation (Dincer & Linde, 2003; Tan et al., 2015; Zhang et al., 2014).

Non-acupoints mean faked acupoints that are theoretically not believed to be associated with any particular treatment effects, and those located near true acupoints are commonly selected as the sham acupoints in body acupuncture/acupressure research (Dincer & Linde, 2003; Tan et al., 2015; Zhang & Tang, 2003). Non-acupoints are inactive in producing treatment effects and their locations are sometimes quite near the active true acupoints (Dincer & Linde, 2003; Tan et al., 2015; Zhang & Tang, 2003), which make them good options for achieving a successful blinding design among participants and even care providers. In AT research, non-acupoints have also been employed for sham intervention designs (Zhang et al., 2014). However, different from body acupoints, hundreds of sensitive and active acupoints are concentrated in the very small auricle, which makes it difficult to identify any inactive sham ear acupoints near the active true acupoints. Some AT studies have included some non-acupoints as sham comparisons, and the most frequently selected acupoints were located at the helix of the ear (Berman, Lundberg, Krook, & Gyllenhammar, 2004; Prisco et al., 2013; Usichenko et al., 2005; Usichenko et al., 2007). However, as the majority of the true auricular acupoints in this study were located around the helix crus and in the cymba concha and cavum concha, it would be easy for the study participants to distinguish the difference in acupoint locations between the true AT treatment and sham AT treatment if the non-acupoints located at the helix were adopted for sham AT comparison. Therefore, non-acupoints were not an adequate option for the sham AT design in this study.

Another type of sham AT approach is irrelevant ear acupoints for the treated health conditions (Zhang, et al., 2014). Irrelevant ear acupoints have also been used in body acupuncture/acupressure research, in which the acupoints are true acupoints but are recognized as having no therapeutic effects for the disease being treated (Dincer & Linde, 2003; Tan et al., 2015). However, the TCM theory holds a holism concept of the human acupoint system in that stimulation of any true acupoints will contribute to some specific effects of the cardiovascular and nervous system, as well as the immune and endocrine system (Pan, Chen, Zhao, & Guo, 2014), which could then generate some treatment effects for particular health problems, even though the acupoints are

not specific to the conditions. Therefore, irrelevant acupoints were also not a good sham AT option in this study.

It should be noted that blinding designs can also be problematic when adopting irrelevant acupoints as the sham comparison, as the acupoint locations are totally different between the true intervention group and the sham intervention group. Therefore, in this doctoral research project, the selected sham ear acupoints were the same as the acupoints used in the true AT protocol but no acupoint stimulation was applied. The same acupoints used in both groups helped maintain a successful blinding design among the participants, and details regarding the justifications for the absence of manual acupressure in the sham AT treatment protocol will be described in the next section.

5.4.2.2. Intensity of sham acupressure and preparation of sham acupressure tapes

In body acupuncture/acupressure research, adopting sham acupoints that are the same as the acupoints used in the true intervention with light or no additional stimulation has been commonly recognized as an appropriate sham intervention design, as this kind of stimulation will not trigger the acupoint response, and therefore eliminates the possibility of any therapeutic effects generated from adequate acupoint stimulation (Dincer & Linde, 2003; Pan et al., 2014; Tan et al., 2015; Zhang & Tang, 2003). Therefore, in this study, to minimize the specific treatment effects generated from acupoint stimulation in the sham AT group, no acupressure was scheduled and the taped seeds were replaced by another Chinese herb named Junci Medulla, which is soft in texture and is unble to produce sufficient stimulation of the acupoints to evoke potential therapeutic effects on the conditions been treated. Junci Medulla is the stem tissue of Juncus effusus (Wang, 2013). Different from vaccaria seeds, which are hard in texture, Junci Medulla is quite soft and cannot be used as a medium to create constant stimulation of the targeted acupoint. The selection of Junci Medulla as the sham AT tapes was also based on its physical texture, and it is not believed to be associated with any particular treatment potentials when used in AT interventions (Suen, Wong, & Leung, 2002). The treatment duration in the sham AT group was the same as in the true AT group, which was five days in total.

Since no manual acupressure was scheduled for the participants in the sham AT group, participants with previous experience of AT would easily be able to distinguish the differences in AT between groups. Therefore, the study recruited only those patients who did not have any AT experience before participating in the pilot RCT to maintain a successful blinding design between the true and sham AT groups. The sham ear acupressure tapes were prepared by the doctoral researcher. Junci Medulla was cut into small pieces similar in size to the vaccaria seeds, and each of the Junci Medulla pieces was placed into each of the small holes on a specific plate to make auricular acupressure tapes. Medical desensitization tape was used to cover the plate, and the tape was then cut into small pieces similar in size to the vaccaria seed tapes, with each Junci Medulla piece attached to each tape. The appearance of the sham AT tapes was almost identical to the ear acupressure tapes used in the true AT group. **Figure 5.6** below shows the procedure for preparing the sham ear acupressure tapes, and **Table 5.2** following summarizes the AT treatment protocols used in the true AT and sham AT groups:

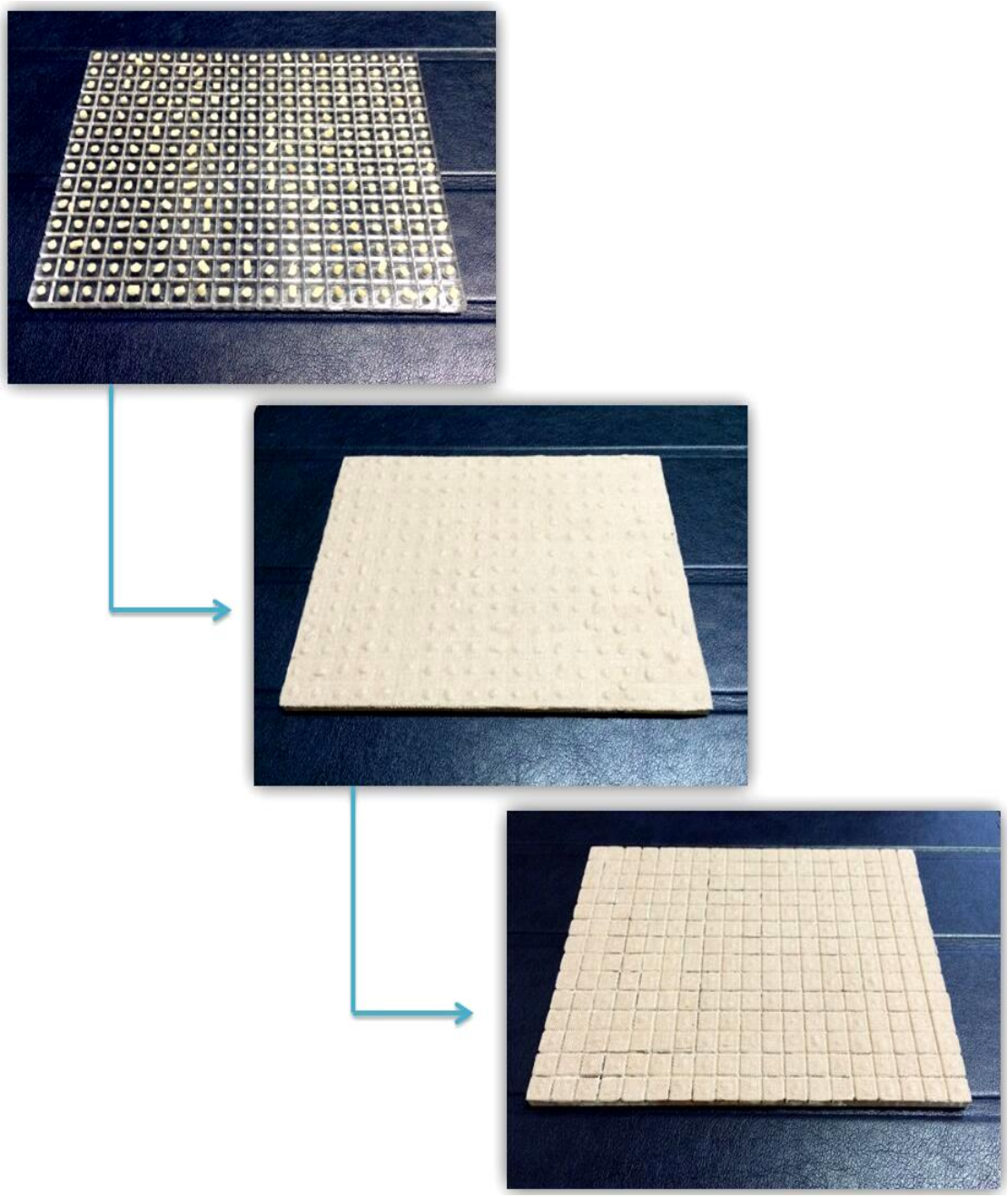


Figure 5.6 Procedure for preparing the sham acupressure tapes used in this study

Table 5.2 AT treatment protocols used in the true AT group and the sham AT group

	True Auricular Acupressure	Sham Auricular Acupressure
Types of taped seeds	Vaccaria seeds	Junci Medulla
Selected ear acupoints	Cardia, Stomach, Spleen, Liver, *Shenmen*, Sympathetic, and Subcortex	Cardia, Stomach, Spleen, Liver, *Shenmen*, Sympathetic, and Subcortex
Acupressure intensity	Pressed the taped seeds by gradually adding pressure until receiving the *de qi* sensation, and further located the most sensitive points for further acupressure	No pressure was scheduled
Treatment frequency and session	Regular acupressure: three times daily, with each time lasting 4 to7 minutes (all acupoints); Additional acupressure: when feeling the symptom of nausea or emesis; Acupressure for each acupoint: 20 to 30 seconds after receiving *de qi* sensation	No pressure was scheduled
Treatment duration	Five days	Five days

Note: AT=auricular therapy

5.4.3 Validation of the AT treatment protocol via a convent validity study

Content validity of the AT treatment protocol was evaluated by a panel of experts specialized in AT and TCM. As recommended by Lynn (1986), three to 10 experts are usually required for a content validity study. Using a content validity index (CVI) of 0.83 as a satisfactory cut-off value of content validity for each item of the AT treatment protocol (item-level CVI, which will be described in detail later) (Lynn, 1986), the number of experts needed for the content validity study was determined to be six. We therefore invited six experts who were specialized in both AT and TCM from the United States and Mainland China to determine the content validity of the AT treatment protocol. The six experts worked at either a university (n=3) or a university teaching hospital (n=3). All had at least 10 years of working experience related to AT and TCM, and half of the experts had more than 20 years of working experience. Among the six experts, one was appointed as a full professor and chief physician at a university teaching hospital, three were associate professors who worked at a university, and the other two held the positions of both associate professor and associate chief physician and worked at a university teaching hospital. The characteristics of the six invited experts are presented in **Table 5.3** below:

Table 5.3 Characteristics of the experts for the content validity study of the AT treatment protocol

Characteristics of the Experts (N=6)	Number (%)
Types of working institutions	
University	3 (50.0%)
University teaching hospital	3 (50.0%)
Age	
50-60 years old	1 (16.7%)
40-50 years old	5 (83.3%)
Highest academic qualification	
Doctorate degree	2 (33.3%)
Master's degree	3 (50.0%)
Bachelor's degree	1 (16.7%)
Academic and professional rank	
Full professor and chief physician	1 (16.7%)
Associate professor	3 (50.0%)
Associate professor and associate chief physician	2 (33.3%)
Years of working experience	
20 years or above	3 (50.0%)
16-20 years	2 (33.3%)
11-15 years	1 (16.7%)

A telephone or email invitation was delivered by the doctoral researcher to formally invite the identified experts to participate in the convent validity study. The experts were invited to respond to the invitation within seven days after receiving it (Rubio, Berg-Weger, Tebb, Lee, & Rausch, 2003), and all experts agreed to take part in the study. The doctoral researcher then delivered or emailed the content validity assessment form together with a cover letter to the six experts (see Appendix I). Information related to the content validity study, including the study aim and objectives, the inclusion criteria of the experts, the content of the assessment form (the AT treatment protocol), and the instructions for rating each assessment item, were included in the cover letter (Rubio et al., 2003).

On the content validity assessment form, five items were used to describe the true AT protocol and the sham AT protocol, respectively, which included the selected auricular acupoints, the scheduled approach for auricular acupressure, the technique for manual acupressure, the frequency and sessions of the AT treatment, and the total duration of the AT treatment. The experts were asked to independently assess the scientific and practical appropriateness of each item on a 4-point Likert scale from 1 to 4 (1 = "totally inappropriate", 2 = "inappropriate", 3 = "appropriate" and 4 = "very appropriate"). The experts were also invited to offer some comments and/or suggestions for further improvement if the item was rated as "inappropriate" or "totally inappropriate," and necessary

references that supported their comments and/or suggestions were also encouraged to be included in the assessment. The doctoral researcher asked that the assessment form be returned within two weeks, and all six experts sent back their completed evaluation within five days after receiving the assessment form.

The content validity of each of the items and the whole AT treatment protocol were evaluated using the CVI (Lynn, 1986; Rubio et al., 2003). The content validity of each item of the AT protocol, the item-level CVI, was evaluated by the panel experts who assessed the item as "very appropriate" (score of 4) or "appropriate" (score of 3) (Lynn, 1986; Rubio et al., 2003). To reach a satisfactory item-level CVI of 0.83, at least five out of the six experts had to rate the item as "very appropriate" or "appropriate" (Lynn, 1986). The CVI of the whole AT treatment protocol, the scale-level CVI, was judged based on the percentage of items that received a "content valid" score of 3 ("appropriate") or 4 ("very appropriate"), and the satisfactory value of the scale-level CVI had to be no less than 0.80 (Davis, 1992; Lynn, 1986). If no consensus could be reached after the first round of assessment, the AT treatment protocol would be revised based on the experts' comments and/or suggestions, and further rounds of rating would be performed until either the item-level CVI or the scale-level CVI reached the predefined satisfactory value.

Only one round of content validity assessment was conducted in this doctoral research project as either the item-level CVI or the scale-level CVI was deemed adequate after completing the first round of panel rating. The results of the content validity assessment are presented in **Table 5.4**. All the items from the true and sham AT protocols were determined to be content valid, with the item-level CVI ranging from 0.83 to 1.00. The scale-level CVIs for the true AT treatment protocol and the sham AT treatment protocol were also identified as excellent, with all at 1.00. Although satisfactory agreement regarding the AT treatment protocol was generally achieved among the panel, one expert held different ideas in terms of the approach for the sham AT intervention. The expert mentioned that the two different AT materials (vaccaria seeds and Junci Medulla) used in the true and sham AT groups may contribute to some variations and further suggested using vaccaria seeds in both groups but applying no additional stimulation in the sham AT group. After a discussion between the doctoral researcher and his two supervisors, who both work in the AT and acupuncture/acupressure research area, no further modification was made to

the sham AT protocol. The use of vaccaria seeds can create some constant stimulation of the acupoints (even without any manual acupressure) and subsequently produce some potentially specific treatment effects on nausea and vomiting. This could significantly reduce the value of the sham AT design in this study, which intended to examine the placebo effects of the sham AT when compared with the standard care as well as distinguish the specific treatment (true) effects of AT from the non-specific treatment (placebo) effects.

Table 5.4 Results of the content validity assessment of the AT treatment protocol

Item	Description of the Item[a]	Content Validity Assessment (total number of experts=6)			
		Number of experts rating "very appropriate" (4)	Number of experts rating "appropriate" (3)	Number of experts rating content valid (3 or 4)	CVI[b]
True AT treatment protocol					
1	Selected auricular acupoints	4	2	6	[Item-level] 1.00
2	Approach for ear acupressure	6	0	6	[Item-level] 1.00
3	Technique for ear acupressure	6	0	6	[Item-level] 1.00
4	Frequency and sessions of AT	4	2	6	[Item-level] 1.00
5	Total AT treatment duration	4	1	5	[Item-level] 0.83
Scale-level CVI for the true AT treatment protocol					[Scale-level] 1.00
Sham AT treatment protocol					
6	Selected auricular acupoints	3	3	6	[Item-level] 1.00
7	Approach for ear acupressure	5	0	5	[Item-level] 0.83
8	Technique for ear acupressure	6	0	6	[Item-level] 1.00
9	Frequency and sessions of AT	6	0	6	[Item-level] 1.00
10	Total AT treatment duration	5	0	5	[Item-level] 0.83
Scale-level CVI for the sham AT treatment protocol					[Scale-level] 1.00
Scale-level CVI for the whole content validity assessment form (both true and sham AT protocols)					[Scale-level] 1.00

Note: a=details regarding the description of each item can be found in Table 5.2 (AT treatment protocols used in the true AT group and the sham AT group) (in English) and in Appendix I (in Chinese); b=the item-level CVI was evaluated by the panel experts who assessed the AT item as "very appropriate" (4) or "appropriate" (3) (Lynn, 1986; Rubio et al., 2003), while the scale-level CVI was judged as the percentage of items that received a "content valid" score of 3 ("appropriate") or 4 ("very appropriate") (Davis, 1992; Lynn, 1986); AT=auricular therapy; CVI=content validity index

5.4.4 Summary of part one

This part presented the development process of an evidence-based AT treatment protocol used for CINV management. Following the *MRC Framework for Developing and Evaluating Complex Interventions*, research evidence and related AT theories and standards included in several well-recognized AT handbooks were retrieved for the development of the evidence-based AT treatment protocol. The characteristics of cancer symptoms were also considered in determining the AT treatment frequency and duration. The AT treatment protocol was then validated by a group of experts specialized in AT and TCM. The design of the pilot trial, which will comprehensively evaluate the feasibility and acceptability of the AT treatment protocol and test the study's methodological procedures, as well as preliminarily evaluate the clinical effects of the AT treatment protocol on CINV and QoL, will be presented in detail in the next part.

5.5 Part two: The pilot randomized controlled trial

5.5.1 Study design

A three-parallel-arm, placebo-controlled randomized trial with a pilot study design was utilized in this phase. Female breast cancer patients scheduled to be treated with their first cycle of chemotherapy were recruited from three provincial medical centers and randomly allocated to three different study arms: true AT intervention plus standard antiemetic treatment and care (true AT group), sham AT intervention plus standard antiemetic treatment and care (sham AT group), and standard antiemetic treatment and care only (standard care group). The AT treatment was administered from day 1 to day 5 of the first chemotherapy cycle in both the true AT group and the sham AT group. Short-term follow-up assessment was performed from the completion of the five-day AT treatment to the end of the first cycle of chemotherapy. Feasibility outcomes related to subject recruitment and the follow-up process, completion of study questionnaires and AT treatment protocol, and the safety of AT were assessed. In addition, clinical outcomes regarding the effects of AT on acute, delayed, and anticipatory CINV as well as QoL were also measured and preliminarily analyzed in the pilot RCT.

5.5.1.1 Identification of appropriate research design to fit the research objectives

The selection of an appropriate research design to address certain research questions and research aims is regarded as the basis of a research project (Draper, 2004). Therefore, the research design should be appropriately selected to fit the predefined research questions and research aims (Draper, 2004). According to Roberts and Dicenso (1999), quantitative research methods are the most suitable approaches to answering research questions that are related to the "cause, prognosis (course), diagnosis, prevention, treatment, or economics of health problems" (p. 4). Qualitative research methods are the most favorable candidates for answering research questions that are focused on the exploration of patients' experiences, attitudes, or meanings related to healthcare issues (Roberts & Dicenso, 1999).

One of the most important study objectives of the current part of the doctoral research project was to preliminarily examine the effects of AT on CINV and QoL in cancer patients allocated to different study groups, which included a cause-and-effect analysis of healthcare intervention. Therefore, a quantitative research design was utilized in this phase. Particularly, the most rigorous approach to exploring cause-and-effect relationships, the RCT, was adopted as the research method (Draper, 2004; Roberts & Dicenso, 1999). Since this current RCT aimed to carry out a preliminary investigation of the AT treatment effects, with a number of other objectives targeting the feasibility of the research methodological procedures, it was conducted only at the pilot study stage in the current doctoral project. Justifications for adopting an RCT and pilot study design will be further elaborated in the following two sections.

5.5.1.2 Reasons for choosing a randomized controlled trial

The cause-and-effect relationships between AT and the clinical outcomes of CINV and QoL were preliminarily investigated in this study, which makes the use of an RCT the most appropriate research approach in this context. Parahoo (1997) (as cited in Draper, 2004) indicated that an RCT can be viewed as the best candidate for exploring the cause-and-effect relationships between an intervention and certain outcomes in a most rigorous manner. Parahoo (1997) (as cited in Draper, 2004) also highlighted that a comprehensive inclusion of randomization, intervention, and control comparison in the research design is the most unique merit of RCTs,

which can basically maintain a reliable analysis of the interventional effects. The two major characteristics of RCTs that ensure the between-group differences in the outcome measures are caused by the study manipulation are the randomization of the study subjects and the longitudinal observation of the outcome assessment (Roberts & Dicenso, 1999). Group allocation following the principle of randomization maintains the similarities of participant characteristics across groups, with the only difference being the study manipulation received, while the longitudinal assessment of the study outcomes helps examine whether certain treatment factors ("manipulation") led to specific changes in the outcome measures (Roberts & Dicenso, 1999).

The comprehensive inclusion of randomization, intervention, and control comparison within the research design also makes RCTs superior to a number of other quantitative research approaches that also focus on the testing of interventional effects (e.g., non-randomized clinical trials or single group pre-post studies) with regard to the rigor of the research methodology. For instance, the absence of randomization in non-randomized clinical trials may lead to some considerable variations in the participants' characteristics across groups, which could seriously deteriorate the correct cause-and-effect analysis between the study intervention and outcomes, as the between-group differences in the effectiveness of the intervention after the longitudinal evaluation could be caused by differences in the participant' socio-demographic and clinical data at the very early stage of group allocation (Roberts & Dicenso, 1999). Single-group clinical trials with a pre-post study design have an absence of both randomization and control comparison, which makes it extremely difficult to judge the cause-and-effect relationships between the intervention and the outcomes (Seers & Critelton, 2001).

The "hierarchy of evidence" has ranked the systematic review of high-quality RCTs and a rigorously-designed multicenter single RCT as the highest level of research evidence for the cause-and-effect evaluation of interventions in healthcare sciences (Evans, 2003). Following the systematic review and multicenter RCT, a rigorously-designed single-site RCT has been ranked second for good research evidence (Evans, 2003). The "hierarchy of evidence" has highlighted the value of rigorously-designed RCTs in contributing to concrete research evidence in terms of the effectiveness of healthcare interventions (Evans, 2003). Given the absence of high-quality research evidence supporting the use of AT for CINV management in cancer patients at present (Tan et al.,

2014a), original research findings from well-designed RCTs are therefore required as the primary sources of research evidence for the further conclusion of definite evidence on the antiemetic role of AT in cancer symptom management. Taking into account all the concerns above, an RCT was utilized in this doctoral research project as it was the most appropriate approach to preliminarily investigating the cause-and-effect relationships between AT and the clinical outcomes of both CINV and QoL in female breast cancer patients undergoing chemotherapy.

5.5.1.3 Reasons for conducting a pilot randomized controlled trial

The significant methodological flaws identified in the study designs of current AT trials for CINV management made them impossible to serve as appropriate evidence and references for rigorously designing a new clinical trial to examine the effects of AT on CINV (Tan et al., 2014a). It has also been pointed out that the implementation of an RCT requires a large amount of time, energy, and money (Roberts & Dicenso, 1999; Thabane et al., 2010), so preparatory work should be conducted to estimate and manage the budget and time schedule and to ensure that the study procedure can proceed smoothly (Thabane et al., 2010). Therefore, before a formal evaluation of an intervention in a large-scale RCT, it is necessary to test the feasibility and acceptability of the intervention and study procedure in advance to ensure that the intervention is feasible and acceptable for use in the targeted population and study settings, and that the research methodological procedures are scientifically and practically adequate for implementation in a future main study (Craig et al., 2008; Thabane et al., 2010). As emphasized by Thabane et al. (2010), the primary and most crucial aim of a pilot study is to evaluate the feasibility and acceptability of the intervention "so as to avoid potentially disastrous consequences of embarking on a large study—which could potentially 'drown' the whole research effort" (p. 1 out of 10). In the *MRC Framework for Developing and Evaluating Complex Interventions*, the preparatory work for testing the feasibility of the intervention and piloting the research methodological procedures has also been highlighted as a crucial phase before proceeding to the further step of formally evaluating the complex intervention (Craig et al., 2008). Considering all the concerns above, a pilot RCT was designed in the doctoral research project to comprehensively assess the feasibility and acceptability of the AT treatment protocol and the research methodological procedure as well as preliminarily evaluate the effects of AT on CINV and QoL among cancer patients undergoing chemotherapy.

The preliminary RCT proposed in this doctoral research project is therefore a pilot trial design, a minimal version of the future main RCT, to examine the effects of AT on CINV in cancer patients, which covers both the feasibility study objectives for testing the feasibility and acceptability of the intervention protocol, subject recruitment, and the follow-up process and the pilot study objectives for preliminarily running all of the study methodological procedures and testing the interventional effects. "Feasibility study" and "pilot study" are two terms used to describe the preparatory work conducted before the main study; they are often used interchangeably in research articles but some differences still exist between the two concepts (Arain, Campbell, Cooper, & Lancaster, 2010; Eldridge & Kerry, 2012). The National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre (NETSCC) (as cited in Arain et al., 2010; Eldridge & Kerry, 2012) defined feasibility studies as some pieces of preparatory works performed prior to initiating the main study that can be used to facilitate the design of the future main study, such as testing the procedures of subject recruitment and randomization, the feasibility of the outcome assessment process, or the participants' compliance with the intervention or study procedure. Pilot studies are regarded as a minimal version of future main studies and are intended to preliminarily perform all of the methodological procedures (e.g., the whole study process, including subject recruitment and group allocation, implementation of the study intervention, outcome assessment, and follow-up evaluation) to see whether the whole study can be conducted in a good manner (Arain et al., 2010; Eldridge & Kerry, 2012). Based on the NETSCC definition, it can be concluded that a feasibility study mostly focuses on part of the study components, while a pilot study mainly emphasizes the methodological procedures of the whole study, and sometimes the feasibility study objectives can even be covered by the pilot study objectives when a pilot study is designed to examine the feasibility of either each research component or the whole study procedure. The *MRC Framework for Developing and Evaluating Complex Interventions* also highlights the value of the implementation of a pilot study at the "feasibility/piloting" phase to assess the feasibility of each study component included in the whole research methodological procedure (Craig et al., 2008).

Both feasibility study objectives and pilot study objectives were included in the current pilot RCT design. Following the *MRC Framework for Developing and Evaluating Complex Interventions* (Craig et al., 2008), and the recommendations for designing and reporting

pilot/feasibility studies as proposed by Arain et al. (2010), Lancaster, Dodd, and Williamson (2004), and Thabane et al. (2010), a pilot RCT was therefore conducted in this doctoral research project to determine the eligibility rate, recruitment rate, retention rate, and attrition rate during the subject recruitment and follow-up process (feasibility study objectives); assess the feasibility and acceptability of the study questionnaires and AT treatment protocol for the study participants (feasibility study objectives); and pilot the methodological procedure of the whole RCT and preliminarily evaluate the effects of AT on CINV and QoL (pilot study objectives). Details of the pilot RCT design, including the study participants and sample size, study settings and trial arms, randomization and blinding, detailed study procedures, outcome measures, and data analysis, will be presented in the following sections.

5.5.2 Study participants and sample size

Cancer patients who were most likely to experience nausea and emesis during chemotherapy were chosen as the target population for participation in the pilot RCT. Based on the treatment- and patient-related risk factors for CINV described in the literature review chapter (Chapter 2), female breast cancer patients undergoing moderately-high to highly emetogenic chemotherapy regimens were selected as the most appropriate study population. The sample size for this pilot study was determined to be 114, with 38 subjects in each of the three study groups.

5.5.2.1 Reasons for choosing female breast cancer patients as the study participants

Female patients are more inclined to experience nausea and emesis during cancer chemotherapy compared with male patients (American Cancer Society, 2016; Chan & Yeo, 2011; Hawkins & Grunberg, 2009; Inrhaoun et al., 2012; Lohr, 2008). According to the latest cancer statistics worldwide, among all types of cancers commonly identified in female patients, breast cancer is currently the most frequently seen cancer (Torre et al., 2015). Meanwhile, the most widely used chemotherapeutic agents in breast cancer, such as cyclophosphamide, doxorubicin, and epirubicin, are generally classified as having moderately-high to highly emetogenic risks (Aapro et al., 2016; Basch et al., 2011; Jordan et al., 2014; NCCN, 2015). When these agents are used in combination with other chemotherapeutic agents, including low emetogenic docetaxel and paclitaxel, the chemotherapy combination regimens are usually regarded as moderately-high to highly

emetogenic. (Note: According to the ONS recommendations, the emetogenic risk of the whole chemotherapy protocol, as determined by the agent with the highest emetogenic potential, increases by one degree when other low emetogenic agents are introduced into the protocol [ONS, May 2017].) Given the reasons listed above, female breast cancer patients with moderately-high to highly emetogenic chemotherapy regimens are most vulnerable to CINV, and they were therefore selected as the targeted study population for the pilot study.

5.5.2.2 Inclusion criteria

Eligible patients were recruited to the trial according to the following inclusion criteria:

(1) Adult female patients aged 18 years or above.

(2) Patients with a confirmed diagnosis of breast cancer at stage I to III (without distant metastasis).

(3) Chemotherapy-naïve patients (patients had not received any type of chemotherapy before participating in the study).

(4) AT-naïve patients (patients did not have any experience of receiving any type of AT before participating in the study).

(5) Patients were able to communicate (both verbally and in writing) in Mandarin Chinese.

(6) Patients had completed at least primary school education.

(7) Patients agreed to participate in the research and were willing to give written informed consent.

(8) Patients were scheduled to receive the first cycle of chemotherapy with moderately-high to highly emetogenic potential: commonly used anthracycline-based chemotherapy regimens including AC combination (doxorubicin plus cyclophosphamide), with or without paclitaxel (AC or AC-T), and EC combination (epirubicin plus cyclophosphamide), with or without paclitaxel or docetaxel (EC, EC-T, or EC-D); TC combination (cyclophosphamide plus docetaxel)]; and other less-frequently used chemotherapy combinations with moderately-high to highly emetogenic potential, including pirarubicin plus cyclophosphamide combination and pirarubicin/epirubicin combined with other chemotherapeutic agents with low to moderately emetogenic risks.

(9) Patients were provided with standard antiemetic medications during chemotherapy, including 5-HT_3 receptor antagonists (granisetron, ondansetron, tropisetron, or palonosetron) and/or dexamethasone.

5.5.2.3 Exclusion criteria

Patients were determined ineligible for participating in the study if they met at least one of the following exclusion criteria:

(1) Patients were extremely weak, disabled, or had immune deficiency.

(2) Patients were unable to follow the study instructions and cooperate with the study intervention and other research procedures.

(3) Patients had concurrent radiotherapy or other kinds of antineoplastic therapy.

(4) Patients were taking part in other clinical studies on antiemetic medications or other types of non-pharmacological interventions to control CINV, or other studies that might have created some interactions with the current pilot RCT.

(5) Patients had other health problems that may affect the symptoms of nausea and emesis during chemotherapy, including gastrointestinal diseases (intestinal obstruction, appendicitis, peptic ulcer, pancreatitis, acute/chronic gastritis, cholecystitis, gastroparesis, gastroesophageal reflux disease, gastric carcinoma, etc.), migraines, liver diseases, Ménière's disease, tinnitus, etc. (Hawthorn, 1995, pp. 37-44; Scorza, Williams, Phillips, & Shaw, 2007).

(6) Patients had ear skin problems that were not appropriate for AT treatment (e.g., ear infections, ear scars and rashes, ear frostbite, ear abrasions, or ear abscess (Abbate, 2004, p. 84; Guan et al., 2002, pp. 113-142).

5.5.2.4 Sample size estimation

As indicated earlier, a pilot study usually puts its primary focus on the feasibility evaluation of the intervention protocol, study questionnaires, and other methodological procedures, but not the hypothesis testing of the interventional effects (Craig et al., 2008; Eldridge & Kerry, 2012; Lancaster et al., 2004; Leon, Davis, & Kraemer, 2011; Thabane et al., 2010). Formal sample size estimation for inferential statistics is therefore not necessary for a pilot study design, and it is suggested that the sample size for a pilot trial should be based on a pragmatic basis for the evaluation of feasibility issues (Leon et al., 2011; Thabane et al., 2010). Given that the secondary focus of this pilot RCT was to preliminarily assess the interventional effects of AT, the study findings of which can be further utilized to inform the design of the future main RCT, the sample

size estimation of the current pilot study should be reasonable enough to provide precise estimates of the parameters used for the future main study sample size estimation (Teare et al., 2014).

Hertzog (2008) suggested that a minimum of 30 subjects per study group would be necessary for a pilot study with effect size and confidence interval (CI) estimations of between-group comparisons for future power analysis. Browne (1995) (as cited in Lancaster et al., 2004) also indicated that a sample size of 30 or more could be considered in a pilot study to estimate a parameter. As recommend by the Chief Scientist Office (CSO) of the Scottish Government Health Directorates (2014), for a pilot study with an RCT design, a minimum of 30 subjects per study group is deemed sufficient for parameter estimation in the future main RCT. Therefore, 30 subjects per group were determined to be an appropriate sample size for this pilot RCT. Allowing for a potential attrition rate of 20% during the whole study process, the total sample size was finally determined to be 114, with 38 subjects in each group.

5.5.3 Study settings

The study was conducted in Fuzhou, the capital city of Fujian Province in Mainland China. A convenience sampling approach was utilized to select the study hospitals, as a random sampling of study hospitals would be difficult and nearly impossible in this study. The study participants were recruited from three large provincial hospitals, which included Fujian Provincial Cancer Hospital, The First People's Hospital of Fujian Province, and The Second People's Hospital of Fujian Province.

(1) Fujian Provincial Cancer Hospital (Study Site I): Fujian Provincial Cancer Hospital is a large cancer center in southeast China, with 28 clinical departments and 1,600 beds. It is the only specialized cancer medical center in Fujian Province and it serves a population of around 38 million across the whole province. The medical oncology department for breast cancer was accessed for subject recruitment, as the majority of breast cancer patients receiving cancer treatment in this hospital would attend this department for chemotherapy.

(2) The First People's Hospital of Fujian Province (Study Site II): The First People's Hospital of Fujian Province is one of the leading medical centers in Fujian Province, with 1,200 beds and 38

clinical departments. It is also a large teaching hospital affiliated with a provincial medical university. The department of medical oncology is responsible for breast cancer chemotherapy in this hospital and part of our study participants were recruited from this department.

(3) The Second People's Hospital of Fujian Province (Study Site III): The Second People's Hospital of Fujian Province is also a large medical center affiliated with a provincial medical university. This hospital has 32 clinical departments and 1,000 beds. The department for breast diseases also accepts breast cancer patients for chemotherapy and part of our study participants were recruited from this department.

5.5.4 Trial arms

Three study arms were designed for this pilot RCT, including the true AT group, the sham AT group, and the standard care group.

5.5.4.1 Reasons for adopting a placebo (sham) comparison and a standard care comparison

In interventional studies utilizing an RCT design, particularly for studies on complex non-pharmacological interventions such as body and ear acupoint stimulation, a placebo comparison (sham intervention) is usually included to help distinguish the specific treatment (true) effects of the intervention from the non-specific treatment (placebo) effects (Dincer & Linde, 2003; Tan et al., 2015; Zhang et al., 2014). The therapeutic effects of acupuncture and acupressure are commonly regarded as a mixture of both specific (true) and non-specific (placebo) effects generated from acupoint stimulation (Dincer & Linde, 2003; Tan et al., 2015; Zhang et al., 2014), and a comparison of the treatment effects between the true intervention and the sham intervention helps determine the degree of the specific effects of the acupoint stimulation.

To examine the size of the non-specific treatment (placebo) effects of acupoint stimulation, a further comparison between the sham intervention group and another group without acupoint stimulation (e.g., the control group, with routine methods of treatment or care only) is also necessary (Tan et al., 2015). As recommended by Dowrick and Bhandari (2012), a study group with routine methods of treatment or care should be considered for healthcare interventional studies that include a

comparison between a true intervention and a placebo (sham) intervention to reflect the "natural course of the disease" (p. 9). Moreover, with the inclusion of comparisons between the placebo (sham) intervention and routine methods of care, the definite placebo effects of the intervention can be captured by "subtracting any benefit of the placebo from usual treatment" (Dowrick & Bhandari, 2012, p. 9).

Given the concerns above, a three-arm design was therefore adopted in this pilot RCT. Specific treatment effects of AT on CINV and QoL were preliminarily examined by comparing the true AT group and the sham AT group, and non-specific treatment (placebo) effects of the sham AT were also preliminarily explored through comparisons between the sham AT group and the standard care group. Detailed information regarding each of these three study groups will be presented in the following sections (see **Table 5.5**).

5.5.4.2 True AT intervention group (true AT group)

Participants allocated to the true AT group received a five-day true AT treatment protocol plus standard antiemetic treatment and care. The true AT treatment was conducted from day 1 to day 5 of the first cycle of chemotherapy. Vaccaria seeds were utilized for acupoint stimulation. AT treatment was scheduled three times daily, with each time lasting about four to seven minutes, pressing all the targeted ear acupoints located on both ears. Daily acupressure was conducted in the morning, afternoon, and evening, respectively, during the five-day AT treatment period, regardless of whether the participants had experienced CINV symptoms or not. In addition to the regular three-times-daily ear acupressure, the participants were also instructed to add pressure to the taped AT seeds as soon as they had the feeling of the coming of nausea and emesis (details can be found in Section 5.4.1 of this chapter, and the AT treatment protocol used in the true AT group was also summarized in Table 5.2). In terms of the standard antiemetic treatment and care, antiemetics (5-HT_3 receptor antagonists and/or dexamethasone) were administered 30 to 60 minutes before the commencement of chemotherapy and the participants continued to receive prescribed antiemetic medications for the following one to two days post-chemotherapy. Daily care for the participants followed routine methods of care at the study sites, such as regular health education, nutritional care, and health assessment.

5.5.4.3 Sham AT comparison group (sham AT group)

Participants allocated to the sham AT group received a five-day sham AT treatment protocol plus standard antiemetic treatment and care. The sham AT treatment was conducted from day 1 to day 5 of the first cycle of chemotherapy. The selected ear acupoints for the sham AT intervention were exactly the same as those in the true AT treatment protocol. Meanwhile, to avoid any potential specific treatment effects generated from the acupoint stimulation, no manual acupressure was scheduled for the participants in the sham AT group, and the vaccaria seeds were replaced by Junci Medulla (details can be found in Section 5.4.2 of this chapter, and the AT treatment protocol used in the sham AT group was also summarized in Table 5.2). In terms of the standard antiemetic treatment and care, antiemetics (5-HT_3 receptor antagonists and/or dexamethasone) were administered 30 to 60 minutes before the commencement of chemotherapy and the participants continued to receive prescribed antiemetic medications for the following one to two days post-chemotherapy. Daily care for the participants followed routine methods of care at the study sites, such as regular health education, nutritional care, and health assessment.

5.5.4.4 Standard care comparison group (standard care group)

Participants allocated to the standard care group were provided only standard antiemetic treatment and care without any AT treatment. Antiemetics (5-HT_3 receptor antagonists and/or dexamethasone) were administered 30 to 60 minutes before the commencement of chemotherapy and the participants continued to receive prescribed antiemetic medications for the following one to two days post-chemotherapy. Daily care for the participants followed routine methods of care at the study sites, such as regular health education, nutritional care, and health assessment.

Table 5.5 Summary of the study arms and interventions

Study Arms	**Intervention Components**		
	AT at specific acupoints with regular acupressure	AT at specific acupoints without any stimulation	Standard antiemetic treatment and routine methods of care
True AT intervention	●		●
Sham AT intervention		●	●
Standard care			●

Note: ●=the intervention component was included in the study arm

5.5.5 Randomization and blinding

5.5.5.1 Randomization

To ensure that patient characteristics were generally comparable between groups as well as to avoid selection bias and minimize accidental bias during the process of group assignment (Suresh, 2011), a randomization procedure was employed. To maintain an equal sample size across the three study groups, the block randomization method was utilized (Efird, 2010; Suresh, 2011), and the online application Research Randomizer (https://www.randomizer.org/) was used to produce the randomization table. Allocation concealment was also utilized to further minimize the risk of selection bias (Suresh, 2011). The randomization table was therefore prepared and kept by a person (a university lecturer) who did not know the study process and was not involved in any other procedures of this study. When a potential participant was identified as eligible for participating in this study and related informed consent was completed, the researchers called the person who was responsible for randomization to receive the corresponding random number to determine the group assignment of the participant.

5.5.5.2 Blinding

To minimize performance bias during the implementation of the study intervention and detection bias during the outcome assessment, it is recommended that an adequate blinding design among the study participants, research personnel (or care providers), and outcome assessors be considered (Furlan et al., 2015). However, a complete blinding design was deemed impossible for this pilot RCT due to the visible nature of the auricular acupressure intervention. A partial blinding design was therefore employed in this study. Particularly, the participants allocated to the true AT group and the sham AT group, as well as the care providers (staff nurses and nurse assistants) working at the study sites, would not know whether the AT treatment was a true or sham approach. In addition, blinding of the outcome assessment for the true AT group and the sham AT group was also maintained given that the outcome measures were self-administered questionnaires and the participants themselves were the outcome assessors. As the participants allocated to the standard care group did not receive any AT intervention, the blinding design was therefore impossible for them because it would also be easy for the care providers to figure out the differences between the standard care group and the two AT groups.

Moreover, to further ensure the successful blinding design among the participants in the true AT group and the sham AT group (e.g., to avoid communication between participants and to prevent those in the sham AT group from observing the regular ear acupressure technique conducted in the true AT group), when the actual AT treatment at the study sites was was about to commence, the oncologists would help separate the participants from the true AT group and the sham AT group into different wards.

5.5.6 Study procedure

Prior to the commencement of the pilot study, a group meeting was held among the researchers (the doctoral researcher and two other nurse researchers who assisted in the subject recruitment and AT intervention, details of which can be found in Section 5.7 in this chapter) and oncology nurses to brief the process of eligibility assessment for study participation. The oncology nurses were responsible for identifying potentially eligible participants based on the study inclusion and exclusion criteria. Patients who were identified as eligible for participation were regarded as potential participants, and they were then invited by the oncology nurses to participate in the study. Potential participants who expressed interest in participating were further introduced to the researchers for more information about the study. The researchers then provided the potential participants with more detail in terms of the study's aim and procedures. Potential participants were well informed that participation in this research was on a voluntary basis and that they had the right to refuse to take part in the research or refuse to continue with the research at any time without affecting their routine cancer treatments and care. For those who agreed to participate, written informed consent was obtained and baseline demographic and clinical data, as well as baseline QoL status (measured by the FACT-B) and anticipatory CINV (measured by the INVR), were then collected. Following the completion of the baseline assessment, the participants were then randomly assigned to one of the three study groups—the true AT group, the sham AT group, or the standard care group—according to a predefined random number table. Subject recruitment and randomization of eligible participants was completed one to two days prior to the commencement of their first cycle of chemotherapy.

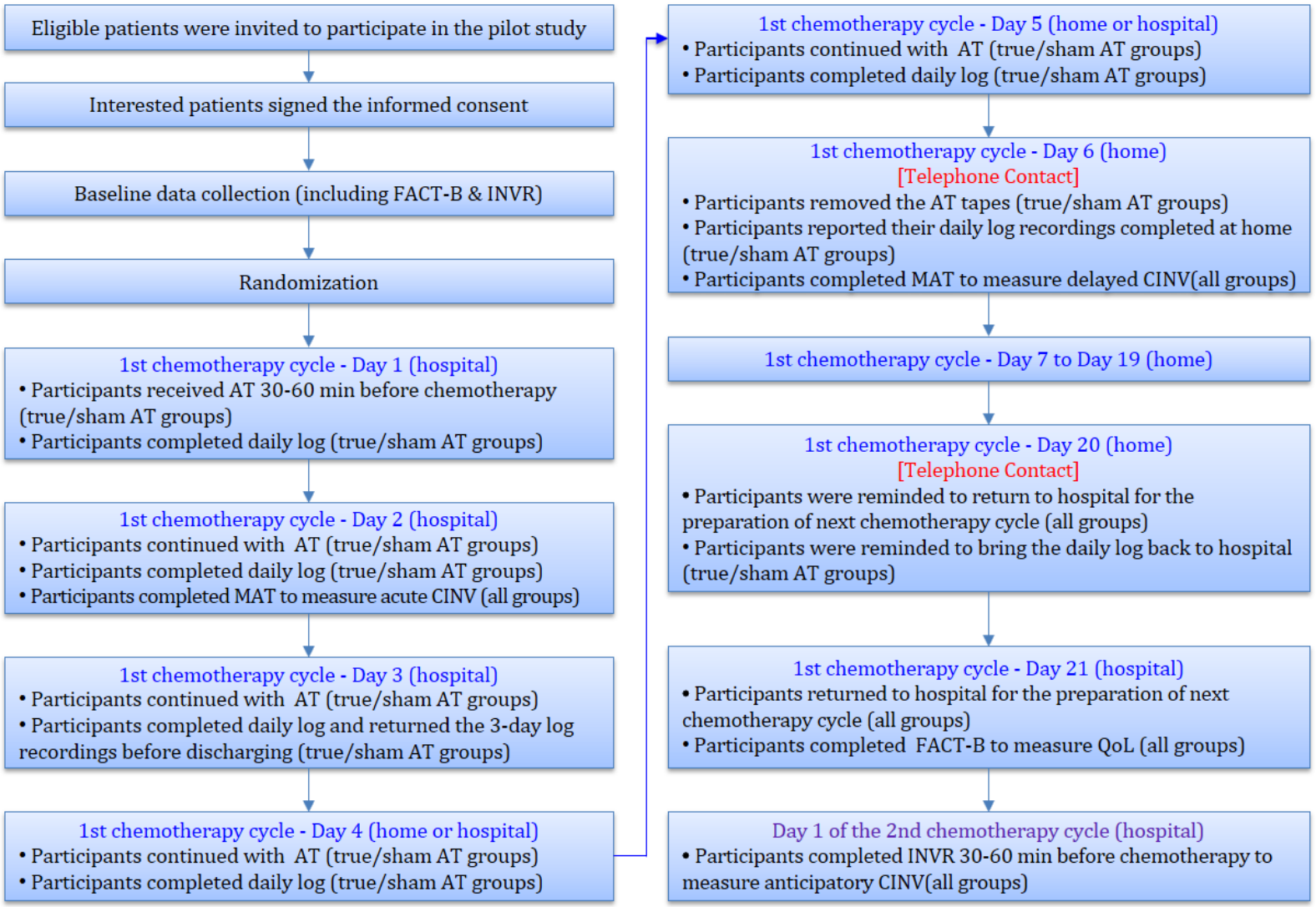
On the first day of the first chemotherapy cycle (**D1**), the participants allocated to the true AT group and the sham AT group received their respective AT treatment 30 to 60 minutes before

the administration of their chemotherapeutic regimens. For those receiving the true AT treatment, the researchers demonstrated the acupressure technique and the participants were then asked to perform a return demonstration to ensure that they had mastered the self-acupressure skills. Instructions and precautions in terms of the AT treatment were given to the participants according to the true and sham AT treatment protocols that were described in detail earlier. The participants in the true AT group were provided with a specifically designed log to record the time, duration, and frequency of ear acupressure daily, as well as possible adverse events associated with the AT treatment. The participants in the sham AT group were given another type of daily log that was designed to record possible AT-related adverse events only. The participants in the true AT group were monitored while conducting regular ear acupressure during the first three to four days of the AT treatment if the participants were still in the hospital, and the participants in the true AT group and the sham AT group were also monitored while completing their daily log if they were still in the hospital (although there were always several participants who did not strictly follow the researchers' instructions to complete the self-acupressure and daily log). The daily logs that were completed at the study sites were returned to the researchers before the participants were discharged from the hospitals.

Acute and delayed nausea and vomiting that occurred during the first five days of the first chemotherapy cycle were measured using the MAT. All participants were asked to complete the acute CINV questionnaire of the MAT on the second day of the first chemotherapy cycle (**D2**) to record the occurrence, frequency, and severity of acute nausea and vomiting experienced during the past 24 hours (the acute phase of CINV, 0-24 h post-chemotherapy). Two research assistants (student nurse helpers) who assisted with the data collection explained to the study participants how to complete the MAT. On the sixth day of the first chemotherapy cycle (**D6**), all participants were again asked to complete the MAT delayed CINV questionnaire to record the occurrence, frequency, and severity of delayed nausea and vomiting experienced during the past four days (the delayed phase of CINV, >24-120 h post-chemotherapy). The delayed CINV assessment was mostly completed by telephone as the majority of the participants were discharged from the hospital on the fourth (**D4**) or fifth (**D5**) day of the first chemotherapy cycle. The research assistants called the participants to ask them to respond to the questionnaire items, and then manually transferred their answers to paper records. For the early-discharged

participants in the true AT group and the sham AT group on **D4** or **D5** of the first chemotherapy cycle, they were asked to take one or two pieces of their daily log to complete at home and bring it back to the hospital when returning for the second chemotherapy cycle. However, the researchers considered that a few participants might forget to complete the daily log at home; therefore, the research assistants who called the participants on **D6** of the chemotherapy cycle for delayed CINV assessment also reminded those in the true AT group and the sham AT group to complete the AT log and asked them to report their recording, and they then manually transferred these to paper records.

Immediately after the completion of the five-day AT treatment, a short-term follow-up was carried out until the end of the first chemotherapy cycle (**D21**), and two telephone calls were made by the research assistants during the follow-up period. The first call was made on **D6** to collect data on delayed CINV assessment, and for the participants in the true AT group and the sham AT group, the research assistant also reminded them to complete and report the daily log of AT treatment as well as to remove the auricular acupressure tapes (details on this procedure were described earlier). The second call was made on the twentieth day of the first chemotherapy cycle (**D20**, one day before the end of the first chemotherapy cycle) to remind participants to return to the hospital on the following day (**D21**) to prepare for the second cycle of chemotherapy. For those allocated to the true AT group and the sham AT group, they were also asked to bring their completed daily log back to the research assistants. Permission for telephone contact was received from the study participants when they were discharged after the first chemotherapy cycle, and the research assistants asked them for the most appropriate time for telephone contact. After returning to the hospital to prepare for the second chemotherapy cycle, all participants were asked to complete the QoL questionnaire (FACT-B) to evaluate their QoL status during the first cycle of chemotherapy. On the first day of the second chemotherapy cycle, 30 to 60 minutes before the administration of the chemotherapeutic regimens, all participants were asked to complete the INVR questionnaire again to indicate their anticipatory nausea and vomiting. The study procedures of the pilot RCT, from subject recruitment to the last time point of data collection, are shown in **Figure 5.7** below:



FACT-B=Functional Assessment of Cancer Therapy-Breast Cancer; INVR=Index of Nausea, Vomiting and Retching; AT=auricular therapy; MAT=MASCC Antiemesis Tool

Figure 5.7 Study procedure for the pilot RCT

5.5.7 Study outcome measures

The main outcomes for this pilot RCT were a series of feasibility outcomes related to subject recruitment and the follow-up process as well as completion of the study questionnaires and interventions. In addition, a number of clinical outcomes in terms of the effects of AT on CINV and QoL, including acute, delayed, and anticipatory nausea and vomiting and breast-cancer-specific QoL, were preliminarily assessed as the secondary outcomes. The outcome measures of this pilot RCT, including baseline assessment, feasibility outcomes, and clinical outcomes, will be described in the following sections.

5.5.7.1 Baseline assessment

The participants' demographic data, medical history, CINV-related risk factors, and other baseline data were collected via a specifically-designed baseline assessment questionnaire (see Appendix II). The demographic data included the patient's age, marital status, education background, employment status, religious background, family monthly income, and source of medical insurance. The patients' medical history and current chemotherapy protocols were retrieved from their medical records, which included the date confirming the diagnosis of breast cancer, the current stage of breast cancer, date and type of breast cancer surgery, scheduled chemotherapeutic agents and combinations, and scheduled antiemetic treatment. Risk factors related to CINV such as a history of morning sickness, motion sickness, and labyrinthitis were measured. In addition, the participants' QoL status and anticipatory nausea and vomiting at baseline were also assessed using the FACT-B and the INVR, respectively.

5.5.7.2 Feasibility outcomes

Several feasibility outcomes were included as the primary outcomes in this pilot RCT, including the feasibility of subject recruitment and the follow-up process, the feasibility of the study questionnaires, the acceptability of the study intervention, the safety of the study intervention, and the participants' satisfaction with the study intervention. Feasibility outcomes regarding the acceptability, safety, and satisfaction with the study intervention were particularly designed for the participants in the true AT group and the sham AT group, and a daily log was used for feasibility data collection.

(1) Feasibility of subject recruitment and follow-up process

Feasibility outcomes in terms of subject recruitment and the follow-up process included: **(1)** the time taken to complete the entire subject recruitment and the average number of subjects recruited per month; **(2)** the eligibility rate of the screened patients (the number of subjects eligible for participation divided by the number of subjects screened for eligibility); **(3)** the recruitment rate (the number of subjects who participated in the study divided by the number of subjects eligible for participation) (Price et al., 2016); **(4)** the retention rate (the number of subjects who completed the study divided by the number of subjects who participated in the study); **(5)** the attrition rate (the number of subjects who dropped out after randomization divided by the number of subjects who participated in the study) (Nour, Chen, & Allman-Farinelli, 2016); and **(6)** the patients' reasons for discontinuing the study after participation.

(2) Feasibility of the study questionnaires

The feasibility of the study questionnaires was measured by calculating the proportion of missing values at both item-level and scale-level for each of the study questionnaires, including the MAT, the INVR, and the FACT-B. Item-level missing values were determined as the percentage of participants who did not respond to each single item, and scale-level missing values were identified as the percentage of participants who did not respond to at least one item in the whole questionnaire.

(3) Acceptability of the study intervention

The acceptability of the study intervention was assessed by: **(1)** the total number of days the AT treatment was performed among the participants in the true AT group and the sham AT group, where the standard duration of the AT treatment should have been five days; **(2)** the number of times that ear acupressure was performed during the AT intervention period by the participants in the true AT group, where the standard number of times should have been 3 times, 12 times, and 15 times for the acute CINV phase (day 1 of chemotherapy), delayed CINV (day 2 to day 5 of chemotherapy), and the five-day AT period (day 1 to day 5 of chemotherapy), respectively; and **(3)** duration of each time of ear acupressure during the acute CINV phase, the delayed CINV phase, and the five-day AT period for the participants in the true AT group, where the standard duration

for each time of ear acupressure should have been four to seven minutes. It should be noted that the standard AT treatment days were five days in total in this pilot study, with a one-day acute CINV phase and a four-day delayed CINV phase. However, a few participants failed to complete the entire five-day AT treatment period, particularly for the AT treatment during the delayed CINV phase; therefore, for those participants who failed to complete the five-day AT treatment period, the computation of their times and average duration of each acupressure was based on the actual number of days (e.g., two days, three days, or four days) they completed the AT treatment. Details will be presented in the results chapter (Chapter 7) in Section 7.2.3.3.2.

(4) Safety of the study intervention

A safety assessment was also included in the feasibility evaluation of the AT intervention, as the *CONSORT for Harms Data Recommendations* indicated that possible harm data (adverse events) associated with an intervention or treatment should be well recorded and reported in clinical studies (Ioannidis et al., 2004). Any possible side effects associated with auricular acupressure in both the true AT group and the sham AT group were recorded by the participants themselves during the five-day AT intervention period. The likelihood of causality between the AT and the reported adverse events was then judged by an experienced acupuncture practitioner. The assessment criteria developed by the WHO-UMC was utilized in this pilot study to determine the causality between the AT intervention and the suspected side effects induced by AT (WHO, 2005). Six grades of causality were used to classify the likelihood, including "certain," "probable/likely," "possible," "unlikely," "conditional/unclassified," and "unassessable/unclassifiable" (WHO, 2005). It should be noted that the WHO assessment tool was originally developed to assess drug-related harm events (WHO, 2005), and the criteria used in the current pilot RCT were slightly modified based on two recent systematic reviews that focused on the potential adverse events associated with the use of AT (Tan et al., 2014b) and cupping treatment (Kim, Kim, Choi & Lee, 2014) (see Appendix III).

(5) Participants' satisfactions with the study intervention

The participants in the true AT group and the sham AT group were required to rate their satisfaction with the intervention after the completion of the five-day AT treatment. Three questions were asked, including their satisfaction with the AT treatment (10-point numeric rating

scale [NRS], where "1" means "very dissatisfied" and "10" represents "very satisfied"), consideration of further AT treatment (10-point NRS, where "1" indicates "absolutely not" and "10" represents "absolutely yes"), and willingness to recommend AT to others (10-point NRS, where "1" represents "absolutely not" and "10" means "absolutely yes").

(6) Daily log

The feasibility assessment data regarding the acceptability, safety, and satisfaction with the AT treatment were recorded in a daily log by participants in the true AT group and the sham AT group. Two types of logs were created specifically for the two groups. For the participants in the true AT group, the log consisted of three sections that the participants were required to complete daily during the five-day AT intervention (see Appendix IV). The first section was the daily schedule for regular ear acupressure and included instructions on how to manually press the taped seeds; the second section was for recording the time, frequency, and duration of daily acupressure; and the third section was about potential adverse events related to auricular acupressure. In addition, the participants' satisfaction with the AT treatment was recorded in the last day's log. As no acupressure was scheduled for the participants in the sham AT group, the log designed for that group did not include information regarding acupressure instructions and the daily recording of acupressure time, frequency, and duration, and only AT-related adverse events and the participants' satisfaction with the AT treatment were recorded (see Appendix V).

