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SELF-ADMINISTERED ACUPRESSURE FOR THE CANCER-RELATED SYMPTOM CLUSTER OF INSOMNIA, DEPRESSION, AND ANXIETY: A FEASIBILITY RANDOMIZED CONTROLLED TRIAL

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Self-Administered Acupressure for the Cancer-Related Symptom Cluster of Insomnia, Depression, and Anxiety: A Feasibility Randomized Controlled Trial

HOANG THI XUAN HUONG

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

July 2020

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_____ (Signed)

Hoang Thi Xuan Huong
_____ (Name of students)

Abstract

Background

About 40% to 60% of cancer patients receiving chemotherapy experienced insomnia during their treatment. Moreover, insomnia correlated with others to form a sleep-related symptom cluster. Our literature review has identified several limitations in previous research that lead to a wide range of insomnia prevalence, unclear risk factors, and the unclear correlation between insomnia and other symptoms in cancer patients. Results from our review also indicated that just a small number of interventions for sleep-related symptom clusters were conducted during the past decade. Nevertheless, most of the current non-pharmacological interventions for sleep-related symptoms clusters require the physical presence of an instructor to deliver the intervention as well as require patients to spend time and effort for administering it. Hence, there is a need to develop an intervention using a self-management approach to manage insomnia and insomnia-related symptom clusters in cancer patients. Among non-pharmacological treatments, self-administered acupressure is a promising approach, but the relevant research evidence is unknown at present.

Aims

This doctoral project was carried out with the following aims:

1. To ascertain the prevalence of insomnia and to identify the risk factors and correlations between insomnia and other symptoms among cancer patients receiving chemotherapy in Vietnam. Data from this study (study one) would highlight the extent of the problem and offer information that should be considered in the development of an intervention trial.
2. To develop a self-acupressure treatment protocol.

3. To test the feasibility of an intervention using self-acupressure to manage the an insomnia-related symptom cluster that will be identified from study one

Methods

This doctoral project covered the first two phases of *The Medical Research Council (MRC) framework for developing and evaluating complex interventions*. In the first phase, a cross-sectional survey was conducted among 214 cancer patients undergoing chemotherapy in three hospitals in Hanoi, Vietnam. The outcome measures included The Insomnia Severity Index (ISI), the Hospital Anxiety and Depression scale (HADS), the Memorial Symptom Assessment Scale (MSAS), the Functional Assessment of Cancer Therapy – General (FATC-G), Actigraph, and a sleep log. Afterward, an acupressure treatment protocol was developed based on the findings of the cross-sectional survey. It was then validated by a panel of six Traditional Chinese Medicine (TCM) experts.

In the second phase of the *MRC framework*, a three-arm parallel randomized control trial (RCT) was adopted. A total of 114 participants scheduled to receive chemotherapy treatment were recruited from two hospitals in Hanoi, Vietnam and were randomly assigned to one of three groups: The true self-acupressure group (True AP), the sham self-acupressure group (Sham AP), and the enhanced standard care group (ESC). Participants in the true and sham self-acupressure group received a self-acupressure training session on how to locate and stimulate acupoints/sham acupoints. They were requested to perform self-acupressure at home once a day for four weeks. Weekly phone calls were made to encourage them to practice self-acupressure at home. Participants in the ESC group received an education training session on ten recommendations to

manage insomnia, depression, and anxiety. They were also requested to practice these recommendations at home for four weeks. During the study period, they also received weekly follow up phone calls. The outcome assessments were the Numeric Rating Scale for each of the symptom (NRS), the ISI, the HADS, the FACT-G, the sleep diary, and the Intervention Rating Scale-15 (IRS-15). Assessments were carried out at baseline (T1), at the end of the intervention (T2) and a month later (T3).

Results

Results from the cross-sectional survey reported a high prevalence of insomnia among participants (42.8%), with one-third of those with insomnia reporting severe insomnia. Insomnia occurrence and severity were not correlated with the participants' characteristics, cancer-related or treatment-related factors, only with the participants' anxiety/depression scores. The principal component analysis showed that insomnia, depression, and anxiety formed a symptom cluster ($p < 0.001$).

Results from the feasibility study indicated the intervention using self-administered acupressure to manage the symptom cluster of insomnia, depression, and anxiety was feasible, with only six months required to recruit and conduct the intervention in 114 cancer patients (recruitment rate 12.6%, attrition rate 35.1%). It was also highly acceptable by participants (the mean IRS-15 was 76.73). Besides, the self-acupressure treatment protocol used in the intervention was safe as associated adverse events were mild, tolerable, and transient. The results indicated that the self-acupressure had clinical significance in improving the targeted symptoms and quality of life. In the true AP group, the SC severity was significantly lower than in the other groups at T2 ($p<0.05$). Insomnia and anxiety severity in the true AP and sham AP group were significantly lower than those in the ESC at T2 and T3 ($p<0.05$).

Conclusion

The doctoral project results provide new knowledge to fill significant gaps related to insomnia prevalence and managing the sleep-related symptom cluster, which includes insomnia, depression, and anxiety in cancer patients undergoing chemotherapy. The results from the feasibility RCT indicated the validated evidence-based acupressure treatment protocol used in the study was demonstrated to be safe, convenient and with promising effectiveness to improve the symptom cluster of insomnia, depression, and anxiety among cancer patients undergoing chemotherapy. However, the effect of self-administered acupressure was a mixture of therapeutic effect and placebo effect. Future full-scale RCT is recommended to examine the promising effect of self-administered acupressure on the symptom cluster of insomnia, depression, and anxiety as well as its effect in improving quality of life status in cancer patients undergoing chemotherapy.

PUBLICATION AND PRESENTATIONS ARISING FROM THE PH.D. STUDY

Referred journal article arising from the thesis

Hoang HTX, Molassiotis A, Chan CW, Nguyen TH, Liep Nguyen V. New-onset insomnia among cancer patients undergoing chemotherapy: prevalence, risk factors, and its correlation with other symptoms. *Sleep Breath*. 2020;24(1):241-251. doi:10.1007/s11325-019-01839-x

Conference presentations

Hoang HTX, Molassiotis A, Chan CW, Nguyen THA (2017). Sleep quality among cancer patients undergoing chemotherapy in Vietnam [poster presentation]. The 20th East Asian Forum of Nursing Scholars (March 09-10, 2017), Hong Kong, SAR

Hoang HTX, Molassiotis A, Chan CW, Vu HA. Self-administered acupressure to manage symptom cluster of insomnia, depression, and anxiety in cancer patients undergoing chemotherapy: a feasibility study [oral presentation]. The 23th East Asian Forum of Nursing Scholars (January 10-11, 2020), Chiang Mai, Thailand

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My very best

Hoang Thi Xuan Huong

Table of Contents

LIST OF FIGURES ..... **xv**

LIST OF TABLES ..... **xvii**

LIST OF ABBREVIATIONS ..... **xxii**

CHAPTER 1. INTRODUCTION **1**

1.1. Introduction **1**

1.2. Background of the study **1**

1.3. Organization of the thesis **5**

CHAPTER 2. LITERATURE REVIEW **6**

2.1. Introduction **6**

2.2. Definition of Insomnia **8**

2.3. Prevalence of Insomnia among Cancer patients **9**

2.4. Factors associated with the development of insomnia in cancer patients ... **18**

2.4.1. Predisposing factors 18

2.4.2. Precipitating factors 20

2.4.3. Perpetuating factors 22

2.5. Impact of Insomnia on cancer patients' quality of life **23**

2.6. Sleep-related symptom clusters in cancer patients 26

2.7. Insomnia's measurement instruments 36

2.7.1. Subjective measurements 36

2.7.2. Objective measurements 40

Polysomnography 40

Actigraph 41

2.8. Managing insomnia in cancer patients 43

2.8.1. Managing insomnia as a single symptom 43

2.8.1.1. Pharmacological treatment for insomnia in the cancer population .. 43

2.8.1.1.1. Hypnotics 44

2.8.1.1.2. Antidepressants 45

2.8.1.1.3. Melatonin 46

2.8.1.1.4. Herbal Medicine 46

2.8.1.2. Non-pharmacological treatments for insomnia in cancer patients ... 50

2.8.1.2.1. Cognitive Behavioral Therapy for Insomnia (CBT-I) 50

2.8.1.2.2. Mindfulness-based interventions 60

2.8.1.2.3. Yoga 62

2.8.1.2.5. Complementary & Alternative treatments: Acupuncture, Acupressure 69

2.8.2. Managing insomnia-related symptom clusters 76

2.9. The effectiveness of self-acupressure in managing sleep-related symptom clusters in cancer patients. **83**

2.10. Gaps in the current literature **84**

2.11. Conclusions of the literature review **86**

CHAPTER 3. THE METHODOLOGICAL AND THEORETICAL FRAMEWORKS UNDERPINNING THE DEVELOPMENT OF THE PROJECT **87**

3.1. Introduction **87**

3.2. The application of the MRC framework for the development of the intervention **87**

3.2.1. Introduction to the MRC framework 87

3.2.2. Application of the MRC framework in the doctoral project 88

3.3. The development of the self-administered acupressure intervention **91**

3.3.1. The theoretical framework of the cross-sectional survey and the feasibility trial 91

3.3.1.1. Introduction to the Theory of Unpleasant Symptoms (TOUS) 91

3.3.1.2. Theoretical framework of the cross-sectional survey 92

3.3.1.3. Theoretical framework of the self-administered acupressure intervention 95

3.4. The aims of the doctoral project 98

CHAPTER 4. INSOMNIA AMONG CANCER PATIENT UNDERGOING CHEMOTHERAPY IN VIETNAM: PREVALENCE, ASSOCIATIONS WITH OTHER SYMPTOMS AND IMPACT ON QUALITY OF LIFE. 99

4.1. Introduction 99

4.2. Methods 100

4.2.1. Study design and settings 100

4.2.1. Sample size estimation 101

4.2.2. Ethical considerations 102

4.2.3. Outcome Measurements 104

4.2.4. Procedures 108

4.3. Data Analysis 109

4.3.1. Data cleaning 110

4.3.2. Assessment of data normality 110

4.3.3. Missing data management 110

4.3.4. Statistical analysis 111

4.4. Results of the study **113**

4.4.1. Sample characteristics 113

4.4.2. Prevalence and Severity of insomnia 118

4.4.3. Feasibility of using Actigraph to measure sleep among participants 119

4.4.4. The impact of insomnia to patient's quality of life (patient's QOL) .. 120

4.4.5. Identification of risk factors for insomnia 121

4.4.6. Identifying a sleep-related symptom cluster 123

4.5. Contribution of the cross-sectional survey to the development of the trial's protocol **125**

CHAPTER 5. DEVELOPMENT OF THE SELF-ACUPRESSURE PROTOCOLS **128**

5.1. Introduction **128**

5.2. The development of the true self-acupressure protocol **129**

5.2.1. Justification of the selected acupoints 129

5.2.2. Justification for the dose of the true self-acupressure treatment 130

5.3. Development of the protocol for the sham self-acupressure **136**

5.3.1. Justification for choosing a sham acupressure approach 136

5.3.2. Sham self-acupressure protocol 136

5.4. Validation of the true self-acupressure and sham self-acupressure protocol 139

CHAPTER 6. THE METHODOLOGY OF THE INTERVENTION FEASIBILITY TRIAL 147

6.1. Introduction 147

6.2. The study design 148

6.3. Setting and study participants 149

6.3.1. Settings 149

6.3.2. Participants 150

6.4. Sample size estimation 151

6.5. Trial arms: Intervention and control arms 152

6.5.1. Enhanced standard care group (ESC) 152

6.5.2. True self-acupressure group [Enhanced standard care + true self-acupressure group] 155

6.5.3. Sham self-acupressure group [Enhanced standard care + sham self-acupressure group] 155

6.6. Study process and data collection 156

6.6.1. Study procedures 156

6.6.2. Randomization, allocation concealment 161

6.6.3. Blinding 162

6.6.4. Fideltity of the study 163

6.6.4.1. Fidelity of the feasibility design 163

6.6.4.2. Training of the interventionists 164

6.6.4.3. Participants training 165

6.6.4.4. Participants' self-delivery of the intervention 166

6.7. Data analysis 167

6.7.1. Outcome measurements 167

6.7.2. Data analysis 172

6.7.2.1. Data cleaning 172

6.7.2.2. Intention-To-Treat (ITT) principle 172

6.7.2.3. Missing data management 173

6.7.2.4. Statistical analysis 174

6.8. Ethical considerations 176

CHAPTER 7. RESULTS OF THE FEASIBILITY TRIAL 179

7.1. Introduction 179

7.2. Participants' characteristic and baseline outcomes data 179

7.2.1. Participants' demographic characteristics 179

7.2.2. Participants' clinical characteristics 181

7.2.3. Participants' baseline outcomes data 183

7.3. Feasibility of the recruitment process 185

7.3.1. Time to recruit participants 185

7.3.2. The recruitment rate, eligible rate, and refusal rate 185

7.4. Attrition rate and differences in characteristic between withdrawn participants and participants who completed the feasibility study 188

7.4.1. Attrition rate and reason for attrition 188

7.4.2. Differences in the characteristics between participants who withdrew and participants who completed the study 189

7.5. The feasibility of the study measurements 190

7.6. Participants' acceptability of the intervention 192

7.6.1. Participants' adherence to the self-acupressure treatment protocol .. 192

7.6.2. Participants' perception of the intervention 193

7.7. Fidelity of the trial 195

7.7.1. Fidelity of the feasibility study design 195

7.7.2. Fidelity of the training of the interventionists 195

7.7.3. Fidelity of the participants' training 195

7.7.4. Fidelity of the participants' self-delivery of the intervention 196

7.8. Adverse events associated with self-acupressure.....197

7.9. Evaluating the preliminary effects of the intervention on the severity of the symptom cluster, individual symptoms, and participants' quality of life.....197

7.9.1. Preliminary effects of the intervention on individual symptoms and the symptom cluster score (measured by NRS) 197

7.9.1.1. Preliminary effects of the intervention on the insomnia score (measured by NRS) 197

7.9.1.2. Preliminary effects of the intervention on the depression severity (measured by NRS) 199

7.9.1.3. Preliminary effects of the intervention on the anxiety severity (measured by NRS) 201

7.9.1.4. Preliminary effects of the intervention on the symptom cluster severity measured by NRS.....203

7.9.2. Preliminary effects of the intervention on the individual symptoms in the cluster (measured by ISI, sleep diary, and HADS) 205

7.9.2.1. Preliminary effects of the intervention on the ISI and sleep parameter 205

7.9.2.2. Preliminary effects of the intervention on the depression severity (measured by HADS 212

7.9.2.3. Preliminary effects of the intervention on anxiety 214

7.9.3. Preliminary effects of the intervention on the patients' quality of life (QOL) 216

7.10. Effect size and sample size calculation 218

***Note: AP: self-acupressure, ESC: Enhanced Standard Care; ISI: Insomnia Severity Index, HADS: Hospital Anxiety and Depression Scale* 218**

7.11. Summary of the results of the feasibility trial 219

CHAPTER 8. DISCUSSION AND CONCLUSIONS 222

8.1. Introduction 222

8.2. Insomnia prevalence and its risk factors 223

8.2.1. Insomnia prevalence 223

8.2.2. Risk factors of insomnia 223

8.3. The symptom cluster of insomnia, depression, and anxiety 224

8.4. The impact of insomnia and the insomnia related-symptom cluster on participants' quality of life 225

8.5. The appropriateness of subjective measurement for insomnia in cancer patients 226

8.6. The feasibility of the intervention 228

8.6.1. The feasibility of the recruitment process 228

8.6.2. Attrition rate and reasons for attrition 230

8.6.3. Feasibility of the study measurements 230

8.6.4. Adverse events from self-acupressure 233

8.6.5. Acceptability of the intervention 234

8.6.5.1. Self-acupressure treatment completeness 234

8.6.5.2. Participants' acceptability of the intervention 236

8.7. Fidelity of the intervention 237

8.7.1. Intervention design 237

8.7.2. Intervention training and monitoring of the intervention delivery 238

8.7.3. Monitoring of patients receiving the intervention 240

8.8. Selection of control groups 241

8.9. Preliminary effectiveness of the intervention 243

8.9.1. Effectiveness of the intervention on the symptom cluster severity 243

8.9.2. Effects of the intervention on individual symptoms 246

8.9.2.1. Effects of the intervention on insomnia 246

8.9.2.2. Effects of the intervention on depression 248

8.9.2.3. Effects of the intervention on anxiety 250

8.9.3. Effects of the intervention on participants' Quality of life (QoL) 251

8.9.4. Clinical significance of the intervention on insomnia, depression, anxiety severity, and quality of life 253

8.9.5. Placebo effects of Self-acupressure 256

8.10. Strengths and limitations 259

8.10.1. Study's strengths 259

8.10.2. Study limitations 261

8.11. Changes for a future trial 263

8.12. Implications 265

8.12.1. Implications for future research 265

8.12.2. Clinical implications 266

8.12.3. Educational implications 267

8.13. Conclusions 269

REFERENCES 272

Appendix 1. Information Sheet for the feasibility study (English and Vietnamese) 313

Appendix 2. Consent form for the feasibility study (English and Vietnamese Version)..... 317

Appendix 3. Assessment and Evaluation form for the feasibility study (English and Vietnamese version)..... 319

Part 1. Demographic data 319

Part 2. Health history 319

Part 4. Insomnia Severity Index 321

Part 5. Assessment depression and Anxiety 322

Part 6. Assessment Quality of Life 324

Part 7. Sleep diary 326

Appendix 5. The intervention rating profile-15 (English and Vietnamese version) 338

Appendix 6. Protocol for the self-acupressure training session for participants 340

Appendix 7. Interventionist Skill Check of Self-acupressure and Sham Self-acupressure (English and Vietnamese version) 342

Appendix 8. Self-acupressure Skill Check Forms for participants (English and Vietnamese version)..... 346

Appendix 9. Protocol for education session for participants in the enhanced standard care group. 350

Appendix 10. Acupresssure Protocol Validation Form (English and Vietnamese) 351

Appendix 4. Self-acupressure Record Form (English and Vietnamese version) 354

Appendix 11. Information sheet of the cross-sectional survey 358

Appendix 12. Consent form for the cross-sectional survey study (English and Vietnamese Version).....359

Appendix 13. Ethical approval memo for the cross-sectional survey.....360

Appendix 14. Ethical approval memo for the feasibility study 361

Appendix 15. Sleep log (use in the cross-sectional survey) 362

LIST OF FIGURES

Figure 1. The MRC's framework for Developing and Evaluating Complex Intervention 88

Figure 2. Process of study design following the MRC framework for Developing and Evaluating Complex Interventions 90

Figure 3. The Theory of Unpleasant Symptoms (Lenz & Pugh, 2003, p. 170) 92

Figure 4. Conceptual Framework of the cross-sectional survey 94

Figure 5. The theoretical framework of the intervention 97

Figure 6. The flowchart of the cross-sectional survey 115

Figure 7. The flowchart of the feasibility trial 160

Figure 8. The CONSORT diagram of the feasibility trial 187

Figure 9. Changing of insomnia score (measured by the NRS) over time in study groups 198

Figure 10. Changing of depression score (measured by the NRS) over time in study groups 200

Figure 11. Changing of anxiety score (measured by the NRS) over time in study groups 202

Figure 12. Reduction of symptom cluster severity (measured by the NRS) in study groups over time. 204

Figure 13. Reduction of insomnia severity (measured by ISI) in study groups over time. 206

Figure 14. Changing of depression severity (measured by HADS) in study groups over time 212

Figure 15. Changing of anxiety severity (measured by HADS) in study groups over time 214

Figure 16. Changing of Quality of Life score in study groups over time 216

LIST OF TABLES

Table 1. Large-scale Studies of insomnia in Cancer Patients 12

Table 2. Cancer treatments that cause insomnia 21

Table 3. Impact of Insomnia to Quality of Life among cancer patients..... 24

Table 4. Studies to determine sleep-related symptom clusters in Cancer Patients 27

Table 5. Hypnotics for insomnia Approved by FDA 44

Table 6. Pharmacological treatments for Insomnia in Cancer patients..... 48

Table 7. Studies on the effectiveness of CBT-I treatment for insomnia in Cancer Patients 51

Table 8. Sleep hygiene components 58

Table 9. Effectiveness of mindfulness training on insomnia in cancer patients 61

Table 10. Studies of Yoga intervention for Insomnia in cancer patients 65

Table 11. Studies of exercise intervention for insomnia in cancer patients. 68

Table 12. Studies of acupuncture for insomnia in cancer patients..... 72

Table 13. Studies of Acupressure for Insomnia in Cancer Patients. 74

Table 14. Interventions to improve sleep-related symptom clusters in cancer patients 77

Table 15. Demographic and Clinical Characteristics of the patients 116

Table 16. Prevalence and Severity of insomnia 118

Table 17. Measuring sleep parameters in patients with insomnia and non-insomnia 119