5.5.7.3 Clinical outcomes

The clinical outcomes regarding the effects of AT on nausea, vomiting, and QoL were included as secondary outcomes in this pilot RCT. The MAT was employed to measure acute and delayed nausea and vomiting during the five-day AT intervention. The FACT-B was used to measure QoL at baseline and the end of the first chemotherapy cycle. In addition, anticipatory nausea and vomiting was also assessed at baseline and on the morning of the commencement of the second chemotherapy cycle using the INVR questionnaire.

5.5.7.3.1 Instruments for measuring acute, delayed, and anticipatory CINV

(1) Selection of adequate instruments for measuring CINV

A number of instruments are currently available in both research and practice to assess nausea and vomiting during cancer chemotherapy, and the most commonly used ones are the MANE, the FLIE, the INVR, and the MAT (Brearley et. al., 2008; Wood, Chapman, & Eilers, 2011). The selection of the most appropriate tool for CINV assessment in this pilot study comprehensively considered the issues of psychometric properties in research and clinical utility in practice (Brearley et al., 2008; Wood et al., 2011). That is to say, the selected CINV measurements should be able to precisely and accurately capture patients' nausea and vomiting symptoms with satisfactory psychometric properties identified through rigorous research, and the selected instruments should also be convenient for use on cancer patients within real clinical practice and optimal for facilitating efficient communication among clinical oncologists, researchers, and patients to reach appropriate CINV symptom management strategies (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Wood et al., 2011).

To capture a full picture of patients' CINV symptom experience, information such as symptom onset (occurrence), frequency, duration, and intensity (severity) during different CINV phases should be comprehensively measured (Brearley et al., 2008; Wood et al., 2011). Meanwhile, according to Brearley et al. (2008), adequate psychometric properties are regarded as the core of a well-designed research instrument, as they can ensure that the scale "consistently measures what it was designed to measure" (p.1215). Moreover, in terms of the clinical utility of the CINV measurements, the expected time and energy used for training the research/clinical staff who are responsible for collecting data, completing the whole questionnaire, and calculating different domain scores for nausea and vomiting should also be taken into consideration when selecting the most appropriate CINV measurements (Brearley et al., 2008).

The MANE mainly focuses on the assessment of the anticipatory phase and the acute phase of nausea and emesis, not the delayed symptoms (Brearley et al., 2008). The psychometric properties of the MANE, including test-retest reliability, content validity, convergent validity, and discriminant validity, were examined and reported to be acceptable, but evidence regarding

its clinical applications has been scanty (Brearley et al., 2008). The FILE and its modified version (FILE 5-day recall) cover both the acute phase and the delayed phase of nausea and vomiting during cancer chemotherapy, but its primary focus is on patients' functional status, especially QoL affected by the CINV symptoms, not on the occurrence, frequency, and intensity of nausea and vomiting symptoms (Brearley et al., 2008). The INVR is a popular instrument used to assess CINV, and it was designed to measure the amount, intensity, duration, and distress of nausea, vomiting, and retching symptoms without distinguishing the acute and delayed symptoms (Brearley et al., 2008; Wood et al., 2011). The psychometric properties of the INVR were examined but were identified as insufficiently reported in the literature (Brearley et al., 2008). The INVR can be rated every 12 hours or 24 hours for a daily record of CINV symptoms, and repeated administration of the questionnaire (about five to 10 times) can also facilitate the assessment of acute and delayed nausea and vomiting symptoms (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Moradian, 2013); however, this could result in a large amount of missing values and produce considerable burden for cancer patients. The MAT is currently the only instrument particularly designed to record the occurrence, frequency, and severity of nausea and vomiting at both the acute phase and the delayed phase of CINV, with well-documented psychometric properties and clinical utility (Brearley et al., 2008; Molassiotis, Coventry et al., 2007). Acute and delayed CINV symptoms are separately recorded at two different time points and there is no need to repeatedly administer the questionnaire to assess delayed CINV symptoms that occurred across several days (Brearley et al., 2008; Molassiotis, Coventry et al., 2007).

Given all the concerns above, the MAT was adopted in this study as the most appropriate instrument for measuring acute and delayed CINV during the first five days of the first chemotherapy cycle. As anticipatory CINV was also planned to be measured at both baseline and post-intervention, the INVR was therefore administered twice in this study to assess anticipatory CINV.

(2) The MASCC Antiemesis Tool (MAT)

The MAT was developed by the MASCC, and it's a short, self-administered instrument that can be used in clinical practice (Brearley et al., 2008; Molassiotis, Coventry et al., 2007) (see Appendix

VI). The MAT is the only available instrument at present to separately record CINV symptoms in the acute phase and the delayed phase, which could "assist cancer treatment centers in understanding the overall effectiveness of their antiemetic strategies" (Molassiotis, Coventry et al., 2007, p. 150). The MAT has only eight items; the first four items measure acute symptoms and the other four items assess delayed episodes (Molassiotis, Coventry et al., 2007). In the acute and delayed symptom domains, each of the four questions measures the onset of vomiting ("yes" or "no"), frequency of vomiting (number of episodes), onset of nausea ("yes" or "no"), and intensity of nausea (0-10 NRS, a higher score represents a worse CINV symptom), respectively (Molassiotis, Coventry et al., 2007; Tan, Suen, & Molassiotis, 2016). On the first day post-chemotherapy (D2 of the chemotherapy cycle), patients respond to the first four questions to rate their acute CINV conditions that occurred during the past 24 hours (0-24 h after receiving the chemotherapy), while on the fifth day post-chemotherapy (D6 of the chemotherapy cycle), patients complete the other four questions to report their delayed CINV symptoms that occurred during the past four days (>24 to 120 h after receiving the chemotherapy) (Tan et al., 2016).

When used in clinical practice, each item of the MAT is assessed on its own without the need to calculate its total and domain scores. This scoring system has been utilized in only two MAT psychometric assessment studies so far (Molassiotis, Coventry et al., 2007; Tan et al., 2016). Particularly, the total score of the CINV experience can be produced by summing up all eight MAT item scores (Molassiotis, Coventry et al., 2007; Tan et al., 2016). The acute CINV scores and the delayed CINV scores can then be calculated by summing up the respective four item's scores within each domain, and the acute nausea/vomiting and delayed nausea/vomiting scores can also be separated by summing up related item scores within the acute and delayed symptom domains, respectively (Tan et al., 2016). In addition, all four items related to nausea and all four items related to vomiting can also be summed up respectively to calculate the MAT total nausea score and total vomiting score (Molassiotis, Coventry et al., 2007; Tan et al., 2016).

The original English version of the MAT was validated in the UK and USA, with satisfactory psychometric properties reported (Molassiotis, Coventry et al., 2007). The reliability of the MAT was reported to be adequate, with the Cronbach's alpha coefficient (internal consistency reliability) of 0.77 in a cancer patient sample and 0.82 in a caregiver sample, and item-to-total correlations of

0.60 to 0.91 (all at $p<0.001$) (Molassiotis, Coventry et al., 2007). Contrasted-group validity analysis based on the younger age risk factor demonstrated a good discrimination of the MAT for CINV symptoms experienced between patients with different emetogenic risks (Molassiotis, Coventry et al., 2007). Good content validity, face validity, and cultural equivalence and congruence of the MAT were identified, and concurrent validity of the MAT was also found to be excellent when tested against the INVR (Molassiotis, Coventry et al., 2007). A variety of language versions of the MAT is now available for use in different countries and populations, such as Arabic, Armenian, Chinese, French, German, Greek, Indonesian, Italian, Japanese, Korean, Russian, and Spanish (http://www.mascc.org/MAT). The Chinese version of the MAT (see Appendix VII) was utilized in this study, and it was applied in the assessment of nausea and emesis among cancer patients in a recent prospective observational research (Hsieh et al., 2015). However, no psychometric assessment of the MAT, Chinese version, has been reported so far. Therefore, before using the MAT, Chinese version, in this pilot RCT, a psychometric assessment study was performed first to identify the validity, reliability, and clinical feasibility of the MAT, Chinese version, used for Chinese patients with different cancer diagnoses, and details of this preparatory study will be presented in the next chapter (Chapter 6: Preparatory study: Psychometric properties of the MAT, Chinese version).

(3) The Index of Nausea, Vomiting, and Retching (INVR)

The INVR is a patient-administered instrument with a total of eight questions and three domains ("symptom experience," "symptom occurrence,"and "symptom distress") (Rhodes & McDaniel, 1999, 2001, 2004) (see Appendix VIII). The eight questions are answered using a 5-point (0 to 4) Likert scale, with three questions assessing the frequency (number of episodes) of nausea, vomiting, and retching, one measuring the amount of vomiting, one addressing the duration of nausea, and three assessing distress related to nausea, vomiting, and retching (Brearley et al., 2008; Rhodes & McDaniel, 1999, 2001, 2004). The total INVR score can range from 0 to 32, with a higher score representing a more unpleasant CINV outcome, and patients can rate the INVR every 12 hours or 24 hours to record their symptom experience daily (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Moradian, 2013; Rhodes & McDaniel, 1999, 2001).

The INVR was developed from the original Rhodes Index of Nausea and Vomiting (INV-2) questionnaire (Rhodes & McDaniel, 1999, 2001). Spearman's correlation coefficients were utilized to measure the reliability of the INVR, with a value of 0.87 for the total questionnaire and 0.71 to 0.95 for single items, and the internal consistency reliability of the original version of the INVR (INV-2) was reported to be 0.98 (Brearley et al., 2008; Rhodes & McDaniel, 2004). The INVR is a popular instrument used in both research and practice for the assessment of nausea and vomiting, and the original English version has been translated into several languages, including Chinese, Japanese, and Korean (Brearley et al., 2008; Rhodes & McDaniel, 2004). The INVR, Chinese version, was used in this study to measure anticipatory nausea and vomiting (see Appendix IX). It was translated by Fu, Rhodes, and Xu (2002) and tested among a group of 177 Chinese cancer and obstetric patients. The Cronbach's alpha coefficient of the INVR, Chinese version, at the morning assessment and evening assessment was 0.95 and 0.94, respectively, while for the Spearman's correlation coefficient of the whole questionnaire, it was 0.98 and 0.97 for the morning assessment and evening assessment, respectively (Fu et al., 2002). The internal consistency reliability of the INVR, Chinese version, has also been examined in Chinese patients with gastrointestinal cancer, and the Cronbach's alpha of the entire questionnaire was 0.897 and the split-half reliability was 0.947 (Fu, 2008).

According to the *Instructions for Administering and Scoring the INR-2 or the INVR* provided by the original author, items 1, 3, 6, and 7 must be reversed when computing the INVR total and domain scores. A numeric value should then be allocated to each item, ranging from 0 to 4, where "0" represents the absence of symptoms and "4" indicates the most severe conditions. The INVR total score can be produced by summing up all eight item scores, with the possible score ranging from 0 to 32. The following table (**Table 5.6**), as originally listed in the INR-2/INVR instructions, shows the computation of the INVR total and domain scores:

Table 5.6 Scoring system of the INVR

Symptom experience subscale score		
	INVR Items	**Score Range**
Nausea experience	Items 4 + 5 + 7	0-12
Vomiting experience	Items 1 + 3 + 6	0-12
Retching experience	Items 2 + 8	0-8
Total experience score	All items	0-32
Symptom occurrence subscale score		
Nausea occurrence	Items 4 + 7	0-8
Vomiting occurrence	Items 1 + 6	0-8
Retching occurrence	8	0-4
Total occurrence score	All items	0-20
Symptom distress subscale score		
Nausea distress	Item 5	0-4
Vomiting distress	Item 3	0-4
Retching distress	Item 2	0-4
Total distress score	All items	0-12

Note: This table was originally listed in the *Instructions for Administering and Scoring the INR-2 or the INVR* provided by the original author, and it has been slightly modified from the original version.

5.5.7.3.2 Instruments for measuring QoL

(1) Selection of adequate QoL instrument

QoL status has been viewed as a crucial outcome measure at endpoint assessment in cancer-related healthcare interventional studies (Niu, Niu, Wang, Zhang, & He, 2014). The evaluation of QoL in clinical research focusing on cancer management can help provide more information in terms of the interventional efficacy and impact (Ferrans, 2010; Holzner et al., 2006). The advances in cancer diagnosis and treatment during the past few decades have enabled cancer patients to live a relatively longer life, but a series of cancer-associated symptoms and antineoplastic treatments have been found to be closely linked with the deterioration of patients' QoL (Niu et al., 2014). As indicated in the literature review chapter on CINV (Chapter 2), cancer patients suffering from nausea and emesis during chemotherapy often experience impairment of their QoL (Cohen et al., 2007; Farrell et al., 2013). Given the close relationship between CINV and QoL, as well as the importance of QoL measurement in cancer studies, QoL was included as one of the clinical outcomes in this pilot RCT.

QoL instruments used in research and practice are typically categorized into two types, including generic measurements and disease-specific measurements (Ferrans, 2010). The QoL

generic instruments cover different aspects of QoL that are closely related to a person's whole life, and they can be used in both the general population and other populations with different types of diseases, which could facilitate a possible comparison between them (Ferrans, 2010). One of the possible disadvantages of QoL generic instruments is the weakness in performing in-depth exploration of particular domains in life, as these generic measurements are primarily designed to capture a broad picture of QoL (Ferrans, 2010). While the disease-specific QoL instruments used in the cancer population generally place their major foci on particular types of cancer diagnoses or antineoplastic approaches, which could facilitate a more precise and reliable understanding of QoL associated with typical symptoms or therapeutic approaches, other important QoL domains or the global impact on QoL may be omitted (Ferrans, 2010; Longworth et al., 2014). The two most popular families of QoL measurements used in cancer research and practice, the FACT-G and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), have unique "core instruments" (Ferrans, 2010, p. 6) that are used for a wide assessment of QoL in different types of cancer patients (Ferrans, 2010; Holzner et al., 2006). To be more specific for some particular types of cancer (or treatment), additional modules have been designed for use in combination with the "core instruments" (Ferrans, 2010), such as the FACT-B for breast cancer and the EORTC QLQ-LC13 for lung cancer (Bergman, Aaronson, Ahmedzai, Kaasa, & Sullivan, 1994; Fallowfield, Leaity, Howell, Benson, & Cella, 1999).

Three QoL scales have been frequently utilized in cancer research, including the FACT-G, the EORTC QLQ-C30, and the Short Form (36) Health Survey (SF-36) (Ferrans, 2010). Among these QoL scales, the SF-36 is a generic assessment of QoL (Ware & Sherbourne, 1992), while the other two scales are cancer-specific. In this study, a cancer-specific instrument was utilized for QoL assessment, as it was regarded to be more appropriate for detecting QoL changes associated with particular cancer symptoms (Ferrans, 2010). Among the three QoL measurements mentioned, only the FACT-G and the EORTC QLQ-C30 have included a specific question to assess global QoL, which is viewed as the most essential component of QoL assessment (Ferrans, 2010). The FACT-G and the EORTC QLQ-C30 questionnaires share four similar QoL domains, including physical, social, emotional, and functional status (Holzner et al., 2006). Moreover, both the FACT-G and the EORTC QLQ-C30 include an additional breast cancer

module to form breast-cancer-specific QoL instruments, which are the FACT-B and the EORTC QLQ-BR23, and the psychometric properties of these two assessments have been identified as satisfactory (Niu, et al., 2014). Furthermore, according to Holzner et al. (2006), the EORTC QLQ-C30 scores can be transformed into the FACT-G scores, and vice versa, which indicates that the two instruments can be equated to promote a more reliable comparison between them and more efficient communication between clinical oncologists and researchers using different QoL assessments.

Either the FACT-B or the EORTC QLQ-BR23 seemed appropriate for use in this pilot study. However, compared with the FACT-B, which has only 37 items, the total number of items for the EORTC QLQ plus the breast cancer module BR23 exceeds 50, which may create a relatively greater burden on the participants in completing the entire questionnaire and contribute to a higher proportion of missing data among the questionnaire items. In addition, according to Wan et al. (2003), both the domain and total scores of the FACT-G (with different cancer modules) can be computed, which enables the questionnaires to reflect either specific changes in different QoL dimensions or global QoL status via the comprehensive combination of different aspects of QoL, while for the EORTC QLQ-C30 and its additional modules, only domain scores are available for computation. Given all the concerns above, the FACT-B was adopted in this pilot RCT as the most appropriate instrument for QoL assessment among breast cancer patients undergoing chemotherapy.

(2) The Functional Assessment of Cancer Therapy-Breast (FACT-B)

The FACT-B is a breast-cancer-specific QoL assessment that belongs to the instrument family of the Functional Assessment of Cancer Therapy (FACT) (Brady et al., 1997; Webster, Cella, & Yost, 2003). It is a self-administered questionnaire that has two major parts, including the FACT-G scale and the breast-cancer-specific subscale (Breast Cancer Subscale, BCS) (Brady et al., 1997; Webster et al., 2003). The FACT-G (version 4) used in this pilot RCT consisted of 27 questions that could generally be used for different cancer patients, and four QoL subscales were incorporated into this scale, including the "Physical Well-Being (PWB)" subscale (7 items), the "Social/Family Well-Being (SWB)" subscale (7 items), the "Emotional Well-Being (EWB)" subscale (6 items), and the "Functional Well-Being (FWB)" subscale (7 items) (Brady et al., 1997;

Webster et al., 2003). The BCS module used in this study had 10 questions addressing breast-cancer-specific concerns (Ng et al., 2012). Each FACT-B question was assessed using a 5-point Likert scale from 0 to 4, where "0" represents "not at all" and "4" indicates "very much" (Ng et al., 2012; Wan et al., 2007).

The psychometric properties of the FACT-B original English version (see Appendix X) have been well-documented in the literature (Brady et al., 1997). The internal consistency reliability of the FACT-B was adequate, as the Cronbach's alpha coefficient for the total instrument was 0.90 (Brady et al., 1997). The FACT-B subscales also demonstrated acceptable internal consistency, with the Cronbach's alpha coefficient ranging from 0.63 to 0.86 (Brady et al., 1997). The test-retest reliability was high, as the correlation coefficient was 0.85 for the whole questionnaire (Brady et al., 1997). The convergent validity of the FACT-B was tested with the Functional Living Index-Cancer (FLIC) and the correlation coefficient was identified as good, with a value of 0.87 (Brady et al., 1997). The FACT-B, Chinese version (version 4, the most updated version at the time of data collection), was utilized in this study (see Appendix XI), and it has demonstrated good psychometric properties in the breast cancer population in Mainland China (Wan et al., 2007). The test-retest reliability coefficient ranged from 0.82 to 0.91 for the five subscales, while it was 0.91 for the whole instrument (Wan et al., 2007). The internal consistency reliability (as measured by the Cronbach's alpha coefficient) ranged from 0.59 to 0.85 for the five subscales, and the construct validity and criteria-related validity were also deemed appropriate for Chinese breast cancer patients (Wan et al., 2007).

According to the *FACIT Administration and Scoring Guidelines* provided by the original author, when computing the FACT scores, those obtained from negatively-stated items must be reversed by subtracting the patients' rating score from "4", and then the total and subscale scores can be calculated accordingly. Particularly, item scores within each FACT-B subscale can be summed up to achieve a domain score for each subscale (PWB, SWB, EWB, FWB, and BCS); the subscale scores from the PWB, FWB, and BCS can also be summed up to compute the Trial Outcome Index (TOI) score (the total score ranges from 0 to 96); a summing-up of the PWB, SWB, EWB, and FWB scores can generate the FACT-G total score (ranging from 0 to 108); and the total FACT-B score is calculated by summing up all five subscales (the total score ranges

from 0 to 148). A higher FACT-B score reflects a better QoL status (Ng et al., 2012; Wan et al., 2007). Subscale scores for domains with missing values can also be computed using the following formula:

Prorated subscale score = [Sum of item scores of the subscale] **x** [N of items in subscale] ÷ [N of items answered]
(as directly quoted from the *FACIT Administration and Scoring Guidelines*)

It should be noted that the formula above is appropriate for use only in subscales with missing values of less than 50%. Only when the completion rate of the total questionnaire items exceeds 80% can the FACT-B be used as a valid measure for reflecting the QoL status of breast cancer patients. The computation of the overall score of the questionnaire is only applicable when all five FACT-B subscales have valid domain scores. (Note: Information provided in this paragraph was adapted from the *FACIT Administration and Scoring Guidelines*).

5.5.8 Time points for data collection

The pilot study data collection, including baseline assessment and evaluation of acute, delayed, and anticipatory CINV and QoL, was performed at five different time points **(T0** to **T4)**. Baseline data (demographic data, medical history, current chemotherapy protocol, antiemetic medications, QoL, anticipatory nausea and vomiting, etc.) were collected after eligible participants who agreed to participate in this study signed the informed consent **(T0)**. On the second day of the first chemotherapy cycle (D2), the participants were required to record the occurrence, frequency, and severity of nausea and vomiting during the acute phase of CINV (0 to 24 h post-chemotherapy) **(T1)**. On the sixth day of the chemotherapy cycle (the day after finishing the five-day AT treatment, D6), the participants were reminded to record their delayed CINV (>24 to 120 h post-chemotherapy) **(T2)**. At the end of the first chemotherapy cycle (D21), the participants returned to the hospital to prepare for the next cycle of treatment, and QoL was measured accordingly **(T3)**. On the morning of the first day of the second cycle of chemotherapy **(T4)**, all participants were asked to indicate their anticipatory CINV 30 to 60 minutes before receiving the chemotherapeutic agents. The questionnaires used for data collection were all self-rated by the study participants, with some additional assistance provided by the two research assistants when necessary. **Table 5.7** below summarizes the times points of data collection for this pilot study:

Table 5.7 Time points of data collection for the pilot RCT

Study Days		Time Points	Measures
D0 prior to the first chemotherapy cycle (hospital)		**T0**	Baseline data, **FACT-B & INVR**
5-day AT (D1 to D5)	**D1** First chemotherapy (hospital)		Daily log
	D2 Post-chemotherapy (hospital)	**T1**	**MAT** & daily log
	D3 Post-chemotherapy (hospital)		Daily log
	D4 Post-chemotherapy (home or hospital)		Daily log
	D5 Post-chemotherapy (home or hospital)		Daily log
Follow-Up (D6 to D21)	**D6** Post-chemotherapy (home) ▵	**T2**	**MAT**
	D7-D19 Post-chemotherapy (home)		
	D20 Post-chemotherapy (home) ▫		
	D21 End of first chemotherapy cycle (hospital)	**T3**	**FACT-B**
The first day of the second chemotherapy cycle (hospital)		**T4**	**INVR**

Note: RCT=randomized controlled trial; FACT-B=Functional Assessment of Cancer Therapy-Breast; INVR=Index of Nausea, Vomiting, and Retching; MAT=MASCC Antiemesis Tool; ▵=first telephone follow-up; ▫=second telephone follow-up

5.5.9 Data analysis

Data were entered into statistical software to create datasets for statistical analysis. Both descriptive statistics and inferential statistics were utilized for data analysis using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Data cleaning was conducted before initiating the data analysis. The analysis of the pilot study clinical outcomes was based on the principle of ITT analysis and missing data were managed using the last observation carried forward (LOCF) approach. Details of the approaches to data analysis will be presented in the following sections.

5.5.9.1 Data cleaning

Data cleaning is an important procedure as it maintains the validity of the statistical analysis (Portney & Watkins, 2000, p. 626). The datasets were checked against the paper recordings of raw data to ensure that the data coding was correct. The datasets were double-checked by the doctoral researcher and another doctoral candidate at The Hong Kong Polytechnic University School of Nursing. A further data cleaning process was conducted by the doctoral researcher and one of his academic supervisors. Categorical data (nominal and ordinal variables) were checked by generating frequency counts to identify the frequency of codes as well as possible missing values for each outcome variable (Portney & Watkins, 2000, p. 626). Continuous data (interval

variables) were checked by generating the corresponding descriptive statistics, such as the maximum value, minimum value, and mean score, to see whether the score range fell within the normal scope (Portney & Watkins, 2000, p. 626).

5.5.9.2 Management of missing data

The LOCF approach was adopted to handle missing values associated with subject dropout that occurred across different time points of data collection. The LOCF method is one of the most popular and frequently used approaches to dealing with missing values in healthcare interventional studies with ITT analysis, in which the last observations of outcome assessment for participants who dropped out from the study are carried forward to the endpoint of data collection and the data analysis is conducted on the basis of "treating carried-forward data as observed data at the last time point" (Shao & Zhong, 2003, p. 2430). In this study, LOCF was adopted for the INVR and the FACT-B questionnaires of the participants who dropped out before the completion of the related assessment. Since only two time points were included in this study for the assessment of the INVR and the FACT-B, baseline data of the INVR and the FACT-B were therefore carried forward to the post-intervention assessment. The LOCF method using baseline data in this setting is also called baseline observation carried forward (BOCF), and it is viewed as a relatively conservative method as it may potentially minimize false-positive interpretation of the interventional effects when an intervention/treatment is claimed to be more effective than a comparison (Barnes, Mallinckrodt, Lindborg, & Carter, 2008). LOCF was not used for the MAT assessment as the CINV symptoms assessed at the two time points of the MAT, the acute phase and the delayed phase, were different in terms of pathophysiological mechanisms. Data analysis of the MAT outcomes was based on the actual number of participants who completed the acute CINV assessment or the delayed CINV assessment.

5.5.9.3 Statistical analysis

The statistical analysis plan for the pilot RCT included both descriptive statistics and inferential statistics. The IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was applied and the significance level was determined to be $p<0.05$ for a two-tailed test.

Statistical analysis of the demographic data, the feasibility outcomes, and the pilot trial clinical outcomes will be described separately in the following sections.

5.5.9.3.1 Statistical analysis of the demographic data

For nominal and ordinal data from demographic characteristics, including education background, marital status, employment status, religious background, family monthly income, medical insurance, cancer stage, type of surgery, type of chemotherapy combination, type of antiemetic medication, risk factors for CINV (Yes/No), number of risk factors for CINV, and occurrence of anticipatory nausea and vomiting (based on the INVR), the Chi-square test or Fisher's exact test was utilized to perform baseline comparisons between groups. For interval data from demographic characteristics, including patients' age and baseline FACT-B and INVR scores, one-way Analysis of Variance (ANOVA) was considered first. The assumption of normality was checked by the Shapiro-Wilk test, and the assumption of homogeneity of variance was measured by Levene's test. If all of these assumptions were not violated, a one-way ANOVA was conducted; if only the homogeneity assumption was violated, the Welch ANOVA was performed instead. Otherwise, the Kruskal-Wallis test was utilized for analysis.

5.5.9.3.2 Statistical analysis of the feasibility outcomes

(1) Feasibility of subject recruitment and follow-up process

Descriptive statistics (absolute number of patients and related percentage) were used to present the eligibility rate and the recruitment rate during subject recruitment, and the retention rate and the attrition rate during the whole study period. Differences in the proportion of subject recruitment at different study sites were examined by the Chi-square test (or Fisher's exact test).

(2) Feasibility of the study questionnaires

Descriptive statistics were used to demonstrate the completion rate of the study questionnaires (the INVR, FACT-B, and MAT) among all the study subjects. The percentage of missing values for each single item on the questionnaires as well as the whole scale was computed respectively to determine the feasibility of the study questionnaires.

(3) Acceptability of the study intervention

Descriptive statistics were used to present the total number of days of AT treatment in the true AT group and the sham AT group, and times of ear acupressure and durations for each time of ear acupressure during the acute CINV phase, the delayed CINV phase, and the five-day total AT period in the true AT group. The Chi-square test or Fisher's exact test was performed to investigate the difference in the total number of AT days between the true AT group and the sham AT group. Spearman's correlation coefficient was utilized to explore the correlations of the number of days of AT treatment, times of ear acupressure, and average duration of each ear acupressure with the AT treatment effects for CINV (based on the MAT scoring system). The correlation is determined to be weak if the correlation coefficient (*r*) is lower than 0.30, moderate if the *r* ranges from 0.30 to 0.59, and strong if the *r* is higher than 0.60 (Martínez-Martín et al., 2007).

(4) Safety of the study intervention

Descriptive statistics (absolute number of events and related percentage) were used to present different potential adverse events associated with AT identified in both the true AT group and the sham AT group, such as minor pain, discomfort, and itching at the local ear skin or around the AT site. The causality between the reported adverse events and AT was assessed by an experienced acupuncture practitioner using the *WHO-UMC System for Standardized Case Causality Assessment*.

(5) Participants' satisfaction with the study intervention

Patient satisfaction scores in terms of "satisfaction with AT treatment," "consideration of further AT treatment," and "willingness to recommend AT to others" were presented as mean and standard deviation, and the differences in satisfaction scores between the true AT group and the sham AT group were assessed by the Independent t-test or the Mann-Whitney U test as determined by normality examination via the Shapiro-Wilk test.

5.5.9.3.3 Statistical analysis of the pilot RCT clinical outcomes

Statistical analysis of the pilot study clinical outcomes was conducted based on the principle of ITT analysis, with an LOCF approach to handle missing data. ITT is a kind of approach that includes all the randomized participants in the final data analysis (Shao & Zhong, 2003).

According to Shao and Zhong (2003), the aim of using the ITT approach in RCTs is "to ensure that the observed clinical results are valid and applicable to the target patient population under the randomization scheme" (p. 2430). Continuous data were presented as mean, standard deviation (SD), standard error (SE), and median, while nominal and ordinal data were presented as absolute number and percentage. The statistical analysis plans for the acute and delayed CINV, anticipatory CINV, and QoL will be described separately in the following sections.

(1) Acute and delayed nausea and vomiting as measured by the MAT

-Analysis based on each single MAT item

The number of participants with a complete response (CR) of CINV, which means the absence of nausea and vomiting symptoms, was computed based on the MAT single items. The CR of CINV symptoms in this study included the CR of overall CINV (a response of "no" to the MAT items for acute nausea, acute vomiting, delayed nausea, and delayed vomiting), the CR of acute CINV (a response of "no" to the MAT items for acute nausea and acute vomiting), the CR of delayed CINV (a response of "no" to the MAT items for delayed nausea and delayed vomiting), the CR of overall nausea (a response of "no" to the MAT items for acute nausea and delayed nausea), and the CR of overall vomiting (a response of "no" to the MAT items for acute vomiting and delayed vomiting). Differences in the CR of CINV among the three groups were assessed using the Chi-square test (or Fisher's exact test). For comparisons showing statistically significant differences, a post-hoc test with partitioning Chi-squared statistics was further conducted to examine the differences between each of the two groups (true AT vs. sham AT, true AT vs. standard care, and sham AT vs. standard care).

Based on the items of the MAT, the Chi-square test (or Fisher's exact test) was utilized to compare the differences in the occurrence of nausea and vomiting among the three study groups during either the acute or delayed CINV phase. For comparisons showing statistically significant differences, a post-hoc test with partitioning Chi-squared statistics was further conducted to examine the differences between each of the two groups. For the differences in the frequency of acute and delayed vomiting as well as the severity of acute and delayed nausea among the three groups, one-way ANOVA was considered first. The Shapiro-Wilk test and Levene's test were

adopted to examine the assumptions of normality and the assumptions of homogeneity of variance, respectively. If all these assumptions were not violated, a one-way ANOVA was conducted; if the homogeneity assumption was violated, the Welch ANOVA was chosen accordingly. Otherwise, the Kruskal-Wallis test was utilized instead. For comparisons showing statistically significant differences via ANOVA, a post-hoc comparison using Tukey's test (homogeneity assumption achieved) or the Games-Howell test (homogeneity assumption violated) was conducted to examine the differences between each of the two groups. If statistically significant differences were detected via the Kruskal-Wallis test, a post-hoc comparison using the Dunn-Bonferroni test was utilized instead.

-Analysis based on the MAT scoring system

By summing up different MAT items, the MAT total and domain scores can be produced, which include the MAT overall total score, the MAT total nausea score, the MAT total vomiting score, the MAT acute CINV score, the MAT acute nausea score, the MAT acute vomiting score, the MAT delayed CINV score, the MAT delayed nausea score, and the MAT delayed vomiting score (Molassiotis, Coventry et al., 2007; Tan et al., 2016). For the differences in the MAT total and domain scores among the three groups, one-way ANOVA was considered first. The Shapiro-Wilk test and Levene's test were adopted to examine the assumptions of normality and the assumptions of homogeneity of variance, respectively. If all these assumptions were not violated, a one-way ANOVA was conducted; if the homogeneity assumption was violated, the Welch ANOVA was chosen accordingly. Otherwise, the Kruskal-Wallis test was utilized instead. For comparisons showing statistically significant differences via ANOVA, a post-hoc comparison using Tukey's test (homogeneity assumption achieved) or the Games-Howell test (homogeneity assumption violated) was conducted to examine the differences between each of the two groups. If statistically significant differences were detected via the Kruskal-Wallis test, a post-hoc comparison using the Dunn-Bonferroni test was utilized instead.

(2) Anticipatory nausea and vomiting as measured by the INVR

Following the INVR scoring system described earlier, the INVR scores used for data analysis in this study included the symptom experience score, the symptom occurrence score, and the

symptom distress score. In addition, the INVR item scores that were related to vomiting symptom and nausea symptom were also computed respectively to create the the INVR total vomiting score and the INVR total nausea score (Molassiotis, Coventry et al., 2007; Tan et al., 2016). For among-group comparisons of the INVR scores at either baseline assessment (absolute value) or post-intervention (follow-up) assessment (i.e., change in scores from baseline), one-way ANOVA was considered first. The Shapiro-Wilk test and Levene's test were adopted to examine the assumptions of normality and the assumptions of homogeneity of variance, respectively. If all of these assumptions were not violated, a one-way ANOVA was conducted; if the homogeneity assumption was violated, the Welch ANOVA was chosen accordingly. Otherwise, the Kruskal-Wallis test was utilized instead. For comparisons showing statistically significant differences via ANOVA, a post-hoc comparison using Tukey's test (homogeneity assumption achieved) or the Games-Howell test (homogeneity assumption violated) was conducted to examine the differences between each of the two groups. If statistically significant differences were detected via the Kruskal-Wallis test, a post-hoc comparison using the Dunn-Bonferroni test was utilized instead.

In addition, the occurrence of anticipatory nausea and the occurrence of anticipatory vomiting at baseline and post-intervention (follow-up) assessments were also recorded using the INVR if the participants scored any INVR item related to nausea or vomiting as "1" or above. Differences in the occurrence of anticipatory nausea and occurrence of anticipatory vomiting among the three study groups were examined using the Chi-square test (or Fisher's exact test). For comparisons showing statistically significant differences, a post-hoc test with partitioning Chi-squared statistics was further conducted to examine the difference between each of the two groups.

(3) Quality of life as measured by the FACT-B

Based on the FACT-B scoring system described earlier, the FACT-B scores used for data analysis in this study included the PWB subscale score, the SWB subscale score, the EWB subscale score, the FWB subscale score, the BCS subscale score, the TOI subscale score, the FACT-G total score, and the FACT-B total score. For among-group comparisons of the FACT-B scores at either baseline assessment (absolute value) or post-intervention (follow-up) assessment (i.e., change in score from baseline), one-way ANOVA was considered first. The Shapiro-Wilk test and Levene's test were adopted to examine the assumptions of normality and the

assumptions of homogeneity of variance, respectively. If all of these assumptions were not violated, a one-way ANOVA was conducted; if the homogeneity assumption was violated, the Welch ANOVA was chosen accordingly. Otherwise, the Kruskal-Wallis test was utilized instead. For comparisons showing statistically significant differences via ANOVA, a post-hoc comparison using Tukey's test (homogeneity assumption achieved) or the Games-Howell test (homogeneity assumption violated) was conducted to examine the difference between each of the two groups. If statistically significant differences were detected via the Kruskal-Wallis test, a post-hoc comparison using the Dunn-Bonferroni test was utilized instead.

(4) Effect size estimations

For the comparisons of the pilot study clinical outcomes among the three study groups, related effect sizes were estimated accordingly. For comparisons involving the Chi-square test or Fisher's exact test, Cramer's V was adopted for effect size estimation (Liao & Meskin, 2015; McHugh, 2013); for comparisons using the Kruskal-Wallis H test, the effect size was estimated by eta-squared (η^2) with the formula "χ^2/N-1", where "χ^2" means the Chi-square value as generated from the Kruskal-Wallis H test and "N" indicates the total number of study participants (Coolican, 2014; Simoens & Tervaniemi, 2013); and for comparisons utilizing ANOVA, the partial eta-squared (partial η^2) was used for effect size estimation (Fritz, Morris, & Richler, 2012; Simoens & Tervaniemi, 2013). In terms of the interpretations of the effect sizes, for Cramer's V with a degree of freedom (df) of 2, a value of 0.07 means a small effect size, 0.21 represents a medium effect size, and 0.35 indicates a large effect size (Cohen, 1988; Medical Research Council Cognition and Brain Sciences Unit [MRC CBSU], July 2016); for η^2, values of 0.01, 0.06, and 0.14 indicate a small, medium, and large effect size, respectively (Cohen, 1988; MRC CBSU, July 2016), while the interpretation of the effect size of a partial η^2 is the same as that of η^2 (Buczkowski et al., 2017; Dempster, 2011).

5.5.9.3.4. Additional secondary analysis of the potential confounding effects at baseline

(1) Reasons for addressing potential confounding effects at baseline

Variations in patient characteristics between groups may contribute to different CINV experiences among cancer patients. The potential confounding effects induced by the variations

of CINV risk factors at baseline could affect the correct cause-and-effect analysis between AT and CINV. As presented in the baseline comparison in the results chapter (details can be found in Chapter 7: Results, Section 7.2.2 Baseline characteristics of the study participants), although the patients' baseline clinical characteristics were comparable across groups and Fisher's exact test did not reveal any statistically significant differences in any clinical data among the three groups (*p* value=0.12 to 0.99), it was noted that the proportion of patients' CINV risk factors, especially younger age, history of morning sickness, and history of motion sickness, still showed insignificant variations across groups, with relatively more CINV risk factors identified in the true and sham AT groups than in the standard care group. There is a possibility that the participants in the true and sham AT groups may have experienced more severe nausea and vomiting symptoms than in the standard care group, which might subsequently underestimate the potential treatment effects of AT. In the study sample, it remained uncertain whether these insignificantly imbalanced CINV risk factors across groups could really produce any obvious confounding effects on the cause-and-effect analysis between AT and CINV. Therefore, apart from the preliminary data analysis of the pilot study clinical outcomes, an additional secondary analysis was also performed to explore the potential confounding effects of baseline CINV risk factors on the cause-and-effect analysis between AT and CINV (as measured by the MAT scoring system).

(2) Selection of appropriate approach to address potential confounding effects

Several approaches have been commonly recommended to control the confounding effects at the statistical analysis stage, including stratification, analysis of covariance (ANCOVA), logistic regression, and linear regression (Braga, Farrokhyar, & Bhandari, 2012; Pourhoseingholi, Baghestani, & Vahedi, 2012). The stratification method simply categorizes each study group into different layers according to the potential confounding factor, and a further comparison between the adjusted effect size based on these layers and the unadjusted effect size without stratification can then help identify the potential confounding effect (Braga et al., 2012; Pourhoseingholi et al., 2012). However, stratification was not appropriate in this pilot trial because the sample size was extremely small and imbalanced within each layer, which could further underestimate the statistical power of the pilot study data analysis. ANCOVA is also a popular approach to dealing with confounding factors (Pourhoseingholi et al., 2012). However, assumptions for ANCOVA

state that both the confounding variables (covariates) and the outcome measures (dependent variables) need to be continuous data in nature, which was inappropriate for use in this study. Logistic regression and linear regression are other options in which multiple confounding factors can be introduced to explore their relationships with one single outcome measure (Braga et al., 2012; Pourhoseingholi et al., 2012). However, these kinds of approaches need to fulfill a number of assumptions that may not fit the current study data. For instance, logistic regression analysis requires that the outcome measure (dependent variable) be dichotomous data, which was not suitable for the MAT scoring system, while normal residuals are usually required for linear regression analysis, but relevant data in this pilot study failed to meet this assumption. Given the concerns above, the commonly adopted approaches to managing confounding effects were deemed not appropriate for use in this pilot study data, and the generalized estimating equation (GEE) model was therefore used instead to investigate the potential confounding effects of baseline CINV risk factors.

(3) The generalized estimating equation (GEE) model

The GEE model has been viewed as an extension of traditional approaches to regression analysis, which can generate a more reliable regression model for the analysis of outcome data that violate the assumption of normality (Ballinger, 2004; Ghisletta & Spini, 2004). The GEE model has been frequently applied in healthcare research as an efficient statistical method for analyzing different types of outcome data, such as continuous, dichotomous, and ordinal variables (Ghisletta & Spini, 2004). In healthcare interventional studies, suspected confounding factors can be introduced as covariates into the GEE model to adjust the interventional (treatment) effects, and a number of clinical trials have adopted this model at the data analysis stage to control the potential confounding effects of the baseline demographics and (or) clinical data for the outcome assessment (Aisen et al., 2008; DiClemente et al., 2004; DuHamel et al., 2010; Kim et al., 2014). In the current analysis, the three CINV risk factors (younger age, history of morning sickness, and history of motion sickness) were introduced one-by-one as a potential confounding factor (covariate) into the GEE model, and the covariate-adjusted between-group mean differences and relevant effect sizes (as measured by Cohen's d) for the MAT total and domain scores were then compared with the corresponding statistics in the covariate-unadjusted GEE model to examine whether there were any significant variations in those statistics before and after controlling the

potential confounding factor. For the effect size interpretation of Cohen's d, a value of 0.2, 0.5, and 0.8 reflects a small, medium, and large effect size, respectively (Cohen, 1988). A summary of the data analysis approaches utilized in the pilot RCT is presented in **Table 5.8** below:

Table 5.8 Data analysis approaches utilized in the pilot RCT

Outcomes	Data Analysis Approaches		
	Statistical Approach	**Post-hoc Analysis**	**Effect Size**
Baseline characteristics			
Nominal and ordinal data	Chi-square test (or Fisher's exact test)	NA	NA
Interval data	One-way (or Welch) ANOVA	NA	NA
	Kruskal-Wallis test	NA	NA
Feasibility outcomes			
Eligibility rate & recruitment rate	Descriptive statistics	NA	NA
Retention rate & attrition rate	Descriptive statistics	NA	NA
Subject recruitment at different sites	Chi-square test (or Fisher's exact test)	NA	NA
Missing values in study questionnaires	Descriptive statistics	NA	NA
Total number of days of AT	Descriptive statistics	NA	NA
Times of ear acupressure	Descriptive statistics	NA	NA
Duration of each acupressure	Descriptive statistics	NA	NA
Associations of AT feasibility outcomes with MAT outcomes	Spearman's correlation coefficient	NA	NA
Adverse events of AT	Descriptive statistics	NA	NA
Satisfaction with AT	Independent t-test	NA	NA
	Mann-Whitney U test	NA	NA
Pilot study clinical outcomes			
Acute and delayed CINV (MAT)			
Complete response of CINV	Chi-square test (or Fisher's exact test)	Partitioning Chi-square	Cramer's V
Occurrence of acute nausea & vomiting	Chi-square test (or Fisher's exact test)	Partitioning Chi-square	Cramer's V
Severity of acute nausea & frequency of acute vomiting	One-way (or Welch) ANOVA	Tukey's (or Games-Howell) test	Partial η^2
	Kruskal-Wallis test	Dunn-Bonferroni test	η^2
Occurrence of delayed nausea & vomiting	Chi-square test (or Fisher's exact test)	Partitioning Chi-square	Cramer's V
Severity of delayed nausea & frequency of delayed vomiting	One-way (or Welch) ANOVA	Tukey's (or Games-Howell) test	Partial η^2
	Kruskal-Wallis test	Dunn-Bonferroni test	η^2
MAT total & domain scores	One-way (or Welch) ANOVA	Tukey's (or Games-Howell) test	Partial η^2
	Kruskal-Wallis test	Dunn-Bonferroni test	η^2
Anticipatory CINV (INVR)			
INVR scores	One-way (or Welch) ANOVA	Tukey's (or Games-Howell) test	Partial η^2
	Kruskal-Wallis test	Dunn-Bonferroni test	η^2
Occurrence of anticipatory nausea & vomiting	Chi-square test (or Fisher's exact test)	Partitioning Chi-square	Cramer's V
QoL status (FACT-B)			
FACT-B total & domain scores	One-way (or Welch) ANOVA	Tukey's (or Games-Howell) test	Partial η^2
	Kruskal-Wallis test	Dunn-Bonferroni test	η^2
Additional analysis for baseline potential confounding effects	GEE model	NA	Cohen's d

Note: RCT=randomized controlled trial; NA=not applicable; AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting; MAT=MASCC Antiemesis Tool; INVR=Index of Nausea, Vomiting, and Retching; FACT-B= Functional Assessment of Cancer Therapy-Breast

5.5.10 Summary of part two

This part presented the design of the pilot study. The preliminary RCT adopted a three-parallel-arm, placebo-controlled pilot trial design. Three study sites were involved for subject recruitment and the sample size was determined to be 114, with 38 subjects in each study arm. Female breast cancer patients scheduled to be treated with their first cycle of chemotherapy were randomly allocated to three different study groups. The AT treatment was administered during the first five days of the first chemotherapy cycle. Short-term follow-up was performed from the completion of AT treatment to the end of the first cycle of chemotherapy. The primary outcomes for this pilot RCT were a series of feasibility outcomes related to subject recruitment and the follow-up process and completion of the study questionnaires and interventions. In addition, clinical outcomes in terms of the effects of AT on CINV and QoL, including acute and delayed CINV (as measured by the MAT), anticipatory CINV (as measured by the INVR), and QoL (as measured by the FACT-B), were also preliminarily assessed. Both descriptive statistics and inferential statistics were utilized for data analysis. The analysis of the pilot study clinical outcomes was based on the principle of ITT analysis and missing data were managed using the LOCF approach. The GEE model was utilized to address potential confounding effects of CINV risk factors at baseline. The nested qualitative study design and the design of the semi-structured interview will be presented in the following part.

5.6 Part three: The qualitative study nested within the pilot trial

5.6.1 Reasons for adopting the nested qualitative study

As recommended by the *MRC Framework for Developing and Evaluating Complex Interventions*, a combination of quantitative and qualitative research approaches is usually necessary when evaluating the feasibility of a complex intervention and piloting its methodological procedures (Craig et al., 2008). Qualitative research combined with a healthcare interventional study can help enrich the overall design of the study and further add important information on "patients' experiences of receiving trial interventions and their perceptions of treatment effects" (Hughes et al., 2013, p. 2 out of 10). According to Verhoef and Vanderheyden (2007), the inclusion of the qualitative approach in healthcare interventional studies is of crucial significance for clinical research related to CHAs, as this combination can help "adequately capture whether an intervention

works, how and in what context, in a manner that respects the unique healing philosophy of an intervention and that also produces generalisable results" (p. 76). Meanwhile, it has been emphasized that one of the most important reasons for combining qualitative research with CHA interventional studies is to reach an optimal approach to help strengthen the interpretation of the research findings and neutralize the potential risk of bias from each researcher's perspective and subsequently facilitate the researchers to reach more reliable, valid, and useful study conclusions and implications (Sandelowski, 2000; Verhoef & Vanderheyden, 2007). Therefore, in this doctoral research project, a qualitative research component was designed and conducted following the completion of the preliminary RCT to explore breast cancer patients' experiences of participating in the pilot trial and receiving the AT intervention.

5.6.2 Reasons for choosing the semi-structured interview

Interviews and focus groups are two qualitative research approaches that are frequently utilized in studies related to health sciences (Britten, 1999; Legard, Keegan, & Ward, 2003). According to Gill, Stewart, Treasure, and Chadwick (2008), the use of interviews in research can help "explore the views, experiences, beliefs and/or motivations of individuals on specific matters" (p. 292), and there are three types of interview designs commonly used in research, including structured interviews, semi-structured interviews, and unstructured interviews.

Structured interviews are usually performed via the verbal use of questionnaires, and the interview items included in the questionnaire are predefined and fixed without allowing any changes and modifications during the implementation of the interview (Gill et al., 2008). Moreover, in structured interviews, follow-up questions are usually not performed, which makes it difficult to further explore the participants' experiences or perceptions in depth (Gill et al., 2008). The structured interview can be used for a fast data collection of particular research concerns within a relatively short period of time, or for qualitative data collection among participants who have some difficulties in reading and writing, but the nature of the structured interview makes it inappropriate for an in-depth exploration of certain research questions (Gill et al., 2008). Unstructured interviews, on the contrary, do not include any predefined questions, which makes the whole interview process weak in management and organization, and it often takes a great deal of energy and time for both the researchers and the participants (Gill et al., 2008). As pointed out by

Gill et al. (2008), an unstructured interview design is necessary only for research questions that require a very intensive depth of exploration, or those questions that are totally new topics that have not been documented in current literature. Semi-structured interviews are currently the most popular and commonly used qualitative interview approach in healthcare research (Gill et al., 2008), as they combine the strengths and eliminate the weaknesses of both structured interviews and unstructured interviews, respectively. The interview guide for semi-structured interviews not only includes a number of predefined questions that are regarded as essential questions for dealing with certain research topics, but also leaves some space for researchers to further explore some particular aspects of the research questions, which can enable an in-depth understanding of the participants' experiences and/or perceptions of the focused research topics (Britten, 1999; Gill et al., 2008).

Focus groups are another type of qualitative data collection method, and many similarities in research designs can be seen between focus groups and semi-structured/unstructured interviews (Gill et al., 2008, p. 293). However, different from other interview designs that are usually on an individual basis, focus groups use a group interview approach to trigger interactions among participants, and qualitative data are collected from a group of participants at one time point (Gill et al., 2008; Kitzinger, 1995). Focus groups can be utilized in healthcare research to explore participants' attitudes, views, experiences, and needs regarding particular research topics (Gill et al., 2008; Kitzinger, 1995). This kind of approach requires that a sufficient number of participants (around six to eight per group) be gathered at a particular time point and location to run the group interview (Gill et al., 2008), which could be problematic in this study. Most of the study participants in this doctoral research project came from rural areas and the majority of them stayed in the hospital for around three to four days after receiving chemotherapy, and the average number of patients participating in the pilot RCT was less than eight in each month at each study site. All of these factors made it difficult to reach a satisfactory size of patients gathered at once for focus groups.

Given all the concerns above, the semi-structured interview seemed to be the most appropriate approach for use in this doctoral project to explore the patients' experiences of participating in the pilot RCT and receiving the AT treatment. Therefore, the semi-structured interview approach was utilized in the qualitative study nested within the pilot RCT, and the study design will be described in the following sections.

5.6.3 Design of the semi-structured interview

5.6.3.1 Study sample and setting

A purposive sampling method was adopted to recruit participants until data saturation was reached. Breast cancer patients who participated in the pilot RCT were recruited from one of three study groups if they: **(1)** had a high, moderate, or low expectation of the therapeutic effects of AT (as determined by the participants themselves using a 0 to 10 numerical scale, where "0" indicates a very low expectation and "10" represents a very high expectation); **(2)** had or had not strictly followed the study protocol for the AT treatment (as determined by the doctoral researcher using an answer of "yes" or "no"); and **(3)** had or had no previous experiences of receiving CHAs other than AT (as determined by the participants themselves using an answer of "yes" or "no"). The interviews took place in an interview room, demonstration room, or other places convenient for the interviewees at the study hospital to ensure the participants' privacy.

5.6.3.2 Study procedure

As the qualitative study was part of the research design nested within the pilot RCT, information in terms of the semi-structured interview was included in the pilot RCT information sheet and consent form. All breast cancer patients who agreed to participate in the pilot trial were also informed in advance about the aims and procedures of the nested semi-structured interview when they met with the researchers the first time, and those who expressed an interest in participating in the doctoral research project (both the pilot RCT and the semi-structured interviews) were provided with written informed consent forms. After the completion of the pilot study data collection on the first day of the second chemotherapy cycle, the participants were asked to indicate their expectations of the AT treatment effects and whether they had any previous experiences of using CHAs (other than AT) for the purposive sampling procedure. The participants who met the purposive sampling criteria (as described in the section above) were put on a "potential interviewees" list and they were then invited again to take part in the semi-structured interviews. The potentially eligible participants were included in the interviews if they felt comfortable with the individual interview and were willing to share their views and experiences with the doctoral researcher. The doctoral researcher then negotiated with each participant to arrange the most appropriate time and location to conduct the interview.

The interviews were performed within two months after the study participants had completed the pilot trial. All of the interviews were conducted by the doctoral researcher. Prior to the commencement of each interview, the doctoral researcher gave a brief self-introduction (again) and repeated the aims and procedures of the interview to the participant. An interview guide was employed to direct the study process, which was developed by the doctoral researcher based on a series of qualitative studies or mixed-methods studies that investigated patients' views and/or perceptions of using acupressure, acupuncture, or Chinese medicine in clinical practice or research (Cassidy, 1998a, 1998b; Gould & MacPherson, 2001; Hughes et al., 2013, 2014). The development of the interview guide also followed the recommendations and suggestions provided by the two academic supervisors of the doctoral researcher, who are familiar with qualitative research. The interview guide consisted of twelve open-ended questions, which are listed in **Table 5.9** (English version only; for the Chinese version of the interview guide, see Appendix XII). Some questions listed in **Table 5.9** were partially adapted from an interview guide related to an AT interventional study provided by one of the academic supervisors of the doctoral researcher. The participants were invited to express their experiences, thoughts, and feelings in terms of participating in the pilot RCT. For those allocated to the true AT group and the sham AT group, their experiences of receiving the AT treatment and their perceptions of the AT treatment effects were also explored. Probes were used by the doctoral researcher during the interview process to ask the participants to further elaborate their thoughts and ideas or to give some examples when describing certain issues. Pilot interviews were conducted with the first three participants to check whether the interview guide was feasible for the participants and whether they understood the interview questions. During the pilot interviews, the doctoral researcher also explored whether any modifications were needed for the interview guide. Prior to the commencement of the doctoral research project, the doctoral researcher had completed a qualitative research methodology course and had gained some experience in conducting a qualitative study and analyzing qualitative study data.

Table 5.9 Open-ended questions incorporated into the semi-structured interview guide

Items	Participants	Questions[a]
Q1	For all participants	What was your overall experience of participating in the pilot RCT?
Q2	For all participants	What is your opinion about using complementary health approaches?
Q3	For all participants	How would you evaluate the instruments/questionnaires that you completed during the study periods? Including: -the MAT, which you were asked to complete on day 2 and day 6 of the first chemotherapy cycle to assess acute and delayed CINV; -the INVR, which you were required to complete before the first and second chemotherapy cycles to evaluate anticipatory CINV; and -the FACT-B, which you were asked to complete before and at the end of the first chemotherapy cycle to measure QoL status.
Q4	For participants in true/sham AT groups	How would you evaluate the daily AT log that you were asked to complete daily during the five-day AT treatment period?
Q5	For participants in true/sham AT groups	To what degree do you believe that the AT treatment helped relieve your nausea and vomiting symptoms during chemotherapy?
Q6	For participants in true/sham AT groups	What changes (improved symptoms [in terms of nausea, vomiting and psychological conditions], lifestyle, attitudes, or behaviors) did you experience after receiving the AT treatment?
Q7	For participants in true/sham AT groups	What kinds of burdens or difficulties did you encounter related to the AT treatment in terms of: -duration of the AT intervention? -keeping the ear acupressure tapes in place? -precautions for the use of AT, for instance, preventing the ear acupressure tapes from getting wet when taking a shower, prudently cleaning your ears to prevent the auricular acupressure tapes from falling off, and avoiding rolling the auricular seeds to prevent ear skin breakdown? -adverse events associated with AT, such as allergic reactions to the ear acupressure tapes (itching and redness), local discomfort, pain, and swelling at the AT site?
Q8	For participants in true/sham AT groups	Apart from the issues mentioned above in Q7, are there any other reasons that made it difficult to continue with the five-day AT treatment?
Q9	For participants in true/sham AT groups	How satisfied are you with the AT treatment?
Q10	For participants in true/sham AT groups	Will you consider using AT to help manage other health disorders (e.g., sleep disturbance, chronic pain and fatigue)? Why?
Q11	For all participants (for participants in true/sham AT groups)	What are your recommendations/suggestions to help us improve the study design (and the AT treatment arrangement in the future)?
Q12	For all participants	Is there anything else related to the study that has not been discussed?

Note: a=some questions listed in this table were partially adapted from an interview guide related to an AT interventional study provided by one of the academic supervisors of the doctoral researcher; RCT=randomized controlled trial; MAT=MASCC Antiemesis Tool; CINV=chemotherapy-induced nausea and vomiting; INVR=Index of Nausea, Vomiting, and Retching; FACT-B=Functional Assessment of Cancer Therapy-Breast; QoL=quality of life; AT=auricular therapy

5.6.3.3 Data analysis

The interviews were conducted in Mandarin Chinese and were audio-taped using a digital recorder. Field notes were also made by the doctoral researcher during and immediately after the semi-structured interviews. The interview data were transcribed verbatim by a postgraduate nursing student helper who was not involved in any other procedures of the qualitative study, the doctoral researcher, and another independent researcher (another nursing doctoral researcher with a qualitative research background at The Hong Kong Polytechnic University), and then the transcripts were checked against the original audio-taped records to make sure that all the records were correctly and accurately transcribed. Thematic analysis, a frequently utilized descriptive approach to qualitative data analysis, was employed in this study for data analysis. Particularly, the "six-phase thematic analysis" method proposed by Braun and Clarke (2006) was employed to guide the qualitative data analysis, which includes "familiarizing yourself with your data (phase one)," "generating initial codes (phase two)," "searching for themes (phase three)," "reviewing themes (phase four)," "defining and naming themes (phase five)," and "producing the report (phase six)" (p. 87). Details of the thematic analysis process are presented in **Figure 5.8**.