Table 18. Differences in insomnia and non-insomnia patients with Quality of Life (QOL) score and QOL domains 120

Table 19. ISI score classification by demographic and clinical characteristic of patients 121

Table 20. Correlations between insomnia score and anxiety/depression score 123

Table 21. Identifying symptom clusters (SCs) by MSAS, ISI, and HADS 124

Table 22. The proposed true self-acupressure treatment protocol for insomnia, depression, and anxiety..... 134

Table 23. The proposed sham self-acupressure protocol 137

Table 24. Characteristics of experts in the panel for validating acupressure treatment protocols 139

Table 25. Components of the proposed acupressure protocols that did not meet the agreement level in the first round of the validation study 143

Table 26. Results of the true self-acupressure protocol validation 144

Table 27. Results of the sham self-acupressure protocol validation 145

Table 28. The final true and sham self-acupressure protocols 146

Table 29. Summary of the study arms and intervention..... 156

Table 30. Time points for data collection during each participant's involment in the feasibility trial 161

Table 31. Baseline demographic information of the participants (n=114) 180

Table 32. Baseline clinical characteristics of the participants (n=114) 182

Table 33. Participants' baseline outcomes data 184

Table 34. Subject recruitment at different study sites 186

Table 35. Reasons for attrition 188

Table 36. Demographic, clinical characteristic, and baseline assessment different between participants who withdrew and who stayed in the feasibility trial 189

Table 37. Missing data for the FACT-G-GS7 and Sleep Diary at different time points of data collection 191

Table 38. Reasons for not completing 28 days of treatment in true and sham acupressure groups 192

Table 39. Participants' perception of the acceptability of the intervention 194

Table 40. Wrong acupoints identified by the participants after the true self-acupressure training sessions 196

Table 41. Pairwise comparison of insomnia score (measured by the NRS) within-group over time (Post-hoc test adjustment) 198

Table 42. Pairwise comparison of insomnia score (measured by the NRS) between-group over time (Post-hoc test adjustment) 199

Table 43. Pairwise comparison of depression score (measured by the NRS) within-group over time (Post-hoc test adjustment) 200

Table 44. Pairwise comparison of depression score (measured by the NRS) between-group over time (Post-hoc test adjustment) 201

Table 45. Pairwise comparison of anxiety score (measured by the NRS) within-group over time (Post-hoc test adjustment) 202

Table 46. Pairwise comparison of anxiety score (measured by the NRS) between-group over time (Post-hoc test adjustment) 203

Table 47. Pairwise comparison of symptom severity (measured by the NRS) within-group over time (Post-hoc test adjustment) 204

Table 48. Pairwise comparison of symptom cluster severity (measured by the NRS) between-groups over time (Post-hoc test adjustment) 205

Table 49. Pairwise comparison of insomnia severity (measured by ISI) within-group over time (Post-hoc test adjustment) 206

Table 50. Pairwise comparison of insomnia severity (measured by ISI) between-group over time (Post-hoc test adjustment) 207

Table 51. Descriptive analysis of participant's sleep parameters 209

Table 52. Changes of sleep parameters in each study group over time 210

Table 53. Changes in sleep parameters of participants at post intervention (T2) and post follow-up (T3) 211

Table 54. Pairwise comparison of depression score (measured by HADS) within-group over time (Post-hoc test adjustment) 213

Table 55. Pairwise comparison of depression score (measured by HADS) between-group over time (Post-hoc test adjustment) 213

Table 56. Pairwise comparison of anxiety score (measured by HADS) within-group over time (Post-hoc test adjustment) 215

Table 57. Pairwise comparison of anxiety severity (measured by HADS) between-groups over time (Post-hoc test adjustment) 215

Table 58. Pairwise comparison of quality of life (measured by FACT-G) within study group over time (Post-hoc test adjustment) 217

Table 59. Pairwise comparison of quality of life index (measured by FACT-G) between study groups over time (Post-hoc test adjustment) 217

Table 60. Effect size of the intervention calculated based on post-intervention assessment results 218

LIST OF ABBREVIATIONS

AA	Auricular therapy
AP	Self-acupressure
AT	Acupuncture therapy
BDI	Beck Depression Inventory
CBT-I	Cognitive behavioral therapy for insomnia
CES-D	Center for Epidemiological Studies Depression scale
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials statements
CR	Cognitive restructuring
CRF	Cancer related-fatigue
DBAS	Dysfunctional Beliefs and Attitudes about Sleep
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EA	Electro acupuncture
ECOG	Eastern Cooperative Cancer Group
EORTC QOL-C30	European Organization for research and treatment of cancer Quality of life
ESAS	Edmonton Symptom Assessment System
ESC	Enhanced Standard Care group
FACT-L	The Functional Assessment of cancer Therapy (for Lung patients)

FACT-O	The Functional Assessment of cancer Therapy (for ovarian patients)
FATC-G	Functional Assessment of Cancer Therapy – General
FDA	The Food and Drug Administration
FSI	Fatigue Symptom Inventory
FWB	Functional Well-Being
GSDS	General Sleep Disturbance Scale
HADS	Hospital Anxiety and Depression scale
ICD-10	International Classification of Diseases, Tenth Edition
ICSD-3	The International Classification of Sleep Disorders 3rd edition
IRS-15	Intervention Rating Scale-15
ISI	Insomnia Severity Index
KMO	Kaise-Meyer-Olkin
LTEQ	Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire
MFI	Multidimensional Fatigue Inventory
MRC:	Medical Research Council
MSAS	Memorial Symptom Assessment Scale
MSAS-GDI	Global Distress Index
MYCAW	Measure Your Self-concern And Well-being

MYMOP	Measure yourself medical outcome profile
NIH-BCC	Behavior change Consortium at the National Institutes for Health
NRS	Numeric Rating Scale
nWASO	Number of nights awaken after sleep onset
PCA	Principal Component Analysis
PHYS	Physical Symptom Distress
PICO	Patient/population/problem, Intervention, Comparison, and Outcomes
PMR	progressive muscle relaxation
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSYCH	Psychological Symptom Distress
RCT	Randomized Control Trial
RT	relaxation training
SCt	Stimulus control
SC	Symptom Cluster
SCSCP	Stanford Cancer Supportive Care Program
SD	Sleep duration
SE	Sleep efficiency
SF-36	Medical outcome survey 36 items short form

SH	Sleep hygiene
SII	Sleep Impairment Index
SMI	Sleep Maintenance Insomnia characterized by middle-of-the-night awakening followed by difficulty returning to sleep
SOI	Sleep onset insomnia
SOL	Sleep Onset Latency
STAI	State-Trait Anxiety Inventory
STRICTA	Standards for Reporting Intervention in Controlled Trials of Acupuncture
TCM	Traditional Chinese Medicine
TOUS	Theory of Unpleasant Symptoms
TST	Total Sleep Time
tWASO	Time awaken after sleep onset
UC	Usual care
US	The United States of American
YOCAS	Yoga program for advanced cancer patients

CHAPTER 1. INTRODUCTION

1.1. Introduction

This chapter begins with the background of the doctoral project, followed by the organization of the thesis.

1.2. Background of the study

Cancer is a leading cause of death worldwide, with approximately nearly one in six deaths being due to cancer globally (World Health Organization, 2017). Cancer is rapidly becoming a global pandemic, and it is estimated that by 2030 there will be 21.7 million cases and 13 million deaths worldwide (American Cancer Society, 2017). Major treatments for cancer include surgery, radiotherapy, and chemotherapy improve patient's survival but also can exert a significant psychosocial and physical impact on patients by producing a variety of unpleasant symptoms (Cleeland, 2007; Dodd et al., 2001; Donovan et al., 2005). Among these symptoms, insomnia is one of the common symptoms in cancer patients; however, it often goes unrecognized and receives little attention compared to other symptoms (e.g., pain, fatigue, depression) by clinicians and researchers (Dahiya et al., 2013; Savard & Morin, 2001). Literature indicated that insomnia reduces patient's quality of life significantly (Clevenger et al., 2013; Davidson et al., 2002; Romito et al., 2014; Vargas et al., 2010). However, previous studies remained many limitations in the methodology including lack of definition of insomnia, using a non-specific scale to measure insomnia, and a small sample size. Hence, the prevalence of insomnia remains variable; its etiology and risk factors were not fully explored.

Up to 40% of cancer patients experienced at least two symptoms during their illness (Esther Kim et al., 2009). Hence, the concept of "symptom clusters" has been developed. A symptom cluster has been first defined as three or more symptoms occurring together, related to each other and may not have the same etiology (Dodd et al., 2001). Later, other research has expanded the concept of symptom clusters and defined it as "two or more symptoms that are clinically meaningful together, related to each other at a given time and share a significant variance in their cluster" (Molassiotis et al., 2010). Although the above definitions share the same viewpoint on how symptoms coexist in a group, there are conceptual disagreements in terms of the number of symptoms in a cluster. Applying the concept of identifying symptom cluster by the correlation between symptoms, different sleep-related symptom clusters among cancer patient have been identified across studies such as fatigue, depression, and insomnia (Ho et al., 2015; Roscoe et al., 2007); pain, fatigue and insomnia (Chen & Tseng, 2006; Cleeland et al., 2000; Ivanova et al., 2005; Romito et al., 2014) or pain, depression, and insomnia (Savard et al., 2005). However, most of the previous studies were conducted in a small sample size and did not use a validated questionnaire to measure insomnia. Nevertheless, other symptoms were measured by a wide range questionnaire which was only measured 13 to 15 symptoms while cancer patients can experience up to 32 symptoms (Lobchuk, 2003). Therefore the correlation between insomnia and other symptoms has not been fully addressed yet in the current research.

Previous studies have indicated insomnia and sleep-related symptom clusters significantly reduced participant's quality of life (Clevenger et al., 2013; Davidson et al., 2002; Romito et al., 2014; Vargas et al., 2010). Hence, managing insomnia can place a significant positive impact on cancer patients' quality of life. Two approaches have

been employed to manage cancer-related insomnia which are managing insomnia as a single symptom and managing the whole sleep-related symptom clusters. The approach of targeting the entire cluster seems to be more reasonable, and recent studies have been used this approach to develop their intervention. During the past decades, several studies have been conducted to examine the effect of non-pharmacological treatment on sleep-related symptom clusters. Interventions to manage sleep-related symptom clusters are still infancy in the literature. To date, only eight studies have tested an intervention designed to handle a sleep-related symptom cluster. In those randomized control trials, non-pharmacological treatments (psycho-education, cognitive-behavioral strategies, and acupressure) were used to managing the pain, fatigue, and sleep disturbance symptom cluster with some initial evidence of success (Kwekkeboom, 2016). However, most of these trials were pilot studies with a small sample size that make their effectiveness on sleep-related insomnia is inconclusive. Besides, most of the current interventions for sleep-related symptoms clusters require the physical presence of an instructor to deliver the intervention as well as require patients to spend time and effort on administering.

Acupressure is a component of Traditional Chinese Medicine (TCM). In acupressure, physical force is stimulated on the acupoints on the body with finger pressure instead of needle insertion (Zick et al., 2011). A patient can get their acupressure treatment from a TCM professional or can be trained to treat themselves. Unlike other non-pharmacological treatments, acupressure can be performed at home, which is convenient for patients. Acupressure appeared to be an effective treatment for insomnia and other symptoms (nausea and vomiting, pain, fatigue) in both cancer and non-cancer populations (Hmwe et al., 2016; Lee et al., 2011). It is also known as a safe treatment

with mild adverse events (Hmwe et al., 2016). However, the effectiveness of acupressure in improving sleep-related symptom clusters in cancer patients is unknown.

Considering all the issues above, more high-quality researches are needed to provide a concrete prevalence of insomnia in the oncology population as well as to identify the risk factor and correlation between insomnia and other symptoms. Nevertheless, non-pharmacological treatment with favorable impact to improve sleep-related symptom clusters should also be tested in cancer patients in clinical practice. The optimal non-pharmacological treatment should have promising potential in improving sleep-related symptom clusters, less burden, and safe to cancer patients, of which self-acupressure could be a good option.

The doctoral project therefore conducted two studies. The Medical Research Council (MRC) framework developing and evaluating complex intervention was employed to guide the research design. The two studies in this project cover the first two phases of the MRC framework. The first study is the cross-sectional survey to ascertain the prevalence of insomnia and clarify risk factors and the correlation between insomnia and other symptoms. The result of the survey indicated a high prevalence of insomnia (42.8%). It also demonstrated that anxiety and depression severity were the risk factors of insomnia. Further analysis confirmed insomnia, depression, and anxiety formed a symptom cluster among participants (Hoang et al., 2019).

The second study was designed to test the feasibility of self-acupressure in managing insomnia, depression, and anxiety in cancer patients undergoing chemotherapy through a three-arm sham-controlled randomized feasibility trial. The two self-acupressure treatment protocol (for true and sham treatment) were developed based on high-quality

systematic reviews, relevant TCM theories, and handbooks. They were then validated by a panel of six TCM experts. Afterward, the feasibility study was carried out to test the feasibility of self-acupressure trial and preliminarily examine the effects of self-acupressure on the severity of the symptom cluster of insomnia, depression, and anxiety, as well as the severity of individual symptoms, and participants' quality of life. To our knowledge, this is the first intervention that targets the symptom cluster of insomnia, depression, and anxiety among cancer patients.

1.3. Organization of the thesis

The overall structure of the proposal takes the form of seven chapters, including this introductory chapter. Chapter two provides a literature review related to the research topic, which identifies what is known so far and what are the gaps in the literature that need further attention. Chapter three is the theoretical framework of the study. Chapter four reported the design and results of the cross-sectional survey. Chapter five provides information about the development of the acupressure protocol. Chapter six reports the design and results of the feasibility study. Lastly, the discussion of the thesis is presented in chapter seven.

CHAPTER 2. LITERATURE REVIEW

2.1. Introduction

As briefly described in chapter 1, the prevalence of insomnia in cancer patients remains variable, and its risk factors and correlation with other symptoms are unclear. In addition, evidence of the effective self-treatment for insomnia and sleep-related insomnia in cancer patients was inconclusive. Thus, the literature review in this chapter focuses on different areas related to insomnia in people with cancer, including prevalence, causes, risk factors, correlation with other symptoms, impact on patient's quality of life, measurements, and managing insomnia/sleep-related symptom cluster. The review aims to provide the context of insomnia to illustrate how this topic has been studied previously to indicate flaws and outline gaps in previous researches. **The search strategies undertaken** for the review included an electronic database search of PubMed, PsycINFO, and Cumulative Index of Nursing and Allied Health Literature (CINAHL). The literature review begins by presenting the definition of insomnia (section 2.2). Then the prevalence of insomnia in cancer patients is reviewed (section 2.3). Afterward, the causes and risk factors associated with insomnia and its impact on patient's quality of life are explored in sections 2.4 and 2.5, respectively. It is then followed by reviewing the sleep-related symptom clusters in cancer patients in section 2.6. Section 2.7 lists out the measurement of insomnia followed by the current treatments of insomnia (2.8). Section 2.9 reports the effectiveness of self-administered acupressure in managing sleep-related symptom clusters. In the last two sections, the research and conclusion of the literature review are presented.

The search terms used for searching publication in different areas related to insomnia were:

- Prevalence of insomnia: insomnia, sleep disorder, sleep disturbances, sleep difficulties, cancer, prevalence.
- Causes, risk factors, and correlation with other symptoms: insomnia, sleep disorder, sleep disturbances, sleep difficulties, cancer, risk factor, causes, correlation, symptom cluster.
- Measurement of insomnia: insomnia, sleep disorder, sleep disturbances, sleep difficulties, cancer, measurement, objective measurement, subjective measurement.
- Managing insomnia/sleep-related symptom cluster: The search strategy was developed by applying PICO categories (Patient/population/problem, Intervention, Comparison, and Outcomes). The initial searching term was broken down into its components: Population (cancer patients), intervention (pharmacological treatment or non-pharmacological treatment), and outcome (the measurement of insomnia). The initial search result helped to determine available therapies for insomnia in the cancer patient. Then, additional searches were conducted with the search term included: non-pharmacological treatment, pharmacological treatment, cognitive behavioral therapy, mindfulness, yoga, acupuncture, acupressure, exercise, symptom cluster, symptom cluster management. An extensive search was conducted, including a search of systematic reviews, meta-analyses, and evidence-based practice guidelines.
- The inclusion criteria for articles were articles published in the English language from 2000 to 2019.

2.2. Definition of Insomnia

Insomnia can be categorized as either a symptom or a disease (Billiard & Bentley, 2004). When being categorized as a disease, there are three classification systems define insomnia: *The International Classification of Sleep Disorders 3rd edition (ICSD-3),* the "*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition" (DSM-5) and the "International Classification of Diseases, Tenth Edition (ICD-10)"*. In these classification systems, insomnia is defined by (1) persistent sleep difficulty (such as cannot sleep after 30 minutes, waking up after sleep onset or earlier than desired), (2) lacking adequate sleep opportunity and (3) related daytime tiredness and impaired daytime function (e.g., impaired working performance, fatigue, mood disturbance). These sleep disturbances must occur at least three times per week for one month to meet the diagnostic criteria for insomnia. Insomnia can be detected by using standard questionnaires such as the Insomnia Severity Index or Pittsburgh Sleep Quality Index which follows the criteria for insomnia of DSM-IV and ICSD (Savard et al., 2005).

In the previous studies on insomnia in cancer patients, these terms such as "sleep disturbance," "insomnia," "impaired sleep," and "sleep-wake disturbances" are being used interchangeably due to lack of insomnia definition (Lowery, 2015). Lacking a definition of insomnia leads to the unclear distinction between symptoms of poor sleep and insomnia reflects a problematic issue in assessing insomnia in cancer patients. This has also led to the use of various questionnaires to assess insomnia resulting in a wide range of insomnia prevalence in the literature. A recent review pointed out that just 10.2% of the included studies defined insomnia, and 31.9% of them used a standardized scale to measure insomnia (Otte et al., 2015). The prevalence of insomnia is presented in the next section.

2.3. Prevalence of Insomnia among Cancer patients

In the general population, insomnia is one of the most common sleep disorders (Neubauer, 2018). A systematic review indicates that the prevalence of insomnia in the general population is approximately 10% to 20% (Buysse, 2013). In cancer patients, insomnia is also one of the most common complaints with prevalence ranges from as low as 8.9% to as high as 93.3% (Davis et al., 2014; Shao et al., 2016). The wide range of insomnia prevalence is perhaps due to variable assessment times, cancer diagnosis, lacking a formal definition of insomnia, and the use of various questionnaires to assess insomnia. In this section, we include studies that had at least 100 participants which are the minimum sample size to obtain any kind of meaningful results (Rumsey, 2005). As such, 17 studies were included to discuss the prevalence of insomnia in cancer patients.

Among cancer patients before receiving treatment, the prevalence of insomnia ranged from 26% to 57% (Phillips et al., 2012; Van Onselen et al., 2010). With patients undergoing treatment, the prevalence is reported to be slightly higher ranging from 30% to 68% (Cheng & Yeung, 2013; Davidson et al., 2002). Advanced cancer patients under palliative treatment have the highest prevalence of insomnia, with up to 93.9% experiencing insomnia (Shao et al., 2016). Insomnia is a problem to not only cancer patients but also to cancer survivors, with nearly 39% to 65% reporting difficulties sleeping during the cancer survivorship period (Clark et al., 2004; Savard & Morin, 2001).

Also, patients with different types of cancer reported different rates of insomnia. Research indicated higher insomnia prevalence in breast and lung cancer in comparison with other cancer types. A study pointed out that lung cancer patients had the highest prevalence of insomnia syndrome, and patients with breast cancer had the highest

number of overall insomnia complaints (Palesh et al., 2010). Another study found 37.8% of patients with breast cancer, and 36.8% of the patients with lung cancer reported insomnia, significantly higher than other cancers (Davidson et al., 2002). Results from those studies indicated that insomnia is a high prevalence problem among cancer patients that need more awareness.

Although this sleep disorder is a significant problem among cancer patients, studies conducted to assess the prevalence of insomnia in cancer patients often have methodological limitations such as: using non-specific questionnaires to measure insomnia, lacking objective measurement, not including a working definition for insomnia, etc**.** **Table 1** details the 17 studies included in this section.

The majority of studies (16/17 studies) did not include a definition of insomnia or sleep problems. Only the study conducted by Davidson et al. (2002) defined insomnia by the combination of patient's perception of sleep disturbances and associated daytime function impairments, which is consistent with the definition of insomnia in ICD-10. Lacking insomnia definition resulted in various questionnaires were used to assess the symptom. Eight questionnaires were used to measure insomnia in studies, among these questionnaires, only three questionnaires (Pittsburgh Sleep Quality Index, Insomnia Severity Index, Athens Insomnia Scale) are specific measurement for insomnia, other scales are not (The Hamilton Depression Inventory, Symptom Distress Scale, Edmonton Symptom Assessment System, Eastern Cooperative Oncology Group). Pittsburgh Sleep Quality Index was used in six studies (Akman et al., 2015; Mercadante et al., 2004; Miaskowski et al., 2011; Phillips et al., 2012; Romito et al., 2014; Van Onselen et al., 2010); Insomnia Severity Index was used in three studies (Davis et al., 2014; Morris et al., 2015; Savard et al., 2015) and Athens Insomnia Scale was used in

one study (Mercadante et al., 2015). Non-specific questionnaires were used to measure poor sleep symptoms (decreased sleep duration, increased sleep latency, sleep disruptions and daytime dysfunction) were used in five studies (Barata et al., 2016; Cheng & Yeung, 2013; Palesh et al., 2010; Sela et al., 2005; Shao et al., 2016). Two studies used the sleep survey questionnaire to measure insomnia, but the authors did not indicate whether these questionnaires were validated (Davidson et al., 2002; Savard et al., 2011). Nevertheless, 16/17 studies did not use objective measurement to provide more information on patient's sleep patterns such as total sleep time, delayed sleep time, sleep efficiency, etc., to provide more detail of the sleep problems among this population. Actigraph was used in only one study (Miaskowski et al., 2011); however, the duration of objective measurement was 48 hours, which was shorter than the recommendation of standard objective measurement for insomnia (Ancoli-Israel et al., 2015).

Another limitation of these studies was regarding the data collection method, as 2/17 used secondary data analysis lacking information about the purpose and sampling method of the primary studies that affect the quality of the data (Cheng & Yeung, 2013; Palesh et al., 2010). Besides, none of the above studies was guided by a theoretical framework. Only three studies were conducted in patients undergoing chemotherapy (Akman et al., 2015; Palesh et al., 2010; Romito et al., 2014). In addition, most of the studies did not discuss the etiology of sleep problems.

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Table 1. Large-scale Studies of insomnia in Cancer Patients

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Phillips et al., 2012)	300 mixed-type cancers/US	Before Chemotherapy	PSQI, LTEQ, CES-D, FSI	Cross-sectional survey	26% of participants were poor sleepers, sleep efficiently was 83%	Strengths: various cancer diagnoses, disease stages, prior treatments. Limitations: the ability to perform subgroup analysis due to a wide range of participants' characteristics, unable to calculate the globe PSQI score due to using the abbreviated version. Not including a working definition for insomnia, lack of objective measurements.
(Miaskowski et al., 2011)	185, mixed type cancers/US	Before radiation therapy	PSQI, GSDS + Actigraph for 48 hours	Cross-sectional survey	More than 56% had PSQI score > 5 (indicated poor sleep quality). The GSDS indicated that 95% of participants reported insufficient sleep amount on four days or more per week.	Strengths: Using both subjective and objective measurements. Limitations: The duration for objective measurement was not long enough (48 hours only). Not including a working definition for insomnia
(Van Onselen et al., 2010)	179 breast/prostate /lung/brain cancer The US	Before radiation therapy	PSQI CES-D, The Spielberg State-Trait Anxiety Inventories	Cross-sectional survey	57% of the patients reported insomnia, and the mean score of PSQI is 6.7 ± 3.8 Patients with clinically significant levels of anxiety and depression reported the highest levels of sleep disturbance.	Strengths: evaluated differences in various components of sleep quality, various cancer diagnoses, disease stages. The relationship between insomnia, depression, and anxiety was investigated. Limitations: Not include a working definition of insomnia, lack of objective measurements. The causal relationship between insomnia, depression, and anxiety was not determined. Unable to conduct subgroup analysis due to the small size of each group.

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Morris et al., 2015)	500, mixed diagnosis, Australia	NA	ISI, Distress Thermometer	Cross-sectional survey	59.4% of patients reported insomnia, among them 27.6% reported moderate to severe levels of insomnia	Strengths: various cancer diagnoses, disease stages. Limitations: participants were recruited through a care helpline. Not including a working definition of insomnia, lack of objective measurements, lacking information regarding the time of assessment.
(Romito et al., 2014)	403 mixed diagnosis/Italia	Undergoing Chemotherapy	PSQI, HADS EORTCQ-QOL-C30 FACT-F	Multi-center observational study	66 % had insomnia. The mean PSQI score was 7.4±4.38. Duration of sleep disturbances: 48 months Insomnia was correlated with global quality of life, physical functioning, and psychological distress.	Strengths: Using standardized tools to measure insomnia, recruited participants from multiple sites. Limitations: Not included a working definition for insomnia, lack of objective measurements, the interview question to explore the patient's attitude regarding sleep problem had not been validated.
(Akman et al., 2015)	314 mixed-type cancers/Turkey	Undergoing Chemotherapy	PSQI	Cross-sectional survey	40.4% of patients had insomnia (PSQI > 5)	Strengths: various cancer diagnoses, disease stages, used standardized tools to measure insomnia. Limitation: lack of objective measurements. Types of Chemotherapy that patients had taken and other symptom accompanying with insomnia were not evaluated

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Davidson et al., 2002)	982 mixed-type cancers/US	During cancer treatment (Chemotherapy, radiotherapy, hormonal therapy)	The sleep survey questionnaire consisted of 16 items.	Cross-sectional survey	31% had insomnia. Insomnia commonly involved multiple awakenings (76% of cases), and duration was >/= 6 months (75% of cases). In 48% of cases, insomnia onset was reported to occur within the period 6 months' pre-diagnosis to 18 months' post-diagnosis). The age of 50-60 years old had the highest proportion of insomnia.	Strengths: Included a working definition of insomnia, various cancer diagnoses, and cancer treatment, participants were recruited from multiple sites. Type, duration and associated factors with insomnia were investigated Limitations: The questionnaire was not validated, lacking objective measurements, information regarding cancer stages, and severity of insomnia.
(Palesh et al., 2010)	823 mixed-type cancers/US	Undergoing Chemotherapy	The Hamilton Depression Inventory (evaluated 23 symptoms included insomnia)	Secondary data analysis among cancer patients with fatigue	Chemotherapy cycle 1: 65.3% had insomnia, and 25% had one or more insomnia symptoms Chemotherapy cycle 2: 28.4% had insomnia, and 53.3% had one or more insomnia symptoms. Lung cancer patients had the highest prevalence of insomnia, and breast cancer had the highest number of overall insomnia complaints. Male patients had a lower rate of insomnia but were not significant. Patients >=58 years had a significantly lower rate of insomnia. Patients with insomnia had significantly more symptoms of depression and fatigue	Strengths: various cancer diagnoses, disease stages Limitations: Not using standardized tools and objective measurements to measure insomnia, secondary data analysis. Just provide information of insomnia for 2 chemotherapy-cycles

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Cheng & Yeung, 2013)	214 mixed-type cancers/Hong Kong	During cancer treatment (chemotherapy or radiotherapy)	Symptom Distress Scale	secondary data analysis	68% had sleep disturbance. 60% suffered from a co-occurrence of any of three or all of the four symptoms: mood disturbance, sleep, fatigue and pain (MSFP) Patients who had a co-occurrence of any of three or all four of the symptoms of MSFP reported the worst functional status and poorest QoL	Strengths: various cancer diagnoses, disease stages, the association between insomnia and other symptoms such as mood disturbance, fatigue, and pain were investigated. Limitations: Not using standardized tools and objective measurements to measure insomnia, secondary data analysis, the questionnaire was a single-item score that could not determine the multidimensional nature of insomnia or address the level of distress caused by insomnia and other symptoms.
(Mercadante et al., 2004)	123, advanced cancer patients/Italy	Receiving pain relief and palliative care	PSQI	cross-sectional study	30% of participants slept less than 5 h in 24 hours Depression and anxiety influenced some sleep disorders.	Strengths: various cancer diagnoses. Difference aspects of sleep and correlation with associated factors were investigated. Limitations: Sleep parameters were measured subjectively. Patients were divided into 2 groups according to sleep duration but not the PSQI score for analysis.
(Sela et al., 2005)	100, advanced cancer patients/ Canada	cancer patients receiving pain and symptom control treatments	9-item sleep questionnaire and ESAS	cross-sectional study	72% reported a wide variety of sleep disturbances after a cancer diagnosis, with the three most frequent elevated symptoms being: not feeling rested in the morning (72%), difficulty staying asleep (63%), and difficulty falling asleep	Strengths: various cancer diagnoses. Limitations: Not using standardized tools and objective measurements to measure insomnia. Participants were recruited from a pain control clinic, implying patients had severe pain and uncontrolled symptoms.

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Davis et al., 2014)	715 Advanced cancer patients/US	Receiving Palliative care	Insomnia Severe Index	cross-sectional study	The median ISI score was 16, and 8.95% had clinical insomnia. Insomnia correlated with depression (r=0.32), pain (r=0.29), and tiredness (r=0.40)	Strength: various cancer diagnoses, large sample size, precipitating, and predisposing factors were described, the relationship between insomnia and depression, pain, tiredness was explored. Limitation: lacking objective measurements. The relationship between insomnia and other symptoms was not fully explored.
(Shao et al., 2016)	289 Advanced cancer patients/China	Receiving Palliative care	ESAS	cross-sectional study	93.3% had insomnia	Strengths: various cancer diagnoses. Limitations: lacking objective measurement, using a non-validation of the Chinese version of ESAS, symptom prevalence, and severity influenced by other confounding factors not assessed in this survey such as treatment type, mood, etc.
(Mercadante et al., 2015)	820 Advanced cancer patient/US	Receiving Palliative care	Athens Insomnia Scale, HADS, ESAS	cross-sectional study	60.8% had insomnia	Strengths: various cancer diagnoses, multi-center study. Correlation between insomnia and other symptoms was explored. Limitations: lacking objective measurement for insomnia.
(Barata et al., 2016)	301 advanced cancer patients/Portugal	Receiving Palliative care	Eastern Cooperative Cancer Group (ECOG) scale Portable Mental Status Questionnaire Confusion Assessment Method	cross-sectional study	46% had insomnia	Strength: various cancer diagnoses, large sample size Limitation: Not using a standardized questionnaire and objective measurement for insomnia

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Findings	Appraisal of study
(Savard et al., 2015)	728 (Breast and Prostate cancer)/Canada	Before, during and after receiving treatment	ISI, Memorial Symptom Assessment Scale	Longitudinal study	At based line: in breast cancer patients ISI mean score was 10.3 and 6.4 in Prostate cancer patients After 18 months: The ISI mean score in breast cancer was 7.0 and in Prostate cancer 5.3	Strengths: large sample size, longitudinal study Limitations: included a variety of treatments but did not assess the differential impact of cancer treatments. Lack of objective measurements, sample size included only breast or prostate cancer patients.
(Savard et al., 2011)	962 mixed-type cancer/Canada	From a preoperative visit to 18 months after surgery	Insomnia interview schedule	Longitudinal study	59% had insomnia at baseline; the prevalence of insomnia generally declined over time but remained pervasive after 18 months (36%)	Strengths: various cancer diagnoses, large sample size, longitudinal study Limitations: included a variety of treatments but did not assess the differential impact of cancer treatments. Lack of objective measurements, not using a standardized questionnaire to measure insomnia.

*Note: **PSQI**: Pittsburgh Sleep Quality Index, **LTEQ:** Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire**; CES-D**: Center for Epidemiological Studies Depression scale; **FSI**: Fatigue Symptom Inventory; **GSDS**: General Sleep Disturbance Scale; **HADS:** The Hospital Anxiety and Depression scale, **EORTCQ-QOL-C30**: European Organization for Research and Treatment of Cancer Quality of life – C30; **FACT-F:** Functional Assessment of Chronic Illness Therapy – Fatigue scale**; ESAS**: Edmonton Symptom Assessment System; **ISI**: Insomnia Severity Index*

Taken together, insomnia is a significant concern in cancer patients. Furthermore, it seems that insomnia is three-fold higher than the rate reported in the general population. Sleep problems can be present at all stages of the cancer process: at the beginning of the treatment, at the time of surgery, during chemotherapy or radiation therapy, and persisting years after the treatment period has ended. So, it is not just a problem with patients who undergo cancer treatments but also with newly diagnosed patients, cancer survivors, and those receiving palliative care. Therefore, insomnia becomes a chronic disease among a substantial proportion of cancer patients. However, previous studies contend many inadequacies in the methodologies, thus the prevalence of insomnia remains variable and the etiology as well as the risk factors of this problem are not fully explored across past studies. However, previous studies have pointed out some possible causes and risk factors of insomnia in cancer patients. This information will be discussed in the next section.

2.4. Factors associated with the development of insomnia in cancer patients

Many factors can contribute to the development of insomnia in cancer patients. According to the Speilman's 3-P model of insomnia, there were three types of risk factors of insomnia in oncology patients which were: predisposing factors, precipitating factors, and perpetuating factors (Induru & Walsh, 2014; O'Donnell, 2004; Savard & Morin, 2001).

2.4.1. Predisposing factors

Predisposing factors increase one's vulnerability to developing insomnia and lower an individual's threshold for insomnia to happen (Lowery, 2015). These include some biological characteristics which do not directly cause insomnia but increase the risk of

developing insomnia. Among cancer patients, two predisposing factors have been identified which are gender and age.

Gender has been identified as a predisposing factor of insomnia in cancer patients and the general population (Lowery, 2015). Large-scale surveys point out that female patients have higher rates of insomnia than males. (Davis et al., 2014; Mercadante et al., 2004; Palesh et al., 2010). On the other hand, several studies showed that there was no significant difference between the two genders regarding insomnia rate (Akman et al., 2015; Morris et al., 2015; Phillips et al., 2012; Romito et al., 2014). Further research should be conducted to determine if gender is a predisposing factor for insomnia in the cancer population.

Aging has been considered as one of the insomnia's predisposing factors in the healthy population, but its role in cancer patients is still unclear. A study conducted in almost 1000 cancer patients during their treatment indicated that 50-60 years old patients had the highest proportion of insomnia (Davidson et al., 2002; Savard & Morin, 2001). More recent research also found that the level of insomnia in patients under 62 years old was more severe than older ones (Khan et al., 2011; Mercadante et al., 2015; Palesh et al., 2010). In contrast, a study in prostate cancer patients reported that young age was a risk factor for the presence of insomnia (Savard et al., 2005). Also, some other studies pointed out that there was no correlation between insomnia and age, as patients in different age groups had similar proportions and severity of insomnia (Akman et al., 2015; Miaskowski et al., 2011; Phillips et al., 2012; Romito et al., 2014). Further research should be conducted to address the role of age in insomnia among cancer patients.

2.4.2. Precipitating factors

The precipitating factors refer to life events, treatment-related factors, lifestyle factors, and hospitalization. These often occur as stressful life events, including being diagnosed with cancer (Lowery, 2015). There is evidence to show that insomnia had its peak during the period after diagnosis and during active treatment (Savard et al., 2013; Savard et al., 2009). Results from a survey indicated a high prevalence of insomnia in patients who were receiving chemotherapy, and this sleep disorder persisted from cycle 1 to 2 in most patients (Palesh et al., 2010). In a longitudinal study in breast and prostate cancer patients found that women undergoing chemotherapy had significantly greater Insomnia Severity Index score than those who did not receive this treatment (Savard et al., 2015). Also, hormonal therapy and biological therapy can cause or worsen existing insomnia (Desai et al., 2013; Liu et al., 2009; Savard et al., 2013). For example, androgen deprivation therapy for prostate cancer and hormonal therapy for breast cancer are often associated with insomnia problems by causing hot flashes, night sweats, and anxiety which result in disturbed sleep (Hanisch et al., 2011). Biological agents such as interferons, interleukins, and tumor necrosis factor-alpha can disturb the sleep-wake circle leading to insomnia (Miller et al., 2008). Corticosteroids increase cortisol levels which also cause insomnia (Hirotsu et al., 2015). Cancer patients who were given dexamethasone to avoid radiation-induced emesis experienced insomnia more often than patients who did not receive this kind of treatment (Kirkbride et al., 2000). Table 2 summarizes cancer treatments that can cause insomnia.

Table 2. Cancer treatments that cause insomnia (Dahiya et al., 2013)

Cancer treatment	Mechanism of insomnia	Examples
Chemotherapy	Cancer-related fatigue, daytime sleepiness, mood disorders, restless leg syndrome	Taxanes, platinum-based chemotherapy
Radiation Therapy	Daytime sleepiness, radiation-induced emesis causing difficulty sleeping, fatigue	
Hormonal Therapy	Hot flashed, night sweats, menopausal symptoms, anxiety	Antiandrogens, aromatase inhibitors
Biological Therapy	Daytime fatigue, malaise	Interferons for malignant melanoma
Corticosteroids	Increase in serum cortisol	Prednisone, dexamethasone
Bone marrow transplantation	Severe anemia causing daytime fatigue and restless leg syndrome	
Surgery	Pain, recovery from surgery, surgery with aesthetic or functional impairments	Mastectomy, debulking surgeries

Hospitalization is also considered as a precipitating factor for cancer inpatients. Most studies that examined sleep quality before and during admission to the hospital found that sleep disturbances increased with the number of days in the hospital. Furlani and Ceolim (2006) pointed out the insomnia rate increase from 52% (at 72 hours after hospital admission) to 80% (at the time of hospital discharge) among breast and gynecological cancer patients. Another study also pointed out that sleep disturbances significantly increased during hospitalization in patients who had undergone a bone marrow transplantation (Anderson et al., 2007). The cause for sleep disturbances during hospitalization is often waking up in the middle of the night to use the toilet and early in the morning due to noise in the hospital and receiving nursing care at night time (Furlani & Ceolim, 2006).

Lastly, lifestyle factors such as smoking and physical activities also take part in precipitating insomnia in cancer patients. A study reported that less physical activity

was associated with more inadequate sleep (r=−0.156, p=0.008). There was also a significant relationship between insomnia and smoking status, with significantly worse sleep among current smokers compared to never smokers (p=0.041) (Phillips et al., 2012).

2.4.3. Perpetuating factors

Perpetuating factors contribute to the maintenance of insomnia over time and might be maladaptive sleep habits, faulty beliefs, and attitudes about sleep (Morin, 1993). Maladaptive sleep behaviors include prolonged bedtime and daytime napping. Cancer patients to cope with sleeplessness, they might try the above sleep behaviors, but as they become habits, insomnia persists for long-term (Lowery, 2015). Besides, individuals with persistent insomnia, possibly including those with cancer, tend to engage in sleep-interfering activities in their bedroom that serve as cues for staying awake rather than inducing sleep (e.g., watching TV, listening to music, eating, working or reading in the bed or the bedroom) (Davis, 2011). These behaviors tend to weaken the association (deconditioning) between certain normally sleep-inducing stimuli (bed, bedtime, and bedroom) and sleep (Morin et al., 2011).

Moreover, when insomnia presented, patients feel stressed that can increase their arousal state to that above a wakeful level. Studies have found that most patients attribute their sleep disturbance to intrusive thoughts (Rumble et al., 2010; Wright et al., 2010). Individuals with insomnia also may have several faulty beliefs and attitudes about sleep and sleeplessness that may contribute to maintaining their problem over-time. These cognitions can be grouped into the following categories: (1) unrealistic sleep requirement expectations (e.g., "I absolutely need 8 hours of sleep each night to feel refreshed and function well during the day"); (2) faulty appraisals of sleep

difficulties (e.g., "I lost control over my ability to sleep"); (3) misattributions of daytime impairments (e.g., blaming their sleep problems for everything that goes wrong during the day); and (4) misconceptions about the causes of insomnia (e.g., exclusive attribution of insomnia to external factors such as aging or hormonal variations) (Morin, 1993). Among breast cancer patients, a study found high levels of cancer-related sleep dysfunctional thoughts and sleep inhibitory behaviors as antecedents of insomnia (Rumble et al., 2010).

To sum up, a variety of factors are associated with the development of insomnia in cancer patients, and these factors may include gender, age, cancer treatments, hospitalization, maladaptive sleep behaviors, and faulty beliefs/attitudes about sleep. However, mixed results were shown across studies about the association of gender, age, with insomnia that needs more studies to explore it further. Although insomnia-associated factors have been recognized, this distressing symptom is still causing adverse effects to many patients. As a result, complications could occur which can affect the patients' quality of life. The consequences of insomnia are explored below.

2.5. Impact of Insomnia on cancer patients' quality of life

Over the past decades, evaluating the quality of life has been important for assessing the quality and outcomes of health care. Most studies on how sleep problems impact the quality of life in patients who are newly diagnosed or undergoing cancer treatment or on cancer survivors showed concrete evidence that sleep problems worsen the quality of life. Some studies regarding the impact of insomnia on HRQoL are shown in Table 3.