The thematic analysis was performed by the doctoral researcher. To ensure the objectivity of the data analysis, ongoing discussions among the doctoral researcher, the study participants, and an independent researcher were performed during the data analysis process, and the independent researcher was invited to do reliability checking. As suggested by Breen (2006), the codes of the qualitative data analysis should be summarized in a file ("list of codes" [p. 472]) and the invited doctoral researcher was then required to match the codes with the related sentences. The reliability of the results was deemed high as the match rate exceeded 80% (Breen, 2006). Meanwhile, the *15-Point Checklist of Criteria for Good Thematic Analysis* proposed by Braun and Clarke (2006, p. 96) was also adopted to ensure that the qualitative data were transcribed, coded, analyzed, and reported in a rigorous manner. Several approaches were also adopted during the processes of study implementation, data analysis, and final report writing to maintain the study quality assurance, and relevant strategies will be described in detail in Section 5.7.

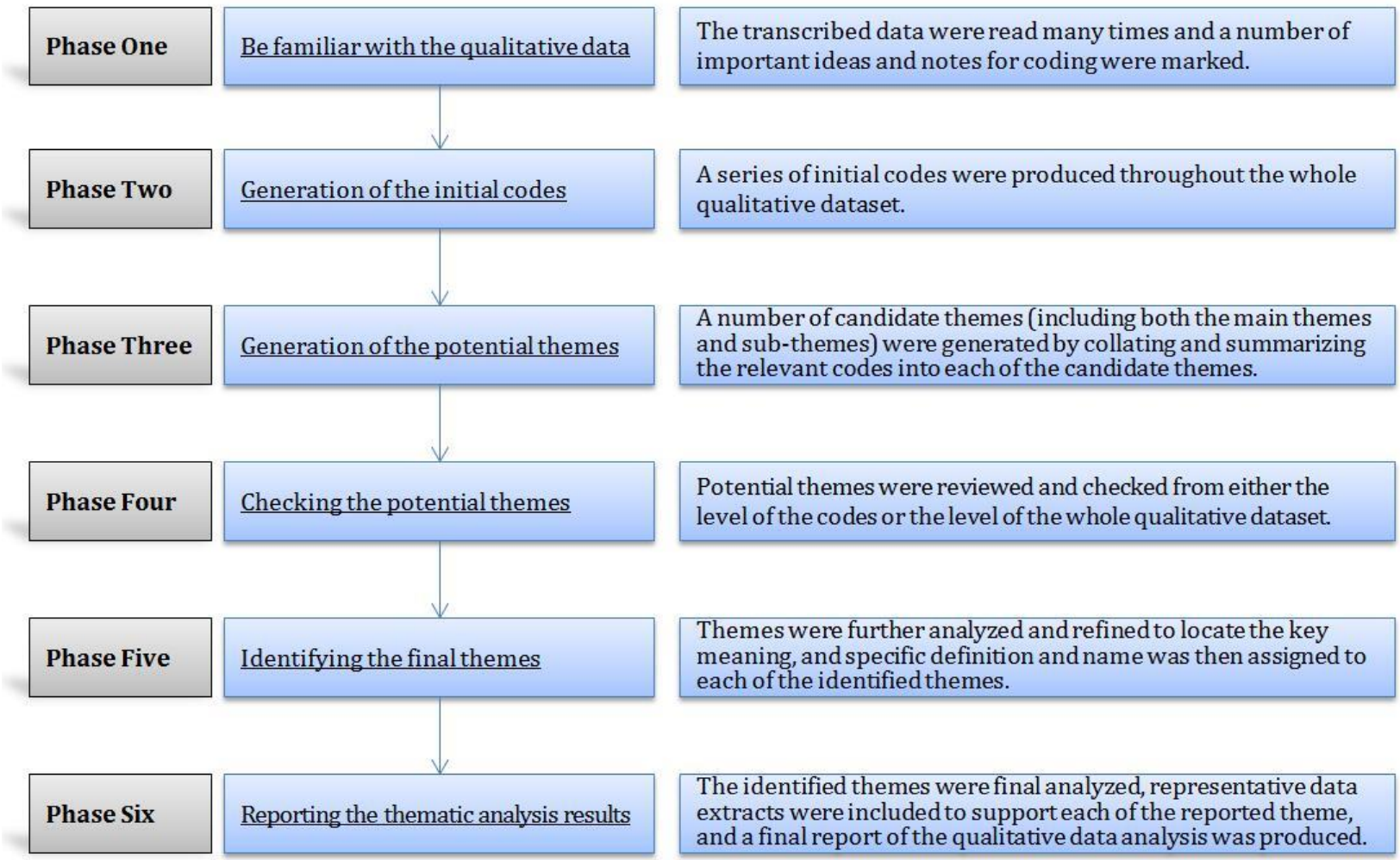


Figure 5.8 The "six-phase thematic analysis" method used in the semi-structured interviews

5.6.4 Summary of part three

This part presented the design of the semi-structured interview nested within the pilot RCT. The purposive sampling approach was utilized for subject recruitment, and a predefined interview guide with several open-ended questions was used to guide the interviews to explore the patients' experiences of participating in the pilot RCT and receiving the AT treatment. The "six-phase thematic analysis" method was adopted for qualitative data analysis and the rigor of the data analysis process was maintained by following the *15-Point Checklist of Criteria for Good Thematic Analysis*. The study team, study quality assurance, and ethical considerations of this doctoral research project will be described in the following sections.

5.7 Study team, study quality assurance, and ethical considerations

5.7.1 Study team

5.7.1.1 Training of study team members

The study team consisted of seven core members, including the doctoral researcher, his two academic supervisors, two nurse researchers, and two research assistants. The study intervention, the AT treatment, was mainly administered by the doctoral researcher, who is a registered nurse in Mainland China, and has a master's degree in Chinese medicine nursing. The doctoral researcher attended AT training courses during his postgraduate study at a Chinese medical university and mastered the technique for auricular acupressure. During his doctoral study at The Hong Kong Polytechnic University, the doctoral researcher also received training on auricular acupressure from his two academic supervisors. One of his supervisors (Associate Professor Lorna Suen) is a certified AT therapist who has accumulated extensive clinical and research experience in using AT to manage different health problems. His other supervisor (Professor Alex Molassiotis) is the chair professor of nursing, with extensive research experience in clinical studies involving acupuncture and acupressure.

The doctoral researcher was primarily responsible for subject recruitment and the administration of the AT treatment for patients in the true AT group and the sham AT group. However, given the possibility that some participants from different study sites may have participated in the study and had scheduled chemotherapy at the same time point, two TCM clinical nurses were

therefore invited to participate in the pilot RCT as the backup researchers to assist in subject recruitment and AT treatment. The two nurse researchers were also registered nurses, and they received auricular acupressure training at their university or hospital. Prior to the commencement of the AT trial, the doctoral researcher and the two backup researchers were trained again by an associate professor who worked at a Chinese medical university. The associate professor had more than 10 years of experience in conducting auricular acupressure and the training was mainly focused on the AT treatment protocol used in the pilot RCT. The doctoral researcher and the two backup researchers were required to follow a standard AT procedure (see Appendix XIII) to perform the AT treatment, including the approach to locating the targeted ear acupoints, the method of attaching the auricular acupressure tapes to the acupoints, and the instructions for regular ear acupressure. Verbal communication between the researcher and the study participants, including an introduction of the AT treatment procedure, instructions for ear acupressure, and precautions of the AT treatment, were also standardized among the researchers. Particularly, the associate professor examined the accuracy of locating the targeted auricular acupoints among the three researchers and the accuracy rate was determined to be 100%.

Two nursing students participated in the pilot RCT as the research assistants to assist in the data collection and telephone follow-ups. Although the outcome measures were all patient-reported instruments and the participants themselves were the outcome assessors, some older patients still had some difficulties in understanding the questionnaire items or had some vision problems and they needed assistance in completing the study questionnaires. The research assistants mainly helped those participants clarify some questionnaire items and, in exceptional cases, read the questions to the participants and asked them to respond. When assisting the participants with the completion of the study questionnaires, the research assistants were not allowed to answer other questions related to the study intervention and procedures, the AT treatment effects, and the scheduled chemotherapy protocols. In fact, apart from assisting in the data collection and telephone follow-ups, the two research assistants were not involved in any other procedures of the pilot RCT. In addition to the seven core members, four clinical staff members also participated in the implementation of the pilot RCT, including three oncology nurses (one at each study site) responsible for the eligibility assessment of the potential participants, and an

acupuncture practitioner responsible for the causality assessment between AT and the reported adverse events.

5.7.1.2 Study quality assurance for the pilot RCT

Several strategies were proposed to control the study quality and to minimize the potential risks of bias that may possibly occur during the implementation of the pilot RCT. These strategies will be described in detail in the following sections.

5.7.1.2.1 Strategies for minimizing selection bias

According to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2008), selection bias can be defined as "systematic differences between baseline characteristics of the groups that are compared" (p. 195). Random assignment and allocation concealment were adopted in this pilot RCT to minimize potential selection bias. The block randomization method was utilized and the online application Research Randomizer was employed to produce the randomization number table. The randomization table was prepared and kept by a person (a university lecturer) who did not know the design of the clinical trial and was not involved in any procedures of the implementation of this study. The doctoral researcher and other study team members did not participate in the preparation of the randomization. Meanwhile, the doctoral researcher and the two backup researchers were also not allowed to participate in the process of identifying the participants' eligibility for study participation. Three oncology nurses (one at each study site) who were not involved in any other procedures of the pilot RCT took responsibility for screening the breast cancer patients and identifying their eligibility for study participation. When a potential participant was identified as eligible for participating in this study and the related informed consent was completed, the researchers called the person who was responsible for randomization to receive the corresponding random number to determine the group assignment for the enrolled participant.

5.7.1.2.2 Strategies for minimizing performance bias

Performance bias indicates "systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest" (Higgins & Green, 2008, p. 195).

A blinding design for the study participants, the researchers, and the outcome assessment and a standard intervention/treatment protocol can help minimize potential performance bias that can occur during a study's implementation (Higgins & Green, 2008). However, given the facts of the visible nature of the study intervention as well as the actual AT treatment at the study hospitals, a complete blinding design was deemed impossible and a partial blinding design was therefore employed in this study. Particularly, the participants allocated to the true AT group and the sham AT group, as well as the care providers working at the study sites, would not know whether the AT treatment was the true or sham approach. Moreover, the blinding of the outcome assessment for the true AT group and the sham AT group was maintained given that the outcome measures were patient-reported questionnaires and the participants themselves were the outcome assessors. In addition, to further ensure the successful blinding design among the participants in the true AT group and the sham AT group, when the actual AT treatment at the study sites was about to commence, the oncologists would separate the participants from the true AT group and the sham AT group into different wards.

The AT intervention protocol used in this study was evidence-based and was developed according to a series of research evidence from several well-designed systematic reviews, AT handbooks and theories, and the characteristics of cancer symptoms, as well as a content validity study among a group of experts specialized in AT and TCM (details can be found in Section 5.4 in this chapter). AT training among the doctoral researcher and the two backup researchers was performed before the commencement of the pilot RCT to minimize variations in the implementation of the AT treatment between different researchers, and all of the researchers were required to strictly follow the standard AT procedures when performing the AT treatment on the study participants. Verbal interactions between the researcher and the participants during the AT treatment were also pre-standardized among the three researchers to avoid increasing the participants' expectations of the potential therapeutic effects of AT. Return demonstration of the self-acupressure technique was also required for the participants in the true AT group to ensure that they had mastered the ear acupressure skills. The co-intervention, particularly, standard antiemetic treatment and care, was similar across the study groups as well as across different study sites. The participants' adherence to regular acupressure of the taped seeds (in the true AT group) and the completion of the study questionnaires was monitored daily by the research assistants during the days when the patients stayed in the hospital. Telephone

follow-ups were also used to further maintain the participants' adherence to the study protocol by reminding them to remove the AT tapes and completing the delayed CINV assessment on time.

5.7.1.2.3 Strategies for minimizing attrition bias and detection bias

In healthcare interventional studies, attrition bias and detection bias may be related to some systematic differences that exist between different study groups in terms of the participants' withdrawal, dropout, and the assessment of outcome variables (Higgins & Green, 2008). In this study, all of the participants were analyzed and reported based on their group allocation, and an ITT analysis with an LOCF approach was utilized for data analysis and missing values management. The participants' withdrawal and dropout rates were low in this study given that the study intervention was a relatively safe and convenient approach in nature, and the majority of the participants were covered by different types of healthcare insurance and were able to afford the medical expenses for the first several cycles of chemotherapy. A partial blinding design was also performed for the outcome assessors (the participants themselves) to minimize potential detection bias during the outcome assessment.

5.7.1.2.4 Strategies for minimizing potential therapeutic effects of the sham AT treatment

In acupuncture/acupressure trials with a design of true and placebo interventions, to investigate the specific treatment effects of the true intervention (the true treatment effects), study investigators must make the greatest effort to minimize the potential treatment effects generated from the sham comparison (Dincer & Linde, 2003; Tan et al., 2015). In this study, the design of the sham AT intervention was based on a series of well-designed systematic reviews on sham approaches used in acupuncture/acupressure trials (Dincer & Linde, 2003; Tan et al., 2015; Zhang & Tang, 2003). The sham AT intervention used in this pilot RCT adopted the same acupoints as those in the true AT group to achieve a successful blinding design among the participants from the true AT group and the sham AT group. To eliminate possible treatment effects generated from acupoint stimulation, no additional acupressure was scheduled for the sham AT tapes. Meanwhile, Junci Medulla instead of vaccaria seeds was utilized for the sham intervention, as vaccaria seeds are hard objects that may create constant physical pressure to the targeted acupoints even when no additional acupressure is applied.

However, this kind of blinding design still may not be sufficient enough even though no acupoint stimulation was applied for patients in the sham AT group. The blinding design could easily be broken if the participants had any previous experience of receiving AT treatment. Therefore, the following strategies were used to minimize the potential risks of breaking the blinding design: **(1)** this pilot study recruited only breast cancer patients who had never received any form of AT treatment before, because AT-naïve participants do not have any previous experience of *de qi* sensation, and it would be somewhat difficult for them to distinguish the difference between the true AT and the sham AT; and **(2)** depending on the actual situation at the study sites, if possible, the oncologists placed the participants from the true AT group and the sham AT group into different wards, which would avoid possible communication between participants from different groups and prevent those in the sham AT group from observing the regular acupressure of taped seeds in the true AT group.

5.7.1.3 Study quality assurance for the semi-structured interview

The rigor of the semi-structured interview was maintained by the following four indicators, which are commonly used in qualitative studies to enhance the "trustworthiness" of the findings: credibility (internal validity), transferability (external validity), dependability (reliability), and confirmability (objectivity) (Lincoln & Guba, 1985; Morse, Barrett, Mayan, Olson, & Spiers, 2002; Shenton, 2004).

The credibility (internal validity) of the semi-structured interview was maintained via the member-checking approach (Lincoln & Guba, 1985; Shenton, 2004). The transcribed scripts were double-checked against the original records by the doctoral researcher and another independent researcher to ensure the accuracy of the transcription. For the representative data extracts listed in the qualitative study results section (details can be found in Chapter 7, Section 7.3), backward translation from English to Mandarin Chinese was performed by the independent researcher to ensure the equivalence of the participants' descriptions between different languages. Meanwhile, the identified themes and sub-themes were returned to some of the participants to check whether these themes really indicated their experiences of taking part in the pilot study and receiving the AT intervention (Lincoln & Guba, 1985; Shenton, 2004). Around half of the participants (13 out of 27) were approached by the doctoral researcher via telephone

and all of them confirmed that their views and ideas were well captured by the identified themes and sub-themes.

The transferability (external validity) of the qualitative study was improved by adding more detailed descriptions of the qualitative research findings and including representative and sufficient data extracts to support each of the identified themes and sub-themes. The findings of this nested qualitative study were also compared with other qualitative studies that explored patients' experiences of participating in acupuncture/acupressure trials to see whether the current study conclusions could be transferred to other research and practice settings (Shenton, 2004). In terms of the strategies for maintaining the dependability (reliability) and conformability (objectivity) of the qualitative study, the design and implementation of the semi-structured interviews and the final data analysis approach were reported in detail in this doctoral thesis to ensure that other researchers have access to sufficient information to repeat the current study. and ongoing communications and discussions among the researcher, the study participants (the informants) and the independent researcher were performed during the processes of generation of the initial codes and potential themes as well as the identification of the final themes to ensure that the interpretations were not based on the preferences of the doctoral researcher but reflect the real thoughts or views of the study participants (Shenton, 2004).

5.7.2 Ethical considerations

Ethical approvals of the doctoral research project were obtained from the Research Committees of The Hong Kong Polytechnic University and the study hospitals (see Appendix XIV). When inviting the potential participants to take part in the study, information regarding the study aims and objectives, procedures of the study, and the potential risks of the intervention approaches were explained in detail by the researchers, and relevant information was also included in an information sheet (see Appendix XV). Potential participants had the chance to carefully read the information sheet and ask any questions regarding the study before making the final decision to participate in the study or not. For these who determined that they would participate in the study, written informed consent forms were obtained accordingly (see Appendix XVI). This study has been registered at ClinicalTrials.gov (https://www.clinicaltrials.gov/) (ClinicalTrials.gov Identifier: NCT02403037). This study has followed the ethical principles for all research that involves human

subjects, which will be described in the following sections (Beauchamp & Childress, 2009; World Medical Association [WMA], 2001).

5.7.2.1 The principle of autonomy (respect for the person)

The principle of autonomy indicates that every study participant has a right to make the decision to participate in a research project or not (Beauchamp & Childress, 2009). When inviting potential participants to join a study, they should be well informed of the aims and objectives of the study, the detailed study procedures, and the potential harms associated with the study intervention. In this study, an information sheet was provided to every potential participant, and the benefits and potential harms associated with the AT treatment were clearly explained by the researchers. A written informed consent was required from every eligible participant who agreed to participate in the doctoral study. All the breast cancer patients eligible for study participation at the study sites were fully informed that their participation was totally based on a voluntary principle, and they all had the right to refuse to take part in the research or to withdraw from it at any time and any stage, and such decisions would not affect their routine antineoplastic/antiemetic treatments and care in the study hospitals.

5.7.2.2 The principle of non-maleficence and beneficence

The essence of the principle of non-maleficence is "do no harm" (Beauchamp & Childress, 2009), which indicates that healthcare interventions should not put the study subjects in a risk position (Andersson et al., 2010). Beneficence means "all forms of action intended to benefit other persons" (Beauchamp & Childress, 2009, p. 197). It cannot be denied that healthcare interventions (particularly some medical procedures) are associated with some potential harms to the patients; however, the greatest effort must be taken to minimize such harms in either practice or research settings. In this study, to minimize the possible harms induced by the use of AT, auricular acupressure was utilized as the study intervention method because it is a non-pharmacological AT modality and research evidence supports its superiority to other AT techniques with regard to its safety and convenience (Tan et al., 2014b). As a frequently utilized therapeutic approach, AT has been shown to be effective in managing different types of health problems, and the antiemetic role of AT in nausea and emesis has been identified as a promising

approach based on current literature (Tan et al., 2014a). This doctoral research project intends to advance the current understanding of the role of "beneficence" in AT for CINV symptom management among cancer patients undergoing chemotherapy.

5.7.2.3 The principle of confidentiality

Participants' information collected for a research project must not be used or disclosed for any purpose without their permission and authorization (Beauchamp & Childress, 2009). Only core members of the research team in this doctoral research project were allowed to access the participants' research records, documents, and any other types of files that had identifiers of the study participants. Several strategies were utilized in this study to secure the confidentiality and anonynimity of the participants' research materials. For instance, a special code with a name acronym was assigned to each of the study participants to replace their names and other important identifiers, such as their personal ID card number and social security card number. All hard copies of the research materials, including the participants' questionnaires, daily logs, and relevant forms, were locked in a cabinet and all electronic files were saved in a compressed file that could only be accessed by the doctoral researcher via passwords.

5.8 Summary of the chapter

This chapter presented the research methodology for this doctoral research project. The study design followed the *MRC Framework for Developing and Evaluating Complex Interventions*, which includes three study phases: the development of an evidence-based AT treatment protocol, the pilot RCT, and the nested semi-structured interviews. Before reporting the relevant study findings from the pilot RCT and the semi-structured interviews, a preparatory study examining the psychometric properties of the MAT, Chinese version, will be presented first, and details of the preparatory work, including the background, study design, results, and discussion, will be presented in the next chapter.

CHAPTER SIX: PREPARATORY STUDY: PSYCHOMETRIC PROPERTIES OF THE MAT, CHINESE VERSION

6.1 Introduction

This chapter will present an instrumental validation study that will examine the psychometric properties of the MAT, Chinese version, for measuring CINV in Chinese cancer patients. The validation study was conducted among a group of Chinese patients with different cancer diagnoses. Different psychometric properties of the MAT, Chinese version, including validity, reliability, and acceptability, were measured and reported. The study's background, methods, results, and discussion will also be reported. It should be noted that this validation study has already been published in an international peer-reviewed journal (Tan, Suen, & Molassiotis, 2016). In this doctoral thesis, the major contents and the styles of text citations and reference list of the published validation study have been slightly modified to fit the whole structure and organization of the doctoral thesis. Permission for the use of the article in this doctoral thesis has been granted by the publisher (Supportive Care in Cancer, Psychometric assessment of the Chinese version of the MASCC Antiemesis Tool (MAT) for measuring chemotherapy-induced nausea and vomiting, 24, 2016, 3729-3737, Jing-Yu Tan, Lorna K. P. Suen and Alex Molassiotis, with permission of Springer).

6.2 Background

As one of the most common and unpleasant side effects among cancer patients undergoing antineoplastic therapies, CINV can create considerable negative impacts on patients' physical and psychological functions (Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; Fernandez-Ortega et al., 2012; Hawkins & Grunberg, 2009). Standard antiemetic medications such as NK-1 receptor antagonists, dexamethasone, and 5-HT_3 receptor antagonists are currently the most recommended treatments for CINV (Chan & Yeo, 2011). However, despite assistance from antiemetic therapies, complete control of CINV remains problematic, as many cancer patients receiving antiemetics still suffer from severe gastrointestinal symptoms during chemotherapy (Cohen et al., 2007; Hsieh et al., 2015; Liau et al., 2005; Valle, Wisniewski, Vadillo, Burke, & Corona, 2006).

Managing CINV (as well as other symptoms) requires regular and appropriate assessment first. Several instruments have been introduced to measure CINV, such as the MANE, the WHO Recommendations for Grading of Acute and Subacute Toxicity, the FLIE, and the INVR

(Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Tan et al., 2014a). However, these measurements are either focused more on the impact of CINV on patients' quality of life rather than on the symptoms themselves, or are long scales that do not properly distinguish between acute and delayed phases of CINV. Meanwhile, some of the instruments lack adequate evidence in terms of their psychometric properties (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Tan et al., 2014a). All of these deficits could limit the application of these measuements and instruments in both research and practice.

As introduced by the MASCC, the MAT is a simple user-friendly instrument for recording nausea and vomiting during chemotherapy (Brearley et al., 2008; Molassiotis, Coventry et al., 2007). The MAT is easily understandable and patients only need to administer it twice during one chemotherapy cycle to record their CINV symptoms. The MAT was developed by a series of rigorous procedures, including critical literature analysis, interviews with clinicians, expert panel discussions, and repeated revisions by healthcare professionals experienced in cancer and chemotherapy (Molassiotis, Coventry et al., 2007). The psychometric properties of the original English version were tested in the UK and USA, with adequate validity, reliability, and cultural transferability and equivalence reported (Molassiotis, Coventry et al., 2007). The MAT has been widely used in research and practice to measure CINV symptoms (Beith, Oh, Chatfield, Davis, & Venkateswaran, 2012; Klafke et al., 2015; Molassiotis et al., 2008; Molassiotis, Russell et al., 2014; Yeh et al., 2014), and it has been translated into several languages, such as Chinese, German, Greek, French, Portuguese, and Spanish, to facilitate its use in different linguistic and cultural contexts.

The Chinese version of the MAT was published in early 2014 (http://www.mascc.org/MAT). Standard translation procedures were employed (Sousa & Rojjanasrirat, 2011), and the equivalence of the original and the Chinese-translated versions of the MAT was maintained by a forward- and backward-translation approach. The MAT, Chinese version, has been used in a recent large observational study across six Asia-Pacific countries (Hsieh et al., 2015). However, its psychometric properties have not been formally examined and reported yet. Therefore, the aim of this study was to determine the psychometric properties of the Chinese version of the MAT, particularly with regard to its validity and reliability, in a heterogeneous group of Chinese cancer patients undergoing chemotherapy.

6.3 Methods

6.3.1 Study design

This psychometric study employed a panel of experts and a prospective observational design. Subject recruitment was conducted using a convenience sampling approach.

6.3.2 Patients and settings

The study sites included three provincial medical centers in Fuzhou, China. Eligible patients were invited to participate in the study if they **(1)** had a confirmed diagnosis of malignancy; **(2)** were aged 18 years old or above; **(3)** were receiving adjuvant chemotherapy at the time of conducting the study; **(4)** were able to communicate in Mandarin Chinese; **(5)** agreed to participate in the study; and **(6)** were willing to provide written informed consent. The Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University reviewed and approved the study protocol. Ethical approvals were also obtained from the study hospitals.

6.3.3 Sample size calculation

Nunnally and Bernstein (1967) indicated that approximately 10 subjects for each item of an instrument are adequate to estimate reliability. Hobart, Cano, Warner, and Thompson (2012) pointed out that the reliability and validity estimation of an instrument becomes robust when the minimum required sample size reaches 20 and 80 subjects, respectively. As Cronbach's alpha was adopted as one of the parameters for assessing the internal consistency of the MAT, according to the formula provided by Bonett (2002) and the study from Moradian et al. (2014), to achieve a coefficient alpha of 0.75 for "an eight-item scale with a 95% confidence interval with a margin-of-error of ±0.1" (p. 814), the required sample size should be 61. The sample size for this study was set at 80 based on the recommendations above. Allowing for a possible 30% dropout rate between the two time points assessing acute and delayed CINV, the final sample size was determined to be 115.

6.3.4 Study procedure

Six experts specialized in cancer treatment/care were invited to identify the content validity and the face validity of the MAT before testing it in clinical settings. CINV was assessed in one

chemotherapy cycle. Patients who met the inclusion criteria were screened and identified by the oncologists at the study sites. Eligible patients were then invited to participate in the study, and details of the study's purpose and procedures were given by the researcher. Eligible patients who agreed to participate signed an informed consent and then provided their demographic data. On the first day (day 1) and the fifth day (day 5) after receiving the most recent chemotherapy, the participants were required to complete the MAT to measure their acute and delayed CINV. Meanwhile, the participants were also asked to complete the INVR daily for five consecutive days (from day 1 to day 5 post-chemotherapy). Detailed instructions for the MAT and the INVR were given to the participants when completing the tools for the first time.

Both the MAT and the INVR were self-completed by the participants. Assistance was offered by the doctoral researcher if the participants had difficulty in filling in the scale by themselves. The participants who stayed in the hospital for five days completed the instruments on site and returned them to the researcher directly after completing them. For those who were discharged, the participants completed them at home and reported their scores to the doctoral researcher through a daily phone call or returned them to the doctoral researcher at their next visit to the hospital.

6.3.5 Study instruments

6.3.5.1 Demographic questionnaire

A questionnaire specific to this study was designed to collect the demographic data of the sample. The classification of the emetogenic potential of the chemotherapeutic agents was categorized into four levels of risk: high, moderate, low, and minimal (Basch et al., 2011; Chambers & Daniels, 2010; Jordan et al., 2014; MASCC, 2013; ONS, May 2017). The emetogenic risk of the chemotherapy protocol with multiple agents was determined by the principles provided by the ONS: **(1)** agents with minimal emetic risk do not make any contribution to the emetogenicity of the whole protocol; **(2)** adding one or more low emetic risk agents makes the highest emetic risk of the whole protocol increase by one degree; **(3)** adding one or more moderate emetic risk agents makes the highest emetic risk of the whole protocol increase by one degree per each agent (ONS, May 2017).

6.3.5.2 MAT

The MAT is comprised of eight items, with four each assessing acute and delayed CINV, respectively (Brearley et al., 2008; Molassiotis, Coventry et al., 2007). Within each phase, the four items include the occurrence of vomiting, frequency of vomiting, occurrence of nausea, and severity of nausea (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Wood et al., 2011). The MAT should be completed on the first day and the fifth day after receiving chemotherapy to measure acute (0 to 24 h post-chemotherapy) and delayed (>24 to 120 h post-chemotherapy) CINV, respectively. The MAT can be completed within a very short time, with an average time of four minutes (Molassiotis, Coventry et al., 2007). For the purpose of psychometric assessment, score summing of the MAT was conducted according to Molassiotis, Coventry et al. (2007). A MAT total score for each subject was computed by summing up the scores of the eight items (Molassiotis, Coventry et al., 2007). The four items rated on day 1 and day 5 post-chemotherapy were summed up respectively to calculate an acute CINV score and a delayed CINV score. Total nausea and total vomiting scores were also produced by summing up the four nausea items and the four vomiting items, respectively (Molassiotis, Coventry et al., 2007). Furthermore, the total nausea and total vomiting scores were reduced to symptom scores for either the acute or the delayed phase (Molassiotis, Coventry et al., 2007).

6.3.5.3 INVR

The INVR has eight items, with three subscales assessing nausea, vomiting, and retching (Rhodes & McDaniel, 1999, 2001). It is a self-completed instrument and each item is rated on a 0- to 4-point Likert scale. The INVR can be used to assess the level of gastrointestinal distress every 12 or 24 hours (Molassiotis, Coventry et al., 2007; Rhodes & McDaniel, 1999, 2001). Good reliability and validity of the INVR has been reported (Brearley et al., 2008; Rhodes & McDaniel, 1999, 2001). The INVR, Chinese version, was validated in Chinese oncology/obstetric patients, with the Cronbach's alpha ranging from 0.94 (evening) to 0.95 (morning) (Fu et al., 2002). Internal consistency was also found to be satisfactory in Chinese gastrointestinal cancer patients (Fu, 2008). The INVR, Chinese version, was utilized in this study to test against the MAT to identify the concurrent validity of the MAT, Chinese version. The eight INVR items were summed up to produce a daily total INVR score, and the five-day INVR scores were also summed up to calculate

an overall CINV score across the five days (Molassiotis, Coventry et al., 2007). The daily total score can be further reduced to daily nausea scores and daily vomiting scores (Molassiotis, Coventry et al., 2007). The INVR total score for day 1 post-chemotherapy was adopted as the acute CINV score, and the INVR total scores in the following four days were summed up to calculate an overall delayed CINV score. In addition, the nausea and vomiting sub-scores were further isolated from the five-day total INVR score, the acute CINV score, and the overall delayed CINV score.

6.3.6 Psychometric assessment

6.3.6.1 Validity

Content validity, face validity, construct validity, and concurrent validity were examined. Content validity was measured using a 4-point Likert scale (4 = "very relevant," 3 = "quite relevant," 2 = "somewhat relevant," and 1 = "not relevant"), and experts were required to evaluate the translation equivalence and cultural relevance of each MAT item used among the Chinese cancer patients (see Appendix XVII). The experts and the patients participating in the study were also asked several questions in terms of the feasibility, clarity, and usability of the MAT to determine its face validity. Construct validity was measured using the contrasted groups approach. As younger age and female gender are regarded as common risk factors for CINV, the patients included in the contrasted groups analysis were divided into two groups based on their age (<50 years old and ≥ 50 years old) and gender (male and female). Concurrent validity is estimated by "how well a test correlates with another test that has already had its validity estimated" (Newman & Newman, 1994; p. 53), and it was measured between the MAT and the INVR by correlation coefficients.

6.3.6.2 Reliability and acceptability

Internal consistency was measured by Cronbach's alpha. Item-to-total correlations were also examined, as this explores the associations between one single item score and the total instrument score without that item (Bohrnstedt, 1969). Test-retest reliability is another attribute of reliability estimation, but it was deemed unsuitable here as patients with CINV violate one of the preconditions for test-retest reliability analysis, which is the "hypothesised stability of the trait being assessed" (Brearley et al., 2008, p. 1215). Completion and dropout rates were assessed to measure the acceptability of the MAT among the participants.

6.3.7 Data analysis

The Statistical Package for the Social Sciences (SPSS) version 20.0 was used for data analysis. Descriptive statistics were adopted to summarize the participants' characteristics. Content validity was measured using the CVI. CVI for each MAT item (item-level CVI) was determined by the proportion of experts who rated the item as "very relevant" or "quite relevant" (Lynn, 1986; Rubio et al., 2003; Waltz & Bausell, 1981). The content validity of an item was deemed appropriate when at least five out of the six experts agreed that it was "very relevant" or "quite relevant" (Lynn, 1986). The content validity of the whole MAT (scale-level CVI) was estimated by calculating the proportion of the items determined to be content valid (Davis, 1992; Lynn, 1986). A value of 0.8 or above is regarded as a satisfactory level of agreement (Davis, 1992).

Half of the MAT items were dichotomous variables in nature, and both the INVR and the MAT scores violated the assumption of normal distribution. Therefore, non-parametric tests were employed in this study. The Mann-Whitney U test was used for the contrasted groups analysis. Spearman's correlation coefficients (r_s) were adopted to explore the relationships between the MAT and the INVR. Reliability was estimated by internal consistency reliability (Cronbach's alpha) and item-to-total correlations. The minimal acceptable Cronbach's alpha is generally regarded as 0.65 to 0.70, and Cronbach's alpha between 0.70 and 0.80 is viewed as acceptable (DeVellis, 1991). A value of 0.4 or above is suggested as an adequate item-to-total correlation (Altman, 1991).

6.4 Results

6.4.1 Demographic and clinical characteristics of the study sample

One hundred and fifteen patients participated in the study and 111 completed it. More than half of the subjects were female, and 42.3% were younger than 50 years old. The majority had completed at least primary school education and most of the subjects were married and employed. The most common diagnoses were breast cancer, stomach cancer, colorectal cancer, and lung cancer. Oxaliplatin-based, anthracycline-based, and cisplatin-based protocols and single-agent paclitaxel were the most commonly used chemotherapeutic agents. The most frequently used antiemetic medications were palonosetron, tropisetron, and ondansetron, either combined with or without dexamethasone. The demographic and clinical data of the study subjects are shown in **Table 6.1** below:

Table 6.1 Demographic and clinical data of the samples (N=111)

Demographic and Clinical Information		n (%)
Gender	Female	66 (59.46%)
	Male	45 (40.54%)
Age (Year)	20-29	1 (0.90%)
	30-39	12 (10.81%)
	40-49	34 (30.63%)
	50-59	34 (30.63%)
	60-69	25 (22.52%)
	70-79	5 (4.50%)
Education background	No formal education	15 (13.51%)
	Primary school	35 (31.53%)
	Secondary school	30 (27.03%)
	High school/vocational school	21 (18.92%)
	College diploma/university degree	10 (9.01%)
Marital status	Single	2 (1.80%)
	Married	109 (98.20%)
Employment status	Professional	19 (17.12%)
	Housewife	29 (26.13%)
	Manual work	34 (30.63%)
	Clerical/admin	11 (9.91%)
	Retired	6 (5.41%)
	Unemployed	2 (1.80%)
	Other	10 (9.01%)
Type of cancer	Stomach cancer	20 (18.02%)
	Lung cancer	17 (15.32%)
	Breast cancer	45 (40.54%)
	Esophageal cancer	5 (4.50%)
	Colorectal cancers	19 (17.12%)
	Lymphoma	1 (0.90%)
	Ovarian cancer	1 (0.90%)
	Small intestine cancer	1 (0.90%)
	Abdominal metastatic cancer	1 (0.90%)
	Tongue cancer + lung cancer	1 (0.90%)
Chemotherapy protocol	Oxaliplatin-based protocols	27 (24.32%)
	Anthracycline-based protocols	20 (18.02%)
	Cisplatin-based protocols	10 (9.01%)
	Carboplatin/Lobaplatin-based protocols	9 (8.11%)
	Single-agent paclitaxel	20 (18.02%)
	Single-agent cyclophosphamide	4 (3.60%)
	Other	21 (18.92%)
Emetogenic risk of the chemotherapy protocol	High risk	50 (45.04%)
	Moderate risk	26 (23.42%)
	Low risk	28 (25.23%)
	Unclear risk	7 (6.31%)
Antiemetic medication	Palonosetron (with/without dexamethasone)	55 (49.55%)
	Tropisetron (with/without dexamethasone)	39 (35.14%)
	Ondansetron (with/without dexamethasone)	10 (9.01%)
	Granisetron (with/without dexamethasone)	5 (4.50%)
	Single-agent dexamethasone	2 (1.80%)

6.4.2 Acceptability and descriptive analysis of the MAT scores

Acceptability of the MAT was generally satisfactory, with a completion rate of 96.5% and a dropout rate of 3.5%. For acute CINV, episodes of acute vomiting were identified in 18 subjects (16.22%), with the frequency of vomiting ranging from 1 to 20 (mean 3.89), while acute nausea was detected in 52 subjects (46.85%), and the severity score ranged from 1 to 8 out of 10 (mean 3.21). Delayed CINV was more commonly reported than acute symptoms, with delayed vomiting reported by 29 subjects (26.13%, frequency ranged from 1 to 40, mean 5.93), and delayed nausea by 60 subjects (54.05%, severity score ranged from 1 to 9 out of 10, mean 3.50).

6.4.3 Content validity and face validity

All of the six experts had more than 16 years of clinical/research experience in cancer-related treatment or care, of which two were professors or associate professors who worked at a medical university, three were senior clinical staff (one chief physician and two associate chief nurses) who worked at a hospital, and the other one held both an academic and a clinical position (professor and chief physician). All experts agreed that the MAT was particularly designed to measure CINV symptoms, and they all agreed that the MAT items were adapted well to the Chinese language. Some minor comments and suggestions were provided by the experts. For instance, one expert suggested changing “vomiting reaction” to “vomiting,” and another suggested changing “stomach contents” (definition of nausea in the MAT instructions) to “food and/or drinks that you have taken in,” which might be more understandable for less-educated patients. All patients participating in the psychometric study agreed that the MAT was useful in recording their CINV symptoms and all the items were quite understandable. They found that the MAT was easier to complete compared with the daily INVR. Two patients (1.8%) who had no formal education found it somewhat difficult to understand the nausea severity items with the 0 to 10 scale. All items were rated by the expert panel as “very relevant” or “quite relevant,” and both the item-level CVI and scale-level CVI reached 1.0, which indicated excellent content validity.

6.4.4 Contrasted groups validity

The results of the contrasted groups analysis are presented in **Table 6.2**. The total MAT score as well as the sub-scores for both acute and delayed CINV were much higher in the younger age

group (indicating more severe CINV symptoms) than those in the group aged more than 50 years old, and the majority of the variables reached statistical significance ($p<0.05$). A similar trend was also detected in the comparison with regard to gender, with female patients having higher CINV scores than males, although not all items showed statistical significance.

Table 6.2 Contrasted groups analysis (N=111)

Score[a]	Age			Gender		
	<50 years old (n=47)	**≥50 years old (n=64)**	***P*** [b]	**Female (n=66)**	**Male (n=45)**	***P*** [b]
Total MAT score	9.83 (1.89)	4.94 (0.80)	0.020	8.36 (1.44)	5.02 (0.93)	0.179
Total nausea score	5.60 (0.74)	3.53 (0.47)	0.030	4.97 (0.58)	3.58 (0.59)	0.130
Total vomiting score	4.23 (1.43)	1.41 (0.43)	0.010	3.39 (1.06)	1.44 (0.45)	0.242
Acute CINV score	3.98 (0.79)	1.88 (0.37)	0.020	3.41 (0.59)	1.82 (0.48)	0.025
Acute nausea score	2.70 (0.40)	1.44 (0.25)	0.014	2.38 (0.31)	1.38 (0.32)	0.026
Acute vomiting score	1.28 (0.52)	0.44 (0.17)	0.091	1.03 (0.38)	0.44 (0.20)	0.248
Delayed CINV score	5.85 (1.20)	3.06 (0.57)	0.041	4.95 (0.96)	3.20 (0.57)	0.693
Delayed nausea score	2.89 (0.42)	2.09 (0.32)	0.131	2.59 (0.36)	2.20 (0.35)	0.667
Delayed vomiting score	2.96 (0.96)	0.97 (0.32)	0.011	2.36 (0.73)	1.00 (0.32)	0.316

Note: a=scores were presented as mean±SE (standard error); b=Mann-Whitney test of mean rank; MAT= MASCC Antiemesis Tool

6.4.5 Concurrent validity

Correlations between the MAT and the INVR were examined by Spearman's correlation coefficients (r_s). The relationships between the daily INVR total score, the daily INVR sub-scores, the MAT total score, and the MAT sub-scores were assessed (see **Table 6.3**). Significantly strong correlations were found between the MAT total and the daily INVR total scores ($p<0.001$), the MAT nausea and the daily INVR nausea scores ($p<0.001$), and the MAT vomiting and the daily INVR vomiting scores ($p<0.001$). The five-day overall INVR score, the INVR nausea scores, and the INVR vomiting scores were then summed up, respectively, to compare them against the MAT total score ($r_s=0.94$), the MAT nausea scores ($r_s=0.90$), and the MAT vomiting scores ($r_s=0.985$), and all were highly significant ($p<0.001$). Lower correlations were observed between the INVR nausea and the MAT vomiting scores ($r_s=0.58$) and the INVR vomiting and the MAT nausea scores ($r_s=0.64$), both at $p<0.001$.

Table 6.3 Correlation coefficients between the MAT and the INVR scores

INVR Scores		MAT Scores		
		Nausea	**Vomiting**	**Total**
Nausea	Day 1 post-chemotherapy	0.827[a]	0.522[a]	0.784[a]
	Day 2 post-chemotherapy	0.760[a]	0.510[a]	0.739[a]
	Day 3 post-chemotherapy	0.664[a]	0.443[a]	0.648[a]
	Day 4 post-chemotherapy	0.613[a]	0.446[a]	0.611[a]
	Day 5 post-chemotherapy	0.586[a]	0.417[a]	0.567[a]
Vomiting	Day 1 post-chemotherapy	0.543[a]	0.741[a]	0.608[a]
	Day 2 post-chemotherapy	0.484[a]	0.753[a]	0.587[a]
	Day 3 post-chemotherapy	0.483[a]	0.711[a]	0.562[a]
	Day 4 post-chemotherapy	0.452[a]	0.664[a]	0.536[a]
	Day 5 post-chemotherapy	0.326[a]	0.581[a]	0.432[a]
Total	Day 1 post-chemotherapy	0.870[a]	0.658[a]	0.865[a]
	Day 2 post-chemotherapy	0.781[a]	0.690[a]	0.821[a]
	Day 3 post-chemotherapy	0.768[a]	0.626[a]	0.784[a]
	Day 4 post-chemotherapy	0.707[a]	0.590[a]	0.727[a]
	Day 5 post-chemotherapy	0.644[a]	0.541[a]	0.665[a]

Note: INVR=Index of Nausea, Vomiting, and Retching; MAT=MASCC Antiemesis Tool; a=significant at 0.01

Further exploration of the correlations of the acute/delayed CINV scores between the MAT and the INVR was conducted (see **Table 6.4**). For the day 1 INVR scores, the INVR total (acute CINV), INVR nausea (acute nausea), and INVR vomiting (acute vomiting) scores were highly and positively correlated with the MAT acute CINV, MAT acute nausea, and MAT acute vomiting scores, respectively. The daily INVR scores in the following four days (representing delayed CINV) were also examined with the delayed MAT scores. The MAT delayed CINV scores were found to be significantly correlated with the daily INVR total score from day 2 to day 5, all at $p<0.001$. The MAT delayed nausea and MAT delayed vomiting scores were also well correlated with the daily INVR delayed nausea and daily INVR delayed vomiting scores, respectively. In addition, the INVR scores from day 2 to day 5 were further summed up to formulate an overall delayed CINV score to explore the correlations with the MAT delayed CINV scores, and all variables were found to be significantly correlated ($p<0.001$). The strong correlations between the two instruments demonstrated high concurrent validity of the MAT, Chinese version.

Table 6.4 Correlation coefficients of acute/delayed CINV scores between the MAT and the INVR

INVR Scores	MAT Scores					
	Acute CINV	Acute Nausea	Acute Vomiting	Delayed CINV	Delayed Nausea	Delayed Vomiting
Day 1 post-chemotherapy [acute CINV]						
Total	0.941[a]	0.910[a]	0.637[a]	0.664[a]	0.636[a]	0.556[a]
Nausea	0.926[a]	0.932[a]	0.512[a]	0.585[a]	0.583[a]	0.435[a]
Vomiting	0.672[a]	0.559[a]	0.996[a]	0.470[a]	0.398[a]	0.558[a]
Day 2 post-chemotherapy [delayed CINV]						
Total	0.555[a]	0.528[a]	0.438[a]	0.867[a]	0.817[a]	0.718[a]
Nausea	0.535[a]	0.529[a]	0.347[a]	0.761[a]	0.792[a]	0.517[a]
Vomiting	0.492[a]	0.425[a]	0.626[a]	0.594[a]	0.429[a]	0.776[a]
Day 3 post-chemotherapy [delayed CINV]						
Total	0.482[a]	0.456[a]	0.386[a]	0.863[a]	0.843[a]	0.655[a]
Nausea	0.366[a]	0.342[a]	0.297[a]	0.726[a]	0.767[a]	0.443[a]
Vomiting	0.412[a]	0.356[a]	0.488[a]	0.605[a]	0.486[a]	0.767[a]
Day 4 post-chemotherapy [delayed CINV]						
Total	0.428[a]	0.386[a]	0.403[a]	0.822[a]	0.814[a]	0.604[a]
Nausea	0.363[a]	0.327[a]	0.335[a]	0.683[a]	0.708[a]	0.436[a]
Vomiting	0.441[a]	0.355[a]	0.603[a]	0.555[a]	0.447[a]	0.699[a]
Day 5 post-chemotherapy [delayed CINV]						
Total	0.390[a]	0.362[a]	0.285[a]	0.740[a]	0.730[a]	0.555[a]
Nausea	0.365[a]	0.339[a]	0.273[a]	0.608[a]	0.651[a]	0.401[a]
Vomiting	0.234[b]	0.172	0.320[a]	0.484[a]	0.372[a]	0.637[a]
Day 2-5 post-chemotherapy [overall delayed CINV]						
4-day overall total	0.532[a]	0.500[a]	0.419[a]	0.936[a]	0.913[a]	0.695[a]
4-day overall nausea	0.511[a]	0.485[a]	0.375[a]	0.880[a]	0.911[a]	0.546[a]
4-day overall vomiting	0.475[a]	0.420[a]	0.533[a]	0.737[a]	0.567[a]	0.966[a]

Note: INVR=Index of Nausea, Vomiting, and Retching; MAT= MASCC Antiemesis Tool; a=significant at 0.01; b=significant at 0.05

6.4.6 Reliability

The internal consistency of the MAT was satisfactory. The Cronbach's alpha for the whole scale was 0.73. Coefficients of the item-to-total scale ranged from 0.50 to 0.71 (mean 0.61), which indicated adequate item-to-total correlations.

6.5 Discussion

The MAT is currently the only scale designed that separately assesses both acute and delayed CINV (Brearley, et al., 2008; Molassiotis, Coventry et al., 2007). The eight-item tool is convenient as it can be completed within a short period of time, which produces less burden on cancer patients. The MAT, Chinese version, was deemed culturally relevant to Chinese patients. Usability and clarity was also supported by experts' and patients' responses. Although one expert suggested

changing “stomach contents” to “food and/or drinks that you have taken in,” a face validity evaluation afterward among the participants revealed that “stomach contents” was actually quite easy to understand, and no change was undertaken for the definition of nausea.

The contrasted group analysis clearly showed that younger and female patients experienced more severe CINV symptoms than older and male ones, respectively. Initial discrimination was adequately presented between groups with known risk factors for CINV. Although all the MAT total and sub-scores were much higher in the female group than those in the male comparison, only a few of them reached statistical significance. One possible explanation might be that the predictive value of gender in CINV was not as strong as the age factor (Molassiotis, Aapro et al., 2014). Meanwhile, the non-parametric test used in the study was less powerful than parametric tests from statistical perspectives.

Excellent concurrent validity of the MAT, Chinese version, was identified. The INVR and the MAT items measuring the same construct were highly correlated with each other, while lower (but significant) correlations were found between corresponding INVR and MAT scores with different concepts (i.e., nausea with vomiting). The discrimination between the different symptom constructs highlights the sensitivity of the Chinese version of the MAT. The findings were consistent with the concurrent validity analysis of the original English MAT version, which also indicated a significantly positive correlation between the INVR and the MAT with the same symptom dimensions (Molassiotis, Coventry et al., 2007). Reliability was also adequate but slightly lower than the original English version, perhaps because the current sample was not as heterogeneous as that in the original validation study, as a more heterogeneous sample could contribute to relatively higher coefficients (Layton, 1986).

The convenience sampling method and the limited geographic distribution of the study subjects (the study was conducted in only one city located in the southeast of Mainland China) may have weakened the generalizability of the study findings. Moreover, factor analysis was considered but finally abandoned because the value of the Kaiser-Meyer-Olkin measure of sample adequacy in our study was low. Additional studies would be useful to further assess factor analysis and other psychometric properties of the MAT, Chinese version, in a larger and more heterogeneous sample

with multiple study sites in different parts of China, and using stratified random sampling to enhance the generalizability of the study results.

Overall, the study provided evidence that the Chinese version of the MAT is a convenient, valid, and reliable scale for measuring nausea and vomiting symptoms in Chinese cancer patients receiving chemotherapy.

6.6 Summary of the chapter

This chapter presented the preparatory study in terms of the psychometric assessment of the MAT, Chinese version, in a group of Chinese patients with different cancer diagnoses. A total of 111 patients completed the study. High content validity was demonstrated, and contrasted groups analysis precisely discriminated different symptom experiences of nausea and vomiting between cancer patients with different ages and genders. Satisfactory concurrent validity of the MAT, Chinese version, was identified when tested against the INVR, and internal consistency and item-to-total correlations also proved to be adequate. The findings of the preparatory study supported the hypothesis that the MAT, Chinese version, can be used as a reliable and valid scale for CINV assessment in Chinese cancer patients. The MAT, Chinese version, was therefore utilized in the pilot RCT to assess acute and delayed nausea and vomiting in breast cancer patients undergoing chemotherapy. The findings of this doctoral research project, including the results from both the pilot RCT and the semi-structured interviews, will be presented in the next chapter.

CHAPTER SEVEN: RESULTS

7.1 Introduction

This chapter consists of four major sections, which will report the study findings from the pilot RCT and the semi-structured interviews, respectively. Section 7.1 (the current section) will offer a general introduction of this chapter. Section 7.2 will present the results of the pilot RCT in six parts. Part one (Section 7.2.1) will summarize the results of the subject recruitment and dropouts. Part two (Section 7.2.2) will report the participants' baseline characteristics, including both demographic data and clinical data. The results of homogeneity of the baseline data among the three study groups will also be reported in part two. The feasibility outcomes of the pilot RCT will be presented in part three (Section 7.2.3), including the feasibility of the study recruitment and follow-up process, the feasibility of the study questionnaires, and the acceptability of the study intervention. The results of the preliminary analysis of the pilot study clinical outcomes, including CINV and QoL, will be reported in part four (Section 7.2.4). Parametric and non-parametric statistical approaches were utilized to examine the among-group differences of the clinical outcomes at baseline, during intervention, and (or) post-intervention. The potential confounding effects of baseline CINV risk factors on the pilot study outcome analysis were investigated using the GEE model and the results will be shown in part five (Section 7.2.5). A brief summary of the study findings from the pilot RCT will be presented in part six (Section 7.2.6). Section 7.3 will report the results of the semi-structured interviews, which include the characteristics of the interviewees, the themes and sub-themes in terms of the study participants' experiences of participating in the pilot RCT and receiving the AT treatment, and a brief summary of the qualitative study findings. A summary of this chapter will be presented in section 7.4.

7.2 Results of the pilot randomized controlled trial

7.2.1 Subject recruitment and dropouts

Subject recruitment was conducted from 2015 to 2016, in a period of 15 months. During this period, 225 patients from three provincial hospitals in Fuzhou, Fujian, China, were screened for eligibility and 76 of them were excluded for the following reasons: the patients were not in the first cycle of chemotherapy (n=44); the breast cancer was at stage IV (metastasis) (n=18); the scheduled chemotherapy protocols were at low to moderate emetogenic risk (n=5); the patients were unable to communicate in Mandarin Chinese (n=3), had gastrointestinal disorders (n=3), or

had previous AT experience (n=1); and the patients had no chemotherapy scheduled (n=2). There were 149 patients who were identified as eligible for inclusion, but 35 of them refused to participate as they did not have any interest in this study. One hundred and fourteen patients provided written informed consent and participated in the pilot trial. After the completion of baseline assessment, the 114 participants were randomly assigned to the true AT group (n=38), the sham AT group (n=38), or the standard care group (n=38). All participants received allocated intervention based on their randomly assigned group, and four participants dropped out during the intervention or follow-up assessment periods, of which one participant from the true AT group failed to respond to the delayed CINV symptom assessment (but indicated her satisfaction scores regarding the AT treatment) via telephone and did not return to the study hospital for the following cycles of chemotherapy, and the other three participants (two from the true AT group and one from the standard care group) also never returned for further chemotherapy, which made it impossible to conduct the post-intervention (follow-up) assessment before the second chemotherapy cycle. A total of 110 participants completed the pilot RCT, and all the randomized participants (n=114) were included in the final data analysis based on the ITT principle (although for a few outcome variables, only per-protocol [PP] analysis was feasible). The procedure of the pilot RCT is summarized in **Figure 7.1**, a flow diagram following the CONSORT guidelines for reporting parallel group randomized trials (Schulz et al., 2010):

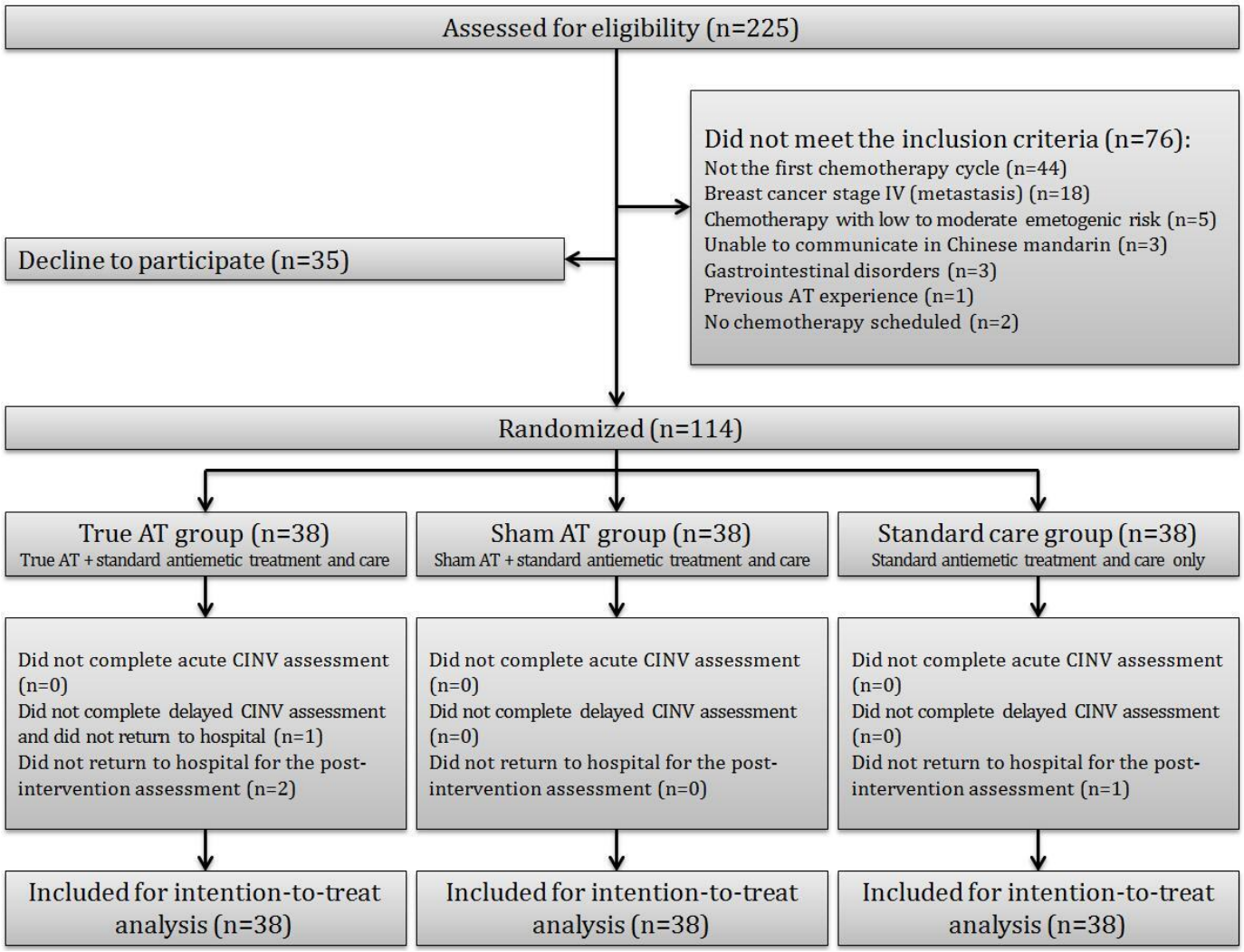


Figure 7.1 CONSORT diagram of pilot study procedure

(**Note:** AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting)

7.2.2 Baseline characteristics of the study participants

7.2.2.1 Participants' baseline demographic data

Table 7.1 presents the patients' baseline demographic characteristics. The mean age for all the participants was 47.5 years (SD=8.8). Around half of the participants (54/114, 47.4%) had primary school education, and only a small number (13/114, 11.4%) received higher education at the college or university level. The majority of the participants (113/114, 99.1%) were married, and only one (0.9%) was single. Forty-seven participants (41.2%) were housewives, while the others were mostly employed and only a few participants (9/114, 7.9%) were retired. More than half of the participants (70/114, 61.4%) did not have any religious beliefs and the rest were Buddhist (38/114, 33.3%) or Christian (6/114, 5.3%). The majority of the participants (106/114, 93%) had a monthly family income of less than 10,000 CNY. One hundred and five of the participants (92.1%) had medical insurance to cover their medical expenses for cancer treatment, of which eight participants (7.0%) had free government medical service, 43 participants (37.7%) were covered by social insurance, and 54 (47.4%) participants received new rural cooperative medical service.