Table 3. Impact of Insomnia to Quality of Life among cancer patients

Author/ Country	**Participants, method**	**Measurement**	**Finding**
(Phillips et al., 2012)/ US	288 Mixed cancer patients, Chemotherapy naive Cross-sectional survey	SF-36	Global PSQI score was significantly associated with depression, fatigue severity, physical and mental health well-being. Poor sleep was related to higher depression and fatigue (r= 0.34 to 0.36)
(Romito et al., 2014)/ US	403 Mixed cancer patients, undergoing chemotherapy Observation study	Modified EORTC QOL-C30	The Quality of life score in good sleepers was significantly higher than poor sleepers (73.2 vs. 55.8). Insomnia was associated with lower global QOL scores, low physical functioning, and psychological distress ($p<0.05$). The findings suggest that sleep problems cause a negative impact on the quality of life, lower the physical function and cause psychological distress but it did not impact on patient's social function
(Clevenger et al., 2013)/US	173 Ovarian Cancer patients Longitudinal study	FACT-O	Compared to the pre-surgery period, after one year, global sleep quality was associated with improvements in QOL score. Sleep disturbance was a risk factor for diminished QOL over time. Women with earlier-stage showed more improvement in sleep than those with advance stage cancer
(Trudel-Fitzgerald et al., 2014)/ Canada	828 mixed cancer patients, longitudinal study	EORTC QOL-C30	Insomnia in a cluster with other symptoms reported the greatest functionals impairment
(Zucca et al., 2012)/US	863 cancer survivors at five-year post-diagnosis Cross-sectional survey	EORTC QOL-C30	Insomnia and other symptoms persisted five years after diagnosis, but at low levejs., patients still experienced insomnia and other symptoms. The quality of life was moderate.
(Vargas et al., 2010)	240 women with Stage I–III breast cancer patients before they had begun adjuvant treatment Cross-sectional survey	PSQI FWB	Higher PSQI Global score was significantly associated with poorer functional well-being, greater fatigue intensity, greater disruptions in social interactions, and lower positive state of mind.

Note: SF-36: Medical outcome survey 36 items short form; EORTC QOL-C30: European Organization for research and treatment of cancer Quality of life, FACT-O: The Functional Assessment of cancer Therapy (for ovarian patients); FACT-L: The Functional Assessment of cancer Therapy (for Lung patients), FWB: Functional Well-Being subscale of the Functional Assessments of Cancer Therapy— Breast Cancer.

Among cancer patients before receiving cancer treatment, a study showed that insomnia adversely affected physical and mental health, as patients with insomnia had higher depression and fatigue (Phillips et al., 2012). Regarding patients undergoing chemotherapy treatments, studies indicated that insomnia significantly reduced the patient's quality of life (Clevenger et al., 2013; Davidson et al., 2002; Romito et al., 2014; Vargas et al., 2010). Findings from the above studies showed the negative effect of insomnia on quality of life, including worsening physical and psychological function in patients by creating greater fatigue and social interaction disruptions as well as lower positive state of mind. With cancer survivors, a study showed that, after 5 to 6-year post-diagnosis, the prevalence of insomnia in 863 cancer survivors was equal to the general population, as the result of the global QOL score was as good as that in the general population (Zucca et al., 2012). This finding suggested improving insomnia can positively impact patient's QOL.

Although being measured with different scales in different cancer populations, the evidence from literature indicated a significantly lower QOL among cancer patients with insomnia. This symptom affects the patient's physical and emotional well-being as well as social function. Therefore, if insomnia can be effectively treated, the quality of life is likely to improve. However, cancer patients may experience several symptoms at the same time during their illness (Esther Kim et al., 2009). Besides, insomnia may not occur alone but in combination with other symptoms. Understanding the relationship between insomnia and other symptoms is a benefit to the development of an effective insomnia treatment to improve cancer patient's quality of life. The following section will provide more details regarding this issue.

2.6. Sleep-related symptom clusters in cancer patients

Recently, results from studies indicated that insomnia does not occur as a single symptom but in combination with other symptoms to form a "symptom cluster." A symptom cluster has been first defined as two or more symptoms occurring together, related to each other and being clinically meaningful together (Dodd et al., 2001; Molassiotis et al., 2010). Up to 40% of cancer patients reported at least a symptom cluster of two symptoms during their illness (Esther Kim et al., 2009). Applying the concept of symptom clusters, different sleep-related clusters have been identified across studies. Table 4 lists out studies that were conducted to determine the sleep-related symptom clusters in cancer patients.

Table 4. Studies to determine sleep-related symptom clusters in Cancer Patients

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Davidson et al., 2002)	982 mixed-type cancer patients/US	During cancer treatment (Chemotherapy, radiotherapy, hormonal therapy)	Sleep survey questionnaire	Cross-sectional survey	Patients who reported fatigue were 2.5 times more likely to have insomnia than others.	Strengths: large sample size, various cancer diagnoses, disease stages, longitudinal study, included insomnia definition. Limitations: The questionnaire was not validated, lacking objective measurements, information regarding cancer stages, and severity of insomnia.
(Okuyama et al., 2000)	134 breast cancer patients/Japan	after surgical treatment	Cancer Fatigue Scale, the Hospital Anxiety and Depression Scale, the Mental Adjustment to Cancer Scale.	Cross-sectional survey	fatigue was significantly correlated with dyspnea, insomnia, and depression.	Strengths: Using standardized tools to measure fatigue and psychological symptoms. Limitations: Not using standardized tools and objective measurement to measure insomnia, focus on breast cancer patients, lack of insomnia definition.
(Palesh et al., 2010)	823 mix type cancer/US	Undergoing Chemotherapy	The Hamilton Depression Inventory	This was a post-hoc analysis of data collected for a large randomized clinical trial	Patients with insomnia had significantly more symptoms of depression and fatigue	Strengths: large-scale study, various cancer diagnoses, disease stages, included insomnia definition. Limitations: Not using standardized tools and objective measurement to measure insomnia, Using secondary data. Just provide information of sleep-related symptom cluster in 2 chemotherapy-cycles

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Bower et al., 2000)	1957 breast cancer survivors	Completed treatment, disease-free	RAND 36-Item Health Survey 1.0; Center for Epidemiologic Studies Depression Scale; Breast Cancer Prevention Trial Symptom Checklist; MOS Sleep Scale;	Cross-sectional survey	1/3 participant reported severe fatigue which was associated with depression, pain, and insomnia.	Strengths: large-scale study, included insomnia definition Limitations: Not using standardized tools and objective measurement to measure insomnia, focus on breast cancer survivors.
(Ho et al., 2015)	134 breast cancer patients/US	Undergoing chemotherapy treatment	Beck Depression Inventory; Hospital Anxiety and Depression Scale; Multidimensional Fatigue Symptom Inventory; PSQI	Longitudinal study	A correlation was found between fatigue, insomnia, and depression.	Strengths: Using standardized measurements, longitudinal Limitations: sample size relatively small, focus on breast cancer patients, lack of insomnia definition.
(Chen & Tseng, 2006)	151 cancer patients/Taiwan	Undergoing cancer treatment	M.D. Anderson symptom inventory (13 symptoms) Hospital Anxiety and Depression Scale	Cross-sectional survey	The correlation was found between pain, fatigue, insomnia	Strengths: Using standardized measurements, various cancer diagnoses. Limitations: sample size relatively small, Not using a standardized tool, and objective measurement to measure insomnia, lack of insomnia definition. Only evaluate the correlation between 13 symptoms.
(Ivanova et al., 2005)	226 cancer patients/Russia	Undergoing cancer treatment	M.D. Anderson symptom inventory (13 symptoms)	Cross-sectional survey	The correlation was found between pain, fatigue, insomnia	Strengths: various cancer diagnoses, large sample size Limitations: Not using a standardized tool and objective measurement to measure insomnia, lack of insomnia definition. Only evaluate the correlation between 13 symptoms

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Hoffman et al., 2007)	80 breast, colon, or lung cancer or non-Hodgkin lymphoma/US		Comorbidity Questionnaire Cancer Symptom Experience Inventory (15 symptoms)	Secondary analysis/ Multinomial log-linear modeling	The correlation was found between pain, fatigue, insomnia	Strengths: include a theoretical framework Limitations: Small sample size and focus on a specific type of cancer, not standardized tools and objective measurement to measure insomnia, lack of insomnia definition, secondary data analysis
(Cheng & Yeung, 2013)	214 mix type cancer/Hong Kong	During cancer treatment	Symptom Distress Scale FACT-G	cross-sectional study used secondary data from a convenience sample	60% suffered from the co-occurrence of any three or all of sleep, mood disturbances, fatigue and pain (MSFP) Patients who had co-occurrence of any three or all four of the symptoms of MSFP reported the worst functional status and poorest QoL	Strengths: various cancer diagnoses, disease stages. Limitations: Not using standardized tools and objective measurement to measure insomnia, secondary data analysis, lack of insomnia definition. The questionnaire was a single-item score which could not determine the multidimensional nature of insomnia or address the level of distressed caused by insomnia and other symptoms
(Denieffe et al., 2014)	94 breast cancer patients/US	Before treatment	Hospital Anxiety and Depression Scale, Insomnia Severity Index, Functional Assessment of Cancer Therapy–Fatigue, Brief Pain Inventory and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30	cross-sectional study	The correlation was found between pain, fatigue, insomnia	Strengths: using standardized tools to measure symptoms Limitations: Small sample size, focus on breast cancer patients, lack of insomnia definition, lack of objective insomnia measurements.

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Savard et al., 2005)	327 prostate cancer patients/Canada	Undergoing radical therapy	Hospital Anxiety and Depression Scale, Insomnia Severity Index, Multidimensional Fatigue Inventory; Prostate Cancer-Specific Module Supplementing European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30	cross-sectional study	pain and depression were associated with insomnia	Strengths: using standardized tools to measure symptoms Limitations: focus on prostate cancer patients
(Davis et al., 2014)	715 Advance cancer patients/US	Receiving Palliative care	Insomnia Severe Index	cross-sectional study	The median ISI score was 16, and 8.95% had clinical insomnia. Insomnia correlated with depression (r=.32), pain (r =.29), and tiredness (r=.40)	Strengths: various cancer diagnoses. Limitations: lacking objective measurement. Only explored the correlation between insomnia and depression, pain, tiredness.
(Romito et al., 2014)	403 mix diagnosis/Italia	Underwent Chemotherapy	PSQI	Multi-center observational study	Complex relationship of mutual influences between insomnia, depression, fatigue, and pain.	Strengths: Using standardized tools to measure insomnia, recruited participants from multicenter. Limitations: Not include a working definition of insomnia, lack of objective measurement.
(Cheng & Lee, 2011)	120 elderly cancer patients/China	Underwent Chemotherapy	Symptom Distress Scale Functional Assessment of Cancer Therapy-General (FACT-G)	cross-sectional study used secondary data	31.2% reported the co-occurrence of all of the four symptoms. They were mild to moderate ($r = 0.29–0.43$, $p < 0.01$)	Limitations: Not include a working definition of insomnia, lack of specific measures for insomnia, using secondary data, moderate sample size.

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Zucca et al., 2012)	863 cancer survivor/US	Survivorship	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-C30)	cross-sectional study	cognitive functioning, fatigue, insomnia, pain, dyspnea, appetite loss, constipation, diarrhea, nausea, and vomiting formed a cluster (α=0.48)	Strengths: large sample size, various cancer diagnoses. Limitations: using EORTC-C30 to measure symptoms, lack of insomnia definition.
(Fodeh et al., 2013)	111 advanced cancer patients/US		Emotional distress thermometer Symptom Distress Scale Enforced Social Dependency Scale (measure daily living activities)	cross-sectional study used secondary data	Outlook, insomnia, appearance, concentration and eating in patient with advanced gastrointestinal diagnosis; nausea, insomnia, eating, concentration and pain in gynecological cancer patients; cough, walking, eating, breathing and insomnia among lung cancer patients	Strengths: various cancer diagnoses. Limitations: small sample size, using secondary data, using none specific questionnaire to measure insomnia, lack of insomnia definition.
(Desai et al., 2013)	413 breast cancer patients	undergoing cancer treatment	Insomnia Severity Index Hospital Anxiety and Depression scale	Cross-sectional study	insomnia, joint pain, and hot flashes formed a symptom cluster	Strengths: large sample size, using validated scale to measure insomnia Limitations: focus on breast cancer patients with postmenopausal symptoms only.
(Liou et al., 2019)	1072 breast cancer patients/US	receiving aromatase inhibitor therapy	Breast Cancer Prevention Trial symptom checklist Insomnia Severity Index	Secondary analysis from a cohort study	insomnia, forgetfulness, difficulty concentrating, distractibility formed a symptom cluster	Strengths: Large sample size, using a standardized scale to measure insomnia Limitation: using secondary data, using none specific questionnaire to measure other symptoms.

Studies	Sample size/country	Time of Assessment	Measure tools	Study design	Finding	Appraisal of study
(Mazor et al., 2018)	398 breast cancer patients/US	Before and 12 months after breast cancer surgery	Self-administered Comorbidity Questionnaire The Menopausal Symptoms Scale	Descriptive, longitudinal study	A symptom cluster of insomnia, psychological, and cognitive symptoms (i.e., anger, anxiety, depression, difficulty concentrating) was found prior and at 12 months after surgery	Strengths: Longitudinal study, large sample size Limitations: focus on breast cancer patients, using none specific questionnaire to measure sleep
(Russell et al., 2019)	145 lung cancer patients /US	undergoing chemotherapy	Self-administered Comorbidity Questionnaire The memorial symptom assessment scale	Descriptive, longitudinal study	A symptom cluster of insomnia, weight loss, worrying, sad, nervous, irritable was found a week before the next cycle of Chemotherapy	Strengths: Longitudinal study, large sample size Limitations: focus on lung cancer patients, using none specific questionnaire to measure sleep
(Albusoul et al., 2017)	219 breast cancer patients/US	From before and after four chemotherapy cycles	Hospital Anxiety and Depression Scale Symptom Experience Scale	Secondary analysis of data from an RCT	Before chemotherapy: sleep disturbance, concentration, anxiety, worried about the appearance After three chemotherapy cycles: Sleep disturbance, nausea, bowel pattern, pain After 4 chemotherapy cycles: Sleep disturbance, fatigue, pain	Strengths: large sample size, measure symptoms at difference time points Limitations: measured only ten symptoms, secondary analysis, most of the symptoms were measured by non-specific scales.

Among different sleep-related symptom clusters, **cancer-related fatigue, depression, and insomnia** seem to be the most commonly identified cluster. Results from a review of 25 studies also indicated a strong interrelationship between cancer-related fatigue (CRF) and insomnia and stated insomnia is a significant cause of CRF (Roscoe et al., 2007). Another review from 16 studies also showed these symptoms were considered concurrently with a mean correlation of 0.55 for fatigue and depression, 0.34 for fatigue and insomnia, 0.45 for depression and insomnia (Donovan & Jacobsen, 2007). To explain the relationship between these symptoms, the authors pointed out that fatigue leads to insomnia (Anderson et al., 2003; Berger & Mitchell, 2008), and insomnia is a risk factor of developing depression and anxiety (Perlis et al., 1997). This cluster was not only experienced in patients undergoing cancer treatment (Davidson et al., 2002; Ho et al., 2015; Okuyama et al., 2000; Palesh et al., 2010) but also reported by cancer survivors (Bower et al., 2000)

The second commonly reported sleep-related symptom cluster was **pain, fatigue, and insomnia**. The significant interaction among these symptoms has been found among cancer patients during cancer treatment (Chen & Tseng, 2006; Hoffman et al., 2007; Ivanova et al., 2005) and breast cancer patients before receiving treatment (Bender et al., 2005; Denieffe et al., 2014; Matthews et al., 2012). Pain is one of the most common physical symptoms reported by cancer patients (Gauthier et al., 2009). Around 52% to 77% of newly diagnosed cancer patients and 62% - 86% of advanced cancer patients experienced this symptom, and a systematic review indicated a pooled prevalence of pain was greater than 50% in all cancer types (van den Beuken-van Everdingen et al., 2007). Patients cannot sleep well with pain, and insomnia can increase the cancer patient’s sensitivity to pain (Smith & Haythornthwaite, 2004).

The cluster that included ***pain, depression, and insomnia*** was also reported among 327 men receiving radical prostatectomy for prostate cancer, pain, and depression were associated with an increased likelihood of insomnia (Savard et al., 2005). In the study of Romito et al. (2014), ***insomnia, depression, fatigue, and pain*** co-occurred as a symptom cluster among 403 patients during their chemotherapy. This symptom cluster was also reported among older cancer patients with the correlation among symptoms of the cluster being weak to moderate ($r=0.29-0.43$, $p<0.01$) (Cheng & Lee, 2011).

Another study also showed that cognitive function, fatigue, insomnia, pain, dyspnea, appetite loss, constipation, diarrhea, nausea, and vomiting form a symptom cluster ($\alpha=0.48$) among cancer survivors with various types of cancer (Zucca et al., 2012). Other symptom combinations also addressed among patients within 100 days from diagnosis with advanced cancer and included: worried about the future, insomnia, distress about the current appearance, concentration, and eating in patients with advanced gastrointestinal cancer; nausea, insomnia, eating, concentration, and pain in gynecological cancer patients and cough, walking, eating, breathing and insomnia among lung cancer patients (Fodeh et al., 2013).

Recently, a longitudinal study found that the major symptom clusters differently depending on the time point of assessment; however, a symptom cluster of insomnia, psychological, and cognitive symptoms (i.e., anger, anxiety, depression, difficulty concentrating, fatigue, forgetful, tension, mood swings) were relatively stable either prior or at 12 months after breast cancer surgery (Mazor et al., 2018). However, another study indicated three different sleep-related symptom clusters among breast cancer patients before starting chemotherapy, and after three and four chemotherapy cycles

(Albusoul et al., 2017). Another longitudinal study in lung cancer patients indicated the sleep-related symptom cluster (insomnia, weight loss, worrying, sad, nervous, and irritable) was found only a week before the next cycle of chemotherapy (Russell et al., 2019). Those findings suggest sleep-related SCs can be different across cancer diagnosis and time points of assessment. Hence, to manage sleep-related symptom clusters, an exploratory study is needed to confirm a sleep-related SCs in the targeted population.

Although previous studies have shown different sleep-related symptom clusters in various cancer patients, the correlation between these symptoms is still not clear due to the limitations of the earlier studies. The first limitation is the cross-sectional nature of the study design. Most studies were conducted at a one-time point and failed to in-depth explore the correlation between symptoms in a cluster such as: which symptom occurs first, whether a symptom in one cluster will aggregate over time and how the cluster will change along with the disease. The second limitation is related to measurement tools to measure insomnia and other symptoms. Many studies did not use validated questionnaires to measure insomnia. Other symptoms (that may be related to insomnia) were measured with a wide range of questionnaires which assessed only 13 to 15 symptoms while the number of symptoms experienced by cancer patients can be up to 32 symptoms (Portenoy et al., 1994). The small sample size and focus on specific cancer populations such as breast cancer patients are also limitations that can compromise the conclusion drawn from previous studies. Furthermore, none of the studies on symptom clusters used objective measurements to measure the sleep patterns of participants to explore whether other symptoms co-occurred with insomnia impaired any specific sleep

pattern. Such information would be helpful in the development of an intervention to manage insomnia/sleep-related symptom clusters in cancer patients.

To sum up, the finding from the literature suggested the correlation between insomnia and other symptoms such as fatigue, pain, and depression. Those findings from the literature indicated that when assessing insomnia, healthcare workers must also assess any co-occurring symptoms. The correlation between insomnia and other symptoms also suggests the need to develop an intervention for the symptom cluster to reduce symptom burden among cancer patients. Nevertheless, different sleep-related symptom clusters were found across studies indicating the need to conduct more studies to ascertain a sleep-related symptom cluster in a cancer population. Such studies must be conducted before the development of an intervention.

2.7. Insomnia's measurement instruments

As mention in section 2.3, a wide range of insomnia prevalence was given across studies due partially to various instruments that have been used to measure insomnia/sleep disturbances among adults. These measurements can be classified into two groups: subjective measurements (self-reported questionnaires, sleep diary) and objective measurements (polysomnography and actigraph). Instruments used to detect insomnia in previous studies will be discussed in this section.

2.7.1. Subjective measurements

There are over 100 instruments for measuring insomnia/sleep problems with different aspects covered and periods evaluated from one day/one night to a maximum of seven weeks (Shahid et al., 2012). Although the number of items or time frame varies across instruments, they are generally used to assess the patient's perception of insomnia and

quantify subjective dimensions of insomnia (Morin et al., 2011). Among them, just a few questionnaires meet the specific needs of investigators conducting epidemiological or clinical trial studies (Morin et al., 2011). Pittsburgh Sleep Quality Index, Insomnia Severity Index, and Daily self-report of Sleep (Sleep diaries, sleep log) are more commonly used than other scales (Buysse et al., 2006; Petit et al., 2003). They are also considered as essential measures for insomnia symptoms.