Table 7.1 Baseline demographic characteristics of the participants (N=114)

Variables	True AT (n=38) Number (%)	Sham AT (n=38) Number (%)	Standard Care (n=38) Number (%)	Total (n=114) Number (%)	Statistics	
					Value	*p*
Age (Mean ± SD)	46.2±7.1	47.9±9.9	48.4±9.3	47.5±8.8	1.22[a]	0.54
Education background						
Primary school	18 (47.4%)	19 (50.0%)	17 (44.7%)	54 (47.4%)	7.56[b]	0.27
Secondary school	6 (15.8%)	10 (26.3%)	8 (21.1%)	24 (21.1%)		
High school/technical school	11 (28.9%)	7 (18.4%)	5 (13.2%)	23 (20.2%)		
College diploma/university degree	3 (7.9%)	2 (5.3%)	8 (21.1%)	13 (11.4%)		
Marital status						
Single	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1.84[b]	>0.99
Married	37 (97.4%)	38 (100%)	38 (100%)	113 (99.1%)		
Employment status						
Professional	8 (21.1%)	5 (13.2%)	6 (15.8%)	19 (16.7%)	4.99[b]	0.91
Manual work	8 (21.1%)	7 (18.4%)	7 (18.4%)	22 (19.3%)		
Housewife	17 (44.7%)	14 (36.8%)	16 (42.1%)	47 (41.2%)		
Admin/clerical	2 (5.3%)	4 (10.5%)	3 (7.9%)	9 (7.9%)		
Retired	1 (2.6%)	4 (10.5%)	4 (10.5%)	9 (7.9%)		
Other	2 (5.3%)	4 (10.5%)	2 (5.3%)	8 (7.0%)		
Religious background						
Buddhist	13 (34.2%)	14 (36.8%)	11 (28.9%)	38 (33.3%)	4.57[b]	0.32
Christian	4 (10.5%)	0 (0.0%)	2 (5.3%)	6 (5.3%)		
None	21 (55.3%)	24 (63.2%)	25 (65.8%)	70 (61.4%)		
Family monthly income						
<3000 CNY	6 (15.8%)	8 (21.1%)	10 (26.3%)	24 (21.1%)	8.09[b]	0.22
3000-6000 CNY	15 (39.5%)	22 (57.9%)	16 (42.1%)	53 (46.5%)		
6001-10000 CNY	13 (34.2%)	5 (13.2%)	11 (28.9%)	29 (25.4%)		
>10000 CNY	4 (10.5%)	3 (7.9%)	1 (2.6%)	8 (7.0%)		
Medical insurance						
Free government medical service	3 (7.9%)	1 (2.6%)	4 (10.5%)	8 (7.0%)	7.98[b]	0.23
Social insurance	12 (31.6%)	14 (36.8%)	17 (44.7%)	43 (37.7%)		
New rural cooperative medical service	22 (57.9%)	17 (44.7%)	15 (39.5%)	54 (47.4%)		
Self-financed	1 (2.6%)	6 (15.8%)	2 (5.3%)	9 (7.9%)		

Note: AT=auricular therapy; SD=standard deviation; CNY=Chinese Yuan; a=Kruskal-Wallis H test; b=Fisher's exact test

7.2.2.2 Participants' baseline clinical data

Table 7.2 lists the participants' clinical characteristics at baseline. More than half of the participants (65/114, 57.0%) were at stage II breast cancer, while stage III and stage I accounted for 29.8% (34/114) and 13.2% (15/114) of the participants, respectively. Most of the participants (81/114, 71.1%) had received modified radical mastectomy prior to chemotherapy, and the most commonly used chemotherapy protocols were the EC (epirubicin and cyclophosphamide) combination (63/114, 55.3%) and the AC (doxorubicin and cyclophosphamide) combination (41/114, 36.0%), with or without sequential adjuvant therapy using paclitaxel or docetaxel. 5-HT_3 antagonists (palonosetron, ondansetron, granisetron, or tropisetron), combined with (67/114, 58.8%) or without (46/114, 40.4%) dexamethasone, were the most frequently prescribed antiemetic medications for controlling nausea and vomiting during chemotherapy.

The participants' risk factors for nausea and vomiting were also measured at baseline, including younger age of less than 50 years old, history of morning sickness, history of motion sickness, and history of labyrinthitis. More than half of the participants (67/114, 58.8%) were at a younger age of less than 50 years old, and 63.2% (72/114) of the participants had a history of morning sickness during their early pregnancy. A history of motion sickness was identified in 41.2% (47/114) of the participants, and the majority of the participants (111/114, 97.4%) had not experienced labyrinthitis. Twenty-five participants (21.9%) had at least three risk factors for nausea and vomiting.

7.2.2.3 Homogeneity of baseline data among the three groups

Non-parametric statistical approaches, including the Kruskal-Wallis H test, the Chi-square test, and Fisher's exact test, were adopted to examine the homogeneity of the participants' baseline data among the three groups (details of the data analysis approaches can be found in Chapter 5, Section 5.5.9). All of the test results are shown in **Table 7.1** and **Table 7.2**. The Kruskal-Wallis H test indicated that there was no statistically significant difference in age among the three groups (p=0.54), and the Fisher's exact test showed that the participants' other demographic data were also comparable across groups, with the p value ranging from 0.22 to >0.99. For the participants' clinical data, there were no statistically significant differences in the proportions of different

stages of breast cancer, types of surgery, types of chemotherapy combinations, and types of antiemetic medication among the three groups (the Chi-square test or Fisher's exact test, *p* value=0.43 to >0.99). Moreover, there were no statistically significant differences in the proportions of CINV risk factors among groups (the Chi-square test or Fisher's exact test, *p* value=0.12 to >0.99). The participants' demographic and clinical characteristics were comparable across groups.

Table 7.2 Baseline clinical characteristics of the participants (N=114)

Variables	True AT (n=38) Number (%)	Sham AT (n=38) Number (%)	Standard Care (n=38) Number (%)	Total (n=114) Number (%)	Statistics	
					Value	*p*
Cancer stage						
Stage I	5 (13.2%)	5 (13.2%)	5 (13.2%)	15 (13.2%)	3.85[b]	0.43
Stage II	19 (50.0%)	26 (68.4%)	20 (52.6%)	65 (57.0%)		
Stage III	14 (36.8%)	7 (18.4%)	13 (34.2%)	34 (29.8%)		
Surgery						
Modified radical mastectomy	24 (63.2%)	30 (78.9%)	27 (71.1%)	81 (71.1%)	7.32[c]	0.50
Simple mastectomy	1 (2.6%)	2 (5.3%)	2 (5.3%)	5 (4.4%)		
Breast-conserving surgery	2 (5.3%)	0 (0.0%)	2 (5.3%)	4 (3.5%)		
Other	3 (7.9%)	1 (2.6%)	4 (10.5%)	8 (7.0%)		
NA	8 (21.1%)	5 (13.2%)	3 (7.9%)	16 (14.0%)		
Chemotherapy combination						
AC/AC-T combination	15 (39.5%)	14 (36.8%)	12 (31.6%)	41 (36.0%)	1.36[c]	0.99
EC/EC-T/EC-D combination	20 (52.6%)	21 (55.3%)	22 (57.9%)	63 (55.3%)		
TC combination	2 (5.3%)	2 (5.3%)	2 (5.3%)	6 (5.3%)		
Other[a]	1 (2.6%)	1 (2.6%)	2 (5.3%)	4 (3.5%)		
Antiemetic medication						
5-HT3 antagonists + dexamethasone	22 (57.9%)	23 (60.5%)	22 (57.9%)	67 (58.8%)	1.93[c]	>0.99
5-HT3 antagonists only	16 (42.1%)	15 (39.5%)	15 (39.5%)	46 (40.4%)		
Dexamethasone only	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.9%)		
Risk factor for CINV						
Aged less than 50 years old	25 (65.8%)	23 (60.5%)	19 (50.0%)	67 (58.8%)	2.03[b]	0.36
History of morning sickness	26 (68.4%)	27 (71.1%)	19 (50.0%)	72 (63.2%)	4.30[b]	0.12
History of motion sickness	18 (47.4%)	16 (42.1%)	13 (34.2%)	47 (41.2%)	1.38[b]	0.50
History of labyrinthitis	1 (2.6%)	1 (2.6%)	1 (2.6%)	3 (2.6%)	0.43[c]	>0.99
Number of risk factor for CINV						
3 risk factors or above	11 (28.9%)	7 (18.4%)	7 (18.4%)	25 (21.9%)	1.64[b]	0.44
Less than 3 risk factors	27 (71.1%)	31 (81.6%)	31 (81.6%)	89 (78.1%)		

Note: AT=auricular therapy; NA=not applicable; AC=doxorubicin + cyclophosphamide; T=paclitaxel; EC=epirubicin + cyclophosphamide; D=docetaxel; TC= cyclophosphamide + docetaxel; a=other less frequently used chemotherapy combinations with moderately-high to highly emetogenic potential, including pirarubicin plus cyclophosphamide combination and pirarubicin/epirubicin combined with other chemotherapeutic agents with low to moderate emetogenic risks; CINV=chemotherapy-induced nausea and vomiting; b=Chi-square test; c=Fisher's exact test.

7.2.3 Feasibility outcomes

7.2.3.1 Feasibility of subject recruitment and follow-up process

The whole subject recruitment process was completed during a 15-month period, with around eight participants recruited per month. The majority of the participants (91/114, 79.8%) were recruited from study site I, while study site II and site III contributed only 23 subjects. A summary of subject recruitment at different study sites is presented in **Table 7.3**. Fisher's exact test indicated no statistically significant differences in the proportions of group allocation among the different study sites (p=0.79). The eligibility rate for the screened patients during the subject recruitment process was 66.2% (149/225), and the recruitment rate for the eligible patients was 76.5% (114/149). The retention rate of the participants during the study period was very high, with 110 out of 114 participants completing the study (96.5%), and this indicated a minimal attrition rate, with only four out of 114 participants dropping out during the study intervention and follow-up period (3.5%). For the four participants who dropped out from the pilot trial, one from the true AT group failed to respond to the delayed CINV assessment (but indicated her satisfaction scores regarding the AT treatment) via telephone and did not return to the hospital for the following cycles of chemotherapy; therefore, the particular reason for discontinuing the study was unknown. For the other three participants who dropped out during the follow-up period (two from the true AT group and one from the standard care group), one apologized for not continuing participation as she had moved back to her hometown and continued her cancer treatment there, which was very far away from Fujian province, and the other two participants changed to local hospitals for further chemotherapy.

Table 7.3 Subject recruitment at different study sites

Study Sites		True AT (n=38)	Sham AT (n=38)	Standard Care (n=38)	Total (n=114)	Statistics[a]	
						Value	*p*
Site I	Number of participants	31	31	29	91	1.95	0.79
	Within group (%)	81.6%	81.6%	76.3%	79.8%		
	Within study site (%)	34.1%	34.1%	31.9%	100.0%		
Site II	Number of participants	3	5	4	12		
	Within group (%)	7.9%	13.2%	10.5%	10.5%		
	Within study site (%)	25.0%	41.7%	33.3%	100.0%		
Site III	Count (Number)	4	2	5	11		
	Within group (%)	10.5%	5.3%	13.2%	9.6%		
	Within study site (%)	36.4%	18.2%	45.5%	100.0%		

Note: AT=auricular therapy; a=Fisher's exact test

7.2.3.2 Feasibility of the study questionnaires

Proportions of missing values at both item-level and scale-level for each of the study questionnaires were used to estimate the participants' acceptability of the study questionnaires. There were no missing values for the INVR questionnaire at either baseline assessment (n=114) or post-intervention (follow-up) assessment (n=110). For the MAT assessment during the first chemotherapy cycle, the participants also responded to all the MAT items without any missing values. For the FACT-B, a number of missing values were identified (see **Table 7.4**). At baseline assessment, missing values were found in 11 of the 37 FACT-B questionnaire items, among which more than half of the participants (68/114, 59.6%) refused to answer question FACT-B-GS7 ("I am satisfied with my sex life"), and 20.2% (23/114) of the participants did not respond to question FACT-B-B4 ("I feel sexually attractive"). Seven participants (6.1%) declined to answer question FACT-B-B9 ("I am able to feel like a woman"). Missing values for other items were minor (0.9% to 3.5%). There were only 38 out of 114 (33.3%) participants who completed all the FACT-B questionnaire items at baseline assessment. Similar findings were reported for the FACT-B questionnaire at the post-intervention (follow-up) evaluation, where 63.6% (70/110) of the participants did not respond to FACT-B-GS7, 23.6% (26/110) did not answer FACT-B-B4, and 7.3% (8/110) failed to respond to FACT-B-B9. Moreover, there were only 38 out of 110 (34.5%) participants who completed all the FACT-B questionnaire items at post-intervention (follow-up) assessment (see **Table 7.4**).

Table 7.4 Missing values for the FACT-B items and total questionnaire[a]

FACT-B	Baseline (n=114)		Post-intervention Evaluation (n=110)[b]	
FACT-B Item-level (item code)	**No. of Participants Responding to the Item**	**Missing (%)**	**No. of Participants Responding to the Item**	**Missing (%)**
FACT-B-GP3	112	2 (1.8%)	109	1 (0.9%)
FACT-B-GP6	113	1 (0.9%)	110	0 (0.0%)
FACT-B-GP7	113	1 (0.9%)	110	0 (0.0%)
FACT-B-GS3	113	1 (0.9%)	109	1 (0.9%)
FACT-B-GS6	110	4 (3.5%)	104	6 (5.5%)
FACT-B-GS7	46	68 (59.6%)	40	70 (63.6%)
FACT-B-GE4	114	0 (0.0%)	109	1 (0.9%)
FACT-B-GE5	114	0 (0.0%)	109	1 (0.9%)
FACT-B-GF3	113	1 (0.9%)	109	1 (0.9%)
FACT-B-B2	113	1 (0.9%)	109	1 (0.9%)
FACT-B-B4	91	23 (20.2%)	84	26 (23.6%)
FACT-B-B5	112	2 (1.8%)	110	0 (0.0%)
FACT-B-B6	114	0 (0.0%)	109	1 (0.9%)
FACT-B-B9	107	7 (6.1%)	102	8 (7.3%)
FACT-B scale-level	**No. of subjects responding to all items**	**Missing (%)**	**No. of subjects responding to all items**	**Missing (%)**
FACT-B total scale	38	76 (66.7%)	38	72 (65.5%)

Note: FACT-B=Functional Assessment of Cancer Therapy-Breast; a=this table only presents items that have missing values at either baseline assessment or post-intervention assessment; b=four participants dropped out before post-intervention assessment of the FACT-B, and therefore the available sample size for the post-intervention assessment was 110

7.2.3.3 Acceptability of the study intervention

7.2.3.3.1 Total number of days of AT treatment

Table 7.5 shows the total number of days of AT treatment in both the true AT group and the sham AT group. The majority of the participants in both the true AT group (29/38, 76.3%) and the sham AT group (32/38, 84.2%) followed the AT treatment protocol to complete the five-day AT treatment. Fisher's exact test indicated that there were no statistically significant differences in the number of days of AT treatment between the true AT group and the sham AT group (p=0.67). It should be noted that one of the three true AT group participants who dropped out from the pilot RCT completed the five-day AT treatment and provided via telephone her five-day AT daily log recordings that she completed at home, while the other two participants completed only a two-day AT treatment and log recordings and a three-day AT treatment and log recordings, respectively.

Table 7.5 Total number of days of AT treatment in the true AT group and the sham AT group

Total Number of Days of AT Treatment	True AT (n=38)[a] Number (%)	Sham AT (n=38) Number (%)	Total (n=76) Number (%)	Statistics[b]	
				Value	*p*
5-day AT treatment **(standard)**	29 (76.3%)	32 (84.2%)	61 (80.3%)	2.07	0.67
4-day AT treatment	5 (13.2%)	5 (13.2%)	10 (13.2%)		
3-day AT treatment	3 (7.9%)	1 (2.6%)	4 (5.3%)		
2-day AT treatment	1 (2.6%)	0 (0.0%)	1 (1.3%)		

Note: AT=auricular therapy; a=Fisher's exact test; b=one of the three true AT group participants who dropped out of the pilot RCT completed the five-day AT treatment and provided via telephone her five-day AT daily log recordings that she completed at home, while the other two participants completed only a two-day AT treatment and log recordings and a three-day AT treatment and log recordings, respectively

7.2.3.3.2 Times and durations of ear acupressure in the true AT group

The AT treatment protocol used in the true AT group required that the auricular tapes be manually pressed at least three times per day, and each single acupoint should be pressed for around 20 to 30 seconds to achieve satisfactory therapeutic effects. Taking into account that there was a total of fourteen acupoints among both ears for acupressure, four to seven minutes should be a satisfactory duration for each total ear acupressure session. The participants in the true AT group recorded the times and durations of ear acupressure in a daily log, and the results are summarized in **Table 7.6**.

During the acute CINV phase (day 1 of the first chemotherapy cycle), most of the participants in the true AT group (32/38, 84.2%) followed the AT treatment protocol of pressing the auricular tapes at least three times per day, and the average duration of performing each acupressure session was found to be satisfactory (four minutes and above) in 71.0% (27/38) of the participants. Six participants (15.8%) performed ear acupressure only once or twice on day 1 of the first chemotherapy cycle, and the average duration of each acupressure session was less than two minutes for five participants (13.2%) and more than two but less than four minutes for six participants (15.8%).

During the delayed CINV phase (four days in total, from day 2 to day 5 of the first chemotherapy cycle, although a few participants failed to complete all of the four-day AT treatment), more than half of the participants (23/38, 60.5%) performed ear acupressure 12 times, and the average duration of each acupressure session was four minutes or more for 65.8% (25/38) of the participants. Five participants (13.2%) performed ear acupressure less than six times

during the delayed phase of CINV, while 10 participants (26.3%) performed ear acupressure six to 11 times during the same phase. The average duration of each acupressure session was less than two minutes for five participants (13.2%) and more than two but less than four minutes for eight participants (21.1%).

During the whole AT treatment period (five days in total, from day 1 to day 5 of the first chemotherapy cycle, although a few participants failed to complete all of the five-day AT treatment), 20 participants (52.6%) performed ear acupressure at least 15 times, while the rest performed ear acupressure only nine to 14 times (13/38, 34.2%) or less than nine times (5/38, 13.2%). An ear acupressure duration of no less than four minutes was found for more than half of the participants (24/38, 63.2%) across the five-day AT treatment, while it was less than two minutes for five participants (13.2%) and more than two but less than four minutes for nine participants (23.7%).

Table 7.6 Times and durations of ear acupressure in the true AT group

Times and Durations of Ear Acupressure	True AT (n=38)[a] Number (%)
Times of ear acupressure during acute CINV	
Less than 3 times	6 (15.8%)
3 times (standard)	30 (78.9%)
More than 3 times	2 (5.3%)
Average duration of each acupressure session during acute CINV	
Less than 2 minutes	5 (13.2%)
More than 2 but less than 4 minutes	6 (15.8%)
4-7 minutes (standard)	26 (68.4%)
More than 7 minutes	1 (2.6%)
Times of ear acupressure during delayed CINV (standard: 4-day)[b]	
Less than 6 times	5 (13.2%)
6-11 times	10 (26.3%)
12 times (standard)	15 (39.5%)
More than 12 times	8 (21.1%)
Average duration of each acupressure session during delayed CINV (standard: 4-day)[b]	
Less than 2 minutes	5 (13.2%)
More than 2 but less than 4 minutes	8 (21.1%)
4-7 minutes (standard)	24 (63.2%)
More than 7 minutes	1 (2.6%)
Total times of ear acupressure during the whole AT treatment (standard: 5-day)[b]	
Less than 9 times	5 (13.2%)
9-14 times	13 (34.2%)
15 times (standard)	12 (31.6%)
More than 15 times	8 (21.1%)
Average duration of each acupressure session during the whole AT treatment (standard: 5-day)[b]	
Less than 2 minutes	5 (13.2%)
More than 2 but less than 4 minutes	9 (23.7%)
4-7 minutes (standard)	23 (60.5%)
More than 7 minutes	1 (2.6%)

Note: AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting; a=one of the three true AT group participants who dropped out of the pilot RCT completed the five-day AT treatment and provided via telephone her five-day AT daily log recordings that she completed at home, while the other two participants completed only a two-day AT treatment and log recordings and a three-day AT treatment and log recordings, respectively; b=it should be noted that the standard AT treatment days were five days in total in this pilot study, with a one-day acute CINV phase and a four-day delayed CINV phase. However, a few participants failed to complete the whole five-day AT treatment, particularly for the AT treatment during the delayed CINV phase, and therefore for those participants who failed to complete the five-day AT treatment, the computation of their times and average duration of each ear acupressure session was based on their actual number of days (e.g., two days, three days, or four days) of AT treatment.

7.2.3.3.3 Relationship between AT treatment effects and AT-related feasibility outcomes

Spearman's correlation coefficients (r_s) were used to investigate the correlations of the number of days of AT treatment, times of ear acupressure, and average duration of each acupressure session with the AT treatment effects for CINV (based on the MAT scoring system). The results are presented in **Table 7.7**. Statistically insignificant correlations were identified between the AT-related feasibility outcomes and the majority of the MAT outcomes (p>0.05). Weakly positive correlations were shown between the MAT scores and the average duration of each ear acupressure session during the acute CINV, the delayed CINV, and the whole AT treatment period, with a few outcomes in the acute CINV phase reaching borderline statistical significance.

Table 7.7 Correlations between AT-related feasibility outcomes and AT treatment effects on CINV

AT-related Feasibility Outcomes	Group	MAT Total and Domain Scores								
		Overall Total	Total Nausea	Total Vomiting	Acute CINV	Acute Nausea	Acute Vomiting	Delayed CINV	Delayed Nausea	Delayed Vomiting
Number of days of AT	**True AT**	-0.012 (*p*=0.94)	0.032 (*p*=0.85)	-0.158 (*p*=0.35)	-0.077 (*p*=0.65)	-0.030 (*p*=0.86)	-0.101 (*p*=0.55)	0.115 (*p*=0.50)	0.090 (*p*=0.60)	-0.012 (*p*=0.94)
Number of days of AT	**Sham AT**	-0.217 (*p*=0.19)	-0.145 (*p*=0.39)	-0.305 (*p*=0.06)	-0.151 (*p*=0.37)	-0.050 (*p*=0.77)	-0.243 (*p*=0.14)	-0.109 (*p*=0.51)	-0.142 (*p*=0.40)	-0.101 (*p*=0.55)
Total times of ear acupressure during acute CINV period	**True AT**	-0.075 (*p*=0.66)	-0.076 (*p*=0.66)	-0.034 (*p*=0.84)	-0.106 (*p*=0.53)	-0.013 (*p*=0.94)	-0.212 (*p*=0.20)	-0.002 (*p*=0.99)	-0.087 (*p*=0.61)	0.156 (*p*=0.36)
Total times of ear acupressure during delayed CINV period	**True AT**	0.076 (*p*=0.66)	0.152 (*p*=0.37)	-0.052 (*p*=0.76)	-0.104 (*p*=0.53)	0.066 (*p*=0.69)	-0.369 (*p*=0.02)	0.267 (*p*=0.11)	0.268 (*p*=0.11)	0.216 (*p*=0.20)
Total times of ear acupressure during the whole AT treatment period	**True AT**	0.078 (*p*=0.65)	0.140 (*p*=0.41)	-0.021 (*p*=0.90)	-0.098 (*p*=0.56)	0.073 (*p*=0.66)	-0.358 (*p*=0.03)	0.266 (*p*=0.11)	0.242 (*p*=0.15)	0.257 (*p*=0.13)
Average duration of each acupressure session during acute CINV	**True AT**	0.281 (*p*=0.09)	0.220 (*p*=0.19)	0.312 (*p*=0.06)	0.298 (*p*=0.07)	0.315 (*p*=0.05)	0.122 (*p*=0.47)	0.152 (*p*=0.37)	0.030 (*p*=0.86)	0.350 (*p*=0.03)
Average duration of each acupressure session during delayed CINV	**True AT**	0.232 (*p*=0.17)	0.186 (*p*=0.27)	0.264 (*p*=0.12)	0.228 (*p*=0.17)	0.261 (*p*=0.11)	0.060 (*p*=0.72)	0.123 (*p*=0.47)	0.027 (*p*=0.88)	0.321 (*p*=0.05)
Average duration of each acupressure session during the whole AT treatment period	**True AT**	0.261 (*p*=0.12)	0.211 (*p*=0.21)	0.285 (*p*=0.09)	0.249 (*p*=0.13)	0.274 (*p*=0.10)	0.086 (*p*=0.61)	0.160 (*p*=0.34)	0.064 (*p*=0.71)	0.333 (*p*=0.04)

Note: AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting; MAT=MASCC Antiemesis Tool

7.2.3.3.4 Safety of the study intervention

Potential adverse events associated with AT were recorded by the participants from both the true AT group and the sham AT group in their daily logs during their AT treatment period. The causality between the reported adverse events and AT was judged by an experienced acupuncture practitioner based on the *WHO-UMC System for Standardized Case Causality Assessment*. **Table 7.8** summarizes the reported AT-related adverse events. A total of 11 participants reported minor to moderate adverse effects associated with AT, and the causalities between all the reported adverse events and the AT treatment were "probable/likely." In the true AT group, nine participants reported adverse reactions associated with AT, of which five participants complained of minor ear pain, two indicated minor discomfort at the AT sites, one reported moderate pain when adding pressure to the taped seeds, and one participant experienced minor to moderate pain when performing the ear acupressure during the AT-treatment period. In the sham AT group, two participants reported minor itching of the ear skin around the AT sites, and no other AT-related adverse events were identified. No serious side effects associated with AT occurred in this pilot RCT. The participants generally viewed that the adverse events were tolerable and transient. The reported side effects gradually disappeared after withdrawing the auricular tapes at the end of the AT treatment period, and no additional treatment was needed to deal with the reported adverse events.

Table 7.8 Summary of AT-related adverse events in the true and sham AT groups

Type of AT-related AE	**True AT (n=38)[a]** Number (%)	**Sham AT (n=38)** Number (%)	**Total (n=76)** Number (%)	**Causality between AT and AE[b]**
Minor itching	0 (0.0%)	2 (5.3%)	2 (2.6%)	Probable/likely
Minor discomfort	2 (5.3%)	0 (0.0%)	2 (2.6%)	Probable/likely
Minor pain	5 (13.2%)	0 (0.0%)	5 (6.6%)	Probable/likely
Moderate pain	1 (2.6%)	0 (0.0%)	1 (1.3%)	Probable/likely
Minor to moderate pain	1 (2.6%)	0 (0.0%)	1 (1.3%)	Probable/likely

Note: AT=auricular therapy; AE=adverse events; a=one of the three true AT group participants who dropped out of the pilot RCT completed the five-day AT treatment and provided via telephone her five-day AT daily log recordings that she completed at home, while the other two participants completed only a two-day AT treatment and log recordings and a three-day AT treatment and log recordings, respectively; b=causality between AT and the reported AE was determined using the *WHO-UMC System for Standardized Case Causality Assessment*

7.2.3.3.5 Participants' satisfaction with the study intervention

The participants in the true AT group and the sham AT group were asked about their satisfaction with the AT treatment and 74 of them responded to the questions (response rate: 74/76, 97.4%), of which the three participants in the true AT group who dropped out of the pilot study were successfully reached by the research assistants via telephone to complete the satisfaction scores, while two participants in the true AT group who completed the pilot RCT failed to indicate their satisfaction with the AT treatment. The participants' satisfaction scores regarding the AT treatment are presented in **Table 7.9**, and they were generally satisfied with the AT intervention, with the mean score of "satisfaction with AT treatment" being 6.8 (SD=1.7) and 7.2 (SD=1.4) in the true AT group and the sham AT group, respectively. For the score of "consideration of further AT treatment," the mean was 6.6 (SD=1.7) in the true AT group and 6.9 (SD=1.7) in the sham AT group. For the item "willingness to recommend AT to others," the mean was 6.2 (SD=1.7) in the true AT group and 6.4 (SD=2.0) in the sham AT group. The Independent t-test and the Mann-Whitney U test did not reveal any statistically significant differences in the satisfaction scores between the two groups (*p* value=0.19 to 0.41).

Table 7.9 Participants' satisfaction scores for auricular therapy

Participants' Satisfaction Scores	True AT (n=36)	Sham AT (n=38)	Statistics	
	Mean/SD [Range]	Mean/SD [Range]	Value	*p*
Satisfaction with AT treatment (0-10)	6.8/1.7 [3-10]	7.2/1.4 [4-10]	-1.33[a]	0.19
Consideration of further AT treatment (0-10)	6.6/1.7 [3-10]	6.9/1.7 [1-10]	-0.82[b]	0.41
Willingness to recommend AT to others (0-10)	6.2/1.7 [2-10]	6.4/2.0 [1-10]	-0.90[b]	0.37

Note: AT=auricular therapy; SD=standard deviation; a=Independent t-test; b=Mann-Whitney U test

7.2.4 Preliminary analysis of the hypothesis testing for the pilot study clinical outcomes

The null hypotheses of the research questions regarding the effects of AT for acute, delayed, and anticipatory CINV and QoL were preliminarily analyzed in the pilot RCT. The statistic and related *p* value of the statistical test for each variable were presented with an estimated effect size. The results of the post-hoc analysis were also presented for outcome variables showing statistically significant differences among the three study groups. The choice of parametric or non-parametric approaches for the analysis of continuous variables was determined by the test of normality (as examined by the Shapiro-Wilk test), and parametric approaches were utilised

when the data in each group were normally distributed; otherwise, non-parametric methods were used instead. Given that the current trial is a pilot study design in nature, the hypothesis testing results of the clinical outcomes should be treated as preliminary findings only (details of the data analysis approaches can be found in Chapter 5, Section 5.5.9).

7.2.4.1 Acute and delayed nausea and vomiting as measured by the MAT

7.2.4.1.1 Complete response of CINV symptoms

The complete response (CR) of CINV symptoms was evaluated by the MAT. The CR rates of overall CINV, acute CINV, delayed CINV, overall nausea, and overall vomiting were computed separately (see **Figure 7.2**) and the results of the among-group comparisons are presented in **Table 7.10**. The participants in the true AT group and the sham AT group had higher CR rates for all the CINV symptoms compared with the standard care group, while the CR rates between the true AT group and the sham AT group were generally similar, with the CR rates ranging from 29.7% to 64.9% in the true AT group, 28.9% to 63.2% in the sham AT group, and 13.2 % to 44.7% in the standard care group.

The Chi-square test indicated a statistically significant difference in the CR of acute CINV among the three study groups, with a medium effect size [χ^2 (2)=7.07, p=0.03, Cramer's V=0.25], and the further post-hoc comparisons using partitioning Chi-square statistics between two study groups revealed that there was a statistically significant difference in the CR of acute CINV between the true AT group and the standard care group [52.6% versus 23.7%, χ^2 (1)=6.75, p=0.01], no statistical difference was identified between the true AT group and the sham AT group [52.6% versus 44.7%, χ^2 (1)=0.47, p=0.49], and between the sham AT group and the standard care group [44.7% versus 23.7%, χ^2 (1)=3.74, p=0.05]. For other variables, no statistically significant differences were found among the three groups and the effect sizes were relatively small (p value=0.15 to 0.68, Cramer's V=0.08 to 0.19).

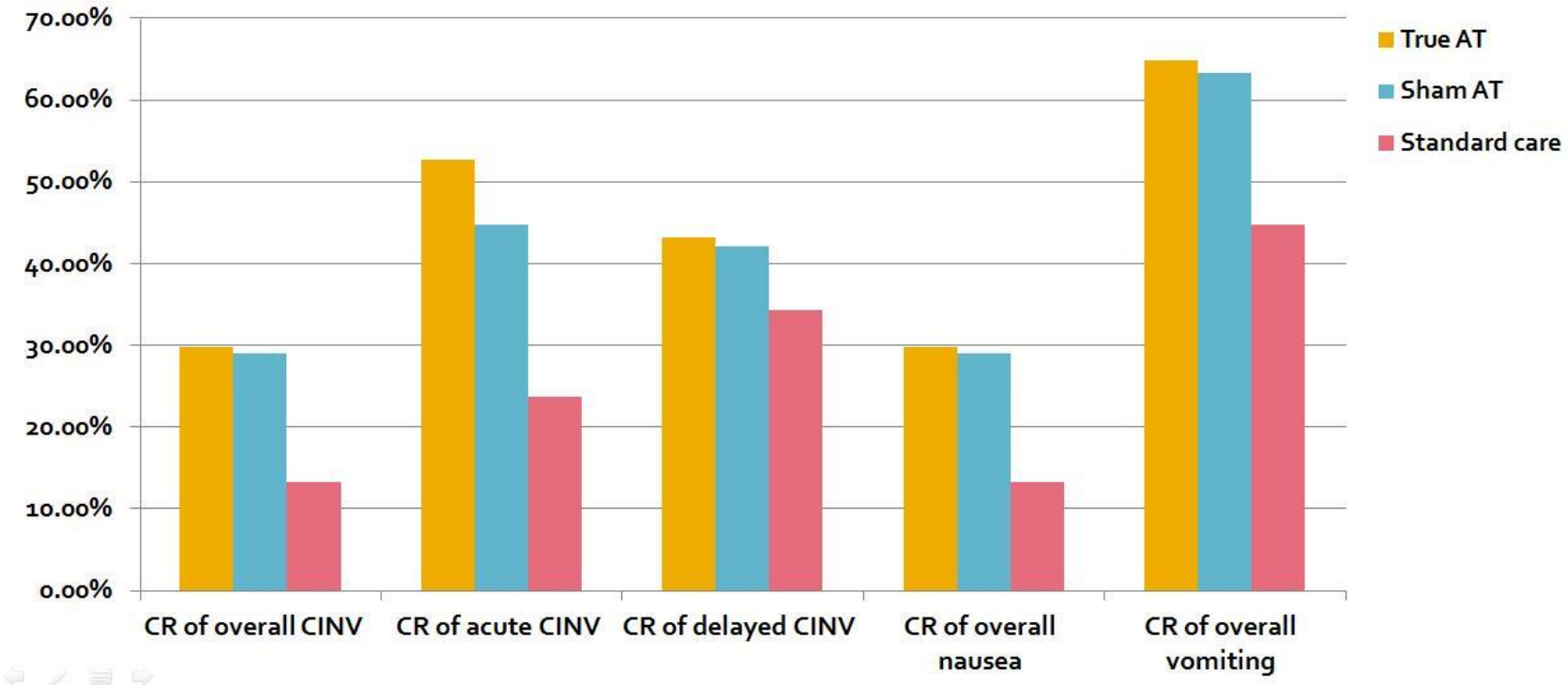


Figure 7.2 Complete response of CINV symptoms
(**Note:** CR=complete response; AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting)

Table 7.10 Differences in the complete response of CINV symptoms among the study groups

MAT Outcomes[a]	True AT		Sham AT		Standard Care		Chi-square Test		Effect Size	Post-hoc Analysis[c] (adjusted *p* value=0.0125)					
										True vs. Sham		True vs. SC		Sham vs. SC	
	n[b]	No. of CR (%)	n	No. of CR (%)	n	No. of CR (%)	Value	*p*	Cramer's V	Value	*p*	Value	*p*	Value	*p*
CR of overall CINV	37	11 (29.7%)	38	11 (28.9%)	38	5 (13.2%)	3.64	0.16	0.18	NA	NA	NA	NA	NA	NA
CR of acute CINV	38	20 (52.6%)	38	17 (44.7%)	38	9 (23.7%)	7.07	**0.03**	0.25	0.47	0.49	6.75	**0.01**	3.74	0.05
CR of delayed CINV	37	16 (43.2%)	38	16 (42.1%)	38	13 (34.2%)	0.76	0.68	0.08	NA	NA	NA	NA	NA	NA
CR of overall nausea	37	11 (29.7%)	38	11 (28.9%)	38	5 (13.2%)	3.64	0.16	0.18	NA	NA	NA	NA	NA	NA
CR of overall vomiting	37	24 (64.9%)	38	24 (63.2%)	38	17 (44.7%)	3.85	0.15	0.19	NA	NA	NA	NA	NA	NA

Note: CINV=chemotherapy-induced nausea and vomiting; MAT=MASCC Antiemesis Tool; AT=auricular therapy; SC=standard care; CR=complete response; NA=not applicable; a=CR of overall CINV: no nausea and vomiting from day 1 to day 5 of the first chemotherapy cycle; CR of acute CINV: no nausea and vomiting during day 1 of the first chemotherapy cycle; CR of delayed CINV: no nausea and vomiting from day 2 to day 5 of the first chemotherapy cycle; CR of overall nausea: no nausea from day 1 to day 5 of the chemotherapy cycle; CR of overall vomiting: no vomiting from day 1 to day 5 of the chemotherapy cycle; b=one participant from the true AT group dropped out during the delayed CINV assessment. ITT analysis using the acute phase data as the delayed outcomes is not appropriate here because the delayed CINV symptom is different from the acute CINV symptom in nature. No ITT approach was utilized in this analysis; therefore, the available sample size for calculating the CR of the overall CINV, delayed CINV, overall nausea, and overall vomiting in the true AT group was 37; c=partitioning Chi-square statistics were applied for the post-hoc analysis. For the post-hoc analysis following the Chi-square test, the *p* value should be adjusted and the formula a'=a/[k(k-1)/2+1] was used accordingly, where a=0.05 and k=3 in this analysis.

7.2.4.1.2 Occurrence of acute nausea and occurrence of acute vomiting

The occurrence of acute nausea and the occurrence of acute vomiting were measured by each of two MAT items, respectively (see **Figure 7.3**). The Chi-square test was utilized for the among-group comparison and the results are presented in **Table 7.11**. During day 1 of the first chemotherapy cycle (acute CINV phase), 17 participants (44.7%) in the true AT group reported acute nausea, while 21 (55.3%) and 28 (73.7%) participants in the sham AT group and standard care group, respectively, experienced acute nausea. The incidence of acute nausea in the true AT group was relatively lower than in the sham AT group, and both were lower than in the standard care group. The Chi-square test indicated statistically significant differences among the three groups, with a medium effect size [χ^2 (2)=6.69, p=0.04, Cramer's V=0.24]. However, the following post-hoc comparisons (partitioning Chi-square statistics) between two groups showed only a statistically significant difference between the true AT group and the standard care group [44.7% versus 73.7%, χ^2 (1)=6.59, p=0.01], while no statistical differences were identified between the true AT group and the sham AT group [44.7% versus 55.3%, χ^2 (1)=0.84, p=0.36], and between the sham AT group and the standard care group [55.3% versus 73.7%, χ^2 (1)=2.82, p=0.09]. For the occurrence of acute vomiting, the true AT group also showed a lower incidence (15.8%) compared with the sham AT group (26.3%). Both the true AT group and the sham AT group reported less acute vomiting than the standard care group (39.5%). A borderline significant difference was found among the three study groups via the Chi-square test, and the effect size was medium [χ^2 (2)=5.41, p=0.07, Cramer's V=0.22].

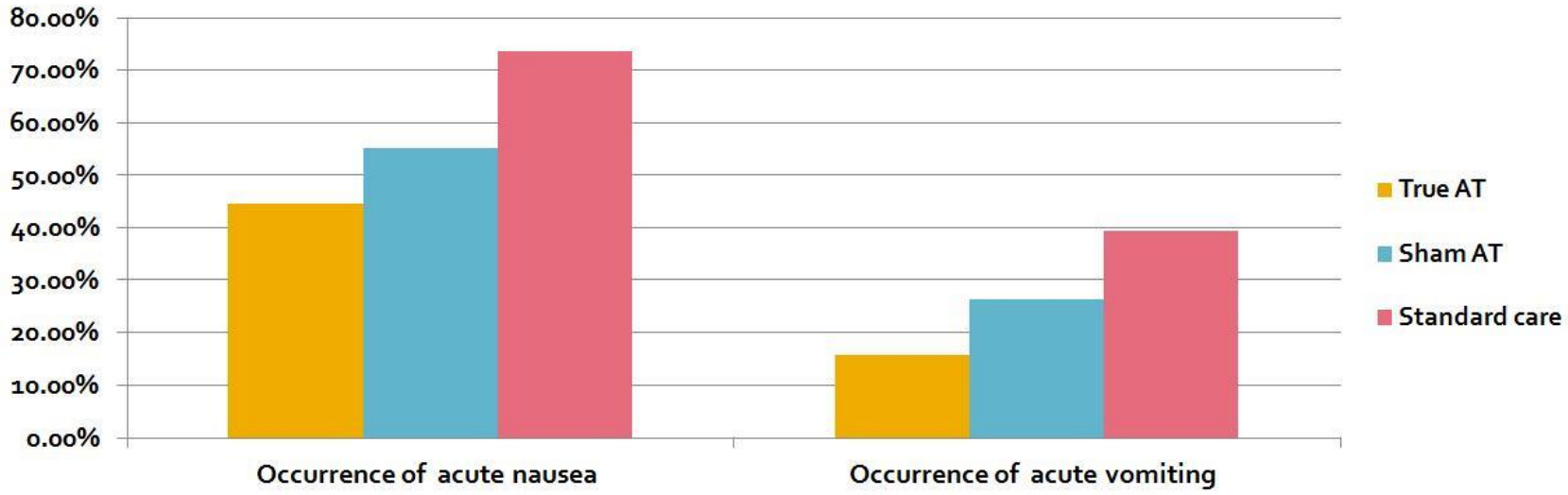


Figure 7.3 Occurrence of acute nausea and acute vomiting
(**Note:** AT=auricular therapy)

Table 7.11 Differences in the occurrence of acute nausea and vomiting among the study groups

MAT Outcomes	True AT		Sham AT		Standard Care		Chi-square Test		Effect Size	Post-hoc analysis[a] (adjusted *p* value=0.0125)					
										True vs. Sham		True vs. SC		Sham vs. SC	
	n	No. (%)	n	No. (%)	n	No. (%)	Value	*p*	Cramer's V	Value	*p*	Value	*p*	Value	*p*
Occurrence of acute nausea	38	17 (44.7%)	38	21 (55.3%)	38	28 (73.7%)	6.69	**0.04**	0.24	0.84	0.36	6.59	**0.01**	2.82	0.09
Occurrence of acute vomiting	38	6 (15.8%)	38	10 (26.3%)	38	15 (39.5%)	5.41	0.07	0.22	NA	NA	NA	NA	NA	NA

Note: MAT=MASCC Antiemesis Tool; AT=auricular therapy; SC=standard care; a=partitioning Chi-square statistics were applied for the post-hoc analysis; for the post-hoc analysis following the Chi-square test, the *p*-value should be adjusted and the formula a'=a/[k(k-1)/2+1] was used accordingly, where a=0.05 and k=3 in this analysis; NA=not applicable

7.2.4.1.3 Severity of acute nausea and frequency of acute vomiting

Two MAT single items were also used to evaluate the severity of acute nausea and the frequency of acute vomiting (see **Figure 7.4**), and the results of the among-group comparisons and the post-hoc tests are shown in **Table 7.12** and **Table 7.13**, respectively. It is worth mentioning that a higher score indicates a more severe acute nausea symptom or more frequent acute vomiting. The mean score for the severity of acute nausea in the true AT group was 1.5 (95%CI=0.9 to 2.1), which was much lower than that in the sham AT group (mean=2.3, 95%CI=1.6 to 3.1) and the standard care group (mean=3.9, 95%CI=2.9 to 5.0). The Kruskal-Wallis H test indicated that there was a statistically significant difference in the severity of acute nausea among the three study groups, and the effect size was near large [χ^2 (2)=14.38, p=0.001, η^2=0.13]. Further post-hoc comparisons using the Dunn-Bonferroni test revealed a statistically significant difference between the true AT group and the standard care group (adjusted p=0.001); no difference was found for the comparisons of the true AT group versus the sham AT group (adjusted p=0.43); and a borderline significant difference was found between the sham AT group and the standard care group (adjusted p=0.07). The frequency of acute vomiting was also found to be less in the true AT group (mean=0.4, 95%CI=0.06 to 0.8) than in the sham AT group (mean=0.8, 95%CI=0.2 to 1.3), and both the true and sham AT groups reported less frequency of acute vomiting compared with the standard care group (mean=1.2, 95%CI=0.6 to 1.7). The Kruskal-Wallis H test showed a borderline significant difference among the three groups, and the effect size was near medium [χ^2 (2)=5.44, p=0.07, η^2=0.05].

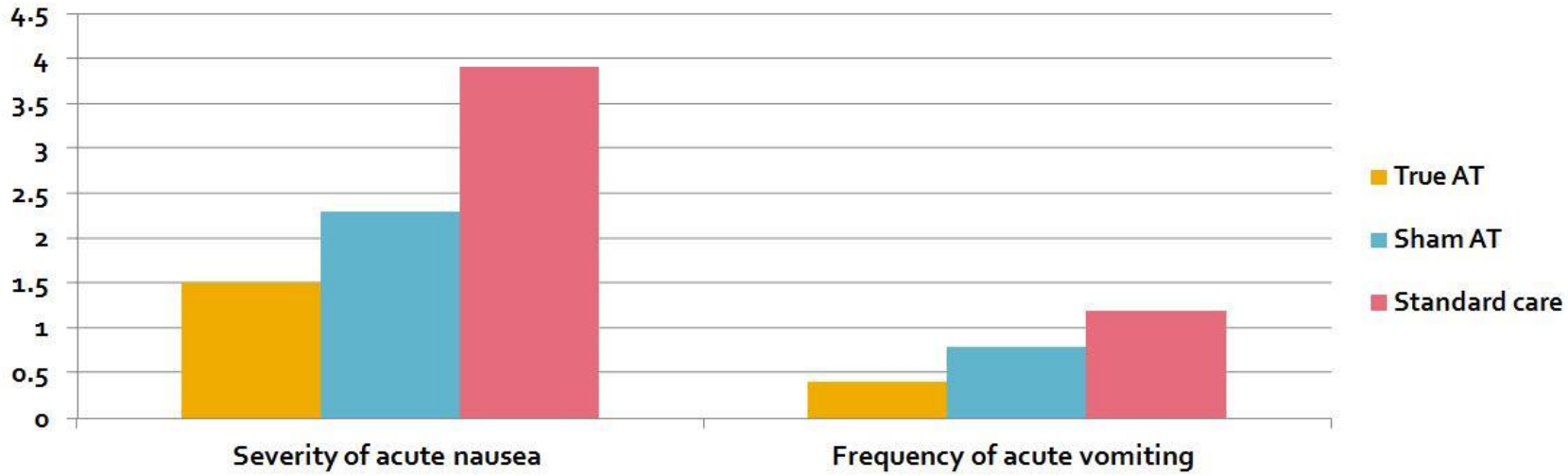


Figure 7.4 Severity of acute nausea and frequency of acute vomiting
(**Note:** AT=auricular therapy)

Table 7.12 Differences in the severity of acute nausea and frequency of acute vomiting among the study groups

MAT Outcomes	True AT		Sham AT		Standard Care		Kruskal-Wallis H Test		Effect Size
	n	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	Value	*p*	η^2
Severity of acute nausea	38	1.5/1.9/0.3/0.0 [0.9-2.1]	38	2.3/2.4/0.4/2.5 [1.6-3.1]	38	3.9/3.1/0.5/4.0 [2.9-5.0]	14.38	**0.001**	0.13
Frequency of acute vomiting	38	0.4/1.1/0.2/0.0 [0.06-0.8]	38	0.8/1.6/0.3/0.0 [0.2-1.3]	38	1.2/1.7/0.3/0.0 [0.6-1.7]	5.44	0.07	0.05

Note: MAT=MASCC Antiemesis Tool; AT=auricular therapy; SD=standard deviation; SE=standard error; CI=confidence interval

Table 7.13 Post-hoc analysis (Dunn-Bonferroni test) for the severity of acute nausea

MAT Outcome	Post-hoc Analysis (Dunn-Bonferroni Test)					
	True AT vs. Sham AT		True AT vs. Standard Care		Sham AT vs. Standard Care	
	Statistic	Adjusted *p* value	Statistic	Adjusted *p* value	Statistic	Adjusted *p* value
Severity of acute nausea	-10.671	0.43	-27.342	**0.001**	-16.671	0.07

Note: MAT=MASCC Antiemesis Tool; AT=auricular therapy

7.2.4.1.4 Occurrence of delayed nausea and occurrence of delayed vomiting

Two MAT items were utilized to assess the occurrence of delayed nausea and the occurrence of delayed vomiting, respectively (see **Figure 7.5**), and the results of the Chi-square test for the among-group differences are shown in **Table 7.14**. The incidence of delayed nausea in the true AT group (20/37, 54.1%) was somewhat lower than in the sham AT group (22/38, 57.9%), and both groups reported a relatively lower incidence of delayed nausea than the standard care group (25/38, 65.8%). There was no statistically significant difference found among the three groups via the Chi-square test, and the effect size was relatively small [χ^2 (2)=1.12, p=0.57, Cramer's V=0.10]. A similar condition was also identified for the occurrence of delayed vomiting, where both the true AT group (10/37, 27.0%) and the sham AT group (10/38, 26.3%) showed a lower incidence of delayed vomiting than the standard care group (16/38, 42.1%). No statistically significant differences were revealed among the three study groups, and the effect size was near medium [χ^2 (2)=2.77, p=0.25, Cramer's V=0.16].

7.2.4.1.5 Severity of delayed nausea and frequency of delayed vomiting

The severity of delayed nausea was measured by one single MAT item (a higher score means a worse condition), and the severity score of delayed nausea in the true AT group (mean=1.7, 95%CI=1.0 to 2.4) was lower than in the sham AT group (mean=2.2, 95%CI=1.4 to 3.0) (see **Figure 7.6**). Both the true AT group and the sham AT group reported lower severity scores of delayed nausea than the standard care group (mean=3.1, 95%CI=2.1 to 4.1). However, the Kruskal-Wallis H test revealed no statistically significant differences among the three groups, and the effect size was near medium [χ^2 (2)=4.23, p=0.12, η^2=0.04]. Similarly, one single MAT item was used to evaluate the frequency of delayed vomiting (a higher score indicates a worse outcome), and either the true AT group (mean=0.7, 95%CI=0.3 to 1.2) or the sham AT group (mean=1.0, 95%CI=0.3 to 1.7) showed a relatively lower frequency of delayed vomiting than the standard care group (mean=1.8, 95%CI=0.9 to 2.7) (see **Figure 7.6**), but the Kruskal-Wallis H test revealed no statistically significant differences among the three groups and the effect size was found to be small [χ^2 (2)=3.39, p=0.18, η^2=0.03]. The results of the Kruskal-Wallis H tests for the among-group differences in the severity of delayed nausea and frequency of delayed vomiting are presented in **Table 7.15**.

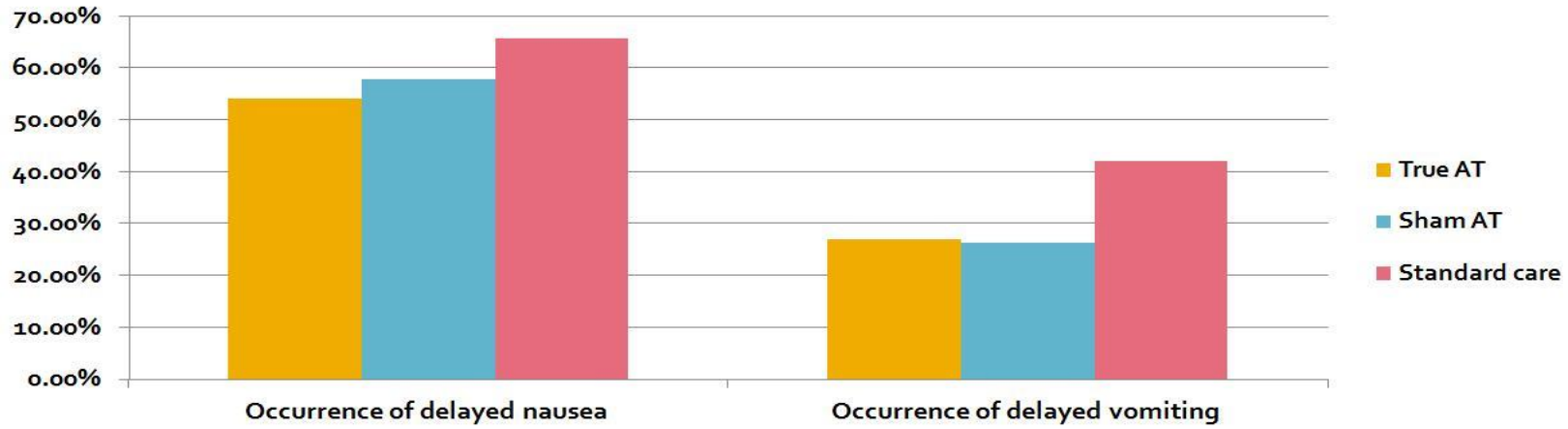


Figure 7.5 Occurrence of delayed nausea and vomiting
(**Note:** AT=auricular therapy)

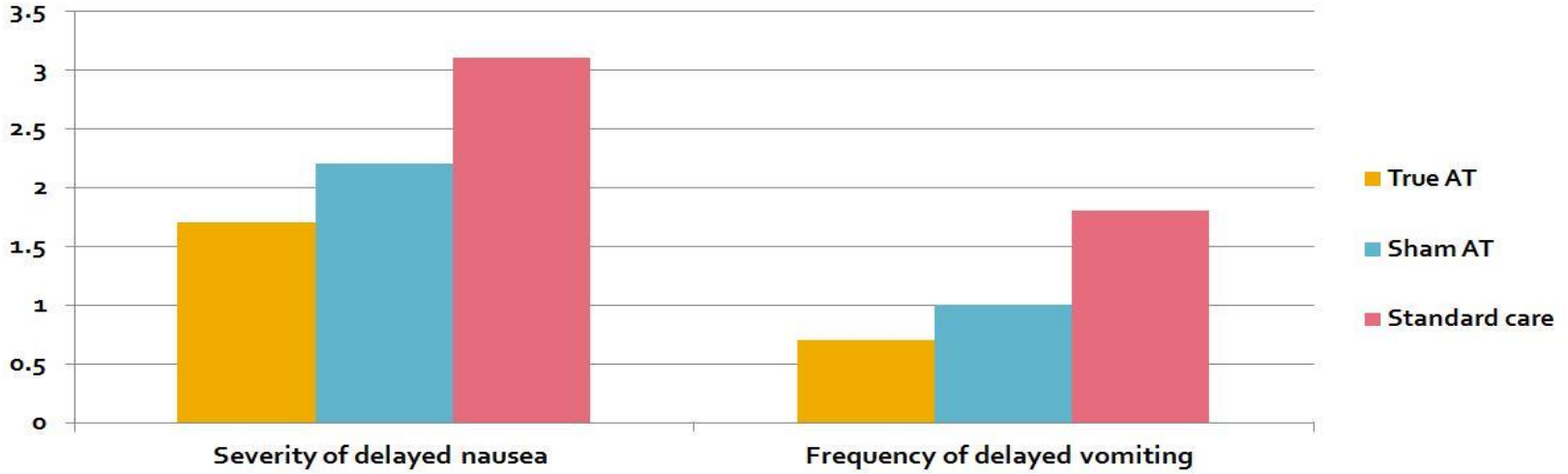


Figure 7.6 Severity of delayed nausea and frequency of delayed vomiting
(**Note:** AT=auricular therapy)

Table 7.14 Differences in the occurrence of delayed nausea and vomiting among the study groups

MAT Outcomes	True AT		Sham AT		Standard Care		Chi-square Test		Effect Size
	n[a]	Number (%)	n	Number (%)	n	Number (%)	Value	*p*	Cramer's V
Occurrence of delayed nausea	37	20 (54.1%)	38	22 (57.9%)	38	25 (65.8%)	1.12	0.57	0.10
Occurrence of delayed vomiting	37	10 (27.0%)	38	10 (26.3%)	38	16 (42.1%)	2.77	0.25	0.16

Note: MAT=MASCC Antiemesis Tool; AT=auricular therapy; a=one participant from the true AT group dropped out during the delayed CINV assessment. ITT analysis using the acute phase data as the delayed outcomes is not appropriate here because the delayed CINV symptom is different from the acute CINV symptom in nature. No ITT approach was utilized in this analysis; therefore, the available sample size for calculating the occurrence of delayed nausea and the occurrence of delayed vomiting in the true AT group was 37.

Table 7.15 Differences in the severity of delayed nausea and frequency of delayed vomiting among the study groups

MAT Outcomes	True AT		Sham AT		Standard Care		Kruskal-Wallis H Test		Effect Size
	n[a]	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	Value	*p*	η^2
Severity of delayed nausea	37	1.7/2.1/0.3/1.0 [1.0-2.4]	38	2.2/2.4/0.4/2.0 [1.4-3.0]	38	3.1/3.0/0.5/2.5 [2.1-4.1]	4.23	0.12	0.04
Frequency of delayed vomiting	37	0.7/1.4/0.2/0.0 [0.3-1.2]	38	1.0/2.1/0.3/0.0 [0.3-1.7]	38	1.8/2.8/0.4/0.0 [0.9-2.7]	3.39	0.18	0.03

Note: MAT=MASCC Antiemesis Tool; AT=auricular therapy; SD=standard deviation; SE=standard error; CI=confidence interval; a=one participant from the true AT group dropped out during the delayed CINV assessment. ITT analysis using the acute phase data as the delayed outcomes is not appropriate here because the delayed CINV symptom is different from acute CINV symptom in nature. No ITT approach was utilized in this analysis; therefore, the available sample size for computing the severity of delayed nausea and the frequency of delayed vomiting in the true AT group was 37.