Pittsburgh Sleep Quality Index (PSQI)

This scale was considered as the most common standardized and validated tool to measure insomnia. In a systematic review of sleep disorders in cancer patients in 254 articles, PSQI was used in 32% of the studies (Otte et al., 2015). The PSQI, which was developed by researchers at the University of Pittsburgh is intended to be a standardized sleep questionnaire for clinicians and researchers. It is a self-rated questionnaire that assesses sleep quality and disturbances. It defines “poor” to “good” sleep by using 19 items which measure seven patterns of sleep in adults: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. Scoring of the answers is based on a 0 to 3 scale. Global PSQI scores range from 0 to 21, a global sum of “5” or higher indicates a “poor” sleeper and sleep difficulty. A cut-off score at 5 points showed insomnia resulted in a sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p<0.001$), the PSQI has internal consistency and a reliability coefficient (Cronbach’s alpha) of 0.83 for its seven components (Buysse et al., 1989). The scale has been translated into over 56 languages including Vietnamese. Subjects may require 5 – 10 minutes to complete it and 3-5 minutes to score it. However, the recall bias may influence the result measured by PSQI since this scale was developed to measure sleep

during the previous month. Yet, respondents can get confused because the questionnaire required patients to estimate many sleep parameters such as how often the patient cannot get to sleep within 30 minutes in the past month. Researchers pointed out there is a high risk to obtain missing data when this instrument is used in cancer populations, for example, many participants would write in “yes” instead of indicating a time for the question about “usual bedtime”(Beck et al., 2004). Besides, PSQI can determine the sleep problem frequency but not its severity.

Insomnia Severity Index (ISI)

Another recommended tool in the assessment of insomnia is the “Insomnia Severity Index” which encompasses 7-items assessing: the perceived severity of insomnia problems, the satisfaction with patient’s current sleep pattern, how sleep problems impair the quality of life and daytime activities and concerns caused by insomnia, each rated on a 0 to 4 points scale. The usual time frame for responding is the last two weeks, patients may spend less than 5 min to complete, and it takes less than 1 min to score the questionnaire (Bastien et al., 2001). ISI scores range from 0 to 28. The total score of ISI indicates the severity of insomnia from no clinically significant insomnia to severe clinical insomnia. The ISI can be used as a screening instrument or as a treatment-outcome measure (Buysse et al., 2006). The questionnaire also has been translated into many languages. A total score of 15 and above indicates that the patient has insomnia. A study stated that this cut-off point detects the majority of cancer patients with insomnia, and this score obtained the sensitivity of 51.3% and the specificity of 90.7% (Savard et al., 2005). However, researchers pointed out, in clinical trials, a cut-off point greater than 14 would be too stringent for enrolling participants and produce many false negatives and suggested a cut-off score of 11 that appears to be the best compromise to

achieve an optimal balance between sensitivity and specificity (Morin et al., 2011). Despite the difference in an optimal cut-off point, the ISI is useful for identifying insomnia cases and documenting the prevalence and burden of the disease since this a brief screening tool with seven items, which is easy for patients to answer. Nevertheless, a positive correlation among total ISI score, subjective sleep estimates, and PSQI score were found, which indicates good convergent validity between ISI and other measurements of sleep (Morin et al., 2011). Also, the ISI can detect changes in sleep difficulties with treatment (Bastien et al., 2001).

Daily self-report of sleep (sleep diary, sleep log)

A sleep diary is useful as a screening or diagnostic tool and as a quantitative dependent measure. Various studies using sleep diaries have been conducted (Buysse et al., 2005; Monk et al., 1994; Morin, 1993; Savard & Morin, 2002), but none of them can provide a preferred sleep diary format. The format of a sleep diary can be designed base on the purpose of the study. Still, it should also address the following daily information:

- Time of going to bed
- Time of final waking and rising from bed
- Sleep onset latency
- Total sleep time
- Number of awakenings
- Wake after sleep onset
- Qualitative aspects of sleep (e.g., sleep quality, sleep depth)
- Daytime dysfunction as a result of insomnia (e.g., difficulty concentrating, irritability)
- Terminal wakefulness

- Medication used
- Napping time
- Alcohol or caffeine consumption.

The usual time frame for responding is 1 to 2 weeks. Patients can complete a sleep diary in paper or through smartphone apps (Min et al., 2014). Although daily self-reports of sleep are used to provide more information about sleep patterns and less sensitive to recall biases, they do not entirely capture the diagnostic criteria for insomnia due to lack of evaluating satisfaction about sleep or addressing the impairment and emotional distress associated with insomnia (Buysse et al., 2006).

2.7.2. Objective measurements

Polysomnography

Polysomnography (PSG) is a test used to diagnose sleep disorders. Polysomnography records patients' brain waves, the oxygen level in the blood, heart rate, and breathing, as well as eye and leg movements during the study. Polysomnography usually is done at a sleep laboratory within a hospital or at a sleep center. A standard set up for Polysomnography includes: the patient lies in a bed with sensors attached to the nose to measure airflow, face, and scalp to measure the movement of eyes and brain waves, chest and belly to measure effort to breathe and on the finger to measure the amount of oxygen in the blood. By using this method, patients must spend some nights in the sleep laboratory. PSG can serve a variety of functions but is primarily used for screening and quantification of sleep disturbance.

In clinical practice, PSG is not recommended for routine assessment, differential diagnosis, or severity assessment (Chesson et al., 2000). However, PSG is beneficial to

evaluate and quantify other sleep pathologies such as sleep apnea or movement-related sleep disorders, which are present among patients with insomnia complaints. More generally, PSG sleep measure is used as a dependent measure to quantify group differences or intervention effects. In this context, it is essential to distinguish between insomnia (defined by a set of symptoms) and sleep disturbances (referring to quantitative measurements of sleep and wake amounts). Patients who have PSG-identified sleep disturbances are the subset of patients that meet the diagnostic criteria for insomnia (Buysse et al., 2006).

Moreover, PSG is only feasible to conduct for one to three nights that raise the possibility that it may provide insufficient sampling to adequately capture the features of insomnia, which may not be present every night. Also, several issues can affect the result of PSG, for example, the change in the sleep environment. Because patients have to sleep in the laboratory in which the environment is different from their home, it can somehow affect their sleep. For those reasons, PSG cannot serve as the sole outcome measure in clinical trials studying insomnia (American Psychiatric Association, 2000) as defined by the standard diagnostic criteria nor should PSG be considered the gold standard quantitative measure of insomnia against which other measures are judged and validated.

Actigraph

Actigraph is a device that uses motion sensors to measure physical movement, typically in a small device worn on the non-dominant wrist (Ancoli-Israel, 2005). Actigraph is dedicated as an objective method to characterize circadian rhythm disturbances, activity levels, or specific sleep disorders including insomnia. It can be used to collect information for a period of days to months in the individual's home

environment and during regular routines. As discussed in two reviews (Ancoli-Israel et al., 2003; Sadeh & Acebo, 2002) and two papers (American Sleep Disorders Association, 1995; Littner et al., 2003), actigraph provides an objective estimate of sleep and the 24-hours sleep-wake rhythm and can detect circadian rhythm disturbances. It is also used to determine whether patients with a sleep disorder are overactive before bedtime or inactive during the day (Hauri & Wisbey, 1992). This function may help healthcare workers to identify some etiologies for sleep problems and provide lifestyle adjustments to the patients. Although actigraph appears to be an ideal method to measure sleep problems, its application to research shows some methodological issues that should be considered. Few studies have compared different sensitivity settings, different devices, and various scoring algorithms, raising questions about reliability and validity across studies. Actigraph is less reliable for distinguishing between quiet wakefulness and sleep, and it tends to overscore sleep in individuals with insomnia while they are lying waiting to fall asleep at the beginning of the night or after waking from sleep (Hauri & Wisbey, 1992). Therefore, actigraph is often used in conjunction with other methods, such as sleep diary to ascertain the time of light out, time to bed, time out of bed, times the device was removed, and times the patients may have been sitting still for quite a long time such as sitting in transportation, watching TV or movie.

To summarize, there are several methods for assessing sleep and determine insomnia among general populations as well as cancer populations. Each method has its advantages and disadvantages. By using self-report questionnaires or sleep diary, patients answer the question by themselves, which is convenient but may have the risk of missing data. Nevertheless, choosing a questionnaire to measure insomnia becomes

a challenge for investigators due to a large number of available sleep questionnaires. By using PSG or actigraph, these devices automatically measure sleep patterns but come with the cost for using PSG service and buying actigraph and also other issues to be considered, such as changing sleep environment, short observation periods (with PSG) or over-scoring with actigraph. Therefore, to avoid the disadvantages of each method, using a combination of subjective and objective measurements is recommended in sleep research (Landry et al., 2015). However, limited studies have been conducted using this combination in the design to detect the prevalence of insomnia as well as evaluate the effectiveness of interventions to manage insomnia in cancer patients.

2.8. Managing insomnia in cancer patients

Two approaches have been adapted to manage insomnia in cancer patients which are managing as a single symptom and managing the insomnia-related symptom clusters. The treatments of insomnia and insomnia-related symptom clusters among cancer patients consists of both pharmacological and non-pharmacological treatments/interventions. Results from studies show that each of them brings advantages as well as disadvantages to patients. Details of each treatment will be discussed in this section.

2.8.1. Managing insomnia as a single symptom

2.8.1.1. Pharmacological treatment for insomnia in the cancer population

Sleep problems are usually treated with drugs, and most of the recommendations for insomnia in cancer patients are based on experience in the general population (Dahiya et al., 2013). However, in cancer patients, the causes of insomnia have some differences that need special consideration (e.g., co-occurring symptoms), so drug treatment should be individually tailored to address these issues too. The choice of pharmacological

treatment is based on the patient's symptoms, response, preferences, cost, and comorbid conditions (Howell et al., 2014). Sleep medicines used for insomnia include hypnotics, melatonin, and herbs.

2.8.1.1.1. Hypnotics

Hypnotics are the most common sleep drugs used for insomnia (Savard & Morin, 2001). Table 5 lists out some hypnotics for insomnia in both the general and cancer patients (approved by The Food and Drug Administration (FDA) – USA).

Table 5. Hypnotics for insomnia Approved by FDA

Drug classes	**Generic names**	**Indications**		**Adverse effects**
		SOI	**SMI**	
Benzodiazepines	Estrazolam	x	x	Drowsiness, confusion, dizziness, trembling, impaired coordination, vision problems, grogginess, headache, respiratory suppression.
	Flurazepam	x	x	
	Quazepam	x	x	
	Temazepam	x	x	
	Triazolam	x		
Benzodiazepine Agonists	Zaleplon	x		Dizziness, drowsiness, short-term memory loss, problems with memory or concentration, lack of coordination, ambles or tingling, headache, nausea, stomach pain, constipation, dry mouth, cramps.
	Zolpidem	x		
	Zolpidem CR	x	x	
	Eszopiclone	x	x	
Antidepressants (H.Antagonists)	Doxepine		x	dizziness, nausea, lethargy, headache, anxiety, and agitation, sexual dysfunction
	Trazodone	x	x	
	Mirtazapine	x		
	Imipramine	x		
Melatonin Agonist	Rametteon	x		Daytime drowsiness, depressed mood, feeling irritable, headache, dizziness

SOI: Sleep onset insomnia, SMI: Sleep Maintenance Insomnia characterized by middle-of-the night awakening followed by difficulty returning to sleep (Asnis et al., 2015)

Hypnotics can improve the quality of sleep by decreasing time to sleep onset, improve sleep efficiency, and impart a sense of restful sleep (Pagel & Parnes, 2001). In the general population, meta-analyses indicated hypnotics decreased sleep latency by 4.2 minutes and significantly improved total sleep duration by one hour in more than 2,600 subjects (Holbrook et al., 2000), statistically significant reductions in subjective and

polysomnographic sleep latency (Huedo-Medina et al., 2012). In cancer patients, among a total of 3018 recorded sleep drugs by 219 breast cancer patients, 46% of them were hypnotics, and 15% to 20% of participants took at least one sleep aid on at least one night before, during, and following adjuvant chemotherapy treatments (Moore et al., 2011). However, using hypnotics, special long-acting hypnotic medication (e.g., Flurazepam, Quazepam) can bring residual effects the next day such as drowsiness, dizziness, light headache and cognitive impairment and risk of fall (Holbrook et al., 2000). Older people experience these effects more frequently because of their slower drug metabolism, and this is important because most of the cancer patients belong to this age group. Drug interactions are also a significant concern in cancer patients. The addition of benzodiazepines to opioids could potentiate respiratory suppression (Savard & Morin, 2001).

2.8.1.1.2. Antidepressants

A review of nice RCTs conducted in the general population found that low-dose of antidepressants improved sleep maintenance and duration of sleep but had no effect on sleep initiation (Yeung et al., 2015). The effect of antidepressants in improving sleep in cancer patients is limited. Some RCTs have been conducted, but the effectiveness and the side effect are not clear. The effect of Mirtazapine in reducing sleep disturbances can persist up to 6 weeks (Cankurtaran et al., 2008), and it can also prolong sleep duration as well as reduce anxiety effectively (Kast, 2001). Trazodone was shown to be effective in reducing insomnia without side effects in advanced cancer patients (Tanimukai et al., 2013).

2.8.1.1.3. Melatonin

Melatonin has been approved by the US Food and Drug Administration for treating insomnia. A systematic review suggested this agent was not recommended in the treatment of chronic insomnia (Howell et al., 2014). However, the result from other trials showed that Melatonin could benefit insomnia in cancer patients. With doses of 3mg/day after four months, patients significantly improved sleep quality, including domains on sleep quality, daytime dysfunction, and total PSQI score (Chen et al., 2014). A study indicated that taking Melatonin was significant to improve insomnia after seven and 14 days (Kurdi & Muthukalai, 2016). Melatonin has demonstrated usefulness in promoting sleep to patients with a circadian rhythm sleep disorder which includes cancer patients. These results from a review suggested that cancer patients can get benefit from Melatonin for their sleep problems, and there was a growing interest in the role that Melatonin may have as an immunogenic agent (Blask et al., 2005). Therefore, further large RCTs need to be conducted to fully ascertain the role of Melatonin in improving insomnia in cancer patients.

2.8.1.1.4. Herbal Medicine

Herbal medicine represents one of the most frequently used complementary and alternative treatments of insomnia. However, the safety and efficacy of herbal medicine for the treatment of this disorder is currently uncertain. In the general population, a recent systematic review showed no statistically significant difference between any herbal medicine (e.g., valerian, chamomile, kava, and Wuling) and placebo (Kishi et al., 2015). Still, none of these herbal medicines were used in any RCTs among cancer patients. Another herb, Mistletoe extracts, stimulates the immune system, improve survival, enhance the quality of life and reduce adverse effects of chemo- and

radiotherapy in cancer patients (Horneber et al., 2008) and also can reduce insomnia in the cancer population. A large randomized control trial among 220 advanced cancer patients showed that, with an average dose of 30mg per week in 12 months, patients with advanced cancer gained weight, reduced appetite loss as well as fatigue, pain, and insomnia with no adverse effects (Troger et al., 2014)

To summarize, pharmacological treatments for insomnia in cancer patients should take into consideration the causes of insomnia that have some similarity to the general population but also some differences that need special attention. Although these sleep drugs are inexpensive and cancer patients with depression and insomnia may benefit, the usage of them is associated with many risks and drug-drug interactions. Therefore, in cancer care, non-pharmacological treatments are being developed to reduce the adverse effects of cancer treatments as well as managing distressing symptoms, such as insomnia, in cancer patients. The next section will focus on the results of non-pharmacological interventions that have previously been trialed for managing insomnia in cancer patients.

Table 6. Pharmacological treatments for Insomnia in Cancer patients

Sleep aid	Authors, year	Participants and Methods	Mean dose (mg/day)	Sleep measurements	Results	Adverse side effects
Hypnotics	(Cankurtaran et al., 2008)	RCT,53 cancer patients divided into three groups Mirtazapine: 20 patients Imipramine: 13 patients Control group: 20 patients Data were collected at baseline, 3rd week and 6th week	Mirtazapine T1:12.2 ± 5.7 T2: 18±7.9 T3: 18.7±9.1 Imipramine T1: 13.8±7.1 T2: 26.5±23.2 T3: 29.4±34.4	Hamilton Depression Rating Scale	No significant differences between the three groups at each visit in terms of insomnia scores. In Mirtazapine group, the percentage of patients having sleep disturbance was significantly decreased at 3rd week and persisted for six weeks.	NA
	(Tanimukai et al., 2013)	An observational study on 30 advanced cancer patients, using trazodone for the treatment of insomnia and nightmares in 7 days	12.5 to 50 mg	NA	Patients did not request an additional hypnotic within seven days after received trazodone. 50% of them gained a satisfactory response to insomnia without side effects.	NA
	(Matsuo & Morita, 2007)	A retrospective study on 163 patients divided into 2 groups Midazolam group: 104 patients Flunitrazepam group: 59 patients in	Midazolam: 10mg – 18mg Flunitrazepam: 2mg	NA	There was no difference in terms of efficacy and safety for primary insomnia between intravenous midazolam and flunitrazepam. In terms of cost, Flunitrazepam is cheaper and shows a lower risk of tolerance development.	Hangover, delirium at night or next morning, respiratory depression (apnea, respiratory arrest, decreased respiratory rate)
Melatonin	(Chen et al., 2014)	Double-blind RCT on 91 breast cancer survivors. Divided into two groups Placebo: 45 patients Melatonin: 45 patients Data were collected at baseline and four months after.	3mg/night	Pittsburgh Sleep Quality Index	Compared to subjects on placebo, subjects randomized to melatonin significantly improve sleep quality, including domains on sleep quality, daytime dysfunction, and total score.	Hangover in the morning
	(Kurdi & Muthukalai, 2016)	50 cancer patients were divided into two groups Melatonin group: 25 patients Control group: 25 patients Data were collected at baseline, after 7 and 14 days.	3mg	Athens Insomnia Scale	Patients in the Melatonin group significantly improve insomnia to compare with the control group. The effectiveness of melatonin was seen between 7 and 14 days ($p<0.05$)	Headache, dizziness, nausea, and vomiting

Sleep aid	authors, year	Participants and Methods	Mean dose	Sleep measurements	Results	Adverse side effects
Herbs	(Troger et al., 2014)	220 advanced pancreatic cancer patients were divided into two groups Mistletoe group: 110 patients Control group: 110 patients Data were collected at baseline and once in the 12 following months	Initially: two injections of 0.01mg, then two of 0.1mg, followed by five of 1mg, then eight of 5mg and finally by the constant target dose of 10mg over the remaining duration of the trial Injections were given three times per week.	European Organization for Research and Treatment of Cancer Quality of life – C30-	Patients in the Mistletoe group significantly reduced insomnia and increased quality of life.	NA

2.8.1.2. Non-pharmacological treatments for insomnia in cancer patients

Although using drugs to treat insomnia is common in cancer patients, this approach remains limitations due to adverse events to patients. This unsatisfactory outcome has led healthcare providers and patients to look for other solutions. Various non-pharmacological treatments have been examined to reduce insomnia. These interventions can be categorized as follows:

- Cognitive-behavioral therapy for insomnia (CBT-I)
- Mindfulness-based stress reduction
- Yoga
- Exercise interventions including walking, home-based exercise.
- Complimentary and alternative treatments: Acupuncture, Acupressure.

Each of these will be discussed in the following sections.

2.8.1.2.1. Cognitive Behavioral Therapy for Insomnia (CBT-I)

Cognitive-behavioral therapy (CBT), originated in the 1980s, is an integration of cognitive therapy and behavioral modification techniques. CBT is a psychological treatment modality aimed at changing and solving emotions, behaviors, and cognitive dysfunctions, focusing on achievements of treatment goals and real situations. CBT has been considered as an effective treatment for insomnia, depression, anxiety, obsessive-compulsive, and eating disorders in the general population (Belanger et al., 2006; Reeve & Bailes, 2010). Cognitive behavioral therapy for insomnia (CBT-I) is a treatment which generally includes 4 to 8 sessions in 6 to 10 weeks (Belanger et al., 2006; Espie, 2009; Perlis et al., 2006; Smith et al., 2003). CBT-I adopts a multi-component approach, which are sleep restriction, stimulus control, cognitive therapy, sleep hygiene, paradoxical intention, relaxation training, and they are also the most commonly used strategies for insomnia in cancer patients (Woodward, 2011). Results across reviews considered CBT as the most effective therapy for insomnia (Howell et al., 2014). Table 7 lists out 19 RCTs conducted to test the effectiveness of CBT-I in the cancer population. These studies were included in 3 recent reviews (Garland et al., 2014; Howell et al., 2014; Johnson et al., 2016).