7.2.4.1.6 MAT total and domain scores based on the MAT scoring system

The MAT scoring system was utilized to compute the MAT total and domain scores, including MAT overall total, MAT total nausea, MAT total vomiting, MAT acute CINV, MAT acute nausea, MAT acute vomiting, MAT delayed CINV, MAT delayed nausea, and MAT delayed vomiting scores (see **Figure 7.7**). A higher MAT total or domain score indicates a more severe nausea and/or vomiting symptom. Since all the MAT total and domain scores failed to meet the assumption of normal distribution (as examined by the Shapiro-Wilk test, all at $p<0.05$), the Kruskal-Wallis H test was adopted to examine the differences in the MAT total and domain scores among the three study groups, and the Dunn-Bonferroni test was used as the post-hoc analysis for comparisons showing statistical significance in the Kruskal-Wallis H test. The results of the among-group comparisons for the MAT total and domain scores (mean, SD, SE, median, and 95%CI) and the following post-hoc analyses are presented in **Table 7.16** and **Table 7.17**, respectively.

The MAT total and domain scores in the true AT group were all lower (indicating less nausea and vomiting symptoms) than those in the sham AT group, and the scores in the sham AT group were also lower than those in the standard care group. The Kruskal-Wallis H test indicated statistically significant differences in the MAT overall total [χ^2 (2)=11.09, p=0.004, η^2=0.10], MAT total nausea [χ^2 (2)=11.86, p=0.003, η^2=0.11], MAT acute CINV [χ^2 (2)=12.28, p=0.002, η^2=0.11], and MAT acute nausea [χ^2 (2)=14.38, p=0.001, η^2=0.13] scores among the three groups, and the effect sizes were all near large. The results of the post-hoc tests indicated statistically significant differences in the MAT overall total (adjusted p=0.003), MAT total nausea (adjusted p=0.002), MAT acute CINV (adjusted p=0.001), and MAT acute nausea (adjusted p=0.001) scores between the true AT group and the standard care group, while no statistically significant differences were detected between the true AT group and the sham AT group (adjusted p value ranged from 0.43 to 0.75), and between the sham AT group and the standard care group (adjusted p value ranged from 0.07 to 0.11). For the other MAT domain scores, the true AT group also showed lower scores than the sham AT group, and both the true and sham AT groups reported relatively lower scores compared with the standard care group. However, no statistically significant differences were identified among the three groups via the

Kruskal-Wallis H test (all at $p>0.05$) and the effect sizes were identified as small to medium (η^2 ranged from 0.03 to 0.05).

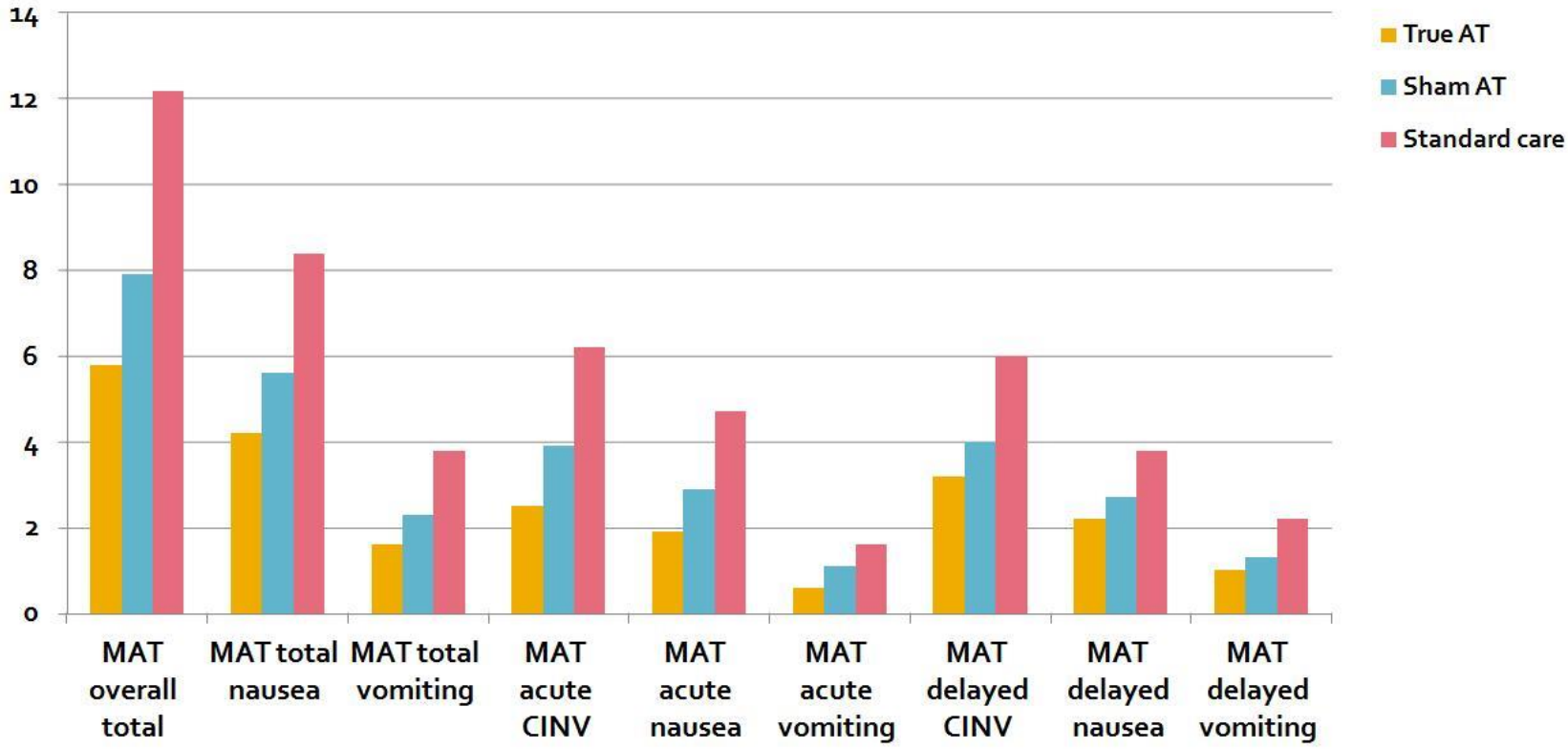


Figure 7.7 MAT total and domain scores
(**Note:** MAT=MASCC Antiemesis Tool; CINV=chemotherapy-induced nausea and vomiting; AT=auricular therapy)

Table 7.16 Differences in the MAT total and domain scores among the study groups

MAT Outcomes[a]	True AT		Sham AT		Standard Care		Kruskal-Wallis H Test		Effect Size
	n[b]	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	n	Mean/SD/SE/Median [95% CI]	Value	*p*	η^2
MAT overall total	37	5.8/5.5/0.9/4.0 [3.9-7.6]	38	7.9/7.3/1.2/5.5 [5.5-10.4]	38	12.2/9.1/1.5/11 [9.2-15.2]	11.09	**0.004**	0.10
MAT total nausea	37	4.2/3.9/0.6/4.0 [2.9-5.5]	38	5.6/4.8/0.8/5.0 [4.1-7.2]	38	8.4/5.8/0.9/8.0 [6.6-10.3]	11.86	**0.003**	0.11
MAT total vomiting	37	1.6/2.6/0.4/0.0 [0.7-2.5]	38	2.3/3.6/0.6/0.0 [1.1-3.5]	38	3.8/4.8/0.8/2.0 [2.2-5.3]	4.47	0.11	0.04
MAT acute CINV	38	2.5/3.1/0.5/0.0 [1.5-3.5]	38	3.9/4.3/0.7/3.5 [2.5-5.4]	38	6.2/4.8/0.8/6.0 [4.7-7.8]	12.28	**0.002**	0.11
MAT acute nausea	38	1.9/2.3/0.4/0.0 [1.2-2.7]	38	2.9/2.9/0.5/3.5 [2.0-3.8]	38	4.7/3.5/0.6/5.0 [3.5-5.8]	14.38	**0.001**	0.13
MAT acute vomiting	38	0.6/1.4/0.2/0.0 [0.1-1.1]	38	1.1/2.0/0.3/0.0 [0.4-1.7]	38	1.6/2.2/0.4/0.0 [0.8-2.3]	5.44	0.07	0.05
MAT delayed CINV	37	3.2/3.6/0.6/2.0 [2.0-4.4]	38	4.0/4.7/0.8/3.0 [2.5-5.5]	38	6.0/5.8/0.9/5.0 [4.1-7.9]	4.27	0.12	0.04
MAT delayed nausea	37	2.2/2.5/0.4/2.0 [1.4-3.0]	38	2.7/2.8/0.5/3.0 [1.8-3.7]	38	3.8/3.4/0.6/3.5 [2.6-4.9]	4.23	0.12	0.04
MAT delayed vomiting	37	1.0/1.8/0.3/0.0 [0.4-1.6]	38	1.3/2.5/0.4/0.0 [0.4-2.1]	38	2.2/3.2/0.5/0.0 [1.2-3.3]	3.39	0.18	0.03

Note: MAT=MASCC Antiemesis Tool; a=for MAT total scale and different symptom domains, a higher score indicates more severe nausea and/or vomiting; AT=auricular therapy; b=one participant from the true AT group dropped out during the delayed CINV assessment. ITT analysis using the acute phase data as the delayed outcomes is not appropriate here because the delayed CINV symptom is different from acute CINV symptom in nature. No ITT approach was utilized in this analysis; therefore, the available sample size for computing the MAT overall total, MAT total nausea, MAT total vomiting, MAT delayed CINV, MAT delayed nausea, and MAT delayed vomiting scores in the true AT group was 37; SD=standard deviation; SE=standard error; CI=confidence interval; CINV=chemotherapy-induced nausea and vomiting

Table 7.17 Post-hoc analysis (Dunn-Bonferroni test) for MAT overall total, MAT total nausea, MAT acute CINV, and MAT acute nausea scores

MAT Outcomes[a]	Post-hoc Analysis (Dunn-Bonferroni Test)					
	True AT vs. Sham AT		True AT vs. Standard Care		Sham AT vs. Standard Care	
	Statistic	Adjusted *p* value	Statistic	Adjusted *p* value	Statistic	Adjusted *p* value
MAT overall total	-8.66	0.75	-24.61	**0.003**	-15.95	0.10
MAT total nausea	-9.68	0.59	-25.56	**0.002**	-15.88	0.10
MAT acute CINV	-10.17	0.49	-25.47	**0.001**	-15.30	0.11
MAT acute nausea	-10.67	0.43	-27.34	**0.001**	-16.67	0.07

Note: MAT=MASCC Antiemesis Tool; a=for MAT total scale and different symptom domains, a higher score indicates more severe nausea and/or vomiting; AT=auricular therapy; CINV=chemotherapy-induced nausea and vomiting

7.2.4.2 Anticipatory nausea and vomiting as measured by the INVR

Anticipatory nausea and vomiting was measured twice during the whole study period using the INVR questionnaire. The first time was at baseline assessment (one day before the first cycle of chemotherapy) and the second time was at post-intervention (follow-up) assessment when the participants returned to the hospital for the next cycle of chemotherapy (30 to 60 minutes prior to administering the chemotherapeutic agents on the first day of the second chemotherapy cycle). A higher INVR score indicates a more severe nausea and/or vomiting condition. As none of the INVR scores (including the absolute score at baseline and post-intervention, and post intervention change value from baseline) met the assumption of normal distribution (as examined by the Shapiro-Wilk test, all at $p< 0.05$), the Kruskal-Wallis H test was utilized for the among-group comparisons of the INVR scores at either baseline assessment or at post-intervention (follow-up) assessment. The occurrence of anticipatory nausea and the occurrence of anticipatory vomiting were also recorded if the participants scored any INVR item related to nausea or vomiting as "1" or above, and the Fisher's exact test was used to examine the differences in the occurrence of anticipatory nausea and the occurrence of anticipatory vomiting among the three study groups.

7.2.4.2.1 Anticipatory nausea and vomiting at baseline assessment

Very few participants (three out of 114, one from each group) experienced anticipatory nausea before the first cycle of chemotherapy, and none of the participants reported anticipatory vomiting. The INVR scores were low for the anticipatory CINV assessment at baseline as the majority of the participants (111 out of 114) rated the INVR total score as "0". No statistically significant differences were found in the INVR domain scores among the three groups (all at $p> 0.99$). The occurrences of anticipatory nausea and anticipatory vomiting before the first chemotherapy cycle did not show any statistically significant differences among the three study groups (anticipatory nausea, Fisher's exact test, statistic=0.43, p=0.99, Cramer's V=0.00).

7.2.4.2.2 Anticipatory nausea and vomiting at post-intervention (follow-up) assessment

For the INVR change scores from baseline, a smaller change value reflects a better outcome. The Kruskal-Wallis H test indicated no statistically significant differences in the INVR scores among the three groups (p value ranged from 0.75 to >0.99). Nine out of 114 participants (ITT analysis)

reported anticipatory nausea before the second cycle of chemotherapy, of which four were from the true AT group (4/38, 10.5%), two were from the sham AT group (2/38, 5.3%), and the other three came from the standard care group (3/38, 7.9%). Fisher's exact test showed no statistically significant difference in the occurrence of anticipatory nausea among the three groups (statistic=0.78, p=0.91, Cramer's V=0.08). Three participants (one from each group) experienced anticipatory vomiting prior to the second cycle of chemotherapy, and no statistically significant difference was found among the three groups (Fisher's exact test, statistic=0.43, p=0.99, Cramer's V=0.00).

7.2.4.3 Quality of life as measured by the FACT-B

The participants' QoL was also measured twice during the whole study period using the FACT-B questionnaire. The first assessment was at baseline (one day before the first cycle of chemotherapy) and the second assessment was at post-intervention (follow-up) when the participants returned to the hospital for the next cycle of chemotherapy. A higher FACT-B score indicates a better QoL. The Shapiro-Wilk test was used to check the assumptions of normality for the absolute value of the FACT-B total and domain scores at baseline and post-intervention, and the post-intervention change scores from baseline. Assumption of homogeneity of variance was measured by Levene's test.

For baseline assessment using the absolute value of the FACT-B scores, the FACT-B functional well-being (FWB) domain, FACT-G total, and FACT-B total scores met both the assumptions of normality and homogeneity of variance (as examined by the Shapiro-Wilk test, all at $p>0.05$); therefore, one-way ANOVA was utilized for the among-group comparison of the FACT-B-FWB, FACT-G total, and FACT-B total scores, while for the other FACT-B domain scores that violated the assumption of normality (as examined by the Shapiro-Wilk test, all at $p< 0.05$), the Kruskal-Wallis H test was used instead for the among-group comparisons. For the post-intervention among-group comparisons of the FACT-B change scores from baseline, following the principles of testing the assumptions of normality and homogeneity of variance above, one-way ANOVA was employed for among-group comparisons of the FACT-B-FWB and the FACT-B total scores, while the Kruskal-Wallis H test was used for the other FACT-B scores.

7.2.4.3.1 Quality of life at baseline assessment

Table 7.18 presents the FACT-B total and domain scores (mean, SD, SE, and 95%CI) at baseline. The FACT-B total and domain scores were generally comparable across the groups. The one-way ANOVA and the Kruskal-Wallis H test did not reveal any statistically significant differences in the FACT-B total and domain scores among the three study groups (all at $p>0.05$).

Table 7.18 Differences in the FACT-B scores among the study groups at baseline assessment

FACT-B Scores	True AT (n=38)	Sham AT (n=38)	Standard Care (n=38)	Statistics	
	Mean/SD/SE/Median [95% CI]	Mean/SD/SE/Median [95% CI]	Mean/SD/SE/Median [95% CI]	Value	*p*
PWB subscale	22.4/3.6/0.6/23.0 [21.2-23.6]	21.0/3.9/0.6/21.0 [19.7-22.3]	20.8/4.2/0.7/20.5 [19.5-22.2]	3.75[a]	0.15
SWB subscale	21.2/5.7/0.9/22.1 [19.3-23.0]	20.5/6.8/1.1/22.1 [18.3-22.8]	20.9/5.8/0.9/22.2 [19.0-22.8]	0.07[a]	0.97
EWB subscale	16.7/3.7/0.6/18.0 [15.4-17.9]	16.6/5.0/0.8/18.0 [15.0-18.3]	15.8/5.9/1.0/18.0 [13.8-17.7]	0.24[a]	0.89
FWB subscale	13.1/5.3//0.9/13.0 [11.3-14.8]	13.1/6.3/1.0/12.5 [11.0-15.2]	13.7/5.6/0.9/14.0 [11.9-15.6]	0.15[b]	0.86
BCS subscale	28.1/5.8/0.9/29.0 [26.2-30.1]	26.9/3.9/0.6/26.0 [25.6-28.2]	26.6/6.1/1.0/29.0 [24.6-28.7]	3.11[a]	0.21
TOI subscale	63.6/10.0/1.6/65.3 [60.3-66.9]	61.0/10.0/1.6/60.0 [57.7-64.2]	61.2/11.2/1.8/62.1 [57.6-64.9]	3.23[a]	0.20
FACT-G total	73.3/11.6/1.9/75.5 [69.5-77.1]	71.3/15.7/2.6/73.0 [66.1-76.5]	71.3/14.0/2.3/72.0 [66.7-75.9]	0.27[b]	0.77
FACT-B total	101.4/14.1/2.3/101.1 [96.8-106.1]	98.2/17.2/2.8/98.5 [92.5-103.8]	97.9/17.9/2.9/99.9 [92.0-103.8]	0.54[b]	0.58

Note: FACT-B=Functional Assessment of Cancer Therapy-Breast; AT=auricular therapy; SD=standard deviation; SE=standard error; CI=confidence interval; PWB=physical well-being; SWB=social/family well-being; EWB=emotional well-being; FWB=functional well-being; BCS=breast cancer subscale; TOI=trial outcome index; FACT-G=Functional Assessment of Cancer Therapy-General; a=Kruskal-Wallis H test; b=one-way ANOVA

7.2.4.3.2 Quality of life at post-intervention (follow-up) assessment

Table 7.19 shows the post-intervention assessment of the FACT-B change scores from baseline (mean, SD, SE, median, and 95%CI). For FACT-B change scores, a larger positive change value from baseline indicates a better improvement of QoL outcome. Relatively lower scores were identified in the majority of the FACT-B domains at post-intervention (follow-up) assessment than at baseline, which indicated deteriorated QoL in the participants after the first cycle of chemotherapy. The results of the one-way ANOVA and the Kruskal-Wallis H test did not reveal any statistically significant differences in the FACT-B total and domain scores among the three study groups (all at $p>0.05$) and the related effect sizes were found to be relatively small.

Table 7.19 Differences in the FACT-B change scores among the study groups at post-intervention (follow-up) assessment

FACT-B Scores	True AT (n=38)	Sham AT (n=38)	Standard Care (n=38)	Statistics		Effect Size
	Mean/SD/SE/Median [95% CI]	Mean/SD/SE/Median [95% CI]	Mean/SD/SE/Median [95% CI]	Value	*p*	Value
PWB subscale	-1.8/4.3/0.7/-1.5 [-3.2- -0.4]	-0.2/3.9/0.6/-1.0 [-1.5-1.1]	-1.6/4.3/0.7/-1.0 [-3.0- -0.2]	2.68[a]	0.26	0.024[c]
SWB subscale	-2.0/6.0/1.0/0.0 [-3.9-0.0]	-1.6/5.7/0.9/0.0 [-3.5-0.3]	-1.7/6.1/1.0/-1.0 [-3.7-0.3]	0.02[a]	0.99	<0.001[c]
EWB subscale	-0.3/4.3/0.7/0.0 [-1.7-1.1]	0.9/4.6/0.7/0.0 [-0.6-2.4]	0.6/5.0/0.8/1.0 [-1.1-2.2]	1.28[a]	0.53	0.011[c]
FWB subscale	-2.3/5.3/0.9/-2.0 [-4.1- -0.6]	-1.0/5.0/0.8/-1.0 [-2.6-0.6]	-1.9/4.4/0.7/-2.0 [-3.3- -0.4]	0.73[b]	0.48	0.013[d]
BCS subscale	0.4/5.8/0.9/-0.05 [-1.5-2.3]	0.5/5.0/0.8/0.0 [-1.1-2.2]	-1.0/5.3/0.9/-0.4 [-2.8- 0.7]	1.27[a]	0.53	0.011[c]
TOI subscale	-3.7/10.7/1.7/-7.0 [-7.3- -0.2]	-0.6/7.8/1.3/-2.0 [-3.2-1.9]	-4.5/9.8/1.6/-3.6 [-7.7- -1.2]	4.59[a]	0.10	0.041[c]
FACT-G total	-6.4/11.6/1.9/-5.0 [-10.2- -2.6]	-1.9/12.4/2.0/-1.5 [-6.0-2.2]	-4.6/13.0/2.1/-5.8 [-8.9- -0.3]	2.10[a]	0.35	0.019[c]
FACT-B total	-6.0/14.6/2.4/-6.5 [-10.8- -1.2]	-1.4/12.2/2.0/-0.7 [-5.4-2.6]	-5.6/15.8/2.6/-4.5 [-10.8- -0.4]	1.22[b]	0.30	0.021[d]

Note: FACT-B=Functional Assessment of Cancer Therapy-Breast; AT=auricular therapy; SD=standard deviation; SE=standard error; CI=confidence interval; PWB=physical well-being; SWB=social/family well-being; EWB=emotional well-being; FWB=functional well-being; BCS=breast cancer subscale; TOI=trial outcome index; FACT-G=Functional Assessment of Cancer Therapy-General; a=Kruskal-Wallis H test; b=one-way ANOVA; c=effect size was measured by η^2; d=effect size was measured by partial η^2

7.2.5 Additional secondary analysis for potential confounding effects at baseline

Although the patients' baseline clinical characteristics were comparable across groups, it was noted that the proportions of patients' CINV risk factors, especially younger age, history of morning sickness, and history of motion sickness, still showed insignificant variations across groups, with relatively more CINV risk factors identified in the true AT group and the sham AT group than in the standard care group. There is a possibility that the patients in the true AT group and the sham AT group may have experienced more severe nausea and vomiting symptoms than those in the standard care group, which might have subsequently underestimated the potential treatment effects of AT. In the study sample, it remained uncertain whether these insignificantly imbalanced CINV risk factors across groups could really produce any significant confounding effects for the cause-and-effect analysis between AT and CINV. Therefore, apart from the preliminary data analysis presented in section 7.2.4, an additional analysis was also performed to explore the potential confounding effects of baseline CINV risk factors for the cause-and-effect analysis between AT and CINV, and the GEE model was used for such analysis (details of the data analysis approaches can be found in Chapter 5, Section 5.5.9).

In the current analysis, the three CINV risk factors (younger age, history of morning sickness, and history of motion sickness) were introduced one-by-one as a potential confounding factor (covariate) into the GEE model, and the covariate-adjusted between-group mean differences and effect sizes for the MAT total and domain scores were then compared with the corresponding statistics in the covariate-unadjusted GEE model to examine whether there were any significant variations in those statistics before and after controlling the potential confounding factor.

7.2.5.1 Analysis of the potential confounding effect of younger age

Table 7.20 presents a covariate's (younger age) unadjusted and adjusted between-group mean differences and effect sizes (as measured by Cohen's d) for the MAT total and domain scores based on the GEE analysis. The changes in the mean differences and related effect sizes in the majority of the between-group comparisons of the MAT total and domain scores were relatively larger in the covariate-adjusted GEE than in the covariate-unadjusted GEE. For instance, the mean difference in the MAT overall total score between the true AT group and the sham AT group

was -2.2 (SE=1.5, p=0.14, Cohen's d=0.34) in the covariate-unadjusted GEE, while it was -2.3 (SE=1.4, p=0.11, Cohen's d=0.37) in the covariate-adjusted GEE. However, there were no obvious variations in those statistics before and after controlling the younger age factor, as the between-group comparisons that showed significant (insignificant) differences in the covariate-unadjusted GEE continued to be significant (insignificant) in the covariate-adjusted GEE. Similarly, effect sizes for the between-group comparisons that revealed small (medium or large) effects in the covariate-unadjusted GEE also continued to be small (medium or large) in the covariate-adjusted GEE.

Table 7.20 Covariate (younger age) unadjusted and adjusted between-group mean differences and effect sizes for the MAT total and domain scores

MAT Scores	Covariate (Younger Age) Unadjusted GEE						Covariate (Younger Age) Adjusted GEE					
	True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC		True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC	
	MD±SE (*p*)	EF[a]	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF
Overall total	-2.2±1.5 (0.14)	0.34	-6.4±1.7 (<0.001)	0.86	-4.3±1.9 (0.02)	0.52	-2.3±1.4 (0.11)	0.37	-6.8±1.7 (<0.001)	0.93	-4.5±1.9 (0.02)	0.56
Total nausea	-1.4±1.0 (0.14)	0.34	-4.3±1.1 (<0.001)	0.88	-2.8±1.2 (0.02)	0.54	-1.5±1.0 (0.12)	0.37	-4.5±1.1 (<0.001)	0.94	-3.0±1.2 (0.01)	0.58
Total vomiting	-0.7±0.7 (0.32)	0.23	-2.2±0.9 (0.01)	0.57	-1.4±1.0 (0.10)	0.35	-0.8±0.7 (0.28)	0.25	-2.3±0.9 (0.01)	0.62	-1.6±1.0 (0.10)	0.38
Acute CINV	-1.4±0.8 (0.09)	0.40	-3.7±0.9 (<0.001)	0.94	-2.3±1.0 (0.03)	0.51	-1.5±0.8 (0.07)	0.41	-3.9±0.9 (<0.001)	0.98	-2.4±1.0 (0.02)	0.54
Acute nausea	-1.0±0.6 (0.10)	0.38	-2.8±0.7 (<0.001)	0.95	-1.8±0.7 (0.01)	0.57	-1.0±0.6 (0.09)	0.39	-2.8±0.7 (<0.001)	0.98	-1.8±0.7 (0.01)	0.59
Acute vomiting	-0.5±0.4 (0.23)	0.27	-1.0±0.4 (0.02)	0.53	-0.5±0.5 (0.29)	0.24	-0.5±0.4 (0.22)	0.29	-1.0±0.4 (0.01)	0.57	-0.5±0.5 (0.24)	0.27
Delayed CINV	-0.8±0.9 (0.41)	0.19	-2.8±1.1 (0.01)	0.58	-2.0±1.2 (0.10)	0.38	-0.9±0.9 (0.35)	0.21	-3.0±1.1 (0.01)	0.64	-2.1±1.2 (0.08)	0.41
Delayed nausea	-0.5±0.6 (0.40)	0.20	-1.5±0.7 (0.02)	0.53	-1.0±0.7 (0.15)	0.33	-0.6±0.6 (0.34)	0.22	-1.7±0.7 (0.01)	0.57	-1.1±0.7 (0.11)	0.37
Delayed vomiting	-0.3±0.5 (0.60)	0.12	-1.2±0.6 (0.04)	0.48	-0.9±0.6 (0.14)	0.34	-0.3±0.5 (0.55)	0.14	-1.3±0.6 (0.03)	0.52	-1.0±0.6 (0.12)	0.36

Note: MAT=MASCC Antiemesis Tool; GEE=generalized estimation equation; AT=auricular therapy; SC=standard care; MD=mean difference; SE=standard error; EF=effect size; a=effect size was measured by Cohen's d; CINV=chemotherapy-induced nausea and vomiting

7.2.5.2 Analysis of potential confounding effect of morning sickness

Table 7.21 presents a covariate's (morning sickness) unadjusted and adjusted between-group mean differences and effect sizes (as measured by Cohen's d) for the MAT total and domain scores based on GEE analysis. For the comparisons of the MAT total and domain scores between the true AT group and the sham AT group, the corresponding between-group mean differences and effect sizes were similar between the covariate-unadjusted and covariate-adjusted GEE. For instance, the mean difference in the the MAT acute vomiting score between the true AT group and the sham AT group was -0.5 (SE=0.4, p=0.23, Cohen's d=0.27) in the covariate-unadjusted GEE, while it was -0.5 (SE=0.4, p=0.24, Cohen's d=0.26) in the covariate-adjusted GEE. For the comparisons of the MAT total and domain scores between the true AT group and the standard care group, and between the sham AT group and the standard care group, the changes on mean differences and the related effect sizes in the majority of the between-group comparisons were relatively larger in the covariate-adjusted GEE than in the covariate-unadjusted GEE. For instance, the mean difference in the MAT total nausea score between the true AT group and the standard care group was -4.3 (SE=1.1, p<0.001, Cohen's d=0.88) in the covariate-unadjusted GEE, while it was -4.6 (SE=1.2, p<0.001, Cohen's d=0.94) in the covariate-adjusted GEE. However, variations did not seem obvious in those statistics before and after controlling the morning sickness factor, as the between-group comparisons that showed significant (insignificant) differences in the covariate-unadjusted GEE continued to be significant (insignificant) in the covariate-adjusted GEE. Similarly, effect sizes for the between-group comparisons that revealed small (medium or large) effects in the covariate-unadjusted GEE also continued to be small (medium or large) in the covariate-adjusted GEE.

Table 7.21 Covariate (morning sickness) unadjusted and adjusted between-group mean differences and effect sizes for the MAT total and domain scores

MAT Scores	Covariate (Morning Sickness) Unadjusted GEE						Covariate (Morning Sickness) Adjusted GEE					
	True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC		True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC	
	MD±SE (*p*)	EF[a]	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF
Overall total	-2.2±1.5 (0.14)	0.34	-6.4±1.7 (<0.001)	0.86	-4.3±1.9 (0.02)	0.52	-2.1±1.5 (0.15)	0.33	-7.1±1.9 (<0.001)	0.94	-4.9±1.9 (0.01)	0.63
Total nausea	-1.4±1.0 (0.14)	0.34	-4.3±1.1 (<0.001)	0.88	-2.8±1.2 (0.02)	0.54	-1.4±1.0 (0.15)	0.32	-4.6±1.2 (<0.001)	0.94	-3.2±1.2 (0.01)	0.63
Total vomiting	-0.7±0.7 (0.32)	0.23	-2.2±0.9 (0.01)	0.57	-1.4±1.0 (0.10)	0.35	-0.7±0.7 (0.32)	0.23	-2.4±0.9 (0.01)	0.63	-1.7±1.0 (0.07)	0.43
Acute CINV	-1.4±0.8 (0.09)	0.40	-3.7±0.9 (<0.001)	0.94	-2.3±1.0 (0.03)	0.51	-1.4±0.8 (0.09)	0.37	-4.0±1.0 (<0.001)	0.99	-2.6±1.1 (0.01)	0.59
Acute nausea	-1.0±0.6 (0.10)	0.38	-2.8±0.7 (<0.001)	0.95	-1.8±0.7 (0.01)	0.57	-0.9±0.6 (0.11)	0.36	-3.0±0.7 (<0.001)	1.01	-2.0±0.7 (0.01)	0.65
Acute vomiting	-0.5±0.4 (0.23)	0.27	-1.0±0.4 (0.02)	0.53	-0.5±0.5 (0.29)	0.24	-0.5±0.4 (0.24)	0.26	-1.0±0.4 (0.02)	0.56	-0.6±0.5 (0.22)	0.29
Delayed CINV	-0.8±0.9 (0.41)	0.19	-2.8±1.1 (0.01)	0.58	-2.0±1.2 (0.10)	0.38	-0.8±0.9 (0.41)	0.19	-3.1±1.2 (0.01)	0.64	-2.3±1.2 (0.05)	0.47
Delayed nausea	-0.5±0.6 (0.40)	0.20	-1.5±0.7 (0.02)	0.53	-1.0±0.7 (0.15)	0.33	-0.5±0.6 (0.40)	0.19	-1.7±0.7 (0.02)	0.57	-1.2±0.7 (0.09)	0.40
Delayed vomiting	-0.3±0.5 (0.60)	0.12	-1.2±0.6 (0.04)	0.48	-0.9±0.6 (0.14)	0.34	-0.3±0.5 (0.60)	0.12	-1.4±0.6 (0.02)	0.54	-1.1±0.6 (0.07)	0.42

Note: MAT=MASCC Antiemesis Tool; GEE=generalized estimation equation; AT=auricular therapy; SC=standard care; MD=mean difference; SE=standard error; EF=effect size; a=effect size was measured by Cohen's d; CINV=chemotherapy-induced nausea and vomiting

7.2.5.3 Analysis of potential confounding effect of motion sickness

Table 7.22 presents a covariate's (motion sickness) unadjusted and adjusted between-group mean differences and effect sizes (as measured by Cohen's d) for the MAT total and domain scores based on GEE analysis. The changes in mean differences and the related effect sizes in the majority of the between-group comparisons of the MAT total and domain scores were relatively larger in the covariate-adjusted GEE than in the covariate-unadjusted GEE. For instance, the mean difference in the MAT overall total score between the true AT group and the standard care group was -6.4 (SE=1.7, p<0.001, Cohen's d=0.86) in the covariate-unadjusted GEE, while it was -6.8 (SE=1.7, p=<0.001, Cohen's d=0.89) in the covariate-adjusted GEE. However, there were no obvious variations in those statistics before and after controlling the motion sickness factor, as the between-group comparisons that showed significant (insignificant) differences in the covariate-unadjusted GEE continued to be significant (insignificant) in the covariate-adjusted GEE. Similarly, effect sizes for the between-group comparisons that revealed small (medium or large) effects in the covariate-unadjusted GEE also continued to be small (medium or large) in the covariate-adjusted GEE.

Table 7.22 Covariate (motion sickness) unadjusted and adjusted between-group mean differences and effect sizes for the MAT total and domain scores

MAT Scores	Covariate (Motion Sickness) Unadjusted GEE						Covariate (Motion Sickness) Adjusted GEE					
	True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC		True AT vs. Sham AT		True AT vs. SC		Sham AT vs. SC	
	MD±SE (*p*)	EF[a]	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF	MD±SE (*p*)	EF
Overall total	-2.2±1.5 (0.14)	0.34	-6.4±1.7 (< 0.001)	0.86	-4.3±1.9 (0.02)	0.52	-2.3±1.4 (0.11)	0.37	-6.8±1.7 (<0.001)	0.89	-4.4±1.9 (0.02)	0.54
Total nausea	-1.4±1.0 (0.14)	0.34	-4.3±1.1 (<0.001)	0.88	-2.8±1.2 (0.02)	0.54	-1.5±1.0 (0.12)	0.36	-4.4±1.1 (<0.001)	0.91	-2.9±1.2 (0.02)	0.56
Total vomiting	-0.7±0.7 (0.32)	0.23	-2.2±0.9 (0.01)	0.57	-1.4±1.0 (0.10)	0.35	-0.8±0.7 (0.25)	0.26	-2.3±0.9 (0.01)	0.60	-1.5±0.9 (0.10)	0.36
Acute CINV	-1.4±0.8 (0.09)	0.40	-3.7±0.9 (< 0.001)	0.94	-2.3±1.0 (0.03)	0.51	-1.6±0.8 (0.05)	0.44	-4.0±0.9 (< 0.001)	1.02	-2.5±1.0 (0.01)	0.55
Acute nausea	-1.0±0.6 (0.10)	0.38	-2.8±0.7 (< 0.001)	0.95	-1.8±0.7 (0.01)	0.57	-1.0±0.6 (0.07)	0.42	-2.9±0.6 (< 0.001)	1.04	-1.9±0.7 (0.01)	0.62
Acute vomiting	-0.5±0.4 (0.23)	0.27	-1.0±0.4 (0.02)	0.53	-0.5±0.5 (0.29)	0.24	-0.5±0.4 (0.19)	0.30	-1.1±0.4 (0.01)	0.57	-0.6±0.5 (0.23)	0.26
Delayed CINV	-0.8±0.9 (0.41)	0.19	-2.8±1.1 (0.01)	0.58	-2.0±1.2 (0.10)	0.38	-0.8±1.0 (0.40)	0.19	-2.8±1.1 (0.01)	0.58	-2.0±1.2 (0.09)	0.38
Delayed nausea	-0.5±0.6 (0.40)	0.20	-1.5±0.7 (0.02)	0.53	-1.0±0.7 (0.15)	0.33	-0.5±0.6 (0.40)	0.19	-1.5±0.7 (0.03)	0.51	-1.0±0.7 (0.16)	0.32
Delayed vomiting	-0.3±0.5 (0.60)	0.12	-1.2±0.6 (0.04)	0.48	-0.9±0.6 (0.14)	0.34	-0.3±0.5 (0.55)	0.14	-1.3±0.6 (0.03)	0.50	-1.0±0.6 (0.12)	0.35

Note: MAT=MASCC Antiemesis Tool; GEE=generalized estimation equation; AT=auricular therapy; SC=standard care; MD=mean difference; SE=standard error; EF=effect size; a=effect size was measured by Cohen's d; CINV=chemotherapy-induced nausea and vomiting

7.2.6 Summary of the pilot RCT results

A total of 114 breast cancer patients were recruited during a 15-month period to participate in the pilot RCT and 110 of them completed the outcome assessment. Analyses of the feasibility outcomes indicated a high completion rate among the study participants (110/114, 96.5%). The feasibility of the study questionnaires was also determined to be adequate among the participants, with missing values identified in only a small number of FACT-B questionnaire items. The AT treatment protocols were found to be acceptible for use in breast cancer patients receiving chemotherapy, as the majority of the participants (61/76, 80.3%) from the true AT group and the sham AT group followed the AT treatment protocol to complete the five-day AT treatment. Adverse events associated with AT, such as minor pain, itching, and discomfort, were identified in a few participants, but the reactions were generally mild, tolerable, and transient.

The preliminary analysis of the pilot study clinical outcomes showed that the participants in the true and sham AT groups had higher CR rates of CINV symptoms than those in the standard care group, with the among-group difference in the CR of acute CINV reaching statistical significance [χ^2 (2)=7.07, p=0.03]. The occurrence and severity of acute CINV in the true AT group was lower than in the sham AT group, and both the true and sham AT groups reported a lower occurrence and severity of acute CINV compared with the standard care group. Statistically significant among-group differences were identified for the occurrence of acute nausea [χ^2 (2)=6.69, p=0.04] and the severity of acute nausea [χ^2 (2)=14.38, p=0.001]. Delayed CINV was also lower in the true AT group and the sham AT group than in the standard care group, but no statistically significant differences were found among the three study groups. The MAT total and domain scores in the true AT group and the sham AT group were all lower (indicating less nausea and vomiting symptoms) than in the standard care group. Statistically significant differences in the MAT overall total [χ^2 (2)=11.09, p=0.004], MAT total nausea [χ^2 (2)=11.86, p=0.003], MAT acute CINV [χ^2 (2)=12.28, p=0.002], and MAT acute nausea [χ^2 (2)=14.38, p=0.001] scores were found among the three groups. There were no statistically significant differences in anticipatory CINV and QoL among the three study groups at post-intervention (follow-up) assessment.

Potential confounding effects of baseline CINV risk factors (younger age, history of morning sickness, and history motion sickness) were examined using the GEE model. There were no significant variations in the between-group mean differences and effect sizes of the MAT total and domain scores before and after adjusting the potential confounding factors, as the between-group comparisons that showed significant (insignificant) differences in the covariate-unadjusted GEE continued to be significant (insignificant) in the covariate-adjusted GEE. Similarly, effect sizes for the between-group comparisons that revealed small (medium or large) effects in the covariate-unadjusted GEE also continued to be small (medium or large) in the covariate-adjusted GEE.

7.3 Results of the semi-structured interviews

7.3.1 Characteristics of the participants

The interviews were held within two months after the invited participants completed the AT trial. Twenty-seven interviewees participated in the semi-structured interviews, of which 10 were from the true AT group, 11 came from the sham AT group, and the other six were from the standard care group. The majority of the interviewees were aged more than 40 years old, had only primary school or secondary school education, and were housewives or manual workers. Breast cancer was at stage II in more than 60% of the participants, and the epirubicin and cyclophosphamide combination was the most frequently utilized chemotherapy protocol. Expectations of the treatment effects of AT varied among the participants receiving the true or sham intervention, with the expectation scores ranging from 1 to 10 (mean=5.95). Over half of the participants had previous experiences of using CHAs. **Table 7.23** below shows the demographic and clinical information of the 27 interviewees:

Table 7.23 Characteristics of the interviewees

Demographic and Clinical Data		Number (%)
Group allocation of the pilot RCT (n=27)	True AT group	10 (37.0%)
	Sham AT group	11 (40.7%)
	Standard care group	6 (22.2%)
Age (years) (n=27)	60-69	4 (14.8%)
	50-59	5 (18.5%)
	40-49	14 (51.9%)
	30-39	2 (7.4%)
	20-29	2 (7.4%)
Education background (n=27)	University/college degree or diploma	2 (7.4%)
	Technical school or high school	1 (3.7%)
	Secondary school	6 (22.2%)
	Primary school	18 (66.7%)
Employment status (n=27)	Professional	2 (7.4%)
	Manual work	8 (29.6%)
	Housewife	14 (51.9%)
	Admin or clerical work	1 (3.7%)
	Retired	1 (3.7%)
	Other	1 (3.7%)
Marital status (n=27)	Married	26 (96.3%)
	Single	1 (3.7%)
Stage of breast cancer (n=27)	Stage III	7 (25.9%)
	Stage II	18 (66.7%)
	Stage I	2 (7.4%)
Chemotherapy protocol (n=27)	Doxorubicin + cyclophosphamide (AC) combination[a]	7 (25.9%)
	Epirubicin + cyclophosphamide (EC) combination[a]	18 (66.7%)
	Docetaxel+ cyclophosphamide (TC) combination	1 (3.7%)
	Pirarubicin+ cyclophosphamide combination	1 (3.7%)
Antiemetic medication (n=27)	5-HT3 receptor antagonists + dexamethasone	14 (51.9%)
	5-HT3 receptor antagonists only	13 (48.1%)
Adherence to AT protocol (n=21)	Rigid adherence	13 (61.9%)
	Not rigid adherence	8 (38.1%)
Expectations of AT treatment effects (0-10 numerical scale, n=21)	Maximum score	10
	Minimum score	1
	Average score (mean)	5.95
Previous experiences with CHAs (n=27)	Yes	16 (59.3%)
	No	11 (40.7%)

Note: RCT=randomized controlled trial; AT: auricular therapy; a=these combinations were administered with or without sequential adjuvant therapy using paclitaxel or docetaxel; CHA: complementary health approach

7.3.2 Theme and sub-themes

Five themes were identified in the interview records describing the participants' experiences of participating in the pilot RCT and receiving the AT treatment: **(1)** views on CHAs; **(2)** experiences of completing the study questionnaires; **(3)** adherence to the intervention protocol; **(4)** safety and convenience of the intervention; and **(5)** perceptions of the intervention effects. Each theme had two to three sub-themes. The main themes and sub-themes generated from the interview data are presented below in **Table 7.24**:

Table 7.24 Main themes and sub-themes

Views on complementary health approaches (CHAs)
• Adjuvant approaches to conventional medicine
• Relatively safe approaches with minor adverse events
• A desire to receive CHAs to manage chemotherapy-induced symptoms
Experiences of completing the study questionnaires
• Convenient and easy to understand
• Recall of acute and delayed nausea and vomiting
Adherence to the intervention protocol
• Adherence to regular auricular acupressure
• Adherence to precautions and treatment duration of AT
Safety and convenience of the intervention
• A relatively safe approach with minor irritations
• A satisfactory approach without disturbing routine treatment and activity
Perceptions of the intervention effects
• Perceptions of the intervention effects for nausea and vomiting
• Perceptions of the intervention effects for emotional well-being
• Perceptions of the placebo effects of the intervention

Note: AT=auricular therapy

7.3.2.1 Views on complementary health approaches (CHAs)

7.3.2.1.1 Adjuvant approaches to conventional medicine

The majority of the interviewees indicated that they or their family members or friends had previously received CHAs, including acupuncture, massage, scraping therapy, and Chinese herbal medicine. The interviewees believed that CHAs could be used as promising adjuvant therapies to conventional medicine for the management of chemotherapy-related adverse reactions. In terms of the role of CHAs, the participants frequently described them as important

treatment components that could contribute to regulating the whole body's functions from a holistic perspective, and to some extent, alleviate the unpleasant symptoms induced by chemotherapy and help the body to restore energy. The participants commonly viewed that the treatment effects of CHAs were usually gradual and slow, and it often took a long time to show their effectiveness. A couple of interviewees also emphasized that the CHAs themselves did not create any therapeutic effects for targeted health problems but only served as supportive roles when used in combination with modern treatment. They stated that CHAs could only assist in "relieving," not "cure" the sickness.

"CHAs can help to regulate my whole body functions. [I feel] so good. A good CHA practitioner can really help to regulate [my health status]. I just believe that CHAs can help to regulate my whole body functions, and [alleviate my] gastrointestinal [reactions]!"
(52 years old, sham AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"The effects of CHAs are not the basis of the treatment effects. It's just a support role! Of course if you say treatment effects…of course the treatment effects should be from the Western medicine! Once the condition has been stabilized by [Western medicine], the CHAs can then [be used] to create some assisting effects."
(60 years old, standard care group, had previous experience of using CHAs)

"I believe that CHAs are effective...but their effects are quite slow to appear…."
(47 years old, true AT group, rigid adherence to AT protocol, had previous experiences of using CHAs)

"CHAs can also help to treat cancer symptoms…but [they] only have some effects to support the treatment. It's just that…[CHAs] can alleviate some symptoms like we have."
(46 years old, sham AT group, not rigid adherence to AT protocol, no previous experience of using CHAs)

7.3.2.1.2 Relatively safe approaches with minor adverse events

Most of the participants viewed CHAs as relatively safe approaches with minor adverse events. Some of them described themselves as having a sense of security when receiving CHAs because of their conviction in the safety of CHAs. However, the interviewees had only a superficial

understanding of the safety issue of CHAs. When the interviewees were asked to describe from what aspects they believed CHAs were safe, none of them could give any details. Moreover, they all failed to name particular adverse events that could be introduced by CHAs. A small number of interviewees only expressed that, from their points of view, CHAs were different from conventional medicine, and they would not induce any severe damage to the human body and *zang-fu* organs (a TCM term to describe human internal organs).

"Everybody says CHAs are good and they're very conservative. It seems that CHAs do not have any side effects. Yes, it should be… Anyway, CHAs do not have that many [adverse events] compared with Western medicine. I think CHAs are better…yes!"

(40 years old, standard care group, had previous experience of using CHAs)

"If you are talking about the side effects…of course CHAs have less side effects [than conventional medicine]."

(44 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"To my understanding, I always choose to visit the CHA practitioners when I feel unwell. [CHAs] are better than Western medicine. It seems that [CHAs] do not hurt our organs. [CHAs] are much safer. To me, they're much safer."

(49 years old, sham AT group, rigid adherence to AT protocol, no previous experience of using CHAs)

7.3.2.1.3 A desire to receive CHAs to manage chemotherapy-induced symptoms

Based on their understanding of the role and safety of CHAs, some participants highlighted that they hoped they could receive CHAs during the current or future chemotherapy cycle to help alleviate the undesirable symptoms (such as nausea and vomiting) induced by antineoplastic treatment. For instance, one interviewee hoped that the cancer hospital would establish a department with a special focus on CHAs, which could provide tailored CHAs to hospitalized patients.

"For CHAs, I've heard from my friends. They said chemotherapy has many side effects. [They told me] I can visit that CHA practitioner to [get some complementary treatments]…eh…to regulate my body a little bit. Especially that [CHAs] do not hurt anything. I hope I can find the CHAs to regulate [my health conditions]…especially for my stomach reactions [nausea and vomiting]. I hope I can eat more and [my] stomach [can be] easier to digest [food]. I hope your hospital can open a complementary medicine clinic or something like that, with good practitioners, I mean someone with relatively better qualifications. They would know our symptoms better, and know our conditions better, and they know how to use CHAs to manage our problems, thus I would feel much safer."

(52 years old, sham AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"For disease [cancer] like the one I have, of course I should get the surgery and chemotherapy first. But after that I also wonder…I should get some CHAs as well. I think that would be great!"

(47 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.2 Experiences of completing the study questionnaires

7.3.2.2.1 Convenient and easy to understand

The majority of the participants felt that the items on the study questionnaires were easy to understand, and there were seldom questions that they felt difficult to answer. A small number of participants who completed the study questionnaires with the assistance of the research assistants also thought the paperwork was convenient and easily understood. The interviewees generally indicated that they did not experience any burden when filling in the study questionnaires, and they agreed that the workload for completing the paperwork was reasonable and acceptable because they were required to answer only a few questionnaires during the whole study period, which was not on a daily basis.

There was one interviewee who complained that the frequent completion of the paperwork would only significantly annoy the patients, as they already suffered from considerable psychological distress during the chemotherapy and they would not be willing to receive any disturbances when they were feeling "really bad." Another participant pointed out that there was

one sensitive item in the QoL questionnaire asking about their sex life. She declined to answer that question as she believed it was more about her personal privacy. However, the participant also emphasized that she was not bothered by the question about her sex life, as there was a clear instruction in the questionnaire that if the patients did not wish to respond to this "sensitive" item, they could directly skip to the next question.

"No, it's quite simple. I don't have any difficulties in understanding [these questionnaires]."

(45 years old, true AT group, rigid adherence to AT protocol, no previous experience of using CHAs)

"Of course I would get so bored if you keep asking me to fill in these questionnaires day by day! No way! Too much! But the questionnaires are not that frequently administered…just occasionally! That's fine. In fact, we have already suffered from great mental distress because of this [cancer treatment], and filling in the paperwork day by day will only make us feel more suffering! Of course! You have to check our conditions before [asking us to do the paperwork]. When I feel really bad [but you still come to ask me to complete these questionnaires], of course I will get bored!"

(60 years old, standard care group, had previous experience of using CHAs)

"Some [questions] are about my personal privacy but I think I can refuse to answer. Other [questions] are very general. That's fine for me."

(28 years old, sham AT group, not rigid adherence to AT protocol, no previous experience of using CHAs)

7.3.2.2.2 Recall of acute and delayed nausea and vomiting

The interviewees were questioned whether they were able to accurately recall the nausea and vomiting symptoms experienced during the first cycle of chemotherapy. Most of them indicated that they could still remember the frequency and severity of acute nausea and vomiting on the first day of the first antineoplastic treatment cycle and delayed sickness during the subsequent three to four days. Some of the interviewees acknowledged that it was appropriate to measure the delayed symptoms with only a one-time assessment. However, a minority of the participants indicated that they could not guarantee an accurate answer for the frequency of nausea and vomiting

because of memory lapses. One interviewee with memory problems expressed that it would be better to check daily with her about the nausea and vomiting experienced during the previous day to get a more precise and accurate record.

"I think it's very reasonable [that you only ask twice about emesis during chemotherapy]. Yes, I can still clearly remember [my nausea and vomiting] for the past two to three weeks. This should be no problem."

(58 years old, standard care group, had previous experience of using CHAs)

"It's just that…I am too old, and you ask me to recall [previous nausea and vomiting], it's really easy to forget things, really…very forgetful. It might be [better if] you could ask me every day [about my symptom experiences]. I really have a very bad memory."

(52 years old, sham AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"I cannot guarantee! Because my memory is not that good now…. If you ask me [about the previous nausea and vomiting], I cannot guarantee that I can give you an accurate answer!"

(44 years old, standard care group, no previous experience of using CHAs)

7.3.2.3 Adherence to the intervention protocol

7.3.2.3.1 Adherence to regular auricular acupressure

The majority of the interviewees allocated to the true AT group confirmed that they had followed the researchers' instructions to regularly add pressure to the taped seeds, and most of them also reported their usual time points for performing acupressure, which were in the morning, at noon (after lunch) or in the early afternoon, and in the evening before sleep. In addition to daily regular acupressure, there was one participant who also pressed the taped seeds when she felt nausea coming on. Two participants demonstrated the acupressure skills to the doctoral researcher, which were deemed correct. There was one interviewee who indicated that she had followed the instructions to regular press the taped seeds on the first day of chemotherapy. However, as she felt the nausea and vomiting symptoms were not alleviated by the regular acupressure, she then decided not to strictly follow the AT protocol for the rest of the intervention

period but only press the seeds occasionally when she was aware that "there was something in the ear."

"Yes, the first [acupressure] is in the morning, then the second one is...at noon, and then in the evening. Totally three times. Yes, yes, yes, three times a day!"

(45 years old, true AT group, rigid adherence to AT protocol, no previous experience of using CHAs)

"I just pressed the taped seeds a little bit when I was aware that there was something in the ear. Because the first day [of chemotherapy]…actually, I do have regularly pressed the seeds but then I still threw up many times! Then again and again! In the following days, I just pressed the ear a little bit...pressed a little bit [occasionally] when I suddenly remember there were acupressure seeds taped in my ear."

(25 years old, true AT group, not rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.3.2 Adherence to precautions and treatment duration of AT

Most of the participants from the true AT group and the sham AT group confirmed that they had kept the auricular tapes in their ears for about five days, and then followed the telephone instructions on the sixth day of the first chemotherapy cycle and removed the tapes. However, a few participants still left the tapes in their ears for more than five days, regardless of the telephone reminder from the research assistants. Most of the interviewees in the true AT group and the sham AT group also had rigid adherence to the precautions of the AT treatment. For instance, the interviewees described that they were very careful to prevent the auricular tapes from getting wet when taking shower or washing their hair, and they also prudently cleaned their ears to prevent the auricular tapes from falling off. Three participants from the sham AT group had inadvertently dropped several auricular tapes when cleaning their face and hair on the third or fourth day of the AT treatment period, but none of them had called the researchers to report this issue, although they had been instructed to contact the researchers for replacements if the auricular tapes fell off.

"Yes! I have pressed [the auricular tapes] for five days!"

(46 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"Yes, I have finished the whole AT treatment. I didn't take the seeds off halfway. Yes, just follow what you said to remove all the seeds at that noon. I told my husband that it's time to remove the seeds. Take the seeds off."

(45 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"I just kept them for about two or three days. Then...I was very careless that I took the tapes off when I was washing my hair. So I took them off! Yes, by myself. I remember it [the AT treatment] should be five days. It's on the third day, I went to the hair salon that day and I forgot to tell the hairdresser that I had ear tapes. Oh, it's all gone! Oh…that's too bad! I have tapes in my ear but I forgot to say [it]."

(28 years old, sham AT group, not rigid adherence to AT protocol, no previous experience of using CHAs)

7.3.2.4 Safety and convenience of the intervention

7.3.2.4.1 A relatively safe approach with minor irritations

Most of the interviewees from the true AT group and the sham AT group did not experience any discomfort or harm associated with AT. A small number of participants identified some minor irritations that might have been attributed to the AT intervention. Three participants from the true AT group experienced minor pain at the ear when adding pressure to the taped seeds, but the pain soon disappeared after withdrawing the acupressure tapes. One interviewee allocated to the sham AT group complained of minor itching of the ear. Another one (sham AT group) identified mild redness at the AT treatment sites after removing the auricular tapes, but she did not record this adverse event in the daily log and did not inform the researchers of this adverse event during the pilot RCT. There was only one participant from the true AT group who complained of obvious pain when she pressed the taped seeds but the pain soon disappeared after she stopped the acupressure. However, this interviewee did not inform the researcher of this AT adverse event during the intervention period, and she continued to finish the AT treatment even

though it felt painful when administering ear acupressure. No other AT-related adverse events were identified among the interviewees.

"Other things are fine. I did not feel anything bad [in my ears]. No, no, no pain and redness, no."
(64 years old, sham AT group, rigid adherence to AT protocol, no previous experience of using CHAs)

"A little painful at the very beginning, just when I began to press [the taped seeds]…maybe [because] I applied too much strength. I just lowered the acupressure intensity a little and then it's all fine! When I got used to the acupressure intensity…then it's okay. No red, no itching, no. I just do [ear acupressure] as usual, lowered the intensity a little bit. Maybe I just pressed [the taped seeds] too hard in the beginning."
(46 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"No discomfort. Just a little itching…itching until finally I took all the tapes off."
(44 years old, sham AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.4.2 A satisfactory approach without disturbing routine treatment and activity

The interviewees in the true AT group and the sham AT group generally viewed AT as a convenient approach without disturbing their routine treatment (e.g., chemotherapy) in the hospital as well as their daily activities. By following the precautions of protecting the auricular tapes, the participants could still wash their hair and take a shower as usual without wetting or dropping the tapes. One participant in the true AT group mentioned that wearing the auricular tapes was somewhat inconvenient when she took the lateral sleeping position, as the pillow pressed against the ear, but another participant (true AT group) indicated that if the pillow was soft enough, the lateral sleeping position did not make her feel an earache and discomfort.

"The AT intervention did not disturb my chemotherapy. I am receiving chemotherapy here, and your assessments did not disturb me at all."
(47 years old, true AT group, rigid adherence to AT, had previous experience of using CHAs)

The participants were generally satisfied with the AT intervention, and more than half of them hoped to continue with the AT intervention to help manage their nausea and vomiting symptoms as well as other health problems for which AT might also create some benefits, such as insomnia and fatigue. There was one interviewee who emphasized that the non-invasive nature of the intervention was the most important motivational factor that drove her to participate in the pilot RCT and consider further AT treatment for other health conditions. A few participants (mostly from the true AT group) expressed that they did not want to receive AT again. When asked about the reasons that made them decide not to continue with the AT treatment, two of them explained that they felt that AT was not very convenient and they would not be willing to receive AT treatment again if they no longer experienced any nausea and vomiting.