Table 7. Studies on the effectiveness of CBT-I treatment for insomnia in Cancer Patients

No	Author	Sample	Diagnosis	Status	Design	Therapy description	Intervention	Follow up	Outcome measure	Result		
										↓	↑	no change
1	(Davidson et al., 2001)	12 M+F	Mixed	Post-treatment	single group	SC, RT, SH, CR	Group, six sessions, weekly, 60-90 min	8 weeks	SD, Sl, NWAK, WASO, TST, SE, SII, HADS, QLQ-C30	NWAK, WASO, sleep-related impairment	TST	
2	(Quesnel et al., 2003)	10F	Breast I-II	Post-treatment	single group	SC, SR, CR, SH fatigue management, RP	Group, 8 sessions, weekly, 90 min	32 weeks	PSG WASO, TST, ISI, BDI, STAI, MFI, QLQ-C30	WASO, ISI	SE,	
3	(Simeit et al., 2004)	229 M+F	Mixed	Post-treatment	3 groups (PMR, AT, UC)	PMR and AT gr were provided information on SC, SR, CR, SH	Group, 3 sessions, weekly, 60 min	34 weeks	PSQL, QLQ-C30	For Interventions gr: SL	SD, SE, daytime function, QOL (3 gr)	
4	(Savard et al., 2011)	11	Breast I-III	Post radiation	single group	SC, SR, CR, SH, RP	Self-administered DVD/booklet, 6 modules, weekly, 60 minutes	18 months	SD; SL, WASO, TST, SE, ISI, HADS, MFI, QLQC30, DBAS	SL, WASO, insomnia severity, depression	SE, quality of life	

No	Author	Sample	Diagnosis	Status	Design	Therapy description	Intervention	Follow up	Outcome measure	Result		
										↓	↑	no change
5	(Roscoe et al., 2015)	96	Mixed	After treatment	2 groups (CBT and placebo)	SR, SC, SH, wakefulness-promoting	Group, 7 sessions, 30-60 min	7 wks	ISI, PSQI		insomnia severity, sleep quality	
6	(Savard et al., 2005)	57	Breast I-III	Post-treatment	2 group s	SC, SR, CR, SH, fatigue and stress management	Group, 8 sessions weekly, 90 min	3,6,12 months	SL, WASO, TST, SE, ISI, HANDS, MFI, QLQC30	SD, insomnia severity, depression, anxiety, fatigue	SE, TST, quality of life	
7	(Epstein & Dirksen, 2007)	72	Breast I-III	Post-treatment	2 groups	T: SC, SR, SH; C: sleep hygiene education	Group, 6 sessions 4 weekly, 30-120 min	none	SL, WASO, TST, SE,	SL, WASO	SE, TST	
8	(Espie et al., 2008)	150 M+F	Mixed	Post-treatment	2 groups	T: SC, SR, CR; C: usually care	Group, 5 sessions weekly, 50 min	6 months	Actigraph, FACT-G, sleep diary	wakefulness of 55 minutes per night, daytime fatigue		
9	(Berger et al., 2009)	219	Breast I-III	Pre, during, post-chemo	2 groups	T: SC, SR, RT, SH; C: diet education	Individual before, biweekly during, 30 days after chemo, 15-30 min	30 days	SL, WASO, TST, SE, PSQI,	WASO, sleep disturbance, fatigue	SE	

No	Author	Sample	Diagnosis	Status	Design	Therapy description	Intervention	Follow up	Outcome measures	Results		
										↓	↑	no change
10	(Ritterband et al., 2012)	28 M+F	Mixed	Post-treatment	2 groups	SR, SC, SH, CR	Individual, 6 sessions, weekly, 45-60 min	none	SL, NWAK, WASO, TST, SE, ISI, HADS, MFSI, MOS-SF-12	SL, insomnia severity, fatigue	SE	
11	(Fiorentino et al., 2009)	14	Breast I-III	Post treatment	2 groups	SR, SC, SH, RT, CR	Individual, 6 sessions, weekly, 60 min	none	SL, WASO, TST, SE, PSQI, ISI	WASO, NWAK, insomnia severity, sleep disturbance	SE, TST	
12	(Garland et al., 2014)	111 M+F	Mixed	Post treatment	2 groups	T1: SR, SC, RT, RP. T2: MBSR	Individual, 8 sessions, weekly, 90 min	5 months	SL, WASO, TST, SE, ISI, PSQI, DBAS, POMS-SF, CSOSI	T1: SL, insomnia severity, sleep disturbance, dysfunction beliefs, Both: WASO, stress and mood symptom	Both: SE, TST	

No	Author	Sample	Diagnosis	Status	Design	Therapy description	Intervention	Follow up	Outcome measures	Results		
										↓	↑	no change
13	(Savard et al., 2014)	260	Breast I-III	Post treatment	3 groups	T1: SR, SC, CR, SH (clinical)	Individual, 6 sessions, weekly,50-60 min	3,6,12 months	SL, WASO, TST, SE, ISI, PSQI, DBAS, MFI, HANDS, EORTC QLQC30	SL, WASO (no diff betweenT1& T2)	SE	
						T2: SR, SC, CR, SH (video)				T1: insomnia severity, dysfunction beliefs, fatigue, depression	T1: TST,	
						T3: usually treatment					QOL in 3 gr	
14	(Matthews et al., 2014)	56	Breast I-III	Post treatment	2 groups	SC, SR, SH, CR	Individual, 6 sessions, weekly, 30-60)	3 & 6 months	Sleep diary, ISI, QLQC30, PFS, AFI, HADS, DBAS, PKT	insomnia severity, SH knowledge	T1: SL, SE	QOL, fatigue, mood
15	(Farrell-Carnahan et al., 2010)	28	Mix	Cancer survivors	2 groups	Self-hypnosis	Web,4 weeks	10 days	Online sleep diary, ISI	Insomnia Severity, SL, WASO (ns)	TST, SE (ns)	
16	(Barsevick et al., 2010)	284	Mix	During Chemotherapy	2 groups	energy and sleep enhancement	Telephone, 3 session weekly,	60 days	Actigraph, PSQI		Sleep disturbance (ns)	

No	Author	Sample	Diagnosis	Status	Design	Therapy description	Intervention	Follow up	Outcome measures	Results		
										↓	↑	no change
17	(Barton et al., 2020)	93	Mix	Cancer survivors	2 groups	SH, SC, SR, 30 mins bedtime short stories	Group intervention or by phone, one session	none	PSQI, BFI, sleep diary	None significant differences were found between intervention and control group		
18	(Savard et al., 2019)	177	mix	NA	2 groups (self-CBT-I and PCBT-I	CBT-I	One group received self-administered CBT-I and other received standard CBT-I	None	ISI, SD	Self-administered CBT-I was as effective as a standard face-to-face CBT-I in improving ISI score and sleep parameters (SE, sleep latency)		
19	(Zachariae et al., 2018)	255	Breast cancer	NA	2 groups	CBT-I	6 online sessions in 9 weeks	6 weeks	SD, ISI, PSQI, FACIT-F	SD, ISI, PSQI		FACIT -F

AT: autogenic training; **BDI**, Beck Depression Inventory; **CR**, cognitive restructuring; **DBAS**, Dysfunctional Beliefs and Attitudes about Sleep; **HADS**, Hospital Anxiety and Depression Scale; **Severity MFI**, Multidimensional Fatigue Inventory; **NWAK**, number of awakenings; **PMR**, progressive muscle relaxation; **PSG**, polysomnography; **PSQI**, Pittsburgh Sleep Quality Index; **QLQ-C30**, Quality of Life Questionnaire – Cancer; **RP**, relapse prevention; **RT**, relaxation training; **SC**, stimulus control; **SE**, sleep efficiency; **SD**, sleep diary; **SH**, sleep hygiene; **SII**, Sleep Impairment Index; **SL**, sleep latency; **SR**, sleep restriction; **STAI**, State-Trait Anxiety Inventory; **TST**, total sleep time; **Tx**, treatment; **UC**, usual care; **WASO**, wake after sleep onset; **FACIT-F:** Functional Assessment of Chronic Illness Therapy for Fatigue; **PCBT-I:** professionally-administered CBT-I; **wk**: week **ns**, non-significant; ↑, increase; ↓, decrease

Results from the above studies suggested that CBT-I is an effective intervention for sleep problems in cancer patients who are at post-treatment period or during treatment as well as in cancer survivors. Among those RCTs for insomnia at post-treatment period, CBT-I has reduced sleep latency significantly (Simeit et al., 2004) as well as wake time after sleep onset, insomnia severity and dysfunctional beliefs, fatigue (Matthews et al., 2014; Savard et al., 2014) and increased sleep efficacy and total sleep time (Farrell-Carnahan et al., 2010). In a large sample size of 219 breast cancer patients Berger et al. (2009) pointed out CBT-I can significantly reduce wake time after sleep onset, the number of awakenings, sleep disturbance, insomnia severity, improved sleep efficacy, and total sleep time up to 1 year after treatment. The effectiveness of CBT-I has been compared with other interventions to reduce insomnia such as mindfulness-based stress reduction (MBSR). The evidence showed that patients receiving CBT-I had shorter sleep latency, lower insomnia severity, sleep disturbances, and dysfunctional beliefs compared with patients receiving MBSR; although patients in both groups increased sleep efficiency, total sleep time, and reduced stress and mood symptoms (Garland et al., 2014). In other comparisons with progressive muscle relaxation, patients received training in CBT-I also reduced significantly sleep latency time (Simeit et al., 2004).

Regarding how CBT-I was delivered to patients, three approaches were used in these above studies including being delivered by a therapist to individuals or small group of patients (12/16 studies); being delivered via telephone (one study), being delivered via educational material (two studies) and internet (one study). There was no difference between CBT-I delivered by a therapist in a face-to-face session or by phone in terms of improving sleep efficiency, wake after sleep onset, sleep quality. However, patients

in the therapist-delivered group significantly decreased dysfunctional beliefs, fatigue, depression, and increased sleep efficacy, total time asleep, and sleep quality (Savard et al., 2014).The results from a study also indicated a similar finding when comparing the effectiveness of CBI-I delivered by a therapist and self-management via video (Savard et al., 2019). Another study also found CBT-I delivered by the internet also appears to be effective in improving the ISI score and sleep parameters, with the additional benefit of reducing fatigue (Zachariae et al., 2018). These findings support the use of self-administered CBT-I when its accessibility is very limited in routine cancer care as there is a lack of qualified practitioners to administer it; also, even when there are such trained professionals, they are insufficient to meet all needs (Savard et al., 2019). The self-help method is the best entry-level to CBT treatment, the second-level being the delivery by a therapist (Espie, 2009; Savard et al., 2011).

Regarding the components included in CBT-I, most of the trials used a combination of sleep restriction (SR), stimulus control (SC), sleep hygiene (SH), and cognitive restructuring (CR). While SC, SR, CR are active components of CBT that need to be delivered by a well-trained therapist, SH is a non-active component that patients can practice at home by themselves. Sleep hygiene is ranked as the most recommended treatment for patients diagnosed with psychophysiological insomnia and inadequate sleep hygiene (such as daytime napping at least twice a week) (Stepanski & Wyatt, 2003). It is the second most commonly recommended treatment for patients with insomnia related to anxiety and mood disorders (Buysse et al., 1997). Nevertheless, sleep hygiene is also recommended as a standard part of best practice for the management of insomnia by The American Academy of Sleep Medicine. Sleep hygiene in past trials was included in the control group as a way to avoid the possible effect of

interpersonal contact impacting outcomes (Shadish et al., 2002) as well as to avoid neglecting the patient in the "usual care" control group (Brink, 2003). Sleep hygiene refers to a list of recommendations for patients to provide information about healthy lifestyles and choices that improve sleep and minimize insomnia. Details of sleep hygiene components are showed in table 8.

Table 8. Sleep hygiene components

Sleep Hygiene components	How the component may work
Regular bedtime, arising time or both	Insomnia among cancer patients is related to abnormal secretion of cytokines that lead to abnormal sleep/wake cycles (Anderson et al., 2003). This rule helps the patient to establish regulating bedtime/waketime that leads to improving the secretion of cytokines.
Avoid naps if possible	Daytime napping decreased the depth of major sleep episode and increased latency to sleep onset and also lower homeostatic sleep pressure that lead to nocturnal sleep onset (Werth et al., 1996). Thus, naps may benefit people who cannot obtain a sufficient sleep hour, but it also lately causes a negative effect on nocturnal sleep.
Curtail time in bed	It is difficult to find experience data to explain why insomniacs should curtail time in bed. However, if people cannot sleep, they tend to produce mental activities such as thinking, planning, and even worried about their sleep. These activities will increase the sleep latency that worsens sleep quality. Therefore, if the patients cannot sleep, they are advised to leave the bed and do their mind racing in a chair and only come back to bed when they feel sleepy
Avoid coffee, alcohol, and nicotine	Coffee is the most recommended for wakefulness and combating sleepiness (Nehlig, 1999). Alcohol intake 6 hours before bedtime is led to significant fragmentation of subsequent sleep (Landolt et al., 1996), and nicotine has been associated with sleep fragmentation (Wetter et al., 1995). For that reason, avoid these stimulants can improve sleep.
Exercise in the late afternoon or early evening.	Although doing exercise can benefit sleep, but exercise near bedtime has been shown to bring a negative effect on sleep. Exercise raises core body temperature, increases heart rate, and prompts the secretion of epinephrine that resulted in causing difficulty to calm down the body to sleep. Data also supported that exercise increases sleep latency (Bonnet & Arand).

Sleep Hygiene components	How the component may work
Eliminate noise from the bedroom	Help to maintain a quiet sleep environment for better sleep quality
Eliminate the bedroom clock Have a comfortable pre-bedtime routine (light snack before bedtime, comfortable bed mattress, appropriated temperature for the bedroom, comfortable sleep clothes)	To avoid patient look at the time and worry about sleep time and create a comfortable sleep environment to support sleep quality.
Inadequate sleep hygiene that patients need to avoid	
Inadequate sleep hygiene	**How they affect sleep**
Variable wake-up times or bedtime	Break the regular sleep/wake cycle
Frequent period (two or three times per weeks) of extended time spent in bed	Break the regular sleep/wake cycle
Engaging in exciting or emotionally upsetting activities too close to bedtime	Make the brain more active while it is supported to be calm and rest to help the sleep occur.
Frequent use of the bed for non-sleep related activities (e.g., watching TV, reading, studying, snacking, etc.)	These activities stimulate the brain, which results in delayed sleep to occur.
Performing activities demanding high levels of concentration shortly before bed	Make the brain more active while it is supported to be calm and rest to help the sleep occur.
Allowing mental activities, such as thinking, planning, reminiscing, etc. to occur in bed	

To summarize, CBT-I is the most common and most effective treatment for insomnia in cancer patients as well as in the general population. However, this treatment needs a well- trained therapist to deliver it to patients, on the other hand, patients will have to spend time to travel to the treatment site as well as pay money to receive the treatment. These limitations make this treatment modality not always be readily available or accessible to all patients, especially to those who live far from the treatment site, and it can also be a costly treatment.

2.8.1.2.2. Mindfulness-based interventions

Mindfulness, based on Buddhist meditation, refers to a "particular way of paying attention," or a "moment-to-moment awareness," where the subject remains non-judgmental and accepting of the different sensations, thoughts, and perceptions that cross one's mind. It has similarly been described as the non-judgmental observation of the ongoing stream of internal and external stimuli as they arise. An operational working definition of mindfulness is "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment" (Kabat-Zinn, 2003, p. 145). Among the cancer population, the most common mindfulness training is mindfulness-based stress reduction (MBSR). This method was shown to be helpful for the mental health of cancer patients, and it improved cancer patients' psychosocial adjustment to their disease in a review from 10 RCTs (Ledesma & Kumano, 2009). A large RCTs was conducted to compare the effectiveness of MBSR and CBT-I, with the results showing that although MBSR produced a clinically significant change in sleep and psychological outcomes (Garland et al., 2014). Table 9 describes three found RCTs on the effectiveness of MBSR on insomnia in cancer patients.

Table 9. Effectiveness of mindfulness training on insomnia in cancer patients

Author	Sample	Diagnosis	Status	Design	Therapy description	Follow up	Outcome measures	Results		
								↓	↑	no change
(Carlson & Garland, 2005)	63	Mix	NA	1 gr	Weekly in 8 weeks, 90 min	none	PSQI	PSQI	sleep quality, mood disturbance, fatigue	
(Lengacher et al., 2015)	79	Breast cancer	NA	2 grs A: MBSR B: Usual care	A: weekly in 6 weeks	12 weeks	Actigraph	At 12 weeks Nighttime awakening,	At 12 weeks: total sleep time, Sleep quality	At 6weeks: insomnia
(Garland et al., 2014)	111	Mix	NA	2 grs A: MBSR B: CBT-I	NA	3 months	Sleep diary	Both: mood disturbance, WASO	A: sleep quality	
(Zhang et al., 2019)	27	Cervical cancer	NA	2 groups A: MBSR B: Usual care	Weekly in 8 weeks	12 months	Sleep diary. Insomnia severity index, Polysomnography	Total wake time	Sleep Efficacy, total sleep time	Sleep parameter measured by Polysomnography

As showed in the above table, the duration for MBSR intervention was from 6 to 8 weeks, and the follow- up was around three months to assess the effect of MBSR. MBSR appeared to be effective in reducing sleep disturbances, increasing sleep quality as well as total sleep time. Still, the result of this method was not rapid. It took at least eight weeks to see the effectiveness of the intervention. This issue can be problematic for cancer patients. For example, due to living far from the treatment site, health issues, and other issues, the refusal rate of a meditation intervention was 80% in one study (Lengacher et al., 2015).

2.8.1.2.3. Yoga

Yoga is an increasingly popular mind-body practice and is also characterized as a mindfulness mode of exercise (Bower et al., 2005). There are many different styles and types of Yoga. They are based on Eastern traditions from India (e.g., Classical, Advaita Vedata, Tantra), Tibet, and China (e.g., Chi Kung, Tai Chi) (Mustian, 2013). Results from systematic reviews show that Yoga improved depression, anxiety, fatigue, and sleep disturbance in the general population as well as in the cancer population (Cramer et al., 2013; Mustian et al., 2014).

We found ten trials using yoga to manage insomnia in cancer patients (Table 10). In those studies, the majority of participants were breast cancer patients. The intervention program was from four to 12 weeks. Yoga sessions usually occurred in 60 to 120 minutes. Results from those studies showed that Yoga could reduce sleep latency and increase sleep quality and sleep duration. Yoga not only was found effective in reducing insomnia but also reduced symptom cluster of fatigue, depression, and anxiety among cancer patient. Among 60 breast cancer patients, 30 of whom were allocated in the control group received yoga training sessions twice per week for eight weeks and

showed a significant reduction in overall fatigue and a non-significant decrease in depression and anxiety (Chao-Jung et al., 2014). A study published in 2004, in which cancer patients were invited to participate in the Stanford Cancer Supportive Care Program (SCSCP). The SCSCP consisted of 11 different activities, including fatigue management, nutrition, massage, and restorative Yoga. Of the 380 participants who participated in restorative Yoga and evaluated their experience, 96% felt it reduced their stress, 74% felt an increase in energy, and 65% reported more restful sleep (Rosenbaum et al., 2004). Another large-scale RCT conducted in 2010 among 410 cancer survivors also indicated that YOCAS (yoga for cancer survivors) improved sleep quality in the intervention group (Mustian et al., 2010). Another large-scale, multicenter trial of YOCAS for sleep difficulties among cancer survivors also indicated yoga participants had significantly improvements in PSQI score, wake after sleep onset, sleep efficiency, and reduce sleep medication usage compared with the controls (Mustian et al., 2013). This is also the only study to used both validated objective and subjective measurements to assess sleep problems in a yoga trial among cancer patients (Danhauer et al., 2019). While results from most of the studies indicated that Yoga is useful for individuals who report mild to moderate sleep quality impairment, clinical insomnia, or continue to report sleep problems after receiving pharmaceutical treatment. A study showed that Yoga had no significant effects on sleep disturbances, but the results must be interpreted with caution due to the small sample size (Cohen et al., 2004).

Although a positive result in managing insomnia among cancer populations is reported, Yoga trials remain with several limitations in the design, such as small sample size. As shown in table 10, 8/10 studies had a small sample size or were a feasibility or pilot study. Due to small participants in each group, the effectiveness of the intervention

cannot fully confirm. Also, as the time for intervention ranged from 4 weeks to 12 weeks, patients need to practice yoga 1 to 2 times per week during the intervention. This therapy requires cancer patients to spend time traveling to the practice site as well as an effort to practice yoga training. These issues could potentially increase the proportion of patients who fail to adhere to the treatment due to inconvenience.

To sum up, previous studies showed a promising effect of Yoga in improving insomnia among patients with cancer. However, due to the small number of studies and limitations in their design, it is difficult to conclude the efficacy of yoga intervention for insomnia in cancer patients. Nevertheless, the inconvenience of practicing Yoga in a fitness center that costs money and time, as well as the effort of patients to participate can become barriers for patients to access this treatment.