"If possible, I hope I can have the AT treatment again. Now I am sick in the hospital, I hope [my conditions] could be better."

(32 years old, sham AT group, not rigid adherence to AT protocol, no previous experience of using CHAs)

"As long as it's not something [experimental drugs] that I have to eat, I will consider [it]. Things [experimental drugs] taken into the stomach…you cannot take them out! Something like that [experimental drugs]…a little scary! It's a pilot testing [of the experimental drugs] so I would be a little scared! A little scared! But for AT, if you say I may throw up, yes I'll have a try. I should have hope, it doesn't matter! But for [an invasive] approach which may enter into my blood...I do have to consider! [Once you get it] you can never take it out!"

(45 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.5 Perceptions of the intervention effects

7.3.2.5.1 Perceptions of the intervention effects for nausea and vomiting

Most of the interviewees allocated to the true AT group and the sham AT group experienced mild or no nausea and vomiting symptoms during the first cycle of chemotherapy, and more than half of them clearly described that they felt that their emesis symptoms were relatively more alleviated during the first chemotherapy cycle with AT than in the subsequent treatment cycles without AT. When the interviewees were asked about whether they believed that the

CINV symptom relief was attributed to the use of AT, most of them were generally pragmatic in their view of the treatment effects of AT, and perceived that AT contributed to some favorable effects in relieving their emesis induced by chemotherapy. Their perceptions of the therapeutic effects of AT came from their own symptom experiences across different chemotherapy cycles with and without using AT, as the nausea and vomiting symptoms became more severe during the second chemotherapy cycle when they no longer received any AT treatment. For a small number of interviewees, their perceptions of the AT treatment effects were from their previous experiences of using other CHAs to manage similar symptoms, or a comparison of their own symptom experiences with other patients' conditions without AT treatment. One interviewee (sham AT group) had used a complementary therapy patch to effectively control motion sickness during travelling, and she believed that the AT must have a mechanism similar to the motion sickness patch to assist her in controlling the chemotherapy-related sickness. Another interviewee from the true AT group stated that a conviction in the treatment effects of AT was the key motivational factor that led her to complete the five-day AT treatment.

"I believe that AT is effective, because I always have travel sickness. I take the motion sickness patch, and it's really effective! So I think this [AT] should be more effective! Yes, I believe! Because…I am really afraid of travelling…but the patch is effective. [Because of that] I believe this [AT] should be more effective! I think the effects of AT are good! You can promote it! The vomiting actually hurts us a lot. We don't want to eat anything and just keep throwing up. It really hurts our stomach and body a lot! If AT can help to relieve [nausea and vomiting], it would be nice! Hope you have those kinds of approaches to help to relieve [nausea and vomiting]."

(52 years old, sham AT group, rigid adherence to AT, had previous experience of using CHAs)

"Yes! I did not throw up. So I just have a belief of the AT. I have hope."

(45 years old, true AT group, rigid adherence to AT, had previous experience of using CHAs)

A minority of the interviewees from the true AT group and the sham AT group experienced relatively severe emesis symptoms during the first and the subsequent cycles of chemotherapy, which made them doubt the benefits of AT. One interviewee from the true AT group complied with the AT protocol at first and performed regular ear acupressure but still experienced severe

nausea and vomiting reactions on the first day of chemotherapy. She emphasized that a failure to see the effectiveness of AT was the main reason for not following the AT protocol during the rest of the intervention period.

"I don't believe [AT can alleviate nausea and vomiting] because…on the first day, I strictly followed your order [to do ear acupressure] but still threw up many times! So I just ignore it! [In the following days of the AT treatment period] I just occasionally did the acupressure when I was aware that there was something in my ear. If hadn't thrown up on the first day, of course I would do it [ear acupressure] regularly then. The AT didn't work on the first day so I just ignored it!"

(25 years old, true AT group, not rigid adherence to AT protocol, had previous experience of using CHAs)

"No it didn't work! I still threw up! I still threw up twice even if I [pressed] the ear tapes! Totally the same! The second chemotherapy cycle [without AT] I also threw up twice!… Of course the AT didn't have effects! How can I still throw up if it [AT] is really effective?"

(48 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.5.2 Perceptions of the intervention effects for emotional well-being

The interviewees who experienced only minor or totally no nausea and vomiting symptoms perceived better emotional status during the first cycle of chemotherapy. The participants described that the minor gastrointestinal reactions experienced during the first chemotherapy cycle did not significantly decrease their appetite, which partly contributed to less physical and emotional burden with regard to routine treatment in the hospital and daily activities after discharge. Two interviewees mentioned that they felt relieved when they did not experience much sickness but saw other patients suffering from severe nausea and vomiting, and they believed that the less physical symptom distress somewhat contributed to better psychological conditions after discharge. In addition to the absence of nausea and vomiting symptoms, support from family members was another important factor that contributed to better psychological well-being among the interviewees with the AT treatment.

"I felt somewhat relieved. I did not throw up but I saw other patients vomit a lot, so I felt much better. After the AT treatment, I felt that I was in a good mood! That…maybe I feel somewhat relaxed."

(45 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"I really felt great in the first chemotherapy cycle! The second cycle…I did not have AT any more, and I just felt not that good! [In the first chemotherapy cycle] my friends [who have the same problems] kept calling me to ask, 'Wwhy the effects are so good? Why the effects are so good?' I really think I was in good mood at that time."

(52 years old, sham AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.2.5.3 Perceptions of placebo effects of the intervention

Importantly, when describing the perceptions of the AT treatment effects, several interviewees emphasized that the effects of AT were only one kind of "psychological comfort" or "psychological effect." They were still uncertain about whether AT could really create some therapeutic effects to help control the nausea and vomiting symptoms, but they believed that there were some non-specific effects of AT from a psychological perspective to increase their expectations of the treatment. One interviewee had heard that she might not experience sickness after receiving CHAs, and this idea further pushed her to convince herself that she would not have any nausea and vomiting once she had received AT treatment. This kind of belief was further strengthened when she did not experience any emesis symptoms but saw other patients without AT suffering from severe nausea and vomiting.

"It's just…I am not sure. But it's just a psychological comfort that I thought I would be fine if I take [AT treatment]…something like that…just something like the psychological effects."

(44 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

"Would I vomit a lot if I hadn't taken the AT? I felt at ease when I attached the tapes to my ears. It's only a psychological effect. I might feel more or less better if I take it [AT treatment], it won't be that easy for me to throw up."

(32 years old, sham AT group, not rigid adherence to AT protocol, no previous experience of using CHAs)

"It might be only a kind of psychological effect. Just because I have a belief in it [AT treatment]…ho ho [laughter]…. Yes, I just have that kind of thought. It might be that, it might be…that other [people] said that AT might have some help, and then I saw other people throw up many time so at that time I was feeling lucky. I had AT and…so I didn't throw up at all! I just have that kind of luck!..... It seemed to have some psychological effects, when I saw other people throw up but I did not!.... Just like that kind of thing to comfort myself."

(45 years old, true AT group, rigid adherence to AT protocol, had previous experience of using CHAs)

7.3.3 Summary of the semi-structured interview results

Twenty-seven interviewees who completed the pilot RCT participated in semi-structured interviews to describe their experiences of participating in the pilot trial and receiving the AT treatment. Five themes were identified in the interview records, including "views on CHAs," "experiences of completing the study questionnaires," "adherence to the intervention protocol," "safety and convenience of the intervention," and "perceptions of the intervention effects." The interviewees generally viewed that the CHAs could be used as convenient and safe adjuvant approaches to conventional medicine. The majority of the interviewees felt that the study questionnaires were easy to understand and that the MAT questionnaire accurately recorded their nausea and vomiting symptoms during the study period. Most of the interviewees from the true AT group and the sham AT group strictly followed the AT treatment protocol to complete the five-day AT treatment, and those in the true AT group also complied with the AT protocol to perform regular ear acupressure. Minor ear irritations were identified in a small number of interviewees, and the majority of interviewees viewed AT as a safe and convenient approach without disturbing their routine treatment and daily activities. Most of the interviewees from the true AT group and the sham AT group perceived that AT produced some favorable effects in relieving their nausea and vomiting symptoms during chemotherapy, while a few of them also believed that AT did not have specific therapeutic effects for CINV but only created some "psychological comforts" to the patients.

7.4 Summary of the chapter

This chapter reported the results of both the pilot RCT and the nested semi-structured interviews. The quantitative research (the pilot RCT) provided reliable evidence in terms of the feasibility of using a five-day AT treatment protocol in female breast cancer patients receiving chemotherapy and preliminary evidence on the effects of AT for the management of CINV. The qualitative research (the semi-structured interviews) explored patients' experiences of participating in the pilot RCT and receiving the AT treatment, which further extended our understanding with regard to the feasibility of the RCT and acceptability of the AT treatment from the patients' perspectives.

The study findings from both the pilot RCT and the semi-structured interviews not only support the feasibility of the AT treatment protocol for use in breast cancer patients undergoing chemotherapy but also highlight the implications for the further refinement of the study protocol, which can be used in a future multicenter large-scale RCT to test the definite effects of AT for the management of nausea and emesis symptoms during cancer chemotherapy. Details of the study's findings and limitations, as well as implications for future research and practice, will be discussed in the next chapter.

CHAPTER EIGHT: DISCUSSION AND CONCLUSION

8.1 Introduction

This chapter is the final chapter of the doctoral thesis, which will present the discussion and conclusion of this doctoral research project. Seven sections are included in this chapter. The study findings from the entire doctoral research project will be briefly summarized in Section 8.2, and the following two sections, Section 8.3 and Section 8.4, will interpret and discuss the study findings from the pilot RCT and the semi-structured interviews, respectively. The strengths and limitations of the doctoral research project will be presented in Section 8.5, and relevant research and practice implications will be listed in Section 8.6. Section 8.7 will summarize the whole discussion in this chapter, highlight the contributions of this study to research and practice, and present the final conclusion of this doctoral research project.

8.2 Summary of study findings of the doctoral research project

This doctoral research project primarily focused on examining the feasibility of running an RCT to explore the effects of AT on CINV and QoL among female breast cancer patients undergoing chemotherapy. To reach the study's aim and objectives, a two-stage study design following the *MRC Framework for Developing and Evaluating Complex Interventions* was utilized, which included the development of the evidence-based AT treatment protocol (phase one) and the pilot RCT and nested semi-structured interview (phase two). The AT intervention protocol was developed using an evidence-based approach, the evidence of which came from several well-designed systematic reviews on AT, acupuncture and acupressure, related AT theories, handbooks and standards, and the characteristics of cancer symptoms. Prior to testing the AT treatment protocol in the pilot RCT, a content validity study was implemented to validate the protocol by a group of experts in AT and TCM. Excellent consensus regarding the scientific and practical appropriateness of the AT treatment protocol was achieved among the panel experts, and the feasibility of using the protocol for CINV management was then examined in the pilot RCT.

The pilot RCT recruited 114 female breast cancer patients and measured a number of feasibility outcomes regarding subject recruitment and follow-up, completion of the study questionnaires and AT treatment protocol, the safety of AT, and the participants' satisfaction with the study

intervention. The study results supported good feasibility and acceptability of the RCT methodological procedures and the AT treatment protocol. The effects of AT on CINV and QoL were also preliminarily investigated in the pilot RCT. AT seemed to have positive effects on the reduction of acute and delayed CINV, particularly for acute nausea symptoms, compared with the standard care group. The antiemetic effects of true AT were also somewhat better than the sham comparison. However, the pilot study did not identify any promising effects of AT on anticipatory CINV and QoL in breast cancer patients undertaking chemotherapy. Following the completion of the pilot RCT, semi-structured interviews were performed by 27 participants to explore their experiences of participating in the pilot RCT and receiving the AT treatment. The participants generally had a positive view toward the use of CHAs, and the majority of them well supported the acceptability and feasibility of the study questionnaires and AT intervention protocol. The antiemetic effects and other beneficial effects of AT on mental well-being were also perceived by most of the participants.

The study findings from both the pilot RCT and the semi-structured interviews supported the feasibility of using the evidence-based AT treatment protocol in an RCT for cancer symptom management, and a number of implications were also retrieved for future research and practice. Details in terms of the study findings, methodological issues, and research and practice implications of this doctoral research project will be interpreted and discussed in the following sections.

8.3 Discussion of the pilot RCT findings

As the primary focus of the pilot RCT was the feasibility of the RCT's methodological procedures and AT treatment protocol, feasibility issues will therefore be discussed first in this section. In addition, the clinical outcomes regarding the effects of AT on CINV and QoL, and issues about the treatment fidelity of AT, the statistical significance and clinical significance of the AT antiemetic effects, the placebo effects of AT, potential confounding effects of baseline CINV risk factors, and sample size estimation for the future main study will also be discussed in this section.

8.3.1 Feasibility issues of the pilot RCT

8.3.1.1 Feasibility of subject recruitment and follow-up process

The pilot study demonstrated a recruitment rate of 76.5% during the subject recruitment process, and it was found to be higher than that in healthcare interventional studies using other non-pharmacological approaches for cancer symptom management, where the recruitment rates were generally lower than 50% (Courneya, Friedenreich et al., 2003; Courneya, Mackey et al., 2003; Courneya, Segal et al., 2007; Daley et al., 2007; Kissane et al., 2007; Lu et al., 2016). For instance, in an RCT using supportive-expressive group therapy in breast cancer patients, the recruitment rate was 46.8% (Kissane et al., 2007); a pilot RCT investigating the effects of acupuncture on swallowing-related QoL in patients with head and neck cancer demonstrated a recruitment rate of only 21% (Lu et al., 2016); and in an RCT using exercise to improve QoL and related health outcomes in female breast cancer patients, the recruitment rate was estimated to be only 28.6% (Daley et al., 2007). Further comparisons of the recruitment rate with other well-designed AT trials in cancer populations are difficult, as existing high-quality RCTs focusing on the use of AT for cancer symptom management are rare (Tan et al., 2014a). Based on the current study's findings, the recruitment rate in clinical research utilizing AT for cancer symptom management seems higher than in studies adopting other non-pharmacological interventions, and a recent pilot RCT using AT for osteoarthritic knees in older people and another pilot trial on AT for the management of cancer symptom clusters (tiredness, pain, and sleep problems) also supported good subject recruitment rates, which were similar to the one in this pilot RCT (Suen, Yeh, & Yeung, 2016; Yeh, Chien, Glick, van Londen, & Bovbjerg, 2015).

Strategies for maintaining satisfactory subject recruitment rates and minimizing dropout rates has been regarded as one of the most important aspects of rigorously-designed clinical studies, and a number of factors have been identified that are associated with subject recruitment and participation in clinical research, which can generally be classified into three categories: **(1)** patient-related factors, including patients' perceptions, uncertainty and concerns in terms of potential benefits and harms associated with the study intervention, patients' concerns of additional healthcare costs associated with study participation, and patients' concerns about the consumption of energy and time based on frequent travel for study participation; **(2)**

study/intervention protocol-related factors, including complexity of the study methodological procedures and intervention protocol, inconvenience and potential harms associated with the study intervention, and insufficient study information; and **(3)** healthcare-professionals-related factors, including a good relationship between healthcare professions and patients (Avis, Smith, Link, Hortobagyi, & Rivera, 2006; Baquet, Commiskey, Mullins, & Mishra, 2006; Castel, Négrier, & Boissel, 2006; Mills et al., 2006; Ross et al., 1999; Yeomans-Kinney et al., 1995).

For patient-related factors, it was indicated that patients with a good perception (less uncertainty) of the potential treatment effects of the study intervention are more likely to accept the invitation for study participation (Avis et al., 2006), while patients who are more concerned about the potential study's drawbacks, including the harms (side effects) of the intervention and the time and costs associated with frequent traveling for study participation, are more likely to refuse to take part in a study (Avis et al., 2006; Castel et al., 2006; Mills et al., 2006; Ross et al., 1999; Yeomans-Kinney et al., 1995). In this pilot RCT, although evidence regarding the effects of AT on CINV was not fully conclusive, the current research literature and underpinning AT theories still support its promising role in antiemetic management, and the AT intervention has also been proved as a convenient and safe treatment method. This information was incorporated into the study information sheet and was well explained by the researchers during the subject recruitment stage to eliminate the participants' concerns regarding the benefits and safety of the study intervention. Moreover, the AT treatment was used as an adjuvant approach to routine cancer treatment at the study sites, all treatments were completed during the patients' normal stay at the hospital, and all outcome assessments were performed on site or collected through telephone contact, which saved the patients' energy, time, and costs during their frequent study participation. The strategies mentioned above may have partially contributed to the relatively high recruitment rate in this pilot RCT. In addition, it was pointed out that having public healthcare insurance is a favorable factor for study participation (Avis et al., 2006; Baquet et al., 2006; Castel, et al., 2006; Mills et al., 2006). In the pilot RCT, the majority of potential participants were covered by different types of healthcare insurance (e.g., free government medical service, social insurance, or new rural cooperative medical service), which may also explain the relatively high recruitment rate identified in this pilot study.

In terms of the study/intervention protocol-related factors, a study protocol with research procedures that are too complicated, insufficient/unclear study information, and an intervention protocol with potential adverse reactions can be barriers to subject recruitment (Mills et al., 2006). In this pilot study, the selection of the most appropriate AT approach was based on a comprehensive analysis of safety, convenience, and effectiveness among different AT modalities, and the daily regular acupressure in the true AT group was designed not to disturb the patients' routine medical treatment and care and daily activities. Apart from routine hospital visits for different cycles of chemotherapy, no additional healthcare appointments were scheduled in this pilot RCT. During the recruitment process, details of the study information were clearly presented both orally and in writing, all of which could have been potential motivators for study participation in this pilot study.

A good relationship between healthcare professionals and patients has been frequently described as an important healthcare-professional-related factor in motivating study recruitment and participation, as patients' decisions to take part in a research or not sometimes depend on their trust in healthcare providers, particularly medical doctors, and patients who receive study information from their doctors have been found to be more inclined to take part in a study (Baquet et al., 2006; Castel et al., 2006; Mills et al., 2006). Although in this pilot study oncologists were not actively involved in subject recruitment and study implementation, the research team's core members were all qualified healthcare professionals (registered nurses), and the oncology nurses responsible for subject screening and invitation were senior staff members at the study sites who had built good relationships with cancer patients, all of which could be viewed as positive healthcare profession factors in facilitating subject recruitment and participation in this study.

Considering all the issues mentioned above, the strategies implemented to eliminate barriers to study recruitment and participation from the aspects of patient-, study/intervention protocol-, and healthcare-professional-related issues may be possible reasons for the good recruitment rate in this pilot study. Meanwhile, this study also demonstrated a high retention rate throughout the whole study process (96.5%), with only four participants dropping out. The strategies mentioned above may partially explain the high retention rate in this pilot study. Apart from one dropout

subject who did not give reasons for discontinuing the study, the other three dropouts were not caused by the inconvenience or complexity of the study procedures and/or intervention protocol but were instead due to personal/family issues that caused them to transfer to other hospitals for further cancer treatment. Another reason for the high retention rate in this study may have been the study design of recruiting breast cancer patients before their first cycle of chemotherapy. It is not surprising that some breast cancer patients at the study sites refused to continue chemotherapy due to the significant side effects and functional status deterioration experienced during the antineoplastic treatment, but this mostly happened after receiving several chemotherapy cycles, and the majority of breast cancer patients did, at least, adhere to the first three to four cycles, according to personal communication with the oncologists and oncology nurses working at the study sites.

Moreover, although an adequate recruitment rate and retention rate were identified in this study, there was a concern about the slow progress of subject recruitment. It was noted that approximately eight subjects were recruited per month and the whole study recruitment took 15 months. This could have been partially due to the strict inclusion and exclusion criteria set for the pilot study, while another reason may have been the selection of the study sites. The majority of the study participants (79.8%) were actually recruited from the provincial cancer hospital and the other two study sites contributed only a small number of participants. Specialized medical centers seem to be more attractive to breast cancer patients than comprehensive medical centers, although the two comprehensive hospitals involved in the study had their own departments for breast diseases. The future main study may consider seeking collaboration with more cancer-specialized medical centers to facilitate the subject recruitment process.

8.3.1.2 Feasibility of the study questionnaires

The participants' acceptability of the study questionnaires was also assessed in the pilot study. Findings from this pilot study indicated that there were no missing values for the MAT during the first cycle of chemotherapy. The participants also responded to all the INVR items at either baseline assessment or post-intervention (follow-up) evaluation. However, for the FACT-B, considerable missing values were identified for several items. Feasibility issues regarding each of

the study questionnaires, including the MAT, the INVR, and the FACT-B, will be discussed in the following sections.

The MAT was employed in this study to measure acute and delayed CINV symptoms. As stated in the research methodology chapter (Chapter 5, Section 5.5.7.3.1), the MAT was selected as the most suitable instrument for acute and delayed CINV assessment given its satisfactory psychometric properties and excellent clinical utility, as well as its unique design of separate measurements of acute and delayed CINV symptoms from the aspects of symptom occurrence, frequency, and severity (Brearley et al., 2008; Molassiotis, Coventry et al., 2007; Wood et al., 2011). Repeated measurements were unnecessary as the patients needed to rate the MAT only twice during one cycle of chemotherapy to assess their acute and delayed CINV symptoms, respectively (Molassiotis, Coventry et al., 2007). The excellent completion rate of the MAT in this pilot study and the patients' positive comments regarding the MAT in the semi-structured interviews (which will be discussed later) well supported its acceptability and convenience to cancer patients. As the MAT was primarily developed for use in clinical practice to facilitate good communication among healthcare professionals, researchers, and patients regarding CINV symptom experiences, the interpretation of the MAT results therefore should be mainly based on single items to inform clinical decision-making (Molassiotis, Coventry et al., 2007). In this study, rich data were generated by analyzing single MAT items, including the complete response of CINV symptoms and occurrence, frequency, and severity of nausea and vomiting at both the acute and delayed CINV phases, which enabled the researchers to gain a comprehensive picture of the patients' symptom experiences by computing the incidence, severity, and frequency score of relevant symptoms and making direct comparisons with other prospective observational study findings on CINV symptoms. The use of the MAT in this pilot study also provided an opportunity to investigate different symptom responses to the AT treatment from the aspects of both statistical importance and clinical importance (details will be discussed later). Analysis based on single items is a unique feature of the MAT, which facilitates its feasibility and usability in clinical practice and prospective observational research (Molassiotis, Coventry et al., 2007; Tan et al., 2016).

Meanwhile, it should be noted that in addition to the single-item analysis, the MAT scoring system was also utilized in this study. The MAT scoring system was first introduced by

Molassiotis et al. and was used twice in psychometric assessment studies to test against the INVR, with excellent concurrent validity identified in cancer patients from the UK, USA, and Mainland China (Molassiotis, Coventry et al., 2007; Tan et al., 2016). The MAT scoring system is not recommended for use in real clinical practice, but in the research setting, the use of the MAT scoring system is necessary as the presentation of total and domain scores of CINV symptom experiences in research articles may facilitate indirect and/or direct comparisons of the MAT scores with other multi-dimensional CINV assessment tools to examine measurement reliability and validity, enable sample size estimations based on the intervention effect size for CINV, and enable possible score transformations with other CINV instruments for secondary-analysis purposes.

Anticipatory nausea and vomiting was measured twice in this pilot study using the INVR, Chinese version. The INVR is a popular instrument for nausea and vomiting assessment, and the psychometric properties of the INVR, Chinese version, have been well documented in literature (Fu, 2008; Fu et al., 2002). The absence of missing values for INVR items identified in the pilot study and the patients' positive comments regarding the study questionnaires during the semi-structured interviews (which will be discussed later) provide evidence in terms of its adequate feasibility and acceptability to cancer patients. There is nothing wrong with adopting the INVR in clinical research to assess anticipatory nausea and vomiting. However, in this pilot study, the INVR scores were found to be extremely low at both baseline and post-intervention (follow-up) assessment given the fact that the majority of the participants did not experience any anticipatory nausea and vomiting symptoms, with only three reporting anticipatory nausea at baseline and nine and three reporting anticipatory nausea and anticipatory vomiting, respectively, at post-intervention (follow-up) evaluation. The INVR items and total scores for the majority of the study participants were therefore rated as "0" in nature, and statistical comparisons of the INVR scores among groups were therefore deemed unnecessary. It seemed that there was no need to use the INVR for anticipatory CINV assessment in this pilot study. In the future main study, the use of the INVR could be replaced by simple polar questions ("yes" or "no") to assess the occurrence of anticipatory nausea and vomiting and to reduce the participants' burden of completing too much research paperwork.

A breast-cancer-specific QoL instrument, the FACT-B, was adopted in this study to assess the participants' QoL status at both baseline and post-intervention (follow-up) assessment. The FACT-B consists of a FACT-G scale for general QoL assessment in cancer populations, which covers the physical, social/family, emotional, and functional dimensions of QoL, and another breast-cancer-specific module to address some particular QoL concerns related to breast cancer patients (Brady et al., 1997; Webster et al., 2003). Adequate psychometric properties in both the English and Chinese FACT-B scales have been identified in the literature (Brady et al., 1997; Wan et al., 2007). However, in this pilot study, considerable missing values were identified for some of the FACT-B items. At the FACT-B baseline assessment, it was found that more than half of the participants (59.6%) refused to answer question FACT-B-GS7 ("I am satisfied with my sex life"), 20.2% did not respond to question FACT-B-B4 ("I feel sexually attractive"), and 6.1% declined to answer question FACT-B-B9 ("I am able to feel like a woman"). Similar results were also identified at post-intervention (follow-up) assessment. As indicated in the semi-structured interviews, these questions were related to "personal privacy," which could have been somewhat sensitive to the participants. Considering the conservative culture in China, particularly for people living in rural areas (around half of the study participants came from rural areas in Fujian Province), it was not surprising that many participants refused to answer these sensitive questions. Significant missing values for FACT-B items related to one's sex life were also mentioned in other studies (Courneya, Mackey et al., 2003; Ng et al., 2012), and a similar situation was also identified in another non-pharmacological pilot study using the EORTC QLQ-C30 for QoL assessment in Iranian breast cancer patients, where the QoL instrument also contained some "sensitive" items related to sexual activities (Moradian, 2013).

In addition, another reason for the significant missing values for the item FACT-B-GS7 may have been the questionnaire instruction itself. As observed during the data collection process, when the participants were hesitant to answer this question, it was the questionnaire's instruction ("If you prefer not to answer it, please mark this box □ and go to the next section.") that made them finally decide to skip this question. This may also indicate that the original author(s) who developed this instrument had foreseen this issue and proposed relevant strategies for handing the missing data. In the scoring instructions, a particular formula (details can be found in Chapter 5, Section 5.5.7.3.2) has been developed to deal with missing values when computing the relevant domain scores. In

this study, the FACT-B total and domain scores were deemed to be valid as no subscale had unanswered items greater than 50%, and the FACT-B item completion rates in all the analyzed questionnaires were higher than 80%. Based on the *FACIT Administration and Scoring Guidelines*, the missing data identified in some of the FACT-B items in this study did not affect the computation of the FACT-B total and subscale scores, and the final scores were valid in reflecting breast cancer patients' QoL status. Given all of the concerns above, the feasibility of the FACT-B was determined to be acceptable (fair), and the future main study may consider using the FACT-B for QoL assessment of breast cancer patients.

8.3.1.3 Feasibility of the AT treatment protocol

The participants' adherence to the AT treatment was examined to determine the feasibility of the study intervention protocol. The total number of days of AT treatment was used to assess the participants' adherence to the AT treatment in both the true AT group and the sham AT group. For participants in the true AT group, their adherence to the AT treatment was further investigated by computing the times and durations of ear acupressure during the whole AT treatment period. The pilot study demonstrated that 80.3% of the participants in the true AT group and the sham AT group completed the five-day AT treatment. Most of the participants in the true AT group (84.2%) followed the study protocol to perform ear acupressure at least three times daily during the acute CINV phase, and the average duration for each acupressure session was four minutes or above for 71.0% of the participants. For the delayed CINV phase, 60.5% of the participants in the true AT group performed ear acupressure 12 times, and the average duration for each acupressure session was four minutes or above for 65.8% of them; for those who did not reach the required dose of ear acupressure, more than half of them still reported performing ear acupressure six to 11 times and an average of two to four minutes for each acupressure session (details can be found in Chapter 7, Section 7.2.3.3). The participants' adherence to the treatment protocol was deemed acceptable and similar findings were also reported in other RCTs using AT to manage different health issues, including breast cancer symptom clusters, smoking cessation, and chronic low back pain (Wing et al., 2010; Yeh, Chien, Lin, Bovbjerg, & van Londen, 2016; Yeh, et al., 2013; Yeh, Morone et al., 2014). For instance, in a pilot RCT using auricular acupressure for chronic pain management, a satisfactory level of adherence to the AT treatment was set as a completion of "at least two-thirds of the suggested pressing time" (p. 5 out of 11), and the

adherence rate was reported to be greater than 85% across the intervention period (Yeh, Morone et al., 2014). The convenience of the AT intervention could be one reason for the adequate adherence rate, but other contributing factors may also have had some effect.

Current literature has listed a number of potential factors that may promote or hinder participants' adherence to a study intervention, and some of them are similar to those factors associated with subject participation and recruitment (details can be found in Section 8.3.1.1 of this chapter). This section will list the factors that were deemed mostly relevant to this pilot study, which are categorized into three types, including patient-related factors, study/intervention protocol-related factors, and healthcare-professionals-related factors.

Different patient-related factors may have affected the participants' adherence to the study intervention. If participants are able to experience the treatment effects within a short period of time after receiving the intervention (immediate treatment effects), their adherence to the study intervention can be high (Ellis et al., 2012), while an increasing concern about the potential harms (adverse reactions) associated with the intervention and a negative perception (e.g., doubt or denial) of the treatment effects, on the contrary, may deteriorate their adherence (Kardas, Lewek, & Matyjaszczyk, 2013; Vermeire, Hearnshaw, Van Royen, & Denekens, 2001). These factors were reflected in this study. Comments from most of the participants in the semi-structured interviews indicated that a perception of the promising effects of AT on nausea and vomiting and the safety of AT were significant motivating factors that led to the completion of the five-day AT treatment, and for the one participant with an unsatisfactory adherence to the AT treatment protocol (as indicated in the semi-structured interview only), the most important reason was a failure to detect the antiemetic effects of the AT treatment on the first day of chemotherapy.

A simple and convenient intervention protocol that can be linked with participants' routine activities may contribute to better adherence (Ellis et al., 2012; Vermeire et al., 2001). As emphasized by DiMatteo, Haskard-Zolnierek, and Martin (2012), the complexity of the intervention is one of the most significant factors in the deterioration of patients' adherence. A complex study protocol with a long intervention duration and frequent intervention sessions may lead to significant non-adherence (DiMatteo et al., 2012; Kardas et al., 2013; Vermeire et al.,

2001). In this pilot study, the AT treatment protocol was designed to be a simple and convenient approach, where the participants could master the self-acupressure technique within a very short time and the total intervention duration was only five days, without disturbing the participants' daily activities (as supported by the qualitative data). Participants' concerns regarding the healthcare costs of the intervention may also negatively affect their adherence (Vermeire et al., 2001), but in this study, the AT treatment was cost-free for the study participants so no financial concerns should have worried them in terms of receiving the study intervention.

A good relationship between healthcare professionals and participants is also regarded as a crucial factor in enhancing adherence to the study intervention (Kardas et al., 2013; Vermeire et al., 2001), and the potential reasons were the same as for those related to study participation and recruitment, which were described earlier in this chapter. The issues mentioned above may partially explain the adequate adherence rate identified in this study. However, it should be noted that the participants' adherence rate for the total times of daily acupressure in the true AT group declined from 84.2% in the acute phase to 60.5% in the delayed phase. A failure to detect positive effects of AT on alleviating CINV symptoms and some AT-related adverse reactions that occurred during the AT treatment may have made some participants discontinue the regular ear acupressure, and another reason may have been insufficient follow-up visits scheduled in the study protocol. As summarized in the review conducted by Kardas et al. (2013), inadequate follow-up approaches and insufficient outpatient visits may deteriorate participants' adherence. In this pilot study, many participants were discharged before the completion of the five-day AT treatment, and those allocated to the true AT group were instructed to do self-acupressure at home for the rest of the AT treatment days without any supervision. Apart from the two follow-up telephone calls made after the AT intervention, no additional telephone contacts were scheduled for the early-discharged participants in the true AT group to monitor their regular ear acupressure at home, which may have negatively affected their adherence to the AT treatment protocol. The future main study may schedule more intensive follow-up support to enhance the participants' adherence to the AT treatment protocol.

The relationship between the AT treatment effects and the AT-related feasibility outcomes was examined using Spearman's correlation, and insignificant correlations were identified between the

AT-related feasibility outcomes and the majority of the MAT outcomes, which indicated that there seemed to be no obvious association between the AT treatment effects and the AT-related feasibility outcomes, but this must be interpreted with caution given the very small sample size (less than 40) included in each analysis, which may have made the data analysis underpowered. The data analysis results showed weakly positive correlations between the MAT scores and average duration of each ear acupressure session during the acute CINV, the delayed CINV and the whole AT intervention period, and a few outcomes in the acute phase reached borderline statistical significance, which revealed that a higher MAT score (a more severe CINV symptom) was positively correlated with a higher frequency of manual acupressure in the true AT group, particularly during the acute CINV phase. This could be explained by the observation that the participants who experienced more severe acute CINV symptoms during the first day of chemotherapy tended to do more ear acupressure to relieve the distressing symptoms, but this should be further clarified in the future main study with a sufficient sample size for more reliable data analysis.

8.3.1.4 Safety of AT and the participants' satisfaction with AT

Potential adverse events associated with AT were recorded by the participants in a daily log, and the causality between the reported adverse events and AT was judged by an experienced acupuncture practitioner. Eleven participants reported a few AT-related adverse events, including itching, discomfort, and pain, but the majority of them were mild and transient. Possible reason for itching might be that some participats were still allergic to the AT tapes. One participant recorded moderate pain (this participant also described it as "obvious pain" during the semi-structured interview), and one reported minor to moderate pain when adding acupressure. No serious adverse reactions were located. The findings supported the assumption that auricular acupressure is a relatively safe approach and the reported adverse reactions were mostly minor. This is in line with previous systematic review findings, which indicated that adverse events in auricular acupressure were minor, transient, and tolerable, and the side reactions disappeared soon after removing the AT tapes (Tan et al., 2014). The participant who recorded moderate pain (also described as "obvious pain" in the semi-structured interview) reported that the pain only occurred when adding acupressure to the taped seeds. Apart from interpreting it as an "adverse event" caused by AT, this could also be explained by the participant being very sensitive to acupoint stimulation, as a sense of "pain" or "aching" at the AT site when adding

acupressure is also regarded as a sign of achieving "*de qi*" sensation (MacPherson & Asghar, 2006; Guan et al., 2002, p. 116).

It must be emphasized that the incidences of AT-related adverse events were highly likely to be underreported in the pilot RCT, as the semi-structured interviews identified three cases of minor pain at the AT sites in a very small sample size (10 participants from the true AT group), but the participants' daily logs in the pilot RCT revealed only five cases of minor pain in the true AT group, and one participant from the sham AT group indicated minor redness at the AT sites during the semi-structured interview but failed to record it in the daily log. The possible non-adherence to the recording of AT-related adverse events during the pilot RCT could be partially explained by the nature of the AT-related adverse events, which were generally mild and transient. Some participants may have ignored the minor side reactions, treating them as "non-adverse events," despite the instructions given by the researchers before receiving the AT treatment.

The participants' satisfaction with the AT intervention was deemed good in this pilot study. However, it should be noted that the participants in the sham AT group actually had relatively higher satisfaction scores than those in the true AT group, although no statistically significant differences were detected between the groups. The data analysis results indicated that both the true AT and sham AT treatment produced some favorable effects in relieving nausea and vomiting compared with the standard care group, although the effects were found to be more profound in the true AT group. The antiemetic effects associated with the sham AT may have partially contributed to the participants' satisfaction with the sham approach. Moreover, there was no manual acupressure scheduled for the sham AT group, which means that the participants only needed to keep the sham tapes in place for five days without performing any manual acupressure. Therefore, the sham AT could be viewed as a "more convenient" approach than the true AT, as at least three-times-daily ear acupressure was required for the patients in the true AT group, which may have occupied some time and caused some inconvenience, and this may also partially explain the relatively higher satisfaction scores in the sham AT group compared with those in the true AT group.

8.3.2 Clinical outcomes regarding CINV and QoL

8.3.2.1 Incidence and severity of CINV in breast cancer patients

The study findings revealed that the incidence of nausea was higher (by nearly twice) than that of vomiting at both the acute CINV phase and the delayed CINV phase, and the incidence of delayed vomiting was somewhat higher than that of acute vomiting. These findings are in line with previous research conclusions, that the control of nausea is much more difficult than the control of vomiting, and delayed CINV symptoms are also more common than acute ones (although this trend was only identified between delayed vomiting and acute vomiting in this pilot study) (Escobar et al., 2015; Hsieh et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Olver, 2015; Rha et al., 2016). The CINV incidence data from the standard care group with antiemetic medication only were used to perform a preliminary comparison with the most recent observational study on CINV in cancer patients with moderately and highly emetogenic chemotherapy (Molassiotis et al., 2016). In the study reported by Molassiotis et al. (2016), incidences of acute nausea and acute vomiting during the first cycle of chemotherapy were identified as 38.3% and 24.5%, respectively, which were much lower than that reported in this study (73.7% for acute nausea and 39.5% for acute vomiting), and similar conditions were also identified for vomiting (39.1% for delayed nausea and 29.5% for delayed vomiting in Molassiotis et al., [2016] vs. 65.8% for delayed nausea and 42.1% for delayed vomiting in this study). The different measurement scales used and imbalanced sample sizes between studies may have partially contributed to the different CINV incidences reported by the studies, but one of the most important reasons for such higher CINV incidences in this pilot study may have been the lack of NK_1 receptor antagonists included in the antiemetic medications. In the study reported by Molassiotis et al. (2016), the antiemetic medications used in part of the study sample followed the MASCC guideline to include the NK_1 receptor antagonist, which is regarded as a strong antiemetic agent for both acute and delayed CINV (Aapro et al., 2012). However, the participants in this doctoral study were recruited from Mainland China, where the NK_1 receptor antagonist (aprepitant) was not commonly used in routine clinical practice at the time of the study implementation and data collection.

This pilot study also demonstrated a 2.6% incidence of anticipatory nausea before the first chemotherapy cycle (data from all three study groups), with an increase to 7.9% before the second cycle (data from the standard care group only), the rates of which were lower than that reported in the study conducted by Molassiotis et al., (2016), where the incidence of anticipatory nausea was 8.3% before the first chemotherapy cycle and 10.1% before the second one. However, both of the study findings indicated a similar trend in that the incidence of anticipatory nausea before the second chemotherapy cycle was higher than that before the first cycle, which supports the idea that nausea and vomiting symptoms experienced during the previous treatment cycle can be a contributing factor in introducing more severe anticipatory nausea in the following cycles (Molassiotis et al., 2016). Given that the current studies on anticipatory CINV in cancer patients are scanty, more research evidence is needed in the future to further explore this issue.

8.3.2.2 QoL status in breast cancer patients

The participants' QoL status in this study was measured using the FACT-B, and baseline data were used to compare with other observational studies using the same scale for QoL assessment in breast cancer patients. Baseline assessment (n=114) in this study revealed a mean score of 99.2 for the FACT-B total score. The mean scores for different subscales were 21.4 (PWB), 20.9 (SWB), 16.4 (EWB), 13.3 (FWB), 27.2 (BCS), and 61.9 (TOI), respectively. The FACT-B total and domain scores identified in this study were mostly consistent with two other observational studies conducted in Japan and South Korea, in which the FACT-B total scores were reported to be 99.5 and 95.5 (for the group of patients aged less than 50 years old), respectively (Park, Lee, Lee, Lee, & Hwang, 2011; Taira et al., 2011). The two studies excluded breast cancer patients with remote metastasis, which was similar to this doctoral research project, although the patients' mean age was a little higher in the Japanese study (53.3 years old) (Taira et al., 2011). However, it was noted that the FWB subscale score in this study (13.3) was much lower than in the Japanese study (17.5) and Korean study (17.4) (Park et al., 2011; Taira et al., 2011), which indicates that breast cancers in this study presented a relatively lower functional status associated with daily life. The participants in this pilot study were newly diagnosed with breast cancer and the majority of them had recently received breast surgery prior to the commencement of their first cycle of chemotherapy, which made them unable to work as they had to stay in bed for a period of time. Disconnections from work and related activities can be an important reason for such a

low FWB score, as nearly half of the participants in this study gave a score of "0" or "1" (indicating a worse condition) on the items related to their work conditions in the FACT-B questionnaire.

8.3.2.3 Effects of AT on acute and delayed CINV

The effects of AT on acute and delayed CINV were preliminarily examined. Regarding the effects of AT on acute CINV, the participants from the true AT group and the sham AT group generally had better CINV outcomes than those in the standard care group, and the true AT treatment usually showed better antiemetic effects than the sham AT treatment. Statistically significant differences were identified in the CR of acute CINV and the occurrence and severity of acute nausea among the three groups, with relevant effect sizes of medium or near large, but further post-hoc analyses showed significant differences only between the true AT group and the standard care group. A borderline significant difference was identified for either the occurrence or frequency of acute vomiting among the three groups, with a medium effect size. For the effects of AT on delayed CINV, all the relevant outcomes indicated relatively better effects of AT in the true AT group and the sham AT group than in the standard care group, but no significant differences were found among the three groups and the relevant effect sizes were deemed to be relatively small (near medium). Analysis based on the MAT scoring system indicated statistically significant differences in the MAT overall total, MAT total nausea, MAT acute CINV, and MAT acute nausea scores among the three groups, but further post-hoc analyses also showed significant differences only between the true AT group and the standard care group. Based on the study findings summarized above, AT seemed to have some positive effects on the reduction of CINV in breast cancer patients, particularly for nausea symptoms in the acute CINV phase.

These study findings support the conclusion of a previous systematic review conducted by the doctoral researcher, that AT can be used as a promising intervention for CINV management in cancer patients (Tan et al., 2014a). The better CINV outcomes identified in the true AT group also support the humuncular reflex theory and the Chinese *zang-fu* organs and meridians theory of AT that abnormal activities of the gastrointestinal system can be well controlled by stimulating particular ear acupoints associated with CINV. The inclusion of auricular acupoints "stomach", "cardia", "spleen" and "liver" in the true AT treatment protocol is based on the understanding that

dysfunctions in the stomach, spleen and liver are the primary causes of CINV, while the selection of acupoints "*shenmen*", "sympathetic" and "subcortex" is mainly because of their potential roles in tranquilizing the mind and regulating the abnormal activities of the gastrointestinal smooth muscles (Bai, 1994, p. 88; Guan et al., 2002, p. 199; L. Huang, 2001, pp. 96-108). The antiemetic effects of AT were well demonstrated in this study by stimulating the above mentioned CINV-specific acupoints, which can be regarded as clinical research evidence to support the close connections between particular ear acupoints and their corresponding internal organs. From clinical perspectives, findings from the pilot RCT support the potential antiemetic mechanisms of AT based on the humuncular reflex theory and the Chinese *zang-fu* organs and meridians theory. However, fully direct evidence from biological perspectives is still needed in future research to provide more reliable explanations of the mechanisms of AT for CINV management.

The findings demonstrated significant positive effects of AT in the reduction of acute nausea during cancer chemotherapy, which highlights the value of using AT as an adjuvant approach to standard antiemetic medications in routine clinical practice for cancer symptom management given the fact that nausea is more difficult to manage than vomiting using current antiemetic treatment strategies (Escobar et al., 2015; Hsieh et al., 2015; Kottschade et al., 2016; Molassiotis et al., 2016; Olver, 2015; Rha et al., 2016). The effects of AT on acute vomiting were also promising given that a borderline significance and medium effect size were identified for either the occurrence or frequency of acute vomiting. The small sample size as well as the small proportion of participants reporting vomiting in this pilot study may have partially contributed to the borderline (insignificant) difference in acute vomiting between groups, and the future main study with a relatively large sample size may help further prove the value of AT in vomiting management.

A further comparison of the current study findings with other well-designed AT trials on CINV management was impossible due to the lack of rigorous studies of this kind in current literature. The most recent crossover RCT conducted in Iran (n=48) examined the effects of AT in breast cancer patients, and frequency and intensity of acute and delayed CINV were compared between the intervention group with auricular acupressure plus antiemetic medications and the control group with antiemetic medications only (Eghbali, Yekaninejad, Jalalinia, Samimi, & Sa'atchi, 2016). The Iranian study indicated that AT was effective in alleviating acute and delayed CINV,

with the majority of outcomes reaching statistically significant differences, except for the intensity of acute vomiting (Eghbali et al., 2016). The findings of the Iranian study also supported a favorable role of AT in CINV management, but the results regarding the effects of AT on delayed CINV symptoms were inconsistent with the results identified in this pilot study. However, the Iranian study results should be prudently interpreted due to a number of methodological flaws; for instance, the study included a very small sample size, with only 48 subjects; procedures regarding randomization and allocation concealment were not reported; acute and delayed CINV were measured by the MANE, which was only appropriate for assessing anticipatory and acute CINV but not for delayed symptoms, and the psychometric properties of the MANE, Iranian version, were also insufficiently tested and reported; and information in terms of patients' adherence to AT was unclear. It should be noted that healthcare interventional studies with limited methodological quality, such as the absence of adequate allocation concealment, are more likely to overestimate the interventional effects (Kunz, Vist, & Oxman, 2007).

This study did not show any significantly positive effects of AT on delayed CINV, which partially reflects the possibility that delayed CINV is more difficult to manage than acute CINV, but other reasons may have also contributed to these results. It was noted that the participants' adherence rates for regular ear acupressure were lower in the delayed CINV phase compared with the acute phase, where nearly 40% of the participants in the true AT group failed to strictly follow the AT protocol to perform ear acupressure at least 12 times during the delayed CINV period, and the average time for each ear acupressure session was found to be less than four minutes for more than 30% of the participants. The non-adherence to regular ear acupressure identified by some of the participants during the delayed CINV phase could have undermined the treatment effects of AT, which may partially explain the "statistically insignificant" results in terms of the effects of AT on the reduction of delayed CINV. Meanwhile, it should be noted that sample size estimation in this pilot study was not power-based and the statistical analysis of the delayed CINV symptoms was underpowered (e.g., the among-group differences for the occurrence of delayed nausea and delayed vomiting revealed insufficient power of less than 0.50), which indicated a high possibility that a type II error occurred and as a result the statistical analysis was unable to detect significant differences in delayed CINV symptoms between groups. Nevertheless, the positive (but insignificant) trend in the reduction of delayed nausea and vomiting in the true

AT group and the sham AT group indicated the potential value of AT for delayed CINV management, and a future main study, with a sufficient sample size, is necessary to further evaluate the definite effects of AT on acute and delayed nausea and emesis in cancer patients.

Given the concerns above, this pilot study provided preliminary evidence that the antiemetic effects of AT are highly suggestive but are still not fully conclusive. In addition, it was noted that the sham AT group showed better CINV outcomes than the standard care group, which also suggested the existence of non-specific treatment (placebo) effects of the AT intervention. Issues regarding the placebo effects of AT will be discussed later in Section 8.3.5.

8.3.2.4 Effects of AT on anticipatory CINV

The effects of AT on anticipatory CINV were also examined in this pilot study, but the results did not show any statistically significant difference among groups. An observational study has identified that the experience of nausea and emesis symptoms during a previous treatment cycle is an important and strong predictive factor in anticipatory nausea that occurs in the following treatments (Molassiotis et al., 2016), which indicates the possibility that better control of CINV using AT during the first cycle of chemotherapy may help reduce anticipatory nausea symptom in the second chemotherapy cycle. However, the data analysis in this study did not reveal any positive effects of AT on anticipatory CINV and several potential reasons may explain this finding. Burish and Carey (1986) (as cited in Roscoe, Morrow, Aapro, Molassiotis, & Olver, 2011) indicated that the complexity of the potential mechanism of anticipatory nausea and vomiting in the development and onset of anticipatory symptoms can be associated with a number of factors, from neurological to psychophysiological aspects, and thus the management of anticipatory nausea and vomiting during cancer treatment is difficult. Complex interventions focused on behavior changes (e.g., hypnosis and progressive muscle relaxation) have been utilized as promising interventions for controlling anticipatory nausea and vomiting, although the research evidence is not fully conclusive yet (Roscoe et al., 2011). However, the AT treatment used in this study was not designed for behavior changes, which may not be the optimal approach for the management of anticipatory CINV. Meanwhile, compared with acute and delayed CINV, the incidence of anticipatory symptoms was relatively lower (Molassiotis et al., 2016), which indicated that a large study sample with sufficient statistical power is necessary to detect the true

effects of an intervention for anticipatory CINV. However, statistical analyses of the among-group differences in the incidence of anticipatory nausea and vomiting in this pilot study were found to be considerably underpowered, and a type II error ("false negative") was highly likely in this case (Button et al., 2013). The effects of AT on anticipatory nausea and vomiting should be further examined in the future main RCT, with a more adequate and reliable sample size.

8.3.2.5 Effects of AT on QoL status

The participants' QoL status was measured at both baseline assessment and post-intervention (follow-up) assessment. It was noted that the participants' QoL deteriorated across the first cycle of chemotherapy, regardless of which group they belonged to, which indicated that the cancer treatment and related distressing effects gradually decreased the participants' functional status. There was no statistically significant difference in QoL status among the three groups at the end of the first chemotherapy cycle, which literally demonstrated that AT seemed to have no effects on the participants' QoL status, but the insignificant changes in QoL among groups may have been attributed to other reasons. The first reason can be the small sample size issue of this pilot study, which was described in early sections of this chapter. The second reason may be the unsatisfactory control of nausea and vomiting symptoms during the delayed phase of CINV, as the ongoing experiences of CINV symptoms with a longer duration have been proven to be linked with more deteriorated QoL (Fernandez-Ortega et al., 2012). The participants in this pilot study continued to suffer from different degrees of delayed CINV symptoms during the first several days after receiving chemotherapy, regardless of receiving AT treatment or not, and the statistically insignificant differences in delayed CINV symptoms among groups (which may have been partially attributed to non-adherence to the AT treatment protocol for some participants during the delayed CINV phase) can be linked with insignificant QoL changes among groups given the close relationship between cancer patients' CINV symptom distress and their QoL status. In addition, it should be noted that the concept of QoL for cancer patients has comprehensively covered different dimensions, from physical, emotional, and social to functional aspects (Holzner et al., 2006); thus, the improvement of QoL status may be more sensitive to those complex interventions with multidimensional components aimed at physical and psychosocial support. The AT intervention protocol designed in this doctoral research project was mainly focused on physical symptom relief, so the selection of the targeted acupoints did not take into

account psychological support for breast cancer patients, and this could be one potential reason for the insignificant results in terms of the effects of AT on patients' QoL status in this pilot study.

The three sections above comprehensively discussed the results of the preliminary analysis regarding the effects of AT on CINV and QoL for breast cancer patients. In general, the statistical analyses indicated that AT can be a promising non-pharmacological approach used in combination with antiemetic medications to deal with CINV, particularly for the alleviation of acute nausea. However, the effects of AT on anticipatory CINV and QoL failed to be detected in this study. The small sample size with underpowered statistical analysis can be one of the reasons for this finding, and non-adherence to the intervention protocols by some participants can be another potential reason, which is related to the issue of intervention fidelity. Moreover, for some outcome comparisons in the preliminary data analysis, although no statistical significance was found, a clinical significance may also exist that could further elaborate the potential value of the AT treatment used in real clinical practice. Placebo effects of the AT intervention were also detected in the data analysis; thus, the distinction between the specific treatment (true) effects and non-specific treatment (placebo) effects of AT should be further clarified and discussed. Issues in terms of intervention fidelity, statistical significance, and clinical significance, as well as the placebo effects of AT, will be discussed in the following sections.

8.3.3 Fidelity of AT intervention

Fidelity can be generally defined as "the extent to which delivery of an intervention adheres to the protocol or program model originally developed" (Mowbray, Holter, Teague, & Bybee, 2003, p. 315). The fidelity of an intervention protocol is of crucial significance for an interventional study design and it often consists of a series of approaches to maintain the validity and reliability of the research intervention (Bellg et al., 2004). It has been emphasized that an accurate examination of the interventional effects and/or a further replication of research design for a certain study could be problematic if the study is linked with "questionable internal and external validity" (Bellg et al., 2004, p. 444). To maintain the intervention fidelity at the stage of research design, several core components should be taken into consideration, including the design of the intervention protocol, training of research personnel (for study implementation), implementation of

the intervention protocol, receipt of the intervention protocol (study participants), and further enactment of techniques gained from the intervention protocol (Bellg et al., 2004; Gearing et al., 2011; Smith, Daunic, & Taylor, 2007). The majority of the key strategies for optimizing intervention fidelity were utilized in this pilot study design to maintain the rigor of the AT treatment protocol.

The component of "design of the intervention protocol" included in intervention fidelity emphasizes that the development of the intervention protocol, including the protocol contents and frequency and duration of the intervention, should follow relevant theories, guidelines, and recommendations; the "dose" of the intervention should be the same across participants in a certain group; and a number of strategies should be prepared in advance to deal with some possible setbacks that night occur during the study implementation, such as the dropout of research personnel (Bellg et al., 2004; Smith et al., 2007). In this pilot study, the fidelity of the AT intervention related to the study design was well maintained, as the AT intervention protocol was developed based on related research evidence, AT theories, several well-known AT handbooks, national standards for locating and identifying auricular acupoints, and the characteristics of targeted cancer symptoms. The content validity of the AT treatment protocol was also supported by a panel of experts specialized in AT and TCM. AT intervention procedures in both the true AT group and the sham AT group were standardized, and the contents and "dose" of the AT treatment (e.g., the selected auricular acupoints, approaches for acupoint location, technique for ear acupressure, and frequency and duration of AT) were also designed to be the same for all the participants within each group. In terms of the planned strategy for handling potential setbacks, such as the possible dropout of research personnel, in addition to the doctoral researcher, two backup researchers with a Chinese medicine nursing background were also invited to participate in the study implementation in case several of the participants who took part in the study received the AT treatment on the same day, or one of the researchers was not available for the study implementation at a particular time point.

The component of "training of research personnel" places its focus on the intensive training of the research personnel for the administration of the study intervention protocol to ensure that the intervention protocol can be implemented "as designed with an acceptable level of quality, or

effectiveness" (Smith et al., 2007, p. 125). For studies involving multiple researchers administering the intervention protocol, the training should also be standardized to ensure that the intervention is performed in the same manner among the different researchers (Bellg et al., 2004). In this pilot study, the three researchers were all registered nurses who had mastered the technique of auricular acupressure during their postgraduate studies or clinical training. Prior to the commencement of this pilot study, all of the researchers were trained again by an associate professor who worked at a Chinese medical university and the training was guided by standard AT treatment procedures. Verbal communication between the researchers and the participants was also pre-standardized to ensure the consistency of the implementation of the AT treatment protocol among the different researchers. Written instructions on the standard AT treatment procedures were given to the researchers to remind them to strictly follow the standard procedures when performing the AT treatment, and the accuracy for locating and identifying the targeted ear acupoints among the researchers was examined by the associate professor before the commencement of the pilot study. During the study implementation period, bimonthly meetings were held among the researchers to discuss and solve any potential inconsistencies in the implementation of the AT treatment protocol. Details regarding the training of researchers for the delivery of the AT treatment can be found in Chapter 5, Section 5.7.1.1.

In terms of the component "implementation of intervention protocol," strategies should include monitoring the process of the intervention protocol delivery to maintain the internal validity of the study (Bellg et al., 2004; Smith et al., 2007). For the component of "receipt of intervention protocol," it must be ensured that the study participants (the recipients of the intervention protocol) well understand the study intervention and are able to follow the standard protocol to complete the intervention as required (Bellg et al., 2004; Smith et al., 2007). Both of these components were addressed in the pilot study. As indicated above, the researchers followed the standard AT treatment procedures with written instructions to maximize the consistency of the implementation of the AT treatment protocols among the different researchers, and peer observations were performed several times during the study period to ensure that the AT treatment was similarly administered among the researchers. For the study participants in the true AT group, after attaching the AT tapes to the targeted acupoints, instructions and techniques for ear acupressure were taught by the researchers, and the participants had to perform a return demonstration afterward to ensure

that they totally understood the study intervention procedures and mastered the self-acupressure techniques. Instructions and techniques for auricular acupressure were also summarized on each page of the daily log so that participants in the true AT group could follow the written instructions to perform self-acupressure. Relevant strategies were also proposed to ensure the participants' adherence to the AT treatment protocol. For instance, the researchers monitored the duration and frequency of regular ear acupressure and the completion of daily logs for the participants in the true AT group during the first three days of the AT treatment period when the participants were staying at the hospital (although there were always several participants who did not strictly follow the researchers' instructions to complete the self-acupressure and daily log), and the research assistants made telephone calls at the end of the five-day AT treatment (day 6 of the first chemotherapy cycle) to remind the participants to remove the AT tapes and to ensure a fixed AT duration was achieved for all the participants in the true AT group and the sham AT group.

The final component of intervention fidelity, "further enactment of techniques gained from the intervention protocol," indicates that strategies should include the dissemination of the techniques and knowledge gained from a research project to routine activities (Bellg et al., 2004; Smith et al., 2007). However, this component was not addressed in this doctoral research project given the pilot design nature of the RCT. The translation of the clinical research evidence into real practice should be based on a precondition that concrete and reliable research evidence has already been concluded from full-powered large-scale RCTs. In this study, the effects of AT on CINV and QoL were not the primary focus of the pilot RCT and related clinical outcomes were only preliminarily analyzed. The enactment of the AT treatment is therefore recommended to be addressed in the future main study, with a long-term observation of the participants' behavior changes.

Although the intervention fidelity of the AT intervention protocol was almost adequately maintained in this pilot study, some drawbacks in the study implementation process were still observed given the gradual decrease in the participants' adherence to the AT treatment protocol during the delayed phase of CINV, which affected the validity and reliability of the study findings. Potential reasons for non-adherence by some of the participants and relevant strategies for improvement have been pointed out in an early section of this chapter (see Section 8.3.1.3), and

those strategies mentioned earlier can also be utilized for further enhancement of the fidelity of AT treatment in the future main study.

8.3.4 Statistical significance and clinical significance

In addition to the statistical significance determined by the statistical hypothesis testing, clinical significance is also an important aspect in the interpretation of the intervention effects (Page, 2014). In healthcare interventional studies, statistical inference is often utilized as the primary approach to determine the possible intervention effects (Jacobson & Truax, 1991). However, the interpretation of the intervention effects from only statistical perspectives may be insufficient given the fact that statistical hypothesis analysis cannot reflect the actual response variability to a certain intervention in a particular study population, and statistical significance identified in the analysis of intervention effects is not necessarily related to clinical importance (Jacobson & Truax, 1991; Jacobson et al., 1999). Cella, Hahn, and Dineen (2002) (also cited in Moradian, 2013) emphasized that statistical analysis with significance testing can provide valuable information on the between- or within-group changes of patient outcomes, but it cannot prove whether the statistically significant changes are really useful to the patients. Peterson (February 2008) (also cited in Moradian, 2013) mentioned that statistical significance testing has its own limitations, as it only provides a judgment of whether a research hypothesis should be accepted or rejected, not whether the statistically significant differences are really relevant to the actual concerns of researchers, clinicians, or patients. The introduction of effect size estimation in statistical inference still cannot remedy the limitations of statistical hypothesis testing; as indicated by Jacobson and Truax (1991), effect size estimation is "relatively independent of its clinical significance" (p. 12).

The clinical significance of healthcare interventions is of crucial importance to patients and healthcare professionals in achieving satisfactory clinical decision-making and for policymakers in developing or changing healthcare policies (Guyatt et al., 2002). Compared with statistical significance, clinical significance is sometimes regarded as the most important indicator in evaluating the effects of an intervention in real clinical practice (Jacobson & Truax, 1991). However, it should be noted that intervention effects with statistical significance do not always reflect clinical significance (Cella et al., 2002; Mariani & Pêgo-Fernandes, 2014; Page, 2014). Freiman et al. (1978) (as cited in Man-Son-Hing et al., 2002) once emphasized that insignificant

research findings merely determined by statistical inference in many academic papers may have ignored the possibility that some of the statistically insignificant outcomes might be clinically significant. All of these findings suggest that both statistical significance and clinical significance should be explored when interpreting the intervention effects in healthcare research.

However, the determination of clinical significance in healthcare research is somewhat difficult (Page, 2014). A literature review conducted by Man-Son-Hing et al. (2002) (also cited in Moradian, 2013) summarized the commonly used approaches to determine clinical significance but concluded that no consensus could be found in the optimal approaches to identifying the clinical significance of intervention effects. This review also presented different opinions on determining clinical significance, including subjective judgments from healthcare professionals and views and preferences from patients based on the observed effects of the healthcare interventions, and the minimal differences that could be detected by patients using different clinical measurement scales (Man-Son-Hing et al., 2002). Pauker and Kassirer (1980) (also cited in Moradian, 2013) posited that the clinical significance of intervention effects could be judged by the clinicians based on a comprehensive estimation between the therapeutic benefits and harms associated with a certain intervention or treatment. Laupacis, Sackett and Roberts (1988) (also cited in Mariani & Pêgo-Fernandes, 2014) once introducted a method named "number needed to be treated" (p. 1729) as one of the approaches to determing clincial benefits associated with the prevention of side reactions. Bellamy et al. (1992) recommended that expert consensus via the Delphi approach could be utilized to determine the clinical importance of the interventional effects. Naylor and Llewellyn-Thomas (1994) (also cited in Moradian, 2013) examined the roles of patients and healthy volunteers in identifying the threshold of clinical significance by exploring their expectations of the potential benefits and harms associated with the studied healthcare intervention or treatment. It is obvious that the identification of clinical significance for a certain intervention may vary across different people or parties as they usually hold different beliefs, preferences, and expectations of the intervention (Man-Son-Hing et al., 2002). The judgment of clinical significance is somewhat arbitrary and can be affected by many factors, including the particular research design and hypothesis, the selection and characteristics of the study participants, the severity of the healthcare problem, the major outcome variables to determine the intervention effects, the features of the study intervention, the possible harms

associated with the intervention, the length of the follow-up assessment, and the accessibility of other replacement approaches (Bellamy et al., 1992; Man-Son-Hing et al., 2002; Sierevelt, van Oldenrijk, & Poolman, 2007).

In this pilot study, the preliminary data analysis placed a major focus on the effects of AT on acute and delayed CINV, and statistical analysis based on MAT single items revealed that statistically significant differences were identified in only a few outcome comparisons related to acute CINV symptoms, particularly acute nausea, while the majority of the MAT outcomes showed statistically insignificant differences among groups although a positive trend of AT on delayed CINV symptoms was shown. Given the issues of clinical significance presented in the paragraphs above, there is a possibility that the statistically insignificant differences identified in some CINV variables in this pilot study may be clinically significant and important to both patients and clinicians, and the antiemetic value of the AT treatment in cancer symptom management could be further enhanced and elaborated from the perspective of clinical importance.

However, current literature regarding the consensus of clinically significant changes in cancer-related nausea and emesis is rare. Several studies that have focused on CINV and postoperative nausea and vomiting have suggested their own thresholds for determining the clinical significance in the change in nausea and vomiting symptoms. A well-designed phase III RCT indicated a widely accepted clinical significance threshold for the change in CINV symptoms in cancer patients, in which a "10% difference between groups in the proportion of patients who had a complete response" of CINV (p. 117) was determined as a clinically important change (Saito et al., 2009). The standard of 10% change in the complete response of CINV was also utilized in a systematic review examining the antiemetic role of palonosetron in CINV management (Popovic et al., 2014). In another RCT focused on postoperative nausea and vomiting, a 12% change in the incidence of nausea was regarded as a potentially significant value, indicating clinical importance (Visalyaputra, Petchpaisit, Somcharoen, & Choavaratana, 1998). In a recent pilot RCT using a non-pharmacological intervention for CINV management in breast cancer patients, the threshold of clinical significance for the change in CINV symptoms was also considered to be 10% (Moradian, 2013). Based on the recommendations above, the clinical significance of the change in

CINV symptoms in this pilot study was therefore determined to be a 10% change in the complete response of CINV symptoms or incidence of nausea and vomiting between groups.

Following the clinical significance threshold of 10% change identified above, it was found that the differences in the CR of overall CINV, CR of acute CINV, CR of overall nausea, CR of overall vomiting, occurrence of acute nausea, occurrence of acute vomiting, and occurrence of delayed vomiting reached clinical significance between the true AT group and the standard care group, and between the sham AT group and the standard care group. Differences in the occurrence of delayed nausea also reached clinical significance between the true AT group and the standard care group. These findings suggest that the changes in the majority of CINV symptoms were clinically important to breast cancer patients and clinicians, even for several outcomes (particularly delayed CINV symptoms) that showed insignificant differences in statistical hypothesis testing. Taking into account both the statistical significance and clinical significance of the effects of AT on CINV symptoms, preliminary research evidence therefore concluded that AT can be used as an effective adjuvant approach to standard antiemetic treatment in routine clinical practice for the management of nausea and emesis symptoms in breast cancer patients undertaking chemotherapy.

8.3.5 Placebo effects of AT

Acupoint stimulations such as acupuncture and acupressure used in research and practice are believed to be associated with different degrees of non-specific therapeutic effects on health conditions, which are usually referred to as placebo effects (Tan et al., 2015). Placebo effects can be described as "the direct therapeutic effects associated with the perception and interpretation of signs" (Miller & Colloca, 2010, p. 515). To distinguish the specific treatment (true) effects of an intervention (treatment) from the non-specific treatment (placebo) effects, a placebo control comparison is usually included in healthcare interventional research (Dincer & Linde, 2003). Moreover, to further measure the size of potential placebo effects in an intervention, a comparison group with routine methods of treatment or care should be included to make comparisons with the true and sham interventions (Dowrick & Bhandari, 2012; Tan et al., 2015). In addition, to accurately separate the specific treatment (true) effects in an intervention from the non-specific treatment (placebo) effects, the placebo comparison approach should be prudently designed to

eliminate or minimize its potential specific treatment effects, although this has been found to be very challenging in acupoint-stimulation research (Dincer & Linde, 2003; Tan et al., 2015).

In this pilot study, the design of the sham AT approach was based on the recommendations of several well-designed systematic reviews on sham acupuncture/acupressure/AT (Dincer & Linde, 2003; Tan et al., 2015; Zhang et al., 2014). An approach using same-ear acupoints utilized in the true AT group without any additional acupoint stimulation was employed in this pilot study as the sham AT comparison because this kind of design can eliminate specific therapeutic effects generated from acupoint stimulation and maintain successful blinding among the participants in the true AT group and the sham AT group to a great extent (Tan et al., 2015). In other words, the sham AT design utilized in this pilot study could, at least to the largest extent, ensure that the effects generated from the sham AT were purely placebo effects, and further comparisons of "true AT vs. sham AT" and "sham AT vs. standard care" could accurately locate the specific effects and placebo effects of AT, respectively.

The findings of this pilot study indicated that both the true AT and sham AT interventions were found to be superior to standard care in the management of CINV symptoms, with a number of outcomes reaching statistical or clinical significance. However, it should be noted that statistically significant differences were identified only between the true AT group and the standard care group, although clinically significant differences were also found in some CINV outcomes between the sham AT group and the standard care group. Meanwhile, a further comparison between the true AT and the sham AT revealed relatively better CINV outcomes (except for the occurrence of delayed vomiting) in the true AT group compared with the sham AT group, but none of the differences reached statistical significance. Clinical significance between the true AT group and the sham AT group was identified only in the occurrence of acute nausea (44.7% in the true AT group vs. 55.3% in the sham AT group) and the occurrence of acute vomiting (15.8% in the true AT group vs. 26.3% in the sham AT group). Based on the study results presented above, it was concluded that both the true AT and sham AT were effective in alleviating CINV symptoms in breast cancer patients and the antiemetic effects were relatively stronger using the true AT treatment. That is to say, the antiemetic effects of the AT treatment mostly consisted of both specific treatment (true) effects and non-specific treatment (placebo) effects. The antiemetic

effects of AT on the occurrence of delayed vomiting were merely placebo effects based on the pilot study findings, as both the true AT group and the sham AT group revealed a similar occurrence of delayed vomiting. Given the clinically significant differences identified in a number of CINV outcomes between the sham AT group and the standard care group, the placebo effects of AT can be judged as very large and clinically important to breast cancer patients and clinicians.

The effects of AT were a mixture of specific treatment effects and placebo effects. This finding is consistent with a recent systematic review that focused on sham approaches in body acupressure, which concluded that true acupressure is more effective than sham comparisons and the effects of sham acupressure is also superior to standard care (Tan et al., 2015). A secondary analysis of a Cochrane review on sham approaches used in clinical research indicated that the effects of sham acupuncture seemed superior to other placebo approaches using pharmacological and physical interventions (Linde, Niemann, & Meissner, 2010). The relatively large placebo effects identified in different acupoint-stimulation methods (e.g., AT, body acupuncture, and body acupressure) may have been partially attributed to the participants' expectations of the study intervention, which produced some non-specific treatment effects for the alleviation of symptoms (Lundeberg, Lund, Sing, & Näslund, 2011; Tan et al., 2015). In this pilot study, the participants were all Chinese who generally held a positive view toward complementary medicine and other traditional treatment approaches. Therefore, the participants may have had relatively high expectations of the AT treatment, and the non-specific psychological effects may have been induced by these expectations, which subsequently contributed to better symptom relief. From a biomedical perspective, it has been found that patients' expectations of the treatment induced by sham interventions could be explained by the activities of the reward system in the brain, which both the prefrontal cortex and ventral striatum play key roles in the mechanisms (Lundeberg et al., 2011). Another reason that can possibly explain the relatively large placebo effects of AT is the patient-reported outcome measures used in this study. All the CINV data in this study were collected from patient-reported questionnaires, which are commonly regarded as subjective measures and the judgments are highly likely to be affected by patients' expectations of the AT intervention (Tan et al., 2015).

Nevertheless, the findings from this pilot study not only support the AT theories that the stimulation of particular auricular acupoints can generate specific treatment effects for the

alleviation of nausea and vomiting during cancer therapy, but also indicate that the treatment effects of AT are not merely generated from specific acupoint stimulation but from a mixture of specific treatment effects and placebo effects. The placebo effects of sham acupoint stimulation are usually found to be relatively large (Linde et al., 2010), and in this study, they even reached the threshold of clinical significance. Based on these considerations, the sham AT treatment, together with other sham acupoint-stimulation methods, including body acupuncture and acupressure, can even be viewed as non-specific but emotion-focused interventions from a psychological point of view, which might help improve symptom management in clinical practice (Lundeberg et al., 2011; Lundeberg, Lund, Näslund, & Thomas, 2008; Tan et al., 2015).

8.3.6 Potential confounding effects of baseline CINV risk factors

Braga et al. (2012) indicated that "confounding" can be described as "a situation when one finds a spurious association or misses a true association between an exposure variable and an outcome variable as a result of a third factor or group of factors referred to as confounding variable(s)" (p. 132). Confounding effects undermine the correct cause-and-effect analysis between an intervention and outcomes, which should be addressed in the study design stage or at the later stage of data analysis (Jager, Zoccali, Macleod, & Dekker, 2008). Randomization has been viewed as an appropriate approach to reduce confounding, as a rigorously-performed randomization procedure can minimize selection bias and help ensure that potential confounders are equally distributed among groups, particularly for RCTs with relatively large sample sizes (Jager et al., 2008). However, even with the help of randomization, patient characteristics and some potential confounding factors may still show some imbalances between groups, but the use of randomization can ensure that the imbalances are caused by chance, not the preference of study researchers (Jager et al., 2008). Some imbalances in patient characteristics and other known/unknown confounding factors may occasionally occur in RCTs with small sample sizes, which could be further addressed at the data analysis stage (Braga et al., 2012).

In this pilot study, the participants' demographic data and clinical characteristics were well comparable across groups, without any statistically significant differences. However, some insignificant variations in the participants' CINV risk factors (younger age, history of morning sickness, and history of motion sickness) were shown at baseline, with relatively more CINV

risk factors identified in the true AT group and the sham AT group than in the standard care group. Although not statistically significant (*p* ranged from 0.12 to 0.50), the imbalance of CINV risk factors might have produced some potential confounding effects in the final analysis. Therefore, in this pilot study, which performed an exploratory analysis of the clinical outcomes, the GEE model was utilized as an additional secondary analysis to examine the potential confounding effects of the three CINV risk factors. The three factors were introduced one by one as a potential covariate into the GEE model, and the covariate-adjusted between-group mean differences and effect sizes (Cohen's d) for the MAT scores were compared with the covariate-unadjusted values to see whether there were any significant variations in those statistics before and after controlling the potential confounding factor.

The findings presented in the results chapter (Chapter 7, Section 7.2.5) indicated that the confounding effects of the three CINV risk factors were deemed to be very small and did not obviously change the between-group mean differences and related effect sizes, as the between-group comparisons that showed significant (insignificant) differences in the covariate-unadjusted GEE continued to be significant (insignificant) in the covariate-adjusted GEE, and the effect sizes for the between-group comparisons that revealed small (medium or large) effects in the covariate-unadjusted GEE also continued to be small (medium or large) in the covariate-adjusted GEE. However, it should be noted that the between-group mean differences and the related effect sizes for the majority of comparisons turned out to be a little higher in the covariate-adjusted GEE model than in the covariate-unadjusted GEE model, which indicated that the "statistically insignificant" imbalance of the CINV risk factors at baseline weakened the true effects of AT on CINV symptoms. Relevant strategies should be considered in the future main study to minimize the possible confounding effects to the utmost extent at the research design stage, and a restricted randomization method could be used to ensure the balance of patients' CINV risk factors and other known risk factors associated with CINV during the randomization procedure.

8.3.7 Sample size estimation for the future main study

The findings of this pilot study provided some information for the future main study sample size estimation. Given that the clinical significance of the CINV outcomes in this study was determined by the 10% change in the complete response of CINV symptoms or incidence of nausea and

vomiting between groups, the effect sizes of those comparisons, which reached both statistical significance and clinical significance in the complete response of CINV and the occurrence of nausea and vomiting, were utilized for sample size estimation using the G*Power version 3.1.9.2 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). Therefore, the effect sizes of the among-group differences in the complete response of acute CINV (effect size=0.25) and the occurrence of acute nausea (effect size=0.24) were used for sample size estimation. Considering a power of 0.8 and an α of 0.05, the total sample size was calculated as 155 for the effect size of 0.25 and 168 for the effect size of 0.24, respectively, and the relatively large size (168, with 56 subjects in each of the three groups) will therefore be utilized for the future main study. Taking into account a relatively conservative attrition rate of 5.0% after the first cycle of chemotherapy, the final sample size for the future main study was determined to be 177, with 59 subjects in each group.

8.4 Discussion of the semi-structured interview findings

The *MRC Framework for Developing and Evaluating Complex Interventions* has recommended a combination of quantitative and qualitative research methods to evaluate the study feasibility and pilot the methodological procedures (Craig et al., 2008). Qualitative research nested within healthcare interventional studies can also enrich the quantitative study findings and collect additional information on the participants' experiences and views of taking part in the interventional study, which can enable a further investigation of the possible explanations that led to the success or failure of the intervention/treatment and can help locate some potential limitations in the research design for future enhancement (Hopton, Thomas, & MacPherson, 2013; Hughes et al., 2013). Nested qualitative studies within RCTs have been utilized in many acupuncture/acupressure trials to further enrich the interpretation of the quantitative research data (Hopton et al., 2013; Huang, Howie, & Robinson, 2012; Hughes et al., 2013, 2014; Moradian, 2013; Paterson, Zheng, Xue, & Wang, 2008). In this doctoral research project, following the completion of the pilot RCT, semi-structured interviews were conducted to explore the participants' experiences of participating in the pilot RCT and receiving the AT treatment. The use of the thematic analysis approach according to the guide described by Braun and Clarke (2006), as indicated by Hopton et al. (2013), "allowed the themes to develop directly from the patients' own voices, and enabled a more accurate representation of their experiences without the

constraint of preconceived ideas" (p. 10 out of 11). The findings from the qualitative studies advanced the understanding of the pilot study feasibility outcomes and effects of AT on CINV symptoms and highlighted some potential limitations of the pilot RCT design, which should be addressed in the future main study. Relevant discussions will be presented in the following paragraphs.

The participants in the semi-structured interviews generally held a positive view toward CHAs and well accepted the adjuvant roles of CHAs to conventional medicine. Their beliefs in the supportive roles of CHAs in health maintenance and symptom management and their convenience and safety were important motivators for study participation. In China, CHAs mostly consist of traditional treatment approaches, including acupuncture, acupressure, massage, scraping therapy, health qigong, and Chinese herbal medicine, and they have been used in clinical practice for thousands of years. CHAs are now widely practiced in different healthcare facilities, such as private clinics, community health centers, TCM-specialized hospitals, and large comprehensive hospitals, and relevant healthcare policies and regulations have been developed to standardize the practice of CHAs across China. Given the wide popularity of CHAs in China, it was not surprising that the majority of the participants were generally familiar with different CHA approaches and expressed their desire to receive AT for their symptom management, which also partially explained the high recruitment rate of the study subjects and acceptable adherence to the study treatment in the pilot RCT. This is also consistent with the qualitative study findings reported by Hopton et al. (2013) and Hughes et al. (2013), in that the patients' willingness to receive the intervention to gain some benefits for their health was an important indicator of their acceptability of study participation and/or receiving the proposed intervention.

The participants' acceptability of the study questionnaires was also well supported by the qualitative data, as the majority of the participants in the semi-structured interviews agreed that the study questionnaires were easy to understand and they did not experience any additional burden in completing the paperwork. Meanwhile, possible reasons for the high missing values rate for several FACT-B items related to sexual activities were also revealed during the interviews, as one participant indicated that these questions somewhat invaded her privacy so she followed the questionnaire's instructions to directly skip the "sensitive items." As indicated earlier in this

chapter, the conservative culture in China (particularly in rural areas) may be the main reason for the high missing values rate for the sexual-activities-related items in the QoL scale. Similar findings were also reported in another qualitative study (focus groups) nested within a non-pharmacological pilot RCT conducted in Iran, in which most of the study participants (female breast cancer patients) refused to answer questions in the EORTC QLQ-C30 questionnaire that were related to their sexual activities and their reasons also related to their cultural background (Moradian, 2013). Regarding the recall of acute and delayed CINV symptoms among the interview participants, although most of the participants indicated that they could accurately recall their CINV symptom experiences during the first several days of the first antineoplastic therapy cycle, several participants could not guarantee an accurate answer for their symptom recording due to memory lapses, particularly for the delayed CINV symptoms, which may have undermined the validity of the symptom recordings using the MAT. For those older participants with memory problems, a simple record of the intensity and frequency of emesis and nausea in a daily log might help solve this problem, which could also be considered in the future main study.

The qualitative study findings regarding the participants' adherence to the AT intervention were consistent with the pilot RCT findings, in that the majority of the participants achieved satisfactory adherence to the AT treatment protocol. The qualitative study also revealed one of the most important reasons for non-adherence to the AT treatment by some participants during the delayed CINV phase, which was a failure to detect favorable treatment effects of AT on nausea and vomiting at the very beginning of the AT treatment. A failure to achieve symptom improvement may have deteriorated the patients' adherence to the study intervention, while better symptom management resulting from the study intervention may have, in turn, enhanced the patients' adherence. This is in line with the qualitative study conducted by Hopton et al. (2013), which pointed out that better control of chronic pain using acupuncture may have (at least partially) contributed to better acceptability of the acupuncture intervention among some participants. The participants' adherence to the AT precautions and treatment durations were deemed satisfactory given that most of them reported that they had followed the study protocol to finish the five-day AT treatment and they carefully protected their AT tapes during daily activities. However, it should be noted that several participants in the interviews reported that they had kept the AT tapes on for more than five days, regardless of the telephone reminders from the research assistants, while some AT

tapes fell off after discharge and these participants did not contact the researchers for replacements. All of of these findings may have weakened the validity of the CINV outcome measures in the pilot RCT. Taking into account that there were already a few cases that showed non-adherence to the AT precautions and treatment durations in the small sample size of the participants in the semi-structured interviews (n=27), it was likely that more participants in the pilot RCT might have had similar situations, which could have consequently undermined the true effects of AT on nausea and vomiting and led to the statistically insignificant results of the effects of AT on delayed CINV. As indicated earlier in this chapter, inadequate follow-up approaches and insufficient follow-up visits may have been partially responsible for the deterioration of the participants' adherence to the study intervention (Kardas et al., 2013), and the future main study may schedule more intensive follow-up support to enhance the participants' adherence to the AT treatment protocol.

Regarding the safety and convenience of the AT treatment, the qualitative study findings were highly consistent with the pilot RCT findings, in that that AT treatment was a safe approach with only a few mild and tolerable adverse events. In line with the pilot study findings, most of the participants in the interviews from the true AT group and the sham AT group expressed that they felt more alleviated of their CINV symptoms during the first chemotherapy cycle compared with the subsequent cycles. However, the participants generally held a very pragmatic view that AT only partially helped to relieve their nausea and vomiting symptoms. This is not surprising because the majority of the participants in the interviews defined the CHAs (including AT) as having only an "adjuvant" and "supportive" role in their routine treatment, which could not replace the role of standard antiemetic medications but instead had a role of complementing conventional medicine in supporting symptom management. In addition, the qualitative study findings highlighted that a belief in the antiemetic effects of the AT treatment was another important motivator for completing the five-day AT treatment.

It was very interesting to see that the interview participants who experienced minor or totally no CINV symptoms also reported better emotional conditions during the first chemotherapy cycle, and the qualitative study findings indicated that less CINV symptom distress may have partially contributed to better psychological conditions in the breast cancer patients; thus, the AT treatment itself may have created some specific effects in improving emotional well-being.

Qualitative studies that have focused on patients' experiences of receiving acupuncture reported that apart from the improvement of the targeted health problems, acupuncture may also produce some additional positive impacts on patients' physical and psychological conditions (Alraek & Malterud, 2009; Hughes, 2009). The additional benefits generated from acupoint stimulation, as explained by Alraek and Malterud (2009), can be viewed as a "positive side-effect" associated with the intervention and the potential reasons could be the "holistic concept" of TCM theory, which focuses on not only the individual symptom but also the entire body's functional status as a whole unit. The AT treatment used in this study also followed the Chinese *zang-fu* organs and meridians theory, and stimulation of the targeted acupoints could have created some additional benefits to other body parts that are internally and externally associated with the targeted *zang-fu* organs. However, the participants' emotional conditions were not measured in the pilot RCT, so a further comparison of the effects of AT on their emotional status between the qualitative study findings and the quantitative study findings was impossible to determine. The additional benefits of AT on patients' emotional conditions offer some implications that patients' psychological status, such as anxiety and depression, should also be included as study outcomes in the future main study.

The placebo effects of AT were also mentioned by a few participants (in both the true AT group and the sham AT group) in the interviews and they believed that the effects of AT were only "psychological comforts," although they did experience CINV symptom relief during the AT treatment. It was also identified that the participants' own expectations of the treatment played an important role in the placebo effects of AT, and this kind of "mental suggestion" could have become stronger if the participants did not experience any CINV symptoms after receiving AT but saw other patients without AT suffering from severe nausea and vomiting. The findings from the pilot RCT suggest that there were strong placebo effects of AT on CINV, and some symptom changes even reached clinical significance, and the qualitative study findings also suggest that the placebo effects of AT were, at least partially, associated with the participants' own expectations of the intervention. This is in line with another qualitative study that focused on acupressure for CINV management, in which the author indicated that the treatment effects of acupressure on nausea and vomiting may have been largely associated with a placebo effect (Hughes et al., 2013), and the study also mentioned the hot debates in healthcare science about whether "placebo effects" can be utilized as one kind of psychological treatment approach. Nevertheless, although a few participants in this

interview thought that the "antiemetic effects" of AT may have been a "psychological comfort" to them, they did acknowledge that AT could really help with CINV management and they were willing to receive AT treatment again in the future. This is consistent with what Segar (2011) said in her article (as cited in Hughes et al., 2013), that the effects of CHAs may be associated with a placebo effect, but that did not make the CHAs less attractive to patients.

The semi-structured interviews nested within the pilot RCT shared a similar limitation with the qualitative study conducted by Hughes et al. (2013), in that study participation was based on a volunteer basis and there was a possibility that the participants who had experienced positive outcomes during the RCT were more likely to take part in the study, and some biases in terms of the participants' experiences and views toward study participation and receiving the AT treatment may have occurred. Although the qualitative study in this doctoral research project used a purposive sampling approach, different CINV symptom experiences after receiving AT treatment were not included in the selection criteria of the purposive sampling method, and this should be further addressed in the future main study.

8.5 Strengths and limitations of the doctoral research project

8.5.1 Study strengths

The strengths of this doctoral research project include the research design and implementation. Different from other AT trials published in current literature, the design of this doctoral research project follows the *MRC Framework for Developing and Evaluating Complex Interventions* (Craig et al., 2008). The MRC framework offers guidance to ensure that the development of a complex intervention protocol is evidence-based, and that the acceptability and feasibility of the proposed intervention and research methodological procedures will be fully examined before moving to the main study stage. The first two stages of the MRC framework were utilized in this doctoral research project. In the first stage, the development of the evidence-based AT treatment protocol (including the most appropriate true and sham AT design, the selection of the targeted auricular acupoints for stimulation, the duration of AT, and the techniques for manual acupressure) was based on widely recognized AT theories and a series of clinical and research evidence retrieved from several well-conducted systematic reviews, which ensured that every single

component of the AT protocol as well as the whole treatment plan were scientifically reasonable. Meanwhile, several popular AT handbooks compiled by experienced AT/acupuncture practitioners and the world-recognized Chinese standard ear acupoint chart were also employed to guide the development of the AT treatment protocol, and the preliminary AT protocol was further validated by a group of experts specialized in AT and TCM prior to formal testing in the pilot RCT, all of which ensured that the developed AT treatment protocol was practically and clinically acceptable and convenient for use in real clinical practice. The evidence-based approach utilized to develop the AT treatment protocol was one of the key strengths of this doctoral research project.

Another strength of this doctoral research project is the combination of quantitative research and qualitative research following the second stage of the MRC framework. The semi-structured interviews nested within the pilot RCT enriched the understanding and interpretation of the feasibility outcomes examined in the pilot RCT, highlighted the potential factors for facilitating and hindering study participation and adherence to the study intervention, and further explored the potential reasons for the placebo effects of the AT treatment. The findings from the pilot RCT and the semi-structured interviews showed mutual complementation, which provided valuable implications for the design of the future main study on the use of AT to control CINV as well as other similar studies using non-pharmacological approaches to cancer symptom management.

The major focus of the pilot RCT was the feasibility and acceptability of the AT treatment protocol and the whole methodological procedures of the RCT. However, the effects of AT on CINV and QoL in breast cancer patients were also preliminarily tested in this pilot study, which provided some preliminary research evidence in this area and advanced the current understanding of the antiemetic role of AT in cancer symptom management. The interpretation of the study findings from both the perspectives of statistical importance and clinical importance enabled a comprehensive understanding of the role of AT in CINV management in both research and clinical settings, and provided valuable information to cancer patients and clinicians in terms of their clinical decision-making on the use of AT in routine practice, although the pilot study data analysis was somewhat underpowered due to the small sample size. The inclusion of the sham AT comparison is also one of the study strengths, as it enabled an analysis of the potential placebo effects of AT and helped

distinguish the specific treatment (true) effects from the non-specific treatment (placebo) effects. The study findings indicated that the antiemetic effects of AT were a mixture of true therapeutic effects and placebo effects, which refutes the claims raised by some scholars that the effects of acupoint stimulation are nothing more than placebo effects (Tan et al., 2015).

Other strengths of this doctoral research project include the high recruitment rate and retention rate identified in the pilot RCT, which may have been due to the wide popularity of CHAs among the Chinese population, the safety and convenience of the non-invasive AT approach used in this study, and the favorable effects of AT on managing nausea and vomiting. The high recruitment rate and retention rate also reflect a promising acceptability and generalizability of the AT intervention among cancer populations, which provides important implications that more well-designed studies are necessary in future research to explore the value of auricular acupressure in cancer symptom management, not only because of its potentially beneficial effects on targeted health conditions but also because of its features of safety and convenience, which have shown excellent acceptability and clinical utility among cancer patients.

8.5.2 Study limitations

This doctoral research project also has a number of limitations. The first limitation is the lack of a definite and proved theoretical background, which failed to fully clarify the mechanism of using AT to manage CINV. The widely accepted AT theories, including the homucular reflex theory and the Chinese *zang-fu* organs and meridians theory, have thus far presented only a possible explanation of the AT mechanisms, without providing fully direct evidence from biological perspectives (Abbate, 2004; Bai, 1994; Oleson, 2014; Shan, 1996; Suen et al., 2001). This is a common dilemma in acupoint-stimulation practice based on the Chinese *zang-fu* organs and meridians theory as well as a number of other non-pharmacological interventions following traditional theories (e.g., health *qigong* and yoga), because the pathways for coordinating the intervention and certain responses in particular body regions are difficult to locate in the human body via current medical technologies. Therefore, the theoretical background of AT to control CINV presented in this doctoral thesis can be described as only a "potential" one, which hinders its acceptability to some researchers.

The convenience sampling approach used in the pilot RCT is also a limitation, because this kind of approach makes the study sample less representative of Chinese breast cancer patients and weakens the generalizability of the research findings to other study settings. As indicated by Farrokhi and Mahmoudi-Hamidabad (2012), convenience sampling is one type of non-probability sampling method that can deteriorate the statistical power analysis of precisely inferring the outcomes to the targeted population. Meanwhile, although three study sites were included in this pilot RCT for subject recruitment, it was the cancer hospital that contributed the majority of the study subjects (79.8%), while the other two study sites provided only a small number of eligible patients. This reflects a limitation in the selection of study sites, in which the slow progress in subject recruitment at two study hospitals delayed the overall research plan and resulted in quite a long duration (15 months) in completing the overall subject recruitment. In addition, another limitation which may have further hindered the generalizability of the study findings is the strict inclusion criteria set in the pilot RCT. Although the strict inclusion criteria generally ensured a homogeneous group of female breast cancer patients in this study to achieve relatively reliable research findings (particularly taking into account the small sample size of this pilot RCT), the exclusion of breast cancer patients at advanced stages or those who had already received multiple treatment cycles, to some extent, hindered the generalizability of the antiemetic benefits of AT to a large breast cancer population with different cancer stages and cycles of chemotherapy.

The randomization procedure utilized in this pilot RCT, without any particular restrictions on known confounding factors for CINV, is an important limitation of this doctoral research project. As indicated by the results of the pilot study data analysis, the statistically insignificant variations in the patients' CINV risk factors across groups at baseline created some confounding effects in the cause-and-effect analysis between the AT treatment and the CINV outcomes, although the confounding effects were determined to be very small. Moreover, it should be noted that the major aim of the pilot RCT was to examine the acceptability and feasibility of the intervention protocol and the RCT methodological procedures, and the sample size estimation was not completely power-based. Therefore, the results drawn from the pilot study's statistical analysis must be prudently interpreted given that the data analysis of the CINV outcomes was generally underpowered, with a high risk of committing a type II error. As emphasized by Lancaster et al. (2004), the statistical

analysis of pilot study data must be viewed as preliminary findings only and "should be taken with extreme caution" (p. 310).

The use of self-reported outcome measures in this pilot study may also be a study limitation. The CINV measures, including the MAT and the INVR as well as the QoL assessment tool FACT-B, were all self-reported outcomes completed by the study participants themselves. A big limitation of self-reported outcome measures is recall bias, as it lowers the accuracy of the data recording of patient-administered instruments, which further deteriorates the internal validity of the outcome measures (Geisen, Strohm, Stringer, Kopp, & Richards, 2012; Hassan, 2005; Short et al., 2009). The degree of recall bias has been identified as the relationship between the characteristics of the study participants and the time frame for recalling an event. For instance, Geisen et al. (2012) pointed out that participants with an older age or lower level of education are more likely to commit recall errors; Short et al. (2009) summarized the research literature and suggested that older age is a crucial indicator that could lead to an inaccurate measurement and an underestimation of the self-reported outcomes; and the underestimation of subjective outcomes sometimes may also be attributed to memory lapses (Short et al., 2009). Particularly, in RCTs, recall bias in self-reported outcome measures may even be obvious in the absence of an adequate blinding design of the group assignment (Hassan, 2005). Findings from the nested semi-structured interviews in this doctoral research project revealed that a few participants with an older age could not accurately recall their delayed CINV experiences, and the nature of the intervention utilized in this pilot RCT made a complete blinding design impossible among those receiving AT and those receiving standard care, all of which could have led to some degree of recall bias in the CINV and QoL outcome measures. As suggested by Hassan (2005), to minimize recall bias in self-reported outcome assessments, researchers may use data from other sources to verify the self-reported data, such as the use of direct observation or other biological variables relevant to the targeted conditions. However, none of the approaches were utilized in the pilot RCT because it was impossible to perform all-day observations of the participants' CINV symptoms, and currently there is still no concrete evidence on the biological indicators that reflect the intensity and incidence of nausea and emesis in cancer patients undergoing chemotherapy.

Although the participants' adherence to the AT treatment was identified as generally acceptable in this pilot RCT, non-adherence was still shown by some participants, particularly during the delayed CINV phase, which can be viewed as another limitation of this doctoral research project. This non-adherence produced some confounding effects on the analysis of AT antiemetic effects, which partially explained the statistically insignificant differences in the effects of AT on delayed CINV among groups. All study limitations presented above provide important implications for the research design of the future main study. Meanwhile, those implications can benefit other healthcare interventional studies focused on the use of non-pharmacological interventions for cancer symptom management. The implications of this doctoral research project for future research and practice, particularly for the refinement of the future main study protocol, will be presented in the next section.

8.6 Research and practice implications

8.6.1 Implications for future research

This doctoral research project has some implications for future healthcare research on non-pharmacological interventions for cancer symptom management. To further enhance the acceptance of CHAs in research and practice, more studies should be conducted to explore the underpinning mechanisms of CHAs and their therapeutic roles in managing various health conditions from biological and psychophysiological perspectives. Meanwhile, future studies are encouraged to follow the *MRC Framework for Developing and Evaluating Complex Interventions* in designing and testing their evidence-based intervention protocols to fit patients' needs from both research and practice perspectives. A combination of quantitative and qualitative research methods is also recommended, which will enable an in-depth understanding of the treatment effects of the study intervention and help explore the facilitating or hindering factors that can lead to the success or failure of the study protocol. In addition to statistical inference based on research hypothesis testing, future studies are also encouraged to interpret the potential clinical significance of the study intervention effects, which can provide valuable information to both patients and clinicians to reach adequate clinical decision-making on a tailored treatment plan. Given the considerable placebo effects associated with the use of non-pharmacological treatments, sham comparisons are also necessary in some circumstances to help distinguish the specific treatment (true) effects of the interventions from the non-specific treatment (placebo) effects.

Apart from the research implications listed above, this doctoral research project also concludes other implications for the refinement of the study protocol used in the future main study. These implications particularly focus on refinements of the subject recruitment plan, the study implementation plan, and the outcome measures and follow-up approaches of the future study protocol.

(1) Subject recruitment

Study sites for future subject recruitment should be specialized hospitals for cancer patients, and inpatient data in terms of the annual intake of breast cancer patients during the previous years should be assessed in advance to estimate the expected number of subjects recruited at each study site and the total length of time for completing subject recruitment. Inclusion criteria should be relatively broader in the future main study; thus, breast cancer patients with distant metastasis and those who have already completed multiple treatment cycles can also have an opportunity to participate in the study and receive the benefits of AT. However, in that case, restricted randomization with stratification must be applied to balance the patients' characteristics and CINV-related risk factors at baseline to minimize possible confounding effects in the final data analysis. Moreover, the future main study may consider inviting oncologists to join the study team. As indicated earlier in this chapter, healthcare professionals, particularly medical doctors, play an important role in subject recruitment and study adherence (Baquet et al., 2006; Castel et al., 2006; Kardas et al., 2013; Mills et al., 2006; Vermeire et al., 2001). The inclusion of oncologists may further facilitate the subject recruitment process and enhance participants' adherence to the study intervention protocol.

(2) Study implementation

Other approaches can also be utilized to enhance participants' adherence to the study intervention protocol. Since the AT intervention duration in one chemotherapy cycle was relatively short, with only one five-day treatment period, daily monitoring of treatment adherence should be continued during the first three days of AT treatment when participants are still in the hospital, while for

those discharged on the fourth day of AT treatment, daily telephone monitoring will be necessary to maintain their adherence to the AT treatment protocol for the following two days.

(3) Outcome measures and follow-up approaches

Apart from acute, delayed, and anticipatory CINV symptoms and QoL status, the participants' emotional conditions, such as anxiety and depression, should also be measured in the future main study using valid instruments such as the Hospital Anxiety and Depression Scale (HADS). The MAT, Chinese version, is still the best candidate for acute and delayed CINV assessment in the future main study given its satisfactory psychometric properties and clinical utility, and its ability to comprehensively evaluate the occurrence, frequency, and severity of nausea and vomiting at both the acute and delayed symptom phases. However, for future study participants with an older age and lower education level, daily checking of their CINV symptom occurrence will be necessary to ensure the accuracy of the MAT self-reported data and eliminate possible recall bias induced by memory lapses. In terms of the assessment of anticipatory CINV in the future main study, specific multidimensional measurements (e.g., the INVR) are unnecessary, as simple polar questions ("yes" or "no") seem adequate enough for measuring the occurrence of anticipatory nausea and vomiting given their extremely low incidences identified in this pilot RCT and another recent large-scale observational study (Molassiotis et al., 2016). In addition, a sufficient follow-up period should be considered in the future main study to investigate the mid-term or long-term effects of AT on CINV symptom control, psychological well-being, and QoL among breast cancer patients.

8.6.2 Implications for future practice

Some practice implications were also concluded in this doctoral research project. Preliminary research evidence on the antiemetic role of AT in CINV management has been identified, and findings from this doctoral research project also support previous literatures' findings that auricular acupressure is a convenient and safe treatment method used in practice. Therefore, future practice may consider introducing auricular acupressure to routine care to manage CINV symptoms. However, it should be noted that research evidence on the antiemetic effects of AT was concluded only from a pilot RCT with a limited sample size; thus, the evidence should only

be interpreted as preliminary, and ongoing assessment of the safety of AT should be emphasized during the AT treatment. The *WHO-UMC System for Standardized Case Causality Assessment* can be utilized to evaluate the causality between the reported adverse events and AT.

8.7 Summary and conclusion

8.7.1 Summary of the discussion

The findings of the pilot RCT and the semi-structured interviews and their related methodological issues, as well as research and practice implications drawn from this doctoral research project, were comprehensively discussed in this chapter. For the feasibility outcomes of the pilot RCT, potential reasons for the satisfactory subject recruitment rate and retention rate as well as adequate adherence rate to the AT treatment protocol were analyzed from the aspects of the study participants, the study/intervention protocol, and healthcare professionals. The feasibility of using the MAT for CINV assessment was well supported by the study findings given its adequate psychometric properties and clinical utility, comprehensiveness in assessing nausea and vomiting at both the acute and delayed CINV phases, and flexibility in interpreting the CINV outcomes from the aspects of both statistical importance and clinical importance. The use of the INVR for anticipatory CINV assessment was deemed unnecessary, and a number of missing values were identified in the FACT-B questionnaire for QoL assessment, but relevant strategies were utilized to handle the missing values and thus the overall validity of the FACT-B scores in this study was not affected. The findings regarding the safety of AT were consistent with a previous systematic review that found that auricular acupressure can be used as a safe and convenient treatment approach, with only minor and tolerable side effects (Tan et al., 2014b).

In terms of the clinical outcome assessment, the incidences of acute and delayed nausea and vomiting were found to be much higher than those in a recent large-scale observational study (Molassiotis et al., 2016), and the absence of NK_1 receptor antagonists in the standard antiemetic treatment was the most important reason for such high CINV incidences in the pilot RCT. QoL status was also comparable with two other Asian studies with similar sample characteristics, but the patients' functional status was found to be much lower in the pilot study compared with other similar studies, and recent breast surgery before receiving the first chemotherapy cycle for

the majority of the study participants in the pilot RCT can be an important reason for this difference. AT plus standard antiemetic medications showed superiority to standard antiemetics alone in alleviating CINV, particularly for the management of nausea symptoms at the acute phase, with a number of MAT outcome variables reaching both statistical significance and clinical significance. The pilot study findings, in line with previous research findings (Dincer & Linde, 2003; Tan et al., 2015), supported the hypothesis that the treatment effects of acupoint stimulation (including AT) are a mixture of specific treatment (true) effects and non-specific treatment (placebo) effects, and the placebo effects of AT were identified as large, which could have been induced by the participants' expectations of the treatment effects of AT. AT did not show any significant effects on anticipatory CINV and QoL, and the relatively small sample size utilized in the pilot RCT may have partially contributed to the insignificant results.

Fidelity of the AT intervention was ensured in the pilot RCT from four aspects, including the design of the intervention protocol, the training of the research personnel, the implementation of the intervention protocol, and the receipt of the intervention protocol. Both statistical significance and clinical significance were utilized to interpret the effects of AT on CINV, and it was found that the changes in the majority of the CINV outcomes were clinically significant for cancer patients and clinicians, even for some variables (particularly delayed CINV symptoms) that showed insignificant differences in the statistical hypothesis testing. The introduction of clinical importance in this doctoral research project highlighted the antiemetic value of AT from a clinical perspective, which could be used to further guide clinical decision-making on the use of AT in routine practice. The statistically insignificant variations in the participants' CINV risk factors at baseline produced some minor confounding effects on the data analysis, which indicated that a restricted randomization procedure with stratification is needed in the future main study to minimize baseline confounding effects.

The semi-structured interviews nested within the pilot RCT enriched the quantitative research data on the feasibility issues of the AT treatment protocol and the pilot RCT's methodological procedures. The participants' positive views toward the role and safety of CHAs and their desire to use CHAs to alleviate their cancer-treatment-related symptoms were found to be important motivation factors for study participation. The participants' acceptability of the study

questionnaires was adequate, which was in line with the pilot RCT findings. However, potential recall bias on the MAT questionnaire for delayed CINV assessment was revealed in the interview data, which may have undermined the validity of delayed symptom recording in the pilot RCT. A failure to achieve symptom relief at the very beginning of AT treatment was identified as an important reason for non-adherence to the AT treatment protocol by some participants, while a high treatment adherence by some participants was attributed to their belief in the promising effects of AT on managing CINV symptoms. In addition to the promising effects of AT on CINV, findings from the semi-structured interviews also revealed a potential role of AT in improving the participants' emotional conditions. The improvement of emotional status may have partially been induced by the alleviation of CINV symptoms. Potentials for adjusting whole body functions of AT treatment based on the "holistic concept" of TCM theory may also help explain the benefits of AT on emotional functions. Based on these observations, psychological well-being should also be included as one of the outcome measures in the future main study. Placebo effects of AT were also reported by some participants in the semi-structured interviews, which were mainly introduced by the participants' expectations of the AT treatment effects.

This discussion chapter also highlighted the strengths and limitations of the doctoral research project. In terms of the study's strengths, the design of the doctoral research project followed the *MRC Framework for Developing and Evaluating Complex Interventions*, and the study design combined both quantitative and qualitative research methods to comprehensively explore feasibility issues regarding the AT treatment protocol and the RCT's methodological procedures. In addition to the feasibility outcomes, the effects of AT on CINV and QoL among female breast cancer patients were also preliminarily analyzed and interpreted from the perspectives of both statistical significance and clinical significance. The inclusion of a sham AT control was also a strength of this doctoral research project, as it enabled an analysis of the potential placebo effects of AT and helped distinguish the true treatment effects of AT from the placebo effects. For the study limitations, the lack of a definite and proved theoretical background to address the antiemetic mechanisms of the AT intervention may have hindered the acceptability of AT practice to some researchers. The convenience sampling approach and the relatively strict inclusion criteria utilized in the pilot RCT weakened the generalizability of the pilot RCT findings. The use of randomization without any restrictions on CINV risk factors contributed to some minor

confounding effects on the cause-and-effect analysis between AT and CINV outcomes. The self-reported outcome measures may have also introduced some recall bias, which could have undermined the internal validity of the outcome assessment, and non-adherence identified in some participants during the delayed CINV phase may also have produced some confounding effects on the data analysis. Given that the sample size estimation of the pilot RCT was not power-based, statistical analysis results should therefore be viewed as preliminary findings only and interpreted with caution.

8.7.2 Contributions to future research and practice

To the best of the doctoral researcher's knowledge, this doctoral project is the first study at present to follow the *MRC Framework for Developing and Evaluating Complex Interventions* in developing an evidence-based AT treatment protocol and examining its feasibility and acceptability among breast cancer patients via a combination of a pilot RCT and semi-structured interviews. The rigorous research design and methodological procedures utilized in this doctoral research project advance the current evidence in terms of the antiemetic role and safety of auricular acupressure in cancer symptom management. The statistical importance and clinical importance of using AT to alleviate CINV highlights the value of AT for cancer patients and clinicians in real clinical settings. Routine clinical practice is therefore recommended to include auricular acupressure as a safe, convenient, and promising non-pharmacological approach to the comprehensive care of nausea and vomiting among breast cancer patients undergoing chemotherapy.

8.7.3 Conclusion of the doctoral research project

The comprehensive interpretation of the doctoral research project findings in this chapter reached a final conclusion, and the findings are presented as follows:

(1) The evidence-based auricular acupressure protocol was demonstrated to be a safe and convenient non-pharmacological intervention for use among female breast cancer patients.

(2) The methodological procedures of the RCT using auricular acupressure to manage CINV was deemed feasible, with a satisfactory recruitment rate and retention rate identified during subject recruitment and the follow-up process, and good acceptability of the study questionnaires and adequate treatment adherence was also identified during the study implementation period.

(3) The use of auricular acupressure plus standard antiemetic medication and care was superior to the use of standard antiemetic medication and care alone in controlling acute and delayed CINV among breast cancer patients undergoing chemotherapy, and the antiemetic effects of auricular acupressure were found to be more profound in alleviating acute CINV symptoms, particularly acute nausea.

(4) The antiemetic effects of auricular acupressure were a mixture of specific treatment (true) effects and non-specific treatment (placebo) effects. The placebo effects of AT on acute and delayed CINV symptoms were found to be very large and even reached clinical significance.

(5) Auricular acupressure seemed to have no significant effects on relieving anticipatory nausea and vomiting in female breast cancer patients prior to the second cycle of chemotherapy.

(6) Auricular acupressure seemed to have no significant effects on improving QoL in female breast cancer patients across the first cycle of chemotherapy.

(7) The preliminary research evidence drawn from this doctoral research project supported the assumption that auricular acupressure is a safe, convenient, and promising non-pharmacological intervention for alleviating acute and delayed nausea and vomiting symptoms in female breast cancer patients undergoing chemotherapy. Future practice is encouraged to utilize auricular acupressure as a promising complementary treatment approach to assisting CINV management in cancer patients.

(8) A future multicenter large-scale RCT is needed to examine the definite effects of AT on CINV and QoL in female breast cancer patients undertaking chemotherapy.

APPENDICES

<u>Appendix I</u>: Content validity assessment form for the AT treatment protocol

Cover Letter
致專家信

尊敬的專家：

您好！首先感謝您能夠在百忙之中抽空參與這份耳穴治療方案的評價。感謝您對我們這一項研究的支持！

此次函詢旨在評價一份針對**控制乳腺癌初次化療患者在第一化療週期急性及延遲性噁心嘔吐的耳穴治療**方案。該方案已經經過本研究團隊初步制定。方案的制定基於了**耳穴治療的相關理論**，**相關系統評價**，**臨床研究**以及**相關耳穴療法論著**的建議。初步擬定的方案尚須經過相關領域的專家進行內容效度的評價，方才能形成最終方案應用到臨床試驗中進行評價。

參與本內容效度測評的專家包括教學科研及臨床實踐兩類專家。教學科研專家須為在高等醫學院校進行針灸/耳穴療法研究的權威教授或副教授（至少具備 10 年以上的研究經歷），並在針灸/耳穴療法相關國際同行評議期刊上發表過高水準學術論文及參編過針灸/耳穴療法相關論著者。臨床實踐專家則為具備副高級及以上職稱的取得資格的註冊針灸治療師（主任醫師或副主任醫師），且具備至少 10 年的針灸及耳穴治療的臨床實踐經驗。

本評價表共分為兩部分，第一部分即為此致專家信，第二部分為耳穴治療方案的內容效度評價表，該表詳細列出了我們初步制定的耳穴治療方案，並根據真耳穴治療方案及假耳穴治療方案的選穴、貼壓工具、按壓時方法，按壓時間及頻率，以及總體治療時間詳細分為了 10 個條目。請您逐條判斷每一條目是否合適並進行評分，每一個條目都按照合適程度分為了四等，即：非常合適（4 分），合適（3 分），不合適（2 分）以及非常不合適（1 分）。請您根據您的判斷在每個條目對應的 4 個分值內進行選擇並在空格內作“✓”標記，同時，針對每一個條目，若您有什麼意見或者建議，請在條目後的空格內補充，同時，若您的意見或者建議來源於相關研究結果或者論著，請您務必提供參考文獻。

此問卷以匿名形式函詢，您的資料僅用於統計分析及研究方案修改，絕不它用，絕對保密。請您在收到問卷的 2 周內發回至研究者電郵，或者聯繫研究者，研究者將在您方便的時候到您的單位取回該表。若您對此方案評價表有疑問或其他諮詢，請撥打電話（852）5432　　或（86）1310763　　（聯繫人：譚景予）；或者發送電郵 jing-yu.tan@　　歡迎您隨時提供寶貴意見。

再次感謝您對本研究的支持。

香港理工大學護理學院

哲學博士研究生 譚景予

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行動電話（香港）：(852) 5432

行動電話（中國）：(86) 1310763

在進行評價之前，請在下列表格中填寫您的基本資訊（請在符合您情況的 □ 內打 “✓”）。

1. 您所在的單位：高等學校 □　醫院 □

2. 年齡： 30～40 歲 □　40～50 歲 □　50～60 歲 □　60 歲以上 □

3. 最高學歷：大專及以下 □　本科 □　研究生 □

4. 最高學位： 學士 □　碩士 □　博士 □　其他 □

5. 職稱: (1) 高校： 副教授 □　副研究員 □　教授 □　研究員 □

(2) 醫院：副主任 (中) 醫師 □　主任 (中) 醫師 □

6. 參加工作的年限： 5～10 年 □　11～15 年 □　16～20 年 □　20 年以上 □

7. 聯繫電話或電子郵箱：

Content Validity Assessment Form
內容效度評價表

說明：請您根據您的判斷在每個條目對應的 4 個分值內進行選擇並在空格內作“✓”標記，同時，針對每一個條目，若您有什麼意見或者建議，請在條目後的空格內補充，同時，若您的意見或者建議來源於相關研究結果或者論著，請您務必提供參考文獻。

條目	條目內容	條目的合適性評分				意見
真穴位貼壓組（干預組）治療方案		非常合適(4)	合適(3)	不合適(2)	非常不合適(1)	**或建議**
1	**選取穴位**：賁門 (CO_3)，胃 (CO_4)，脾 (CO_{13})，肝 (CO_{12})，神門 (TF_4)，交感 (AH_{6a})及皮質下 (AT_4)，雙耳取穴					
2	**貼壓工具**：王不留行籽					
3	**穴位按壓方法**：用食指和拇指的指腹分別置於耳廓的正面及背面，然後相對壓迫貼壓的王不留行籽，逐漸加壓直至出現脹、痛、熱等感覺 (“得氣”感)。此時，輕微移動食指及拇指，尋找穴位貼壓處脹痛感最明顯的部位 (即“敏感點”)，繼續在此“敏感點”持續對壓。					
4	**穴位治療時間及頻率**：每日自行按壓三次 (上午，下午及晚間入睡前，無論是否具備噁心嘔吐的症狀，皆規律按壓)；對於每個穴位，在尋找到“敏感點”以後，則持續對壓 20-30 秒；除規律按壓三次之外，在感到噁心嘔吐的時候可做額外按壓					
5	**總體治療時間**：5 天*****（從首次化療當天持續至首次化療結束後第 4 天）					
假穴位貼壓組（安慰劑組）治療方案						
6	**選取穴位：**賁門 (CO_3)，胃 (CO_4)，脾 (CO_{13})，肝 (CO_{12})，神門 (TF_4)，交感 (AH_{6a})及皮質下 (AT_4)，雙耳取穴					
7	**貼壓工具：**燈芯草					
8	**穴位按壓方法：**不做任何按壓					
9	**穴位治療時間及頻率：**不做任何按壓					
10	**總體治療時間：**5 天*****（從首次化療當天持續至首次化療結束後第 4 天）					

*****：耳穴療程的長短依照所針對的疾病狀態而定。根據耳穴治療學家管遵信教授的建議，非慢性疾病的耳穴治療可以持續至患者的相關症狀消失時為止 (Guan et al., 2002, p. 117)。 化療所致的噁心嘔吐的急性反應通常持續至化療後的 24 小時內，而延遲性反應則持續至化療的第 5 天。因此，本研究擬採用的耳穴療程定為 5 天 (從首次化療當天持續至首次化療結束後第 4 天)。

Appendix II: Baseline data assessment form

基本資料情況表

姓 名	_____	**年 齡**	_____	**科 室**	_____ **床 號** _____
入院日期	_____			**出院日期**	_____
聯繫人	_____	**電 話**	_____	**居住住址**	_____

教育程度	☐ 未接受正式教育 ☐ 小學 ☐ 初中 ☐ 高中或中專 ☐ 大專 ☐ 大學或以上	**婚姻狀況**	☐ 未婚 ☐ 已婚 ☐ 離婚 ☐ 喪偶
職業狀況	☐ 專業技術人員 ☐ 體力勞動者 ☐ 家庭主婦 ☐ 文書或管理工作 ☐ 其他 ☐ 失業 ☐ 退休	**宗教信仰**	☐ 佛教 ☐ 道教 ☐ 基督教 ☐ 天主教 ☐ 伊斯蘭教 其他 _____
家庭收入 (每個月)	☐ 3000 元及以下 ☐ 3000-6000 元 ☐> 6000-10000 元 ☐ 10000 元以上	**醫療費用主要來源**	☐ 公費醫療 ☐ 社會醫療保險 ☐ 新農合醫療 ☐ 自費醫療 其他 _____
主要照顧者	_____ **與患者的關係** _____		**聯繫電話** _

病程及病史

乳腺癌診斷時間及分期	診斷時間 _____年_____月 ☐ Ⅰ ☐ ⅡA ☐ ⅡB ☐ ⅢA ☐ Ⅲ B ☐ ⅢC	**其他診斷**	1 診斷名稱 _____ 2 診斷名稱 _____ 3 診斷名稱 _____	診斷時間 ___年___月 診斷時間 ___年___月 診斷時間 ___年___月
乳腺癌手術類型及時間	手術時間 _____年_____月 ☐ 乳癌改良根治術 ☐乳癌單純切除術 ☐ 乳癌保留乳房術 其他 _____	**其他手術**	1 手術名稱 _____ 2 手術名稱 _____ 3 手術名稱 _____	手術時間 ___年___月 手術時間 ___年___月 手術時間 ___年___月
疾病家族史	☐ 否認 ☐ 有 (若有，填寫疾病名稱) 1_____ 2_____ 3_____ 4_____	**過敏史**	☐ 否認 ☐ 有 (若有，填寫藥物或致敏源) 1_____ 2_____ 3_____ 4_____	

化療方案及用藥

化療週期	第一週期，擬從_____月_____日 到 _____月_____日
化療方案及其劑量療程	☐ AC 方案 劑量療程 _____ ☐AC-T 方案 劑量療程 _____ ☐ EC 方案 劑量療程 _____ ☐ EC-T 方案 劑量療程 _____ ☐ EC-D 方案 劑量療程 _____ ☐ TC 方案 劑量療程 _____ 其他 _____

止吐方案及用藥

止吐藥物及其劑量療程	藥物 1_____ 劑量療程 _____ 藥物 2_____ 劑量療程 _____ 藥物 3_____ 劑量療程 _____ 藥物 4_____ 劑量療程 _____ 其他_____

惡心嘔吐危險因素評估

懷孕初期的嘔吐反應	☐ 有	☐無	**暈動癥病史**	☐ 有	☐無
內耳迷路炎病史	☐ 有	☐無	**既往化療/放療經歷**	☐ 有	☐無

生存質量 (FACT-B) 得分情況_____ **預期性惡心嘔吐 (INVR) 得分情況**_____

<u>Appendix III</u>: WHO-Uppsala Monitoring Centre (UMC) System for Standardized Case Causality Assessment

WHO-Uppsala Monitoring Centre (UMC) System for Standardized Case Causality Assessment (Modified version for the safety assessment of AT)*

WHO-乌普萨拉监测中心系统因果关系评价 [耳穴療法安全性評估修改版]*

Causality Term [因果關係條目]	**Assessment Criteria** [評價標準]
Certain [肯定有關的]	There was a plausible time relationship between the occurrence of side reactions and the use of AT, and there was a plausible response to the withdrawal of AT; thus, it was impossible that these side reactions were attributed to health problems (diseases) or other therapeutic approaches. [存在可信的因果聯繫：不良事件明確發生在接受耳穴療法之後且在祛除刺激后不良事件消失；同時這些不良事件不能由除耳穴療法之外的健康問題或者其他干預方法所解釋]
Probable or Likely [很可能有關]	There was a reasonable time relationship between the occurrence of side reactions and the use of AT, and these side reactions were unlikely to be explained by health problems (diseases) or other therapeutic approaches. [存在貌似可信的因果聯繫：不良事件的產生有極大可能是由耳穴療法導致，且這些不良事件的產生不太可能歸因于健康問題或其他干預方法]
Possible [可能有關]	There was a reasonable time relationship between the occurrence of side reactions and the use of AT, but these side reactions could also be attributed to health problems (diseases) or other therapeutic approaches, and there was no clear information on AT withdrawal. [存在貌似可信的因果聯繫：不良事件的產生有極大可能是由耳穴療法導致，但是也可能是由健康問題或者其他干預方法引起。同時，在祛除干預刺激后的相關信息缺失或者不明確]
Unlikely [不太可能有關]	An improbable time relationship was identified between the reported side reactions and the use of AT. [不太可能的時間序貫關係：耳穴療法和不良事件之間的時間聯繫不太可信]
Conditional or Unclassified [條件的/未分類的]	The side reactions were identified but more reliable information must be collected for an appropriate judgment of the causality between the side reactions and the use of AT. [不良事件發生但是需要更多可靠的信息來判斷其因果聯繫]
Unclassifiable or Unassessable [無法評估的/未分類的]	The side reactions were proposed but the causality could not be assessed because the available information was contradictory or insufficient. [不良事件被提出，但因為相關信息缺乏或者相互矛盾而無法做出判斷]

Note: AT=auricular therapy. *=this tool has been modified for use in AT safety assessment based on two systematic reviews that focused on adverse events associated with the use of AT (reference 1) and cupping treatment (reference 2).