Table 10. Studies of Yoga intervention for Insomnia in cancer patients

Author	Sample	Diagnosis	Design	Status	Type of Yoga	Dose information	Intensive	Outcome measures	Results		
									↓	↑	no change
(Ulger & Yagli, 2010)	20	Breast cancer	1 group	Post-treatment	classical	2/wk/4 wks, 60 min	Low-Moderate	Turkish version of Nottingham health profile		SQ	
(Cohen et al., 2004)	39	Lymphoma	2 groups	mix	Tibetan	1/wk/7 wks	low	PSQI	sleep efficiency	SQ, Sleep duration	
(Danhauer et al., 2009)	44	Breast cancer	2 groups	mix	Integral	1/wk/10 wks, 75 min	low	PSQI		SQ	
(Bower et al., 2012)	37	Breast cancer	2 groups	Post-treatment	Yoga of Awareness	1/wk/8wks, 120 min	Low-Moderate	Daily sleep dairy rating	sleep duration	SQ	
(Vadiraja et al., 2009)	74	Breast cancer	2 groups	During radiotherapy	Integral	3/wk/6wks, 50 min	Low-Moderate	QoL C30		SQ	
(Chandwani et al., 2010)	61	Breast cancer	2 groups	During radiotherapy	Patanjali	2/wk/6 wks, 60 min	Low-Moderate	PSQI			QoL, SQ
(Bower et al., 2011)	31	Breast cancer	2 groups	Post-treatment	Iyengar	2/wk/12wks. 90 min	Low-Moderate	PSQI		SQ	
(Dhruva et al., 2012)	23	mix	2 groups	Receiving	Pranayama	1/wk/12months. 60 min	low	General Sleep Disturbance scale		SQ	
(Mustian et al., 2010)	410	mix	2 groups	Post-treatment	YOCAS	2/wk/4 wks, 75 min	Low-Moderate	PSQI		SQ	
(Mustian et al., 2013)	410	Mix	2 groups	Cancer survivors	YOCAS	2 session/week in 4 weeks	Low-Moderate	PSQI, actigraph	PSQI score WASO	Objective and subjective SQ, daytime function SE	

***PSQI**: Pittsburgh Sleep Quality Index; **SQ**: Sleep Quality, **WASO**: wake after sleep onset, **SE**: Sleep Efficacy ; **YOCAS**: Yoga for cancer survivors; **QoL**: Quality of life; **wk:** week*

2.8.1.2.4. Physical exercise

Studies suggest lifestyle factors such as physical activity and functional status are associated with cancer outcomes. For cancer patients, the most common physical exercise is walking. The effectiveness of walking to improve the quality of sleep among cancer patients has been shown in a systematic review from nine RCTs in nearly 600 patients. In this review, most of the studies used moderate-intensity walking exercise, and walking exercise significantly improved sleep in people with cancer (Chiu et al., 2015). A meta-analysis from 25 studies with 1080 participants also indicated walking is more effective than yoga at improving sleep quality in cancer patients (Tang et al., 2019).

Table 11 lists out found RCTs using physical exercise to reduce insomnia in cancer patients. The results showed that walking exercise alone and walking exercise combined with other forms of interventions yielded comparable effects on sleep improvement and that the effect size did not differ among participants who were at different stages of cancer or any type of cancer (Chiu et al., 2015). Other types of physical exercise like progressive resistance training, stair-stepping, and muscle relaxation also gave better sleep quality, satisfaction with sleep, and reduced difficulty sleeping as well as sleep onset latency, and the number of awakening times. An RCT on cancer survivors also suggested telephone reminders can increase physical activity in this population, which resulted in significant reductions in insomnia (Ligibel et al., 2012).

The existed evidence leads to the conclusion that physical exercise can improve cancer patient's sleep quality. However, due to limitations in small sample size and no follow-up in most studies, more studies should be conducted with well-designed methods to make more reliable evidence to support the effectiveness of physical exercise in

reducing insomnia in the cancer population. Further studies should determine the most effective physical exercise intervention for cancer patients by comparing the effectiveness of walking and resistance training for improving sleep quality in cancer patients as well as the acceptance and safety of the cancer population. Lastly, evidence has shown that doing exercise decreases fatigue and enhances the quality of sleep among cancer patients. Still, most of the studies were conducted in western populations, and only one pilot study about the effect of exercise has been examined in an Asian breast cancer population.

Table 11. Studies of exercise intervention for insomnia in cancer patients.

No	Author	Sample	Diagnosis	Situation	Design	Dose	Follow-up time	Measurements	Results	
									↓	↑
1.	(Mock et al., 1997)	46	Breast cancer	Receiving treatment	Two groups A: self-paced, home-based walking B: Usual care	NA	six weeks	NA	difficulty sleeping	
2.	(Sprod et al., 2010)	40	Breast or prostate cancer	Receiving treatment	Two groups A: walking and progressive resistance training B: Usual care	walking: 4 weeks. Resistance training: 4 set/day/4 weeks	three months	PSQI	PSQI score in A	
3.	(Young-McCaughan et al., 2002)	62	Mix cancer type	Receiving treatment	1 group: walking, stair stepping, upper body exercise	2 day/week/12 wks	none	Cancer Rehabilitation Evaluation System-Short Form	difficulty sleeping	
4.	(Payne et al., 2008)	20	Breast cancer	Receiving treatment	Two groups A: walking B: usual care	4/wk/14wks, 20minutes/day	None	PSQI	PSQI score in group A	
5.	(Ligibel et al., 2012)	121	Mix	Cancer survivors	Two groups A: telephone-based to motivate subject to increase physical activities B: Usual care	NA	16 weeks	EORTC QLQ-C30	insomnia	
6.	(Wang et al., 2011)	160	Breast cancer	Before surgery	A: six wks walking program. 30minutes, 3/wk B: usual care	NA	None	PSQI	PSQI score significantly reduce	

PSQI: Pittsburgh Sleep Quality Index; **EORTC QLQ-C30:** The European Organization for Research and Treatment of Cancer core quality of life questionnaire**; wk**: week

2.8.1.2.5. Complementary & Alternative treatments: Acupuncture, Acupressure

a. Acupuncture

Acupuncture is a therapy that uses fine needles to insert in the skin at strategic points (acupoints) on a body. The actions depend on the function of the acupoint, the characteristics of the needle insertion, the type of needle and point depth, as well as on the body posture and the phrase of the respiratory cycle (Quispe-Cabanillas et al., 2012) This is a key component of Traditional Chinese Medicine. The mechanisms of acupuncture have not been fully clarified. According to the Traditional Chinese Medicine (TCM) theory, the symptoms are caused by pathogenic changes in *Qi*, the imbalance of *Yin and Yang* (Liu, 1998), and the insufficiency of blood circulation to the organs (Li, 2007, p. 1023). *Qi* is considered as the vital energy of life, while *Yin and Yang* are common medicinal traits conflicting as well as in equilibrium with each other (Heinrich et al., 2017). Stimulating acupoints improves the symptom by increasing the blood circulation resulting in enhancing *Qi* and balancing *Yin* and *Yang* (Li, 2007, p. 1023). According to the Chinese *Zang-fu* organs and meridians theory, the enhancement of *Qi* leads to the improvement of physiological functions of body systems or *Zang-fu* in the process (Lu et al., 2004). *Zang-fu* is the term for human organs (five *Zang* organs: heart, liver, spleen, lung, and kidneys, along with six *fu* organs: gallbladder, stomach, small intestine, large intestine, bladder, and *san jiao)* (Mehta & Dhapte, 2015). Evident indicated that acupuncture can impact insomnia by modifying the neurotransmitters linked to stimulation of the central or autonomic nervous systems, including norepinephrine, melatonin, γ-aminobutyric acid, and β-endorphin (Huang et al., 2011; Zhao, 2013). This treatment has been used as a treatment of various physical and mental conditions. Acupuncture must be delivered to patients by a healthcare

worker who holds a certificate in acupuncture. For treatment, patients can receive either regular acupuncture (body or auricular) or electro-acupuncture. In the cancer population, acupuncture is known as treatment to reduce fatigue, pain, nausea, and vomiting, as well as hot flushes (Garcia et al., 2013). However, the role of acupuncture in reducing cancer-related insomnia has yielded mixed results. A systematic review of six RCTs showed that acupuncture increased the number of hours slept and reduced the number of times woken up each night (1 RCT). The three weeks of follow-up in two RCTs showed superior effects of acupuncture compared with conventional drugs, and a meta-analysis showed significant effects of acupuncture. Two RCTs tested the effects of acupuncture on cancer-related insomnia compared with sham acupuncture (placebo acupuncture). One RCT showed favorable outcomes, while the other trial failed to do so. The study indicated a low level of evidence that acupuncture may be superior to sham acupuncture, medications, or hormone therapy (Choi et al., 2016). When compared with CBT-I, acupuncture was less effective in reducing insomnia in a rigorous designed RCT by Garland et al. (2019). However, the results from this trial indicated that participants in the acupuncture group reported clinically significant reductions in the severity of their insomnia, and these effects were well maintained at the 3-month follow-up. Acupuncture also appeared to increase sleep diary reported total sleep time, whereas the CBT-I group did not. Table 12 shows studies evaluating the effectiveness of acupuncture in cancer populations published in English.

Trials using acupuncture to manage insomnia remains with imitations in methodology. A sham control group must be included since the sham acupuncture also has positive treatment effects due to a combination of positive expectancy, patient-interventionist interaction, and active patient engagement (Lund & Lundeberg, 2006; O'Sullivan &

Higginson, 2010; Paley et al., 2011). However, only 2/5 of found studies have had three groups design with a sham control group. In addition, most of the RCTs had a small sample size. Therefore, the results do not have enough statistical power to make a firm conclusion for the effectiveness of acupuncture in improving insomnia in cancer patients. Further larger-scale RCTs should be conducted.

Table 12. Studies of acupuncture for insomnia in cancer patients

Author	Sample	Diagnosis	Design	Therapy description	Used Acupoints	Follow up	Outcome measures	Results		
								↓	↑	no diff
(Bokmand & Flyger, 2013)	94	Breast cancer	3 groups	A: AT, weekly, 15-20 min B: Sham AT C: No treatment	HC6, KI3, SP6, LR3	12 weeks	Sleep log	Sleep disturbance in gr A. effect last of 12 weeks after treatment		
(Mao et al., 2015)	76	Breast cancer	3 groups	A: EA, twice a week in 2 weeks, then 1/wk/6wks, 30 min B: Sham AT C: waitlist	LII5, SI9, ST34, ST35, SP9	12 weeks	PSQI			PSQI score
(Siegel et al., 2015)	29	Mix	2 groups	A: RA 1/wk/8wks, 35 min B: Usual care	ST6, SP6, LI4, LI11, EX-HN3, PC6, TH5, SP15, ST25, UB26, UB60, GB13, LV3	none	MYMOP	Insomnia		
(Otte et al., 2011)	10	Breast cancer	1 group	AT, 3 times/wks in 2 weeks	LU7, SP6, LII1, KD6, KD3, HT6, KD7, Ren4, LI4, ST36, GB34, GB41, HT7, SI3	8 weeks	PSQI, sleep diary	PSQI, WASO, nighttime awakening		TST, SE
(Garland et al., 2019)	160	Cancer survivors	2 groups	Gr 1; 10 treatment sessions of Acupuncture in 8 weeks Gr 2: CBT-I for 8 weeks	Gr 1: HT7, SP6, GV 20, GV 24, HT 7 (auricular), Sympathetic (auricular) Gr2: SR, SC, cognitive restructuring, relaxation training.	4 weeks	ISI, PSQI, SD, BPI, MFI, HASDS, PROM	CBT-I was more effective in improving sleep than acupuncture however, both acupuncture and CBT-I produced clinically meaningful reductions in ISI score		

***AT**: Acupuncture therapy, **SD**: Sleep duration, **TST**: total sleep time, **MYMOP**: Measure yourself medical outcome profile, **EA**: electro-acupuncture; **PSQI**: Pittsburgh Sleep Quality Index; **SE**: sleep efficiency; **TST**: total sleep time; **ISI:** Insomnia severity Index, **BPI**: Brief Pain Inventory; **MFI**: Multidimensional Fatigue Inventory-Short Form; **HADS**: the Hospital Anxiety and Depression Scale; **PROM:** Patient-Reported Outcomes Measurement Information System-Global Health Scale; **wk:** week*

b. Acupressure

Acupressure is a form of touch therapy that utilizes the principles of acupuncture and TCM as presented in the previous section. Acupressure is a non-pharmacological treatment for a wide range of symptoms (Lee et al., 2011). There are two type of acupressure: body acupressure and auricular acupressure. In the body acupressure (normally call as acupressure), physical force is stimulated on the acupoints on the body with finger pressure instead of needle insertion (Zick et al., 2011). In auricular acupressure (AA), the acupoints on the external surface of the ear or auricle are stimulated. In this thesis, we use the term acupressure to refer to the body acupressure. Acupressure is easy to learn through books that illustrate the position of acupoints on the body. It is also very versatile, as it can be performed anywhere. It is also a self-administered treatment method in which healthcare workers can train patients on how to locate and stimulate an acupoint. In this thesis, the term "self-acupressure" or "self-administered acupressure" are both refer to the approach in which patients stimulate acupoints by themselves after being trained. We found six studies using acupressure to improve sleep in cancer patients. Their effectiveness is summarized in table 13.

Table 13. Studies of Acupressure for Insomnia in Cancer Patients.

Author	Sample	Diagnosis	Design	Therapy description	Used Acupoints	Follow up	Outcome measures	Results		
								↓	↑	no diff
(Kumar & Uma, 2015)	60	mix	One gr pre and posttest design	Self-administered every before bedtime in 7 days	3 points (back of the ear, wrist and calf muscle	none	PSQI	PQSI score		
(Yeh et al., 2016)	31	Breast cancer	Two groups	Group 1: self AA weekly in 4 weeks Group 2; Received sham AA weekly in 4 weeks	Shenmen Sympathetic Occiput Sub cortex nervous Anxious Neurasthenia point	none	Sleep diary QOL	Sleep disturbance		
(Hughes et al., 2015)	7	Breast, colorectal cancer	Three groups	A: AA (by therapist) B: Self-administered acupressure C: Usual care	HT7, PC6, GB20, Ex8, KI6, BL62	5 weeks	PSQI, MYCAW	PSQI score (A, B) MYCAW (A,B)		PSQI and MYCAW in C
(Cerrone et al., 2008)	25	Cancer and others disease	One gr pre and posttest design	HT 7 stimulation for at least two consecutive weeks using a medical device	HT7	none			SQ	
(Kuo et al., 2018)	47	Ovarian cancer	Two groups	Group 1: self AA in 2 weeks after chemotherapy (6 weeks) Group 2: SH	Shenmen Heart point Sub cortex point Endocrine point	None	PSQI	PSQI score		
(Yoon & Park, 2019)	46	Breast cancer	Two groups	Group 1: vaccaria seeds were applied in the acupoint in 6 weeks Group 2: vaccaria seeds were applied in the Helix control point in 6 weeks	Shenmen Heart point Occiput Anterior lobe		PSQI Fitbit tracker	PSQI score		All sleep parameters measured by Fitbit tracker

*Note **AA**: Auricular therapy, **QOL**: Quality of life, **MYCAW**: Measure your self-concern and wellbeing; **PSQI**: Pittsburgh Sleep Quality Index; **SQ**: Sleep quality*

As showed in table 13, although the number of studies is rather small, positive results were revealed. Among breast cancer patients, three studies indicated that self-acupressure reduced sleep disturbances and objective sleep parameters (e.g., total sleep time, sleep efficiency, wake after sleep onset). In the mixed type cancer population, two studies showed self-acupressure reduced the PSQI score and improved sleep quality. The result from the small-scale study conducted by Hughes et al. (2015) stated the equivalence of receiving acupressure either by a therapist or by patients themselves. These above RCTs suggest that self-acupressure can reduce sleep disturbances and improve sleep quality among cancer patients. However, the small sample size and other limitations in the design method, such as having no control group, and no follow-up time that makes the results from acupressure RCTs less convincing.

To sum up, several trials using acupuncture and acupressure were conducted. Most of the studies were pilot study with a small sample size which makes the result do not have enough statistical power to confirm the effectiveness of acupuncture/acupressure in improving insomnia in cancer patients. The advantages of being a non-invasive treatment with safety, no cost, and self-management make self-administered acupressure a helpful approach to assist patients in overcoming distressing symptoms during their treatment. However, only a small number of trials with limitations in the design were conducted to explore its efficacy on insomnia in cancer patients.

This section demonstrated the available non-pharmacological treatment for insomnia in cancer patients. However, insomnia in cancer can occur with other physical and emotional symptoms to form a symptom cluster. Therefore, to successfully manage insomnia, interventions focusing on single symptoms only may be limited in their effectiveness. Interventions targeting sleep-related symptom clusters have been

developed. The trials were conducted to examine the efficacy of treatments on sleep-related symptom clusters that will be explored in the next section.

2.8.2. Managing insomnia-related symptom clusters

To manage sleep-related symptom clusters among cancer patients, several interventions that use pharmacological or non-pharmacological approaches have been identified (Berger et al., 2013). However, the side effect of drugs makes pharmacological treatments less common in the cancer population. Therefore, non-pharmacological treatments have received more attention from healthcare professionals as well as cancer patients. Non-pharmacological therapies have been used to manage sleep-related symptom clusters among cancer patients include: Cognitive Behavior Therapy, alternative treatments (Berger et al., 2013). Results from 3 recent reviews (Coolbrandt et al., 2014; Kwekkeboom, 2016; Wenli et al., 2016) indicated that up to date only 12 studies had been conducted aiming to test either the feasibility or effectiveness of non-pharmacological treatment in managing sleep–related symptom clusters in cancer patients. Table 14 describes these above interventions.

Table 14. Interventions to improve sleep-related symptom clusters in cancer patients

Authors	Design and sample	Symptom cluster	Treatment groups	Duration of treatment	Findings	Appraisal of study	Quality assessment/	Strength of evidence
Alternative therapy								
(Yeh et al., 2016)	RCT N=31 breast cancer patient, currently off treatment or receiving adjuvant therapy	Pain Fatigue Sleep disturbance	Auricular acupressure Seeds tapes to points targeting pain, fatigue, sleep disturbance Control Sham acupressure with seeds taped to points unrelated to pain, fatigue or sleep disturbances	Once a week for 4 weeks. Follow up: one month	Within-group improvement in symptoms Between groups – no signification difference compared with sham acupressure	Small sample size	Random: Yes Concealment: ? Sham Control: yes Blinding: ? Dropouts accounted: Yes Follow up: Yes Validation of tools: Yes	Due to the small sample size, the design of the intervention is insufficient to provide adequate statistical power to detect an intervention effect.
(Yun et al., 2017)	RCT N=46 breast cancer patient survivors	Depression Anxiety Perceived stress Sleep disturbances	Intervention group: Received mind subtraction meditation (MSM) Control group: Self-management education on breast cancer survivor (SME)	MSM: once a week in eight weeks SME: once a week in four weeks No follow-up time	Between-group: Significant reduction of the symptom cluster	Lacking information about allocation concealment, blinding and no follow up time	Random: Yes Concealment: ? Control: yes Blinding: yes Dropouts accounted; Yes Follow up: no Validation of tools: yes	Due to the small sample size, the design of the intervention is insufficient to provide adequate statistical power to detect an intervention effect.
(Barsevick et al., 2010)	RCT N=276 cancer patients receiving chemotherapy	Fatigue Sleep disturbance	Intervention group: received three sections with content equivalent to Energy and sleep enhancement (EASE) intervention but focused on nutrition and healthy diet Control group: usual care	43-46 days Follow up time: 60 days	Fatigue and patient-reported sleep disturbances were elevated in both groups at baseline and follow-up.	Lacking information about allocation concealment and blinding	Random: Yes Concealment: ? Control: yes Blinding: ? Dropouts accounted: Yes Follow up: Yes Validation of tools: yes	The sample size is large however, lacking allocation concealment and blinding information create a potential bias to the results of study

Authors	Design and sample	Symptom cluster	Treatment groups	Duration of treatment	Findings	Appraisal of study	Quality assessment/	Strength of evidence
(Yennurajalingam et al., 2017)	One group, feasibility trial N=36 advance cancer patients	Depression Anxiety Sleep disturbance Pain	Patients received a 4-week Cranial Electrotherapy Stimulation (CES) intervention	Frequency: NA No follow-up time	CES improved the score of depression, anxiety, pain and sleep significantly	Lack of control group, small sample size, no follow-up time	Random: No Concealment: ? Control: No Blinding: No Dropouts accounted; Yes Follow up: No Validation of tools: Yes	Limitation in study design and its implementation might affect the findings of the study and also decrease the quality level of evidence
(Zengin & Aylaz, 2019)	RCT N= 176 Cancer patients undergoing chemotherapy	Fatigue Insomnia	Intervention group: received one sleep hygiene education session and 16 session of reflexology including initiation of massage, the stimulation of reflex points and the termination of massage Control group:	Reflexology was provided in eight weeks (two sessions per week)	Participant in the intervention group significantly improve sleep quality and fatigue compared with control group	Large sample size, no blinding	Random: Yes Concealment: ? Control: Yes Blinding: No Dropouts accounted; Yes Follow up: No Validation of tools: Yes	The trial design was rigorous; however, study design did not include an active placebo controlling for specific and nonspecific characteristics. Therefore, the authors cannot assess whether the improvement of study outcomes was specific to the intervention
Cognitive Behavioral Therapy (CBT)								
(Kwekkeboom et al., 2010)	feasibility RCT N=30 advanced cancer patient receiving chemotherapy or radiation	Pain Fatigue Sleep disturbance	Patient selection of guided imagery, relaxation and distraction strategies (used daily)	Two weeks No follow-up time	Within-group: no change in symptoms from baseline to week 2, but the reduction in all 3 symptoms at the time the CBT strategy was used	Lack of control group, small sample size, no follow-up time	Random: No Concealment: ? Control: No Blinding: ? Dropouts accounted: Yes Follow up: No Validation of tools: Yes	Limitation in study design and its implementation might affect the findings of the study and also decrease the quality level of evidence

Authors	Design and sample	Symptom cluster	Treatment groups	Duration of treatment	Findings	Appraisal of study	Quality assessment/	Strength of evidence
(Kwekkeboom et al., 2012)	Pilot RCT N=86 advanced cancer patient receiving chemotherapy or radiation n	Pain Fatigue Sleep disturbance	CBT intervention Education about symptom cluster Patient selection of guided imagery, relaxation and distraction strategies (used daily) Control group Waiting list	Two weeks No follow-up time	Between-group: symptom cluster severity was lower in the treatment compared with the waitlist control group at week 2	Small sample size	Random: Yes Concealment: ? Control: yes Blinding: Yes Dropouts accounted: Yes Follow up: no Validation of tools: Yes	Consider the small sample size, the intervention seems less strong for importance effect.
(Dirksen & Epstein, 2008)	RCT N=72 breast cancer patients	Fatigue Trait anxiety Depression Insomnia	Intervention Group: received CBT-I (stimulus control instruction, sleep restriction. Sleep education. Sleep hygiene) Control group: Received Sleep education and sleep hygiene in 6 weeks	Frequency: NA Duration: Six weeks Follow up: Two weeks	Patients in the intervention group had a significant improvement in fatigue. Trait anxiety, depression and insomnia.	Lacking information about allocation concealment and blinding	Random: yes Concealment: ? Control: yes Blinding: ? Dropouts accounted: Yes Follow up: Yes Validation of tools: Yes	Consider the small sample size, the intervention seems less strong for importance effect.
(Fleming et al., 2014)	RCT N=113 insomnia cancer patient	Fatigue Anxiety Depression Insomnia	Intervention Group: received CBT-I Control group: treatment as usual	Once a week in five weeks Follow up: six months	CBT-I appears to offer generalized a benefit to the symptom cluster as a whole and, specifically, is effective in reducing fatigue.	Small sample size and lacking information about allocation concealment, blinding	Random: Yes Concealment: No Control: yes Blinding: No Dropouts accounted: yes Follow up: yes Validation of tools: yes	Consider the small sample size and lacking allocation concealment, blinding, the intervention seems less strong for importance effect.