[**Reference 1**: Tan, J. Y., Molassiotis, A., Wang, T., & Suen, L. K. (2014). Adverse events of auricular therapy: A systematic review. *Evidence-Based Complementary and Alternative Medicine*, 2014, Article ID 506758, 20 pages. doi:10.1155/2014/506758]

[**Reference 2**: Kim, T. H., Kim, K. H., Choi, J. Y., & Lee, M. S. (2014). Adverse events related to cupping therapy in studies conducted in Korea: A systematic review. *European Journal of Integrative Medicine*, *6*(4), 434-440.]

Adverse Events Assessment Form

不良事件評估表

研究對象編號:____________________ 評價者:__________________ 評價時間:__________________

不良事件	發生時間	結束時間	結局	因果關係分析結果		退出研究
			☐ 自行緩解 ☐ 處理后緩解 ☐ 未緩解 ☐ 不清楚	☐ 肯定有關的 ☐ 可能有關 ☐ 條件的	☐ 很可能有關的 ☐ 不太可能有關 ☐ 無法評估	☐ 是 ☐ 否
			☐ 自行緩解 ☐ 處理后緩解 ☐ 未緩解 ☐ 不清楚	☐ 肯定有關的 ☐ 可能有關 ☐ 條件的	☐ 很可能有關的 ☐ 不太可能有關 ☐ 無法評估	☐ 是 ☐ 否
			☐ 自行缓解 ☐ 处理后缓解 ☐ 未缓解 ☐ 不清楚	☐ 肯定有關的 ☐ 可能有關 ☐ 條件的	☐ 很可能有關的 ☐ 不太可能有關 ☐ 無法評估	☐ 是 ☐ 否
			☐ 自行缓解 ☐ 处理后缓解 ☐ 未缓解 ☐ 不清楚	☐ 肯定有關的 ☐ 可能有關 ☐ 條件的	☐ 很可能有關的 ☐ 不太可能有關 ☐ 無法評估	☐ 是 ☐ 否
			☐ 自行缓解 ☐ 处理后缓解 ☐ 未缓解 ☐ 不清楚	☐ 肯定有關的 ☐ 可能有關 ☐ 條件的	☐ 很可能有關的 ☐ 不太可能有關 ☐ 無法評估	☐ 是 ☐ 否

<u>Appendix IV</u>: Daily log for participants in the true AT group

Daily Log (true AT group, day 1 to day 4, four pages in total, one page for each day)

耳穴治療日誌 (真耳穴治療組，用於第 1 天至第 4 天，共 4 頁，每天填寫一頁)

今天是本次化療週期的第 1 (或 2,3,4) 天

耳穴按壓提示：

● 請每天保證規律按壓耳貼三次，第一次應在上午，第二次在下午，第三次則在晚上您入睡之前，除此之外，當您感覺惡心，想要嘔吐之前，可以額外地按壓耳貼。

● 每個穴位按壓的具體方法：將您的食指及拇指置於耳廓所選穴位的的正面和背面，進行對壓，按壓時須要逐漸地增加壓力，直到感覺到按壓穴位處出現沉重、脹痛或者熱酸的感覺 (即得氣感)，這時，您需要輕微得移動您的手指，尋找穴位處得氣感最強烈的部位，再按壓 20-30 秒。

● 若您的耳貼脫落，請與我們聯繫，在家時也請您與研究人員及時聯繫，并到醫院重新更換耳貼。我們的上班時間是從早上八點至下午六點，您與這個時間段內的任何時間達到醫院，研究人員均會為您更換新的耳貼。

● 若您在治療過程中有何疑問，或者有什麼不舒服的反應，請及時與研究人員聯繫，電話：(86) 13107636830。

● 規律及足夠強度的按壓對於耳穴治療治療效應發揮至關重要，請您遵照我們的要求及指導進行規律及正確的按壓。

今天您有按照要求規律地按壓耳穴嗎？(請在下面的空格處填寫您今天進行耳穴按壓的時間及頻率)

第一次：時間_____，總共按壓了約_____分鐘

第二次：時間_____，總共按壓了約_____分鐘

第三次：時間_____，總共按壓了約_____分鐘

除了按照上述要求進行了規律的按壓之外，您今天是否還進行了額外的按壓，若有，請在，請在以下記錄。

今天共額外按壓了_____次，分別是：

時間_____，總共按壓了約_____分鐘

時間_____，總共按壓了約_____分鐘

更多 _____

若您今天沒有按照上述要求進行按壓，請說明您的理由或者難處：

_____

在進行耳穴治療的過程中，您耳貼的部位及其周圍，是否出現了以下的一些不適的反應？若有，請在與您情況相同的選項後打勾，并填寫症狀出現的時間及持續時間，若您尚發生了我們沒有列出的其他反應，也請您在最後補充。

● 沒有不適的反應（ ）

● 有不適的反應 （ ）（請在以下選擇及填寫）

耳朵局部有不舒服（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部轻微疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部中度疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **<u>若出現此反應，請立即與我們聯繫</u>**

耳朵局部明顯疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **<u>若出現此反應，請立即與我們聯繫</u>**

耳朵局部发红現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部发痒感覺（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部出血現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **<u>若出現此反應，請立即與我們聯繫</u>**

其它_____

Daily Log (true AT group, for day 5)

耳穴治療日誌 (真耳穴治療組，用於耳穴治療第 5 天)

今天是本次化療週期的第 5 天

耳穴按壓提示：

● 請每天保證規律按壓耳貼三次，第一次應在上午，第二次在下午，第三次則在晚上您入睡之前，除此之外，當您感覺惡心，想要嘔吐之前，可以額外地按壓耳貼。

● 每個穴位按壓的具體方法：將您的食指及拇指置於耳廓所選穴位的的正面和背面，進行對壓，按壓時須要逐漸地增加壓力，直到感覺到按壓穴位處出現沉重、脹痛或者熱酸的感覺 (即得氣感)，這時，您需要輕微得移動您的手指，尋找穴位處得氣感最強烈的部位，再按壓 20-30 秒。

● 若您的耳貼脫落，請立即與我們聯繫，在家時也請您與研究人員及時聯繫，并到醫院重新更換耳貼。我們的上班時間是從早上八點至下午六點，您與這個時間段內的任何時間達到醫院，研究人員均會為您更換新的耳貼。

● 若您在治療過程中有何疑問，或者有什麼不舒服的反應，請及時與研究人員聯繫，電話：(86) 13107636830。

● 規律及足夠強度的按壓對於耳穴治療治療效應發揮至關重要，請您遵照我們的要求及指導進行規律及正確的按壓。

今天您有按照要求規律地按壓耳穴嗎？(請在下面的空格處填寫您今天進行耳穴按壓的時間及頻率)

第一次：時間_____，總共按壓了約_____分鐘

第二次：時間_____，總共按壓了約_____分鐘

第三次：時間_____，總共按壓了約_____分鐘

除了按照上述要求進行了規律的按壓之外，您今天是否還進行了額外的按壓，若有，請在，請在以下記錄。

今天共額外按壓了_____次，分別是：

時間_____，總共按壓了約_____分鐘

時間_____，總共按壓了約_____分鐘

更多 _____

若您今天沒有按照上述要求進行按壓，請說明您的理由或者難處：

_____

在進行耳穴治療的過程中，您耳貼的部位及其周圍，是否出現了以下的一些不適的反應？若有，請在與您情況相同的選項後打勾，并填寫症狀出現的時間及持續時間，若您尚發生了我們沒有列出的其他反應，也請您在最後補充。

● 沒有不適的反應（ ）

● 有不適的反應 （ ）（請在以下選擇及填寫）

耳朵局部有不舒服（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部轻微疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部中度疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

耳朵局部明顯疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

耳朵局部发红現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部发痒感覺（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部出血現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

其它_____

感謝您完成了我們整個 5 天的耳穴治療，對於使用耳穴按壓這種方式輔助控制化療所引起的惡心嘔吐：

您是否滿意這樣的治療方式呢？下面 1-10，從 1(非常不滿意) 到 10(非常滿意)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

非常不滿意 非常滿意

你是否會考慮在將來繼續接受耳穴治療？

您是否考虑将来继续接受耳穴治疗？下面 1-10，從 1(絕對不會) 到 10(一定會)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

絕對不會 一定會

您是否會考慮將耳穴療法推薦給您的朋友？下面 1-10，從 1 (絕對不會) 到 10 (一定會)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

絕對不會 一定會

<u>提醒</u>：請您在明天早上移除耳貼，然後完成一份 MAT 問卷。明天您也將接到我們的隨訪電話，請注意接聽。

Appendix V: **Daily log for participants in the sham AT group**

Daily Log (sham AT group, day 1 to day 4, four pages in total, one page for each day)
耳穴治療日誌 (假耳穴治療組，用於第 1 天至第 4 天，共 4 頁，每天填寫一頁)

今天是本次化療週期的第 1 (或 2,3,4) 天
耳穴治療提示： ● 若您的耳貼脫落，請立即與我們聯繫，在家時也請您與研究人員及時聯繫，并到醫院重新更換耳貼。我們的上班時間是從早上八點至下午六點，您與這個時間段內的任何時間達到醫院，研究人員均會為您更換新的耳貼。 ● 若您在治療過程中有何疑問，或者有什麼不舒服的反應，請及時與研究人員聯繫，電話：(86) 13107636830。
在進行耳穴治療的過程中，您耳貼的部位及其周圍，是否出現了以下的一些不適的反應？若有，請在與您情況相同的選項後打勾，并填寫症狀出現的時間及持續時間，若您尚發生了我們沒有列出的其他反應，也請您在最後補充。 ● 沒有不適的反應（ ） ● 有不適的反應 （ ）（請在以下選擇及填寫） 耳朵局部有不舒服（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) 耳朵局部轻微疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) 耳朵局部中度疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫** 耳朵局部明顯疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫** 耳朵局部发红現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) 耳朵局部发痒感覺（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) 耳朵局部出血現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫** 其它_____

Daily Log (sham AT group, for day 5)

耳穴治療日誌 (假耳穴治療組，用於耳穴治療第 5 天)

今天是本次化療週期的第 5 天

耳穴治療提示：

● 若您的耳貼脫落，請立即與我們聯繫，在家時也請您與研究人員及時聯繫，并到醫院重新更換耳貼。我們的上班時間是從早上八點至下午六點，您與這個時間段內的任何時間達到醫院，研究人員均會為您更換新的耳貼。

● 若您在治療過程中有何疑問，或者有什麼不舒服的反應，請及時與研究人員聯繫，電話：(86) 13107636830。

在進行耳穴治療的過程中，您耳貼的部位及其周圍，是否出現了以下的一些不適的反應？若有，請在與您情況相同的選項後打勾，并填寫症狀出現的時間及持續時間，若您尚發生了我們沒有列出的其他反應，也請您在最後補充。

● 沒有不適的反應（ ）

● 有不適的反應 （ ）（請在以下選擇及填寫）

耳朵局部有不舒服（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部轻微疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部中度疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

耳朵局部明顯疼痛（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

耳朵局部发红現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部发痒感覺（ ） 出現時間：_____ 持續時間：_____(按分鐘計算)

耳朵局部出血現象（ ） 出現時間：_____ 持續時間：_____(按分鐘計算) **若出現此反應，請立即與我們聯繫**

其它_____

感謝您完成了我們整個 5 天的耳穴治療，對於使用耳穴按壓這種方式輔助控制化療所引起的惡心嘔吐：

您是否滿意這樣的治療方式呢？下面 1-10，從 1(非常不滿意) 到 10(非常滿意)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

非常不滿意 非常滿意

你是否會考慮在將來繼續接受耳穴治療？

您是否考虑将来继续接受耳穴治疗？下面 1-10，從 1(絕對不會) 到 10(一定會)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

絕對不會 一定會

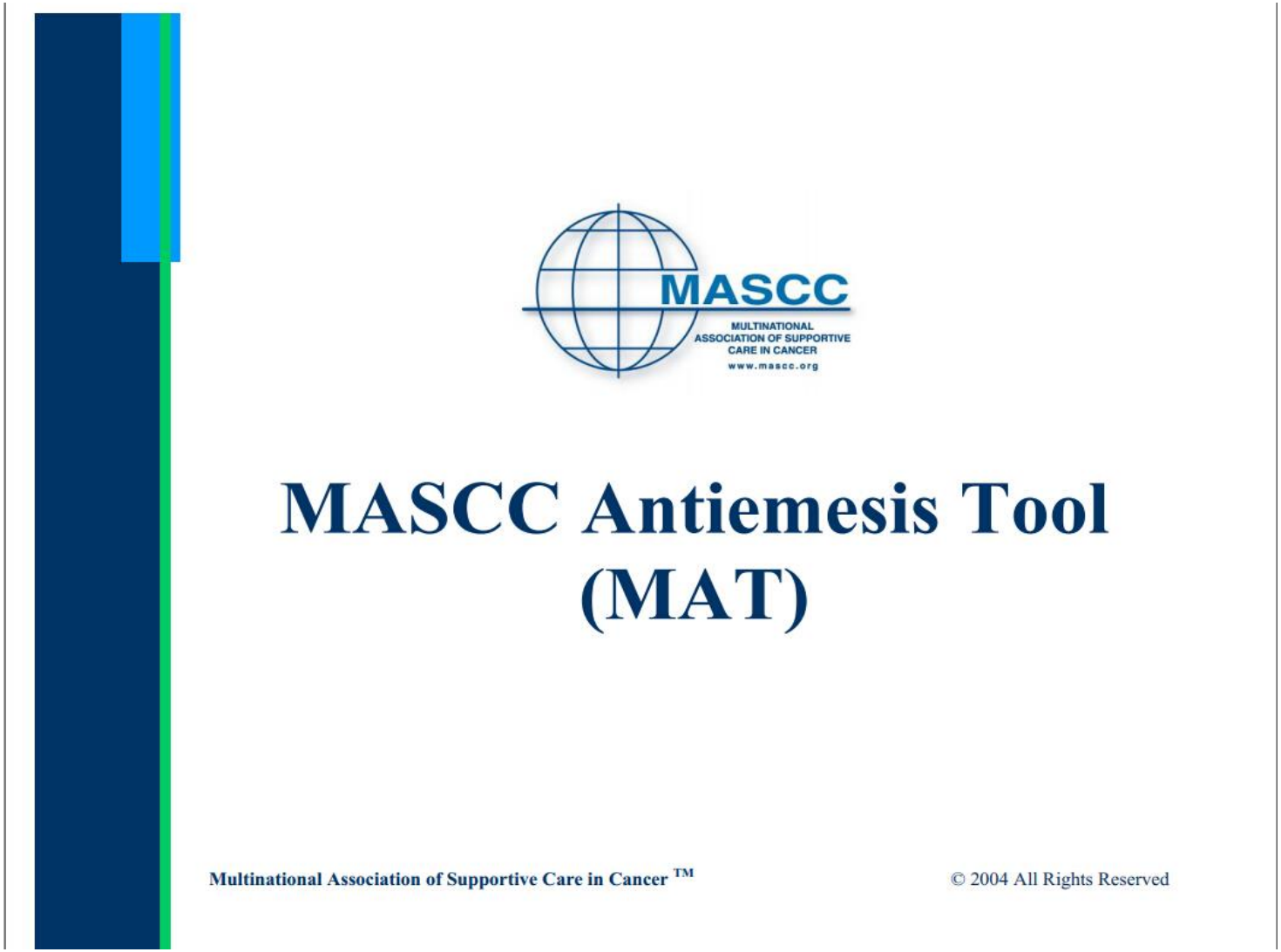
您是否會考慮將耳穴療法推薦給您的朋友？下面 1-10，從 1 (絕對不會) 到 10 (一定會)，請根據您的情況在相應數字上打勾：

1 2 3 4 5 6 7 8 9 10

絕對不會 一定會

提醒：請您在明天早上移除耳貼，然後完成一份 MAT 問卷。明天您也將接到我們的隨訪電話，請注意接聽。

Appendix VI: **The MASCC Antiemesis Tool (MAT), English version**



MASCC Antiemesis Tool: Instructions

Your Name:

Date of Chemotherapy *(this cycle)*:

Day | Month | Day of the Week

Your Oncology Nurse: Phone:

Your Oncology Physician: Phone:

Information about this brief form:

The MASCC Antiemesis Tool (MAT) is a way to help your doctors and nurses be sure you get the best care there is to prevent nausea and vomiting from chemotherapy. By filling out this form, you can help us make sure that you are having the best control of these possible side effects.

Here are the definitions used on this form:

Vomiting: The bringing up of stomach contents.

Nausea: The feeling that you might vomit.

Please answer all questions. There are no right or wrong answers, only your impression.
If you have any concerns about how or when to complete this form, please ask!

Please notice that Question #4 and Question #8 have a different style. These questions are scales.
For this type of question, just circle the number from 0 to 10 that most closely resembles your experience with your nausea and vomiting and write the number in the box to the right. An example of this form of question (but dealing with parking) is given below. Feel free to practice with this example or ask one of us to go over it with you.

How much difficulty did you have parking your car today?

0 1 2 3 4 5 6 7 8 9 10

None — As much as possible

(Write the number in this box)

Please return the form shortly after completing it, as discussed with us. Thank you!

MASCC Antiemesis Tool

Please fill this out the day after chemotherapy on:

Day | Month | Day of the Week

Nausea and Vomiting during the first 24 hours after chemotherapy:

(This page refers to the first 24 hours following chemotherapy):

1) In the 24 hours since chemotherapy, did you have any **vomiting?** **Yes** ☐ **No** ☐ (Select one)

2) If you vomited in the 24 hours since chemotherapy, how many **times** did it happen? ☐ (Write the number of times in this box)

3) In the 24 hours since chemotherapy, did you have any **nausea?** **Yes** ☐ **No** ☐ (Select one)

4) If you had nausea, please circle or enter the number that most closely resembles your experience.
How much nausea did you have in the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10

None — As much as possible

☐ (Write the number in this box)

MASCC Antiemesis Tool

This page asks about the period from the day after to 4 days after chemotherapy.
So it asks about the time after the first 24 hours.

Please fill this out four days after chemotherapy on:

Day ☐ Month ☐ Day of the Week ☐

Delayed Nausea and Vomiting

5) Did you **vomit** 24 hours or more after chemotherapy? **Yes** ☐ **No** ☐ (Select one)

6) If you vomited during this period, how many **times** did it happen? ☐ (Write the number of times in this box)

7) Did you have any **nausea** 24 hours or more after chemotherapy? **Yes** ☐ **No** ☐ (Select one)

8) If you had nausea, please circle or enter the number that most closely resembles your experience.
How much nausea did you have over this time period?

☐ (Write the number in this box)

 3

MASCC Antiemesis Tool (MAT)

Patient Outcomes Score Sheet

Patient Name		Chemotherapy	Date	Antiemetic Regimen	Acute Vomiting		Acute Nausea		Delayed Vomiting		Delayed Nausea		Action Taken
					Question #1	Question #2	Question #3	Question #4	Question #5	Question #6	Question #7	Question #8	
					1=yes 2=no	Frequency	1=yes 2=no	Intensity score	1=yes 2=no	Frequency	1=yes 2=no	Intensity score	
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												
	1			Acute									
	2												
	3			Delayed									
	4												

Appendix VII: **The MASCC Antiemesis Tool (MAT), Chinese version**

MASCC 止吐评价工具 (MAT)

Multinational Association of Supportive Care in Cancer ™

MASCC 止吐评价工具：使用说明

姓名:

化疗日期 *（本周期）*：

日期　月　星期 (几)

您的责任护士：　　电话：

您的管床医生：　　电话：

如何使用本表格：

MASCC 止吐工具（MAT）针对化疗过程中出现的恶心/呕吐而设计，主旨是协助您的医护人员为您提供更好的防治手段。准确填写该表格有助于使该不良反应得到最佳控制。

以下是本表格中涉及的一些名词的定义：

呕吐：胃内容物反流经口吐出。

恶心：一种想要呕吐的感觉。

请您回答所有的问题.根据您本人的看法来回答问题,没有对错之分.如果您对如何完成及何时完成这份表格有任何疑问,请务必提出！

请注意问题 4 和问题 8 的提问形式与其他问题是不一样的——这两个问题用了度量工具。对于这种类型 的问题,您只需要根据您自身恶心与呕吐的体验，从 0-10 中圈出一个与您所感觉到的恶心呕吐严重程度最相符的数字，并把这个数字写在最右边的框内。这里提供了一个此类型问题的范例(有关停车的问题)，您可以先尝试一下回答这一类型的问题，或者通过这个例子让我们帮助您理解如何回答这一类型的问题.。

您今天停车有多困难?

0 1 2 3 4 5 6 7 8 9 10

没有困难　　极度困难

(在方框中填写数字)

请您在填写完该表后立即返还,欢迎与我们讨论.谢谢您的配合!

MASCC 止吐工具

请在化疗后第二 天填写该问卷:

日期 月 星期 (几)

化疗后第一个 24 小时您的恶心与呕吐的情况:

(这一页主要反映您化疗后 **24 小时内** 的情况):

1) 化疗后 **24 小时内**,您是否有**呕吐**的情况? **有** ☐ **没有** ☐ (选择一个)

2) 如果您在化疗后 **24 小时内** 出现呕吐,您呕吐了多少次? ☐ (写下您呕吐的次数)

3) 化疗后 **24 小时内**,您是否有**恶心**的感觉? **有** ☐ **没有** ☐ (选择一个)

4) 如果您有恶心的情况,请圈出或者写下最能够体现您恶心严重程度的数字.在过去的 **24 小时内**, 您恶心的情况有多严重?

☐ (在方框中填写数字)

0 1 2 3 4 5 6 7 8 9 10

没有恶心 极度恶心

MASCC 止吐工具

这一页是要了解您在化疗结束 **24 小时后**到化疗结束后第 **4** 天的情况.
因此所有问题问的都是化疗结束后 **24 小时之后**的情况.

请在化疗结束 4 天后填写这张表:

日期 月 星期(几)

延迟性呕吐与恶心

5) 化疗结束 **24 小时之后**您有**呕吐**反应吗? **有** ☐ **没有** ☐
(选择一个)

6) 如果在此期间您有呕吐,您呕吐了多少次?
(写下您呕吐的次数)

7) 化疗结束 **24 小时之后**您有**恶心**反应吗? **有** ☐ **没有** ☐
(选择一个)

8) 如果您有恶心反应,请圈出或者写下最能够体现您恶心严重程度的数字.在过去这段时期, 您恶心的情况有多严重?

0 1 2 3 4 5 6 7 8 9 10
没有恶心 极度恶心

(在方框中填写数字)

MASCC止吐工具 (MAT)

患者结果得分记录表

患者姓名	化疗	日期	止吐方案	急性呕吐		急性恶心		延迟性呕吐		迟发性恶心		处理措施
				问题1	问题2	问题3	问题4	问题5	问题6	问题7	问题8	
				1=有 2=没有	频次	1=有 2=没有	严重程度分级	1=有 2=没有	频次	1=有 2=没有	严重程度分级	
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
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	3		*延迟性*									
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	1		*急性*									
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	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											
	1		*急性*									
	2											
	3		*延迟性*									
	4											

<u>Appendix VIII</u>: **The Index of Nausea, Vomiting, and Retching (INVR), English version**

The Index of Nausea, Vomiting, and Retching

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please mark **one** mark on each **line**.

	A	**B**	**C**	**D**	**E**
1. In the last 12 hours, I threw up ___ times.	7 or more	5-6	3-4	1-2	I did not throw up
2. In the last 12 hours, from retching and dry heaves I have felt ___distress.	no	mild	moderate	great	severe
3. In the last 12 hours, from vomiting or throwing up, I felt ___ distress.	severe	great	moderate	mild	no
4. In the last 12 hours, I have felt nauseated or sick to my stomach ____.	not at all	1 hour or less	2-3 hours	4-6 hours	more than 6 hours
5. In the last 12 hours, from nausea/sickness to my stomach, I have felt ___ distress.	no	mild	moderate	great	severe
6. In the last 12 hours, each time I threw up, I produced a ____ amount.	very large (3 cups or more)	large (2-3 cups)	moderate (½-2 cups)	small (up to ½ cups)	no
7. In the last 12 hours, I have felt nauseated or sick to my stomach ___ times.	7 or more	5-6	3-4	1-2	no
8. In the last 12 hours, I have had periods of retching or dry heaves without bringing anything up _____ times.	no	1-2	3-4	5-6	7 or more

Appendix IX: **The Index of Nausea, Vomiting, and Retching (INVR), simplified Chinese version**

恶心、呕吐、干呕评分调查表

请您在下表 A、B、C、D、E 五项中选择最与您接近的一项填入:

	A	B	C	D	E
1. 在过去 12 小时内我呕吐___次	7 次以上	5-6 次	3-4 次	1-2 次	未呕吐
2. 在过去 12 小时内干呕给我带来___痛苦	未感到	轻微	中度	很大	非常大
3. 在过去 12 小时内呕吐给我带来___痛苦	非常大	很大	中度	轻微	未感到
4. 在过去 12 小时内我恶心、胃部不适持续时间____	未感到不适	近 1 小时	2-3 小时	4-6 小时	6 小时以上
5. 在过去 12 小时内恶心、胃部不适给我带来___痛苦	未感到	轻微	中度	很大	非常大
6. 在过去 12 小时内我每次呕吐达____杯	非常多 3 杯以上	很多 2-3 杯	中量 ½-2 杯	很少 不到 1 杯	未呕吐
7. 在过去 12 小时我感到恶心、胃部不适____次	大于 7 次	5-6 次	3-4 次	1-2 次	未感到不适
8. 在过去 12 小时内我干呕但没呕吐东西_____次	未干呕过	1-2 次	3-4 次	5-6 次	大于 7 次

※ 1 杯 = 250 cc

<u>Appendix X</u>: The Functional Assessment of Cancer Therapy-Breast (FACT-B) (Version 4), English version

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix XI: **The Functional Assessment of Cancer Therapy-Breast (FACT-B) (Version 4), Chinese version**

FACT-B（第四版）

以下是一些与您患有同样疾病的人所认为重要的陈述。请在每行圈选或标出一个数字来表明适用于您**过去7天**情况的回答。

	生 理 状 况	一点也不	有一点	有些	相当	非常
GP1	我精神不好	0	1	2	3	4
GP2	我感到恶心	0	1	2	3	4
GP3	因为我身体不好，我满足家庭的需要有困难	0	1	2	3	4
GP4	我感到疼痛	0	1	2	3	4
GP5	治疗的副作用使我感到烦恼	0	1	2	3	4
GP6	我觉得病了	0	1	2	3	4
GP7	我因病被迫要卧床休息	0	1	2	3	4

	社 会 / 家 庭 状 况	一点也不	有一点	有些	相当	非常
GS1	我和朋友们很亲近	0	1	2	3	4
GS2	我在感情上得到家人的支持	0	1	2	3	4
GS3	我得到朋友的支持	0	1	2	3	4
GS4	我的家人已能正视我患病这一事实	0	1	2	3	4
GS5	我满意家人间对我疾病的沟通方式	0	1	2	3	4
GS6	我与自己的配偶（或给我主要支持的人）很亲近 ...	0	1	2	3	4
Q1	*不管你近期的性生活的程度，请回答下面的问题* *如果你不愿回答，请在这里注明 □，然后回答下一组问题*					
GS7	我对自己的性生活感到满意	0	1	2	3	4

FACT-B（第四版）

请在每行圈选或标出一个数字来表明适用于您**过去7天**情况的回答。

	情 感 状 况	一点也不	有一点	有些	相当	非常
GE1	我感到悲伤	0	1	2	3	4
GE2	我满意自己处理疾病的方式	0	1	2	3	4
GE3	在与疾病的抗争中，我越来越感到失望	0	1	2	3	4
GE4	我感到紧张	0	1	2	3	4
GE5	我担心我可能会去世	0	1	2	3	4
GE6	我担心自己的病情会恶化	0	1	2	3	4

	功 能 状 况	一点也不	有一点	有些	相当	非常
GF1	我能够工作（包括在家里工作）	0	1	2	3	4
GF2	我的工作（包括在家的工作）令我有成就感	0	1	2	3	4
GF3	我能够享受生活	0	1	2	3	4
GF4	我已能面对自己的疾病	0	1	2	3	4
GF5	我睡得很好	0	1	2	3	4
GF6	我在享受我常做的娱乐活动	0	1	2	3	4
GF7	我对现在的生活质量感到满意	0	1	2	3	4

FACT-B（第四版）

请在每行圈选或标出一个数字来表明适用于您**过去7天**情况的回答。

	附 加 关 注	一点也不	有一点	有些	相当	非常
B1	我一直感到呼吸急促	0	1	2	3	4
B2	我在意自己的衣着	0	1	2	3	4
B3	我的一只胳膊或两只胳膊发肿，或一碰就疼	0	1	2	3	4
B4	我感到自己在性方面有吸引力	0	1	2	3	4
B5	脱发使我烦恼	0	1	2	3	4
B6	我担心家里其他人有一天会得和我一样的病	0	1	2	3	4
B7	我担心紧张对我的疾病造成的影响	0	1	2	3	4
B8	体重的变化使我烦恼	0	1	2	3	4
B9	我能够感到自己象个女人	0	1	2	3	4
P2	我身体的某些部位感到疼痛	0	1	2	3	4

Appendix XII: **Open-ended questions included in the semi-structured interview guide**

姓名縮寫：_____	**RCT Random No.：_____**	**RCT Group：_____**
AT 完成情況：嚴格依從☐ 非嚴格依從☐	**對 AT 效果的期待*：0 1 2 3 4 5 6 7 8 9 10**	**曾接觸其他 CHAs：**是☐ 否☐
訪談編號：_____	**聯繫電話：_____**	**訪談持續時間：____(min)**

* 0-完全沒有期待；10-非常期待

問題編號	問題	現場記錄
1 所有患者	你參加本治療研究的總體體驗如何？	
2 所有患者	你對傳統中醫藥(補充替代療法)的看法如何？(與現代醫學比較)	
3 所有患者	如何評價你在治療期間填寫的幾份問卷，包括： (1) 在初次化療週期的第 2 天(化療后第 1 天)及第 6 天(化療后第 5 天)填寫(或詢問)的關於化療噁心嘔吐情況的 MAT 問卷？ (2) 在接受初次及二次化療前填寫 (或詢問)的關於預期性噁心嘔吐情況的 INVR 問卷？ (3) 在接受初次及二次化療前填寫 (或詢問)的生存品質問卷 FACT-B 問卷？	
4 接受 AT 者	如何評價我們在耳穴治療期間要求你每日記錄的耳穴治療日誌 (以記錄你每天的按壓次數、時間及可能存在的不良反應)？	
5 接受 AT 者	在何種程度上你相信耳穴療法能夠幫助你控制噁心嘔吐的症狀？	
6 接受 AT 者	在接受耳穴治療後，你在以下方面體會到了哪些變化： (1) 症狀改善 (噁心嘔吐症狀及其他精神心理症狀)？ (2) 行為習慣？ (3) 生活態度？	
7 接受 AT 者	接受耳穴治療期間，哪些問題或麻煩導致你難以依從指示進行規律治療？ (1) 因耳穴治療的時間過長而造成不便； (2) 難以使耳穴貼一直保持在原位； (3) 其他常見問題，如：在洗澡時不慎將耳穴貼打濕；清理耳朵時不慎使耳穴貼脫落掉進外耳道；不慎在按壓的同時滾動揉搓了耳穴貼，從而導致耳朵皮膚破損； (4) 出現和耳穴治療相關的副作用，如：對耳穴貼過敏 (出現耳朵局部皮膚發紅及疼痛等症狀)、局部不適、發癢、紅腫或出血等症狀。	
8 接受 AT 者	(除以上原因) 其他哪些原因導致你難以堅持規律完成五天的耳穴治療？	
9 接受 AT 者	你對於耳穴治療的滿意度如何？	
10 接受 AT 者	你在將來是否會考慮採用耳穴療法治療你的其他健康問題 (如睡眠障礙，慢性疼痛及疲勞等)？(採用或不採用)的原因？	
11 所有患者 (接受 AT 者)	你對於研究(及耳穴治療)安排有什麼建議或意見？以便我們在將來能夠進一步提高。	
12 所有患者	你是否還有和治療相關的其他問題 (在前面的訪談中尚未涉及到的)？	

<u>Appendix XIII</u>: Standard AT procedures (for training the doctoral researcher and the two backup researchers)

耳穴貼壓的標準操作流程 [博士研究員及後備研究員培訓用]

<u>組別 1 的耳穴治療方法 [採用王不留行籽耳穴貼]</u>

準備	研究者：六步洗手法洗手并戴口罩.
	物品：治療車、治療盤、75%酒精、棉簽、耳穴探測儀，王不留行籽耳穴貼、鑷子、彎盤等。
	參與者 (患者)：研究者須遵照護理操作流程，核對并確認參與者的相關信息，做好治療目的解釋并描述耳穴治療相關操作流程。
操作過程	備齊用物至床邊，再次核對，取得參與者合作。
	體位：參與者取合適體位。
	定穴：**“胃”，“脾”，“賁門”，“肝”，“神門”，“交感”**及**“皮質下” <u>[雙耳取穴]</u>** 研究者應用耳穴探測儀在相應耳穴區尋找找敏感點或陽性反應點并確定相應耳穴的定位。
	消毒：全耳正面自上而下，用酒精消毒。
	埋籽：正確持鑷，取粘有王不留行籽的脫敏膠布耳穴貼，粘於所選穴位上，並用拇、食指腹按壓片刻。
	按壓：按壓時，力度適中，詢問有無酸、脹、痛等 “得氣”感，在確定“得氣”感以後，再在最為敏感的相應穴位點持續對壓 20-30 秒，按壓強度以患者能耐受為度。研究者向參與者示範按壓操作后，參與者進行自行按壓，研究者須確定其操作正確無誤。
	注意事項：囑參與者保留耳穴貼 5 日，每日清晨、下午 (午休后) 及晚間 (睡前) 規律按壓貼壓的耳穴，以產生得氣感為度。每穴大致按壓 20-30 秒，除每天三次規律按壓之外，參與者在出現噁心感之前亦可進行按壓。同時，囑咐其在洗頭洗澡時候注意保護耳穴貼以防止其打濕并脫落。如耳穴貼有脫落或者貼壓部位出現疼痛發紅瘙癢等不良反應，參與者須及時與研究者聯繫。
	觀察：留籽期間，經常觀察局部皮膚有無紅腫熱痛，及不適症狀，膠布是否脫落。

組別 2 的耳穴治療方法 [採用燈芯草耳穴貼]

準備	研究者：六步洗手法洗手并戴口罩.
	物品：治療車、治療盤、75%酒精、棉簽、耳穴探測儀，燈芯草耳穴貼、鑷子、彎盤等。
	參與者 (患者)：研究者須遵照護理操作流程，核對并確認參與者的相關信息，做好治療目的解釋并描述耳穴治療相關操作流程。
操作過程	備齊用物至床邊，再次核對，取得參與者合作。
	體位：參與者取合適體位。
	定穴：**“胃”，“脾”，“賁門”，“肝”，“神門”，“交感”**及**“皮質下” [雙耳取穴]** 研究者應用耳穴探測儀在相應耳穴區尋找找敏感點或陽性反應點并確定相應耳穴的定位
	消毒：全耳正面自上而下，用酒精消毒。
	埋籽：正確持鑷，取粘有燈芯草的脫敏膠布耳穴貼，粘於所選穴位上. **勿須進行按壓！**
	注意事項：囑參與者保留 5 日，**並囑其勿對耳貼進行按壓！** 同時，囑咐其在洗頭洗澡時候注意保護耳穴貼以防止其打濕并脫落。如耳穴貼有脫落或者貼壓部位出現疼痛發紅瘙癢等不良反應，參與者須及時與研究者聯繫。
	觀察：留籽期間，經常觀察局部皮膚有無紅腫熱痛，及不適症狀，膠布是否脫落。

Appendix XIV: Ethical approvals of the doctoral research project

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Suen Kwai Ping Lorna (School of Nursing)		
From	CHIEN Wai Tong, Chair, Departmental Research Committee		
Email	hschien@j	Date	08-Mar-2015

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 01-May-2015 to 01-Aug-2016:

Project Title:	The Effects of Auricular Acupressure on Chemotherapy-Induced Nausea and Vomiting in Female Breast Cancer Patients: A Pilot and Feasibility Randomized Controlled Trial
Department:	School of Nursing
Principal Investigator:	Suen Kwai Ping Lorna
Reference Number:	HSEARS20150213001

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

CHIEN Wai Tong

Chair

Departmental Research Committee

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Suen Kwai Ping Lorna (School of Nursing)		
From	CHIEN Wai Tong, Chair, Departmental Research Committee		
Email	hschien@	Date	15-Jun-2016

Revision of Ethical Approval for Teaching/Research Involving Human Subjects

Project Title:	The Effects of Auricular Acupressure on Chemotherapy-Induced Nausea and Vomiting in Female Breast Cancer Patients: A Pilot and Feasibility Randomized Controlled Trial
Department:	School of Nursing
Principal Investigator:	Suen Kwai Ping Lorna
Reference Number:	HSEARS20150213001-01

I am pleased to inform you that approval has been given to your revised application for human ethics review of the above project for a period from 01-May-2015 to 31-Oct-2016:

Please be reminded that you are responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI also assumes the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval extension.

You will receive separate email notification should you be required to obtain fresh approval.

CHIEN Wai Tong

Chair

Departmental Research Committee

Appendix XV: Information sheet

Information Sheet (English Version)

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

INFORMATION SHEET

The Effects of Auricular Acupressure on Chemotherapy-Induced Nausea and Vomiting in Female Breast Cancer Patients: A Pilot and Feasibility Randomized Controlled Trial

You are invited to participate in a clinical pilot study supervised by Dr. Lorna Suen and Prof. Alex Molassiotis, and conducted by Mr. Jing-Yu Tan, who is a Ph.D. student at the School of Nursing, The Hong Kong Polytechnic University. Please carefully read this information sheet before making the decision to participate in this study or not. Eligible participants should be female breast cancer patients scheduled to be treated with the first cycle of chemotherapy. If you agree to participate in this pilot research, you will need to sign a written informed consent. Please note that participation in the pilot study is totally on a voluntary basis.

The overall purpose of this pilot study is to assess the feasibility of a randomized controlled trial (RCT) to evaluate the effects of auricular acupressure on nausea and vomiting in a group of female breast cancer patients undergoing chemotherapy. The objectives of this study are to evaluate the feasibility of the procedures of the RCT using a standard auricular acupressure protocol to alleviate chemotherapy-induced nausea and vomiting; to determine the eligibility rate, recruitment rate, retention rate, and attrition rate during the pilot RCT subject recruitment and follow-up process; to determine the feasibility and acceptability of the study questionnaires and auricular acupressure protocols among the study participants; to identify potential adverse events associated with auricular acupressure; to preliminarily examine the effects of auricular acupressure on acute, delayed, and anticipatory nausea and vomiting as well as quality of life (QoL) status in breast cancer patients undergoing chemotherapy; to explore the participants' experiences of participating in the pilot RCT and receiving the auricular acupressure; and to refine the study protocol for a future multicenter, large-scale RCT to examine the definite effects of auricular acupressure on nausea and emesis in breast cancer patients undertaking chemotherapy.

If you agree to participate in this pilot research, you will have an equal chance to be allocated to one of three groups. One group will receive standard antiemetic medications, and for the other two groups, in addition to the standard antiemetic medications, a five-day auricular acupressure program will be provided. The auricular acupressure used in one group was specifically designed to control nausea and vomiting, while the auricular acupressure used in the other group was not emesis-specific but may also produce some potentially non-specific curative effects for emesis. The auricular acupressure treatment will begin on the day that you receive the chemotherapeutic regimens and will continue for the following four days.

For the baseline assessment, you will be asked to complete a demographic questionnaire and another two questionnaires to evaluate your anticipatory nausea and vomiting and QoL before the chemotherapy; you will also be required to complete a self-rated questionnaire on CINV on day 2 and the day 6 of the first cycle of chemotherapy. When you return to the hospital for the next cycle of chemotherapy, you will be asked to complete a QoL questionnaire. In addition, on the morning of the second chemotherapy cycle, you will also be asked to measure anticipatory nausea and vomiting using another self-rated questionnaire.

In addition, we will also invite you to participate in a semi-structured qualitative interview after the completion of the pilot RCT. The interview will be on an individual basis with the doctoral researcher (Mr. Jing-Yu Tan), and it aims to explore the participants' experiences of participating in the pilot RCT and receiving the auricular acupressure. Several questions will be asked during the interview, and the interview will be audio-taped using a digital recorder. You can choose either the interview room or the demonstration room in this department to do the interview or some other place that is convenient for you. After completing the pilot RCT, the doctoral researcher will check with you to arrange a suitable time to conduct the interview.

The treatment approach used in this study, auricular acupressure, is a famous non-pharmacological intervention with the features of being non-invasive and having fewer undesirable reactions, and it will not do harm to your health. Some minor adverse events of auricular acupressure (e.g., minor pain, itching, and discomfort of the ear skin) have been documented in the literature, but most of the reactions are tolerable and transient and will disappear soon after removing the acupressure tapes. You have every right to withdraw from the study before or during the measurement without penalty of any kind. All information related to you will remain confidential, and will be identifiable by codes known only to the researchers.

If you have any complaints about the conduct of this research study, please do not hesitate to contact Dr. Virginia Cheng, Secretary of the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University in person or in writing (c/o Research Office of the University), stating clearly the person and department responsible for this study.

If you would like more information about this study, please contact Mr. Jing-Yu Tan at telephone number (86) 1310763 or his supervisors, Dr. Lorna Suen and Prof. Alex Molassiotis, at telephone number (852) 2766 (Dr. Suen) or (852) 2766 (Prof. Molassiotis).

Thank you for your interest in participating in this study.

Principal Investigators

Dr. Lorna Suen, Prof. Alex Molassiotis, Mr. Jing-Yu Tan

Information Sheet (Simplified Chinese Version)

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

有 關 資 料

耳穴貼壓治療乳腺癌患者化療所致惡心嘔吐的臨床隨機對照預試驗

誠邀閣下參加由 孫桂萍博士及莫禮士教授 負責監督, 譚景予先生 負責執行的研究項目 。譚景予先生是香港理工大學護理學院的博士研究生 。在閣下決定是否參加這個研究之前，請閣下仔細閱讀本研究有關內容，本研究的參加者要求確診為乳腺癌的患者且目前正在接受第一週期的輔助化療。若同意參與此研究，閣下需要簽署知情同意書，您是否參加本研究完全是自願的。

這項預實驗的目的是評價實施一項臨床隨機對照試驗的可行性，這項臨床隨機對照試驗的主要目的是檢驗一項關於耳穴貼壓療法緩解乳腺癌化療患者惡心嘔吐的臨床隨機對照試驗的可行性。在這項預實驗中，和可行性相關的研究目的則包括試行這一臨床隨機對照試驗；評價在整個研究過程中研究對象的納入率及失訪率；評價研究問卷在研究對象中使用的可行性；評價研究干預方法的安全性；初步評價干預方法對化療相關的急性、延遲性及預期性惡心嘔吐以及生存質量的效果；以及探索研究對象完成整個研究過程的體驗。同時，這項預實驗的結果還將為下一步多中心、大樣本的臨床隨機對照試驗干預方案的改善提供啟示。

閣下若有意願參與此研究，則將有均等的機會被隨機分到三個不同組別。一個組接受常規的止吐藥物治療，而另外兩個組除了接受常規的止吐藥物治療外，還將獲得為期 5 天的耳穴貼壓療法。在這兩個接受耳穴貼壓療法的組別中，一個組的耳穴療法是特異性地針對化療所致惡心嘔吐反應的，另一個組則未特異性針對惡心嘔吐但仍可能對惡心嘔吐產生一些非特異性的潛在治療作用。耳穴貼壓治療從本週期化療的第 1 天持續至第 5 天，

除了在同意參加研究的當天做的一系列基線評估 (包含基本情況調查表、化療前的預期性惡心嘔吐及生存質量)之外，閣下需要在本化療週期的第 2 天即第 6 天，填寫一份和評價急性/延遲性惡心嘔吐相關的問卷。同時，當本週期化療結束時，即當閣下返回醫院準備下一階段化療時，尚需閣下再進行一次生存質量問卷調查。最後，在第二個化療週期第 1 天，閣下須要再完成一份問卷以評價您的預期性惡心嘔吐的情況。

除此之外，在閣下完成這個臨床預試驗之後，我們還會邀請閣下參加一個半結構式的訪談。該訪談是一對一的形式，訪談期間僅有閣下和譚先生參加。該訪談的目的在於探索研究參與者參加整個臨床預試驗的體驗以及接受耳穴治療的一些體驗。在訪談的過程中，

譚先生將會問你一些問題，整個訪談過程將全程錄音。閣下可以選擇在科室的訪談室或示教室進行該訪談，或者在閣下認為更加方便的其他地方。在閣下完成臨床預試驗以後，譚先生將會和閣下確認最方便的時間進行訪談。

本研究所採用的耳穴貼壓療法是一種非侵入性的非藥物操作技術，安全方便，副作用小，不會對閣下的健康造成損耗。目前的文獻顯示耳穴貼壓可導致一些輕微的不良反應 (如耳朵皮膚的輕微疼痛、癢或不適)，但這些反應多短暫可耐受，且在移除耳穴貼后可快速消除。閣下享有充分的權利在研究開始之前或之後決定退出這項研究, 而不會受到任何對閣下不正常的待遇或被追究責任 。凡有關閣下的資料將會保密, 一切資料的編碼只有研究人員得悉。

如果閣下對這項研究有任何的不滿, 可隨時與香港理工大學人類實驗對象操守小組委員會秘書 Virginia Cheng 博士聯 絡 (地址 : 香港理工大學研究事務處 轉交) 。

如果閣下想獲得更多有關這項研究的資料，請與 譚景予先生，即實施本項目的博士研究生聯絡，電話（86）1310763 ，或聯絡他的指導教師 孫桂萍博士及莫禮士教授，電話（852）2766 （孫桂萍博士）和（852）2766 （莫禮士教授）。

謝謝閣下有興趣參與這項研究 。

主要研究員 (PI)

孫桂萍 博士

莫禮士 教授

譚景予 先生

Appendix XVI: Written informed consent

Written Informed Consent (English Version)

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

CONSENT TO PARTICIPATE IN RESEARCH

The Effects of Auricular Acupressure on Chemotherapy-Induced Nausea and Vomiting in Female Breast Cancer Patients: A Pilot and Feasibility Randomized Controlled Trial

I _____hereby consent to participate in the captioned research conducted by_____.

I understand that information obtained from this research may be used in future research and published. However, my right to privacy will be retained (i.e., my personal details will not be revealed).

The procedure as set out in the attached information sheet has been fully explained. I understand the benefits and risks involved. My participation in the project is voluntary.

I acknowledge that I have the right to question any part of the procedure and can withdraw at any time without penalty of any kind.

Name of Participant _____

Signature of Participant _____

Name of Researcher _____

Signature of Researcher _____

Date _____

Written Informed Consent (Simplified Chinese Version)

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing
香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

參與研究同意書

耳穴貼壓治療乳腺癌患者化療所致惡心嘔吐的臨床隨機對照預試驗

本人_____同意參與由_____開展的上述研究。

本人知悉此研究所得的資料可能被用作日後的研究及發表，但本人的私隱權利將得以保留，即本人的個人資料不會被公開。

研究人員已向本人清楚解釋列在所附資料卡上的研究程序，本人明瞭當中涉及的利益及風險；本人自願參與研究項目。

本人知悉本人有權利就程序的任何部分提出疑問，并有權隨時退出而不受任何懲處。

參與者姓名_____

參與者簽署_____

研究人員姓名_____

研究人員簽署_____

日期 _____

Appendix XVII: Content validity assessment for the MAT, Chinese version

Cover Letter
致專家信

尊敬的專家：

您好！首先感謝您能夠在百忙之中抽空參與這份中文版 MASCC 止吐工具 (MAT) 的評價。感謝您對我們這一項研究的支持！

此次函詢旨在評價中文版 MAT 各個条目文化適應性的內容效度。參與本內容效度測評的專家包括教學科研及臨床實踐兩類專家。教學科研專家須為在高等院校進行腫瘤支持治療研究的教授或副教授（至少具備 10 年以上的研究經歷），并在腫瘤支持治療國內或國際同行評議期刊上發表過高水平學術論文者。臨床實踐專家則為具備副高級及以上職稱的取得資格的腫瘤科醫師（主任醫師或副主任醫師）及腫瘤科護師（主任護理師或副主任護理師），且具備至少 10 年的腫瘤患者治療/護理經驗。

本評價表共分為兩部分，第一部分即為此致專家信，第二部分為 MAT 文化適應性的內容效度評價表。請您逐條判斷每一條目是否適宜于中國病人進行理解，并進行評分，每一個條目都按照文化相關性程度分為了四等，即：非常合適（4 分），合適（3 分），一般合適（2 分）以及不合適（1 分）。請您根據您的判斷在每個條目對應的 4 個分值內進行選擇并在空格內作"√"標記，同時，尚有幾個關於 MAT 的問題附與評價表后，請一併回答。

此問卷以匿名形式函詢，您的資料僅用於統計分析及研究方案修改，絕不它用，絕對保密。請您在收到問卷的 2 周內發回至研究者電郵，或者聯繫研究者，研究者將在您方便的時候到您的單位取回該表。若您對此方案評價表有疑問或其他咨詢，請撥打電話（852）5432　　或（86）1310763　（聯繫人：譚景予）；或者發送電郵 jing-yu.tan@　　. 歡迎您隨時提供寶貴意見。

再次感謝您對本研究的支持。

香港理工大學護理學院

哲學博士研究生 譚景予

電子郵箱：jing-yu.tan@

移動電話（香港）：(852) 5432

移動電話（中國大陸）：(86) 1310763

在進行評價之前，請在下列表格中填寫您的基本資訊（請在符合您情況的□內打✓）。

1. 您所在的單位：高等學校 □　醫院 □

2. 所從事的研究領域：腫瘤相關治療 □　腫瘤相關護理 □

3. 年齡：30～40 歲 □　40～50 歲 □　50～60 歲 □　60 歲以上 □

4. 最高學歷：大專及以下 □　本科 □　研究生 □

5. 最高學位：學士 □　碩士 □　博士 □　其他 □

6. 職稱: (1) 高校：副教授 □　副研究員 □　教授 □　研究員 □

(2) 醫院：副主任醫師 □　主任醫師 □

副主任護師 □　主任護師 □

7. 參加工作的年限：5～10 年 □　11～15 年 □　16～20 年 □　20 年以上 □

8. 聯繫電話：

Content Validity Assessment Form
内容效度評價表

說明：請您根據您的判斷在每個條目對應的 4 個分值內進行選擇并在空格內作“√”標記。

条目	条目内容		条目的文化适应性评分			
			非常合适(4)	合适(3)	一般合适(2)	不合适(1)
1	**如何使用本表格**：MASCC 止吐工具（ MAT）针对化疗过程中出现的恶心/呕吐而设计，主旨是协助您的医护人员为您提供更好的防治手段。准确填写该表格有助于使该不良反应得到最佳控制。 以下是本表格中涉及的一些名词的定义： 呕吐: 胃内容物反流经口吐出。 恶心: 一种想要呕吐的感觉。 请您回答所有的问题.根据您本人的看法来回答问题,没有对错之分。如果您对如何完成及何时完成这份表格有任何疑问, 请务必提出！ 请注意问题 4 和问题 8 的提问形式与其他问题是不一样的——这两个问题用了度量工具。对于这种类型 的问题,您只需要根据您自身恶心与呕吐的体验，从 0-10 中圈出一个与您所感觉到的恶心呕吐严重程度最相符的数字，并把这个数字 写在最右边的框内。这里提供了一个此类型问题的范例(有关停车的问题)，您可以先尝试一下回答这一类型的问题，或者通过这个例子让我们帮助您理解如何回答这一类型的问题。 您今天停车有多困难? 0 1 2 3 4 5 6 7 8 9 10 没有困难 极度困难 (在方框中填写数字) 请您在填完该表后立即返还，欢迎与我们讨论。谢谢您的配合！					
化疗后第一个 24 小时您的恶心与呕吐的情况 (这一页主要反映您化疗后 24 小时内的情况)						
2	1) 化疗后 24 小时内,您是否有呕吐的情况?	有 □□没有 □ □ (选择一个)				
3	2) 如果您在化疗后 24 小时内出现呕吐, 您呕吐了多少次? □	□ (写下您呕吐的次数)				
4	3) 化疗后 24 小时内, 您是否有恶心的感觉?	有 □□没有 □□ (选择一个)				
5	4) 如果您有恶心的情况, 请圈出或者写下最能够体现您恶心严重程度的数字.在过去的 24 小时内, 您恶心的情况有多严重? 0 1 2 3 4 5 6 7 8 9 10 没有恶心 极度恶心	□ (在方框中填写数字)				
这一页是要了解您在化疗结束 24 小时后到化疗结束后第 4 天的情况. 因此所有问题问的都是化疗结束后 24 小时之后的情况						
6	5) 化疗结束 24 小时之后您有呕吐反应吗?	有 □ 没有 □ □ (选择一个)				
7	6) 如果在此期间您有呕吐, 您呕吐了多少次?	□ (写下您呕吐的次数)				
8	7) 化疗结束 24 小时之后您有恶心反应吗?	有 □ 没有 □□ (选择一个)				
9	8) 如果您有恶心反应, 请圈出或者写下最能够体现您恶心严重程度的数字。在过去这段时期, 您恶心的情况有多严重? 0 1 2 3 4 5 6 7 8 9 10 没有恶心 极度恶心	□ (在方框中填写数字)				
请您同时回答以下三个问题： 1. 该量表是否真正评价了化疗所致恶心呕吐的症状？_____ 2. 该量表的条目是否适合中国的肿瘤患者进行评价？_____ 3. 该量表的条目在理解上是否有困难？若有，请指出并提出您的修改建议。_____						

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