Authors	Design and sample	Symptom cluster	Treatment groups	Duration of treatment	Findings	Appraisal of study	Quality assessment/	Strength of evidence
(Kwekkeboom et al., 2018)	RCT N = 164 advanced cancer patients receiving chemotherapy	Pain Fatigue Insomnia	Intervention group: Received Cognitive-behavioral strategies (CBS) intervention in nine weeks Control group: cancer education in nine weeks	One face-to-face and 12 CBS provided on MP3 player Control group: One face-to-face cancer education sessions	Participant in the CBS group reported less symptom distress at week 6.	Large sample size, using standard scales to measure symptoms	Random: Yes Concealment: Yes Control: yes Blinding: ? Dropouts accounted: yes Follow up: yes Validation of tools: yes	The trial design was rigorous, however, the control condition may have provided some bias to the results.
Yoga								
(Chaoul et al., 2018)	RCT N = 227 Breast cancer patients	Fatigue Insomnia	TYP: received seven Tibetan yoga training session and required to practice at home for six months STP: received seven stretching training session and required to practice at home for six months UC; received usual care	One a week during four weeks and three booster sessions. Follow-up: six months	Participant in TYP group reported s better PSQI score and actigraphy outcomes at 3 and 6 months compared with UC.	Large sample size, measuring sleep objective and subjectively. High attrition rate	Random: Yes Concealment: Yes Control: yes Blinding: ? Dropouts accounted: yes Follow up: yes Validation of tools: yes	The trial design was rigorous, however, the high attrition rate (22%) which may have the trial' s results being underpowered.
(Lin et al., 2019)	RCT N = 410 cancer survivors	Fatigue Insomnia	Intervention: YOCAS yoga for cancer survivors) Control: usual care	YOCAS in four weeks	YOCAS participant improve fatigue, sleep quality and daytime dysfunction significantly	Large sample size, using standard scales to measure symptoms	Random: Yes Concealment: Yes Control: yes Blinding: No Dropouts accounted: yes Follow up: No Validation of tools: yes	The trial design was rigorous, however, study design did not compare yoga with an active behavioral placebo controlling Therefore, the authors cannot assess whether the improvement of study outcomes was specific to yoga. No follow-up assessment was included to see the sustainability of the yoga effect.

Alternative therapies to treat sleep-related symptom clusters included Auricular Acupressure (AA), meditation, Cranial Electrotherapy Stimulation (CES)[1], consultation on Energy and Sleep enhancement (EASE), and reflexology and sleep hygiene education. Among these treatments, AA, meditation, and CES showed a significant reduction in pain, fatigue and sleep disturbance (Yeh et al., 2016); or depression, anxiety, stress, and sleep disturbances (Yun et al., 2017) among breast cancer patients. These treatments also reduced depression, anxiety, sleep disturbances, and pain among advanced cancer patients (Yennurajalingam et al., 2017). Reflexology and sleep hygiene education also indicated a significant improvement of sleep quality and fatigue in cancer patients undergoing chemotherapy (Zengin & Aylaz, 2019). However, a large-scale randomized trial failed to show the effectiveness of EASE in reducing fatigue and sleep disturbance (Barsevick et al., 2010).

Cognitive Behavioral Therapy (CBT) also brought some positive results in managing a sleep-related symptom cluster. A group of researchers used CBT intervention to reduce the cluster of Pain, fatigue, and sleep disturbance among advanced cancer patients undergoing cancer treatment. The results from the feasibility and pilot study of the intervention indicated the cluster severity was lower in the treatment group compared with the control group after two weeks. However, no significant reduction was found (Kwekkeboom et al., 2012). By targeting the sentinel symptom (insomnia) approach, Cognitive Behavioral Therapy for Insomnia (CBT-I) was used to manage the symptom cluster of insomnia, fatigue, anxiety, and depression in people with cancer. A significant improvement was found in the treatment group in a CBT-I conducted among 72 breast cancer patients after six weeks of intervention (Dirksen & Epstein, 2008), however in a larger RCT among various types of cancer patients, this treatment only reduced fatigue (Fleming et al., 2014). A large-scale RCT using Cognitive-behavioral strategies to reduce insomnia, fatigue, and pain indicated a significant symptom distress reduction in the intervention group at post-treatment (Kwekkeboom et al., 2018)

[1] Cranial electrotherapy stimulation uses a cell-phone size? medical devices that sends a pulsed, weak electrical current (<4mA) to the brain via electrodes placed in the ear lobes.

Results from two recent large-scale RCTs using yoga confirmed its effectiveness in reducing the symptom cluster of insomnia and fatigue in breast cancer and cancer survivors. Yoga indicated its effects in improving both subjective and objective outcome measures in the trial conducted Chaoul et al. (2018). In cancer survivors, YOCAS (yoga program for advanced cancer patients) participant improved fatigue, sleep quality and daytime dysfunction significantly (Lin et al., 2019).

Although past trials had some positive results in the effectiveness of non-pharmacological treatment in reducing sleep-related symptom clusters, these mentioned studies remained limited. First of all, most of them are either feasibility or pilot trials with a small sample size (7/12 studies). The aim of conducting a feasibility/pilot study is examining unforeseen problems, such as the feasibility of recruiting subjects, possible randomization method, assessment procedures, and implementation of the main intervention as well as calculate the effect size for the main study rather than testing hypotheses of the study (Kraemer et al., 2006; Leon et al., 2011). Due to the small sample size of studies, the effectiveness of the intervention is inconclusive. Secondly, half of the study's design did not assess the long-term effects of interventions. Lastly, the majority of studies (10/12 studies) did not provide information about blinding resulting in performance bias and detection bias that affect the finding. All of the above limitations decrease the quality of the evidence on the effectiveness of non-pharmacological treatments in improving sleep-related symptom clusters in cancer patients. In addition, most of the interventions were conducted in breast cancer or advanced cancer populations, with only two study conducted in patients undergoing chemotherapy while this population is experiencing a large number of symptoms as an adverse event of chemotherapy treatment.

As this section demonstrated, there are two approaches in managing sleep-related symptom clusters in cancer population: targeting the core symptom of the cluster (insomnia) or targeting the whole cluster. The approach of targeting the entire cluster seems to be more reasonable, and recent studies have used this approach to develop their interventions. Due to the small number and low quality of previous studies, the effectiveness of non-pharmacological treatments to improve insomnia-related symptom

clusters in cancer patients is inconclusive. Several limitations of previous studies are small sample size, lacking follow up assessment, or lacking blinding. Therefore, well-designed studies are urgently needed to determine an effective non-pharmacological treatment for sleep-related symptom clusters among the cancer population.

Moreover, most current non-pharmacological treatments require trained therapies to deliver the intervention for the treatment to be useful as sleep-related symptom cluster management modalities. Most of them also require more time and effort in administering it. Therefore, it is necessary to examine more effective, self-management, less time-consuming, and more cost-effective interventions in this area. For this reason, self-administered acupressure was chosen for the intervention in this project. Further detail of this treatment is presented in the next section.

2.9. The effectiveness of self-acupressure in managing sleep-related symptom clusters in cancer patients.

Self-acupressure appeared to be an effective treatment for various symptoms, including insomnia in both cancer and none cancer population. The findings from a systematic review of 43 studies indicated the effectiveness of self-acupressure in managing nausea and vomiting as well as pain and dyspnea in various populations (Lee et al., 2011). A review from 18 databased also found self-acupressure tended to be effective in relieving fatigue in cancer patients (Ling et al., 2014). The positive effects of self-acupressure for symptom management further include significant improvements in symptom severity in allergic disease, nausea, and vomiting in cancer, respiratory symptoms, pain in dysmenorrhea, stress/fatigue in healthy people were evident in the systematic review conducted by Song et al. (2015).

Nevertheless, self-acupressure appeared to be an effective treatment for insomnia in cancer patients as demonstrated in section 2.8.1.2. (page 73). Finding from systematic reviews also indicated its promising results in managing insomnia. A systematic review of 30 articles indicated that self-acupressure significantly improves sleep quality compared with the control groups (Hmwe et al., 2016). Besides, a review conducted by Song et al. (2015) also stated self-acupressure significantly improved sleep disturbances in the healthy population. A meta-analysis from 13 studies reported self-acupressure

had clinically meaningful improvement in sleep quality by increasing the sleep duration and reducing sleep latency (finding from the objective measurements) (Waits et al., 2016).

Although all of the above reviews indicated acupressure showed the positive effect of self-acupressure in improving insomnia and other symptoms in various populations, it is difficult to conclude due to the quality of the included studies. All of the mentioned reviews concluded that due to the methodological quality (lacking or no blinding, not using a validated scale, lack of objective measurements for insomnia, sham control design) their evidence did not allow to make a conclusion of the effectiveness of self-acupressure. They also highly suggested high-quality randomized control trials with large sample size and rigorous design are necessary to establish the evidence for self-acupressure as an effective treatment.

Self-acupressure has demonstrated its effectiveness in single symptoms in both cancer and non-cancer populations. However, its effectiveness in managing sleep-related symptom clusters in cancer patients is unknown. Nevertheless, the promising results regarding its effectiveness in improving various single symptoms indicated a possibility of acupressure in managing sleep-related symptom cluster in cancer patients. Recently, a positive results was reported in a study using auricular acupressure (stimulating acupoints on the ear instead of on the body with magnetized pellets/seeds) to manage symptom cluster of pain, fatigue, and sleep disturbances in breast cancer (Yeh et al., 2016). Therefore, studies are needed to explore the efficacy of self-acupressure for insomnia-related symptom clusters in cancer patients.

2.10. Gaps in the current literature

Overall, this review of the literature showed that insomnia is a significant problem among cancer population that needs more attention from healthcare providers. However, studies on insomnia in cancer patients remain with limitations in methodology that lead to many research gaps in the literature. Most of the studies on the prevalence of insomnia were conducted in a small sample size with diverse characteristics of participants. This problem can lead to an inability to conduct sub-group analysis to identify potential risk factors, and this makes the risk factors of

insomnia in cancer patients remain unclear. Besides, the lack of using standardized questionnaires to measure insomnia results in a wide range of insomnia prevalence in the literature. The majority of previous studies also did not report sleep parameters (e.g. total sleep time, sleep efficiency, number of nights awaken) of insomnia patients due to lacking of objective measurements.

In the studies on the sleep-related symptom cluster, the relationship between insomnia and other symptoms is still not clear. Due to the nature of cross-sectional design, previous studies fail to explore which symptom occurs first, whether symptoms in one cluster will aggregate over time and how the cluster will change along with the disease. Moreover, studies in different cancer populations suggested different sleep-related clusters, which lead to the impossibility to confirm a sleep-related SC presented in a specific cancer population. And only a small number of studies explored sleep-related symptom clusters in patients undergoing chemotherapy, while this population often experiences the highest number of symptoms due to their treatment.

Regarding studies on non-pharmacological treatment for insomnia in cancer patients, CBT-I is considered as the most effective intervention to improve insomnia. Its efficacy in improving insomnia and other co-occurring symptoms was shown in two RCTs with limited sample size. Alternative treatments and exercise interventions provided promising results. However, due to limitations in the study's design (small sample size, do not include or not proper control group) as well as the small number of trials, their effectiveness on insomnia is inconclusive. Among the above interventions, the majority of them required the physical presence of health care providers. It was costly, time-consuming as well as required effort from participants to receive the treatment except for self-acupressure. However, just a small number of studies was conducted using this approach in cancer patient to improve insomnia.

Regarding studies on non-pharmacological treatment for sleep-related symptom clusters in cancer patients, due to the limitations of trials in this field, the efficacy of non-pharmacological treatments for insomnia is inconclusive. The disadvantages of previous work include the small sample size, lacking the follow-up assessment to explore the long-term effect of the intervention, lacking the blinding design that can

lead to creating performance bias and detection bias. They also focus on some specific cancer populations (advanced cancer and breast cancer) that limited the ability to apply the treatment to other cancer populations. Nevertheless, while most current treatment not only required the physical presence of healthcare providers to deliver but also consume more time, money, and effort for the patient to administer. Hence, there is sufficient evidence to support the development of a self-management intervention that can potentially improve the sleep-related symptom clusters. In addition, there is no evidence to support the effectiveness of a self-acupressure intervention that can potentially improve sleep-related symptom clusters in cancer patients.

2.11. Conclusions of the literature review

Finding from the literature indicated that there is a need to develop an intervention using self-acupressure to manage sleep-related symptom clusters among participants undergoing chemotherapy. However, before developing such intervention, a cross-sectional survey is needed to address these gaps related to insomnia among cancer patients undergoing chemotherapy. This survey also plays an important role in the development of the intervention protocol by identifying what variables can potentially affect the results of the intervention that need to be controlled or managed (i.e., how variables and sample characteristics can potentially affect insomnia). Besides, the study also helps to clarify whether an insomnia-related SC is formed as well as if the outcome measurements are reliable in the targeted population.

Since this doctoral project aims to develop an intervention to manage sleep-related symptom clusters in cancer patients, the Medical Research Council (MRC) framework for developing and evaluating complex interventions is employed to guide the development of the project. The application of the MRC framework to this doctoral project and the theoretical frameworks included in this thesis are presented in the next chapter.

CHAPTER 3. THE METHODOLOGICAL AND THEORETICAL FRAMEWORKS UNDERPINNING THE DEVELOPMENT OF THE PROJECT

3.1. Introduction

The results from our review indicated the need to develop an intervention using self-acupressure to manage insomnia-related symptom clusters among cancer patients. The Medical Research Council's framework for Developing and Evaluating Complex interventions (MRC) is being used as a guideline for the development and evaluation of an intervention protocol. The chapter begins with the application of the MRC framework for the development of the intervention. Afterward, the theoretical frameworks for the two studies included in this doctoral project are presented. The overall aim of the project is shown in the last section of this chapter.

3.2. The application of the MRC framework for the development of the intervention

3.2.1. Introduction to the MRC framework

A complex intervention has been defined as an intervention that contains several interacting components, and this kind of intervention has been used widely in healthcare research (Craig et al., 2008). The Medical Research Council (MRC) has published a framework that guides the development, evaluation, and implementation of an intervention. The MRC framework has four key elements include the development phase, feasibility and piloting phase, evaluation phase, and implementation phase (Figure 1).

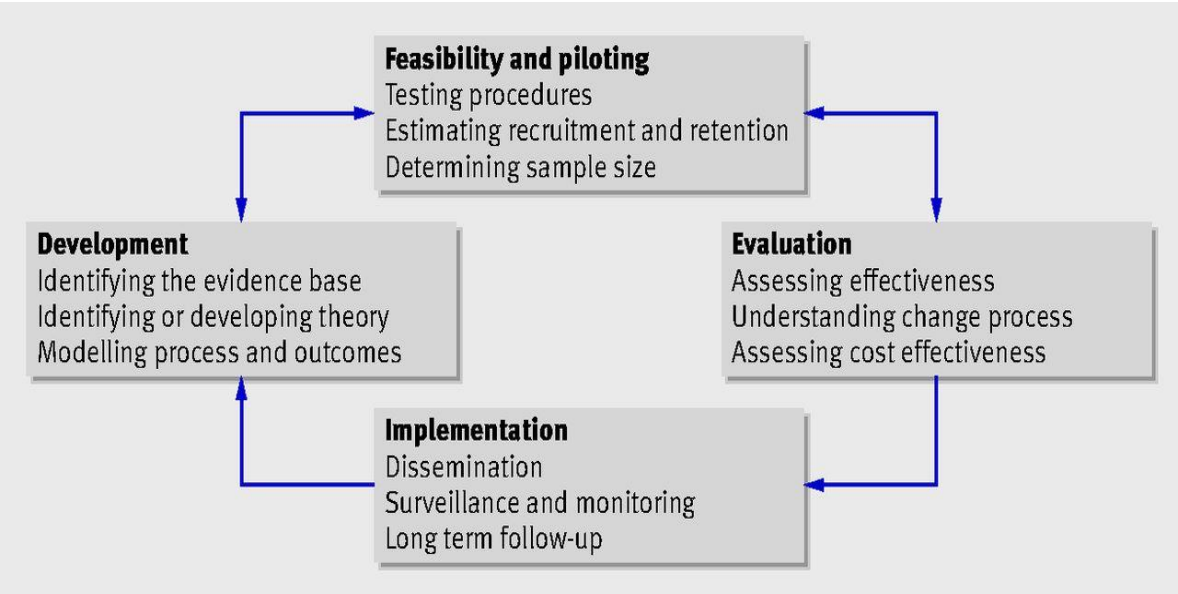

Figure 1. The MRC's framework for Developing and Evaluating Complex Intervention

In the first phase of the MRC framework is the development of the intervention. In this phase, evident and the related theory of the intervention must be identified, and the process and outcomes should also be modeled. The second phase is the feasibility and piloting phase. The procedures of the intervention are tested to make a critical estimation of the future full-scale randomized control trial (e.g., recruitment rate, sample size). In the third phase - evaluation phase, the effectiveness of the intervention is assessed by conducting a full-scale randomized control trial. In the implementation phase, the intervention is disseminated, and also the long-term follow up, surveillance, and monitoring of its effectiveness should be conducted. The four phases are in a cycle in which the study can move backward and forward between the phases. If a problem is identified that makes the study impossible to move to the next stage, the study must be revised and can move back to the previous phase.

3.2.2. Application of the MRC framework in the doctoral project

This doctoral project covers the first two phases of the MRC framework, which are the development and testing the feasibility. In the first phases, two research works have been conducted: the survey and the development of the acupressure protocol. In the second phase, the feasibility trial is conducted.

The cross-sectional survey is conducted to ascertain the prevalence of insomnia among Vietnamese cancer patients, to determine factors that influence the result of the intervention that need to be controlled (e.g., patient's characteristics, treatment-related factors), to determine the correlation between insomnia and other symptoms, to confirm an insomnia-related symptom cluster, and to make the decision on choosing the outcome measurement for the future intervention study. Also, available systematic reviews are used to develop the self-acupressure treatment protocol and sham acupressure protocol.

In the second phase of the MRC framework, the feasibility study is implemented. The objectives of the feasibility study are to assess the feasibility, acceptability of the intervention, and make estimations about the effectiveness of the intervention. The process of the current study design following the *MRC framework for Developing and Evaluating Complex Interventions* is presented in **Figure 2**. The method of the feasibility study will be displayed in the next chapter. In the following sections, the conceptual framework of the cross-sectional survey and the feasibility study are reported.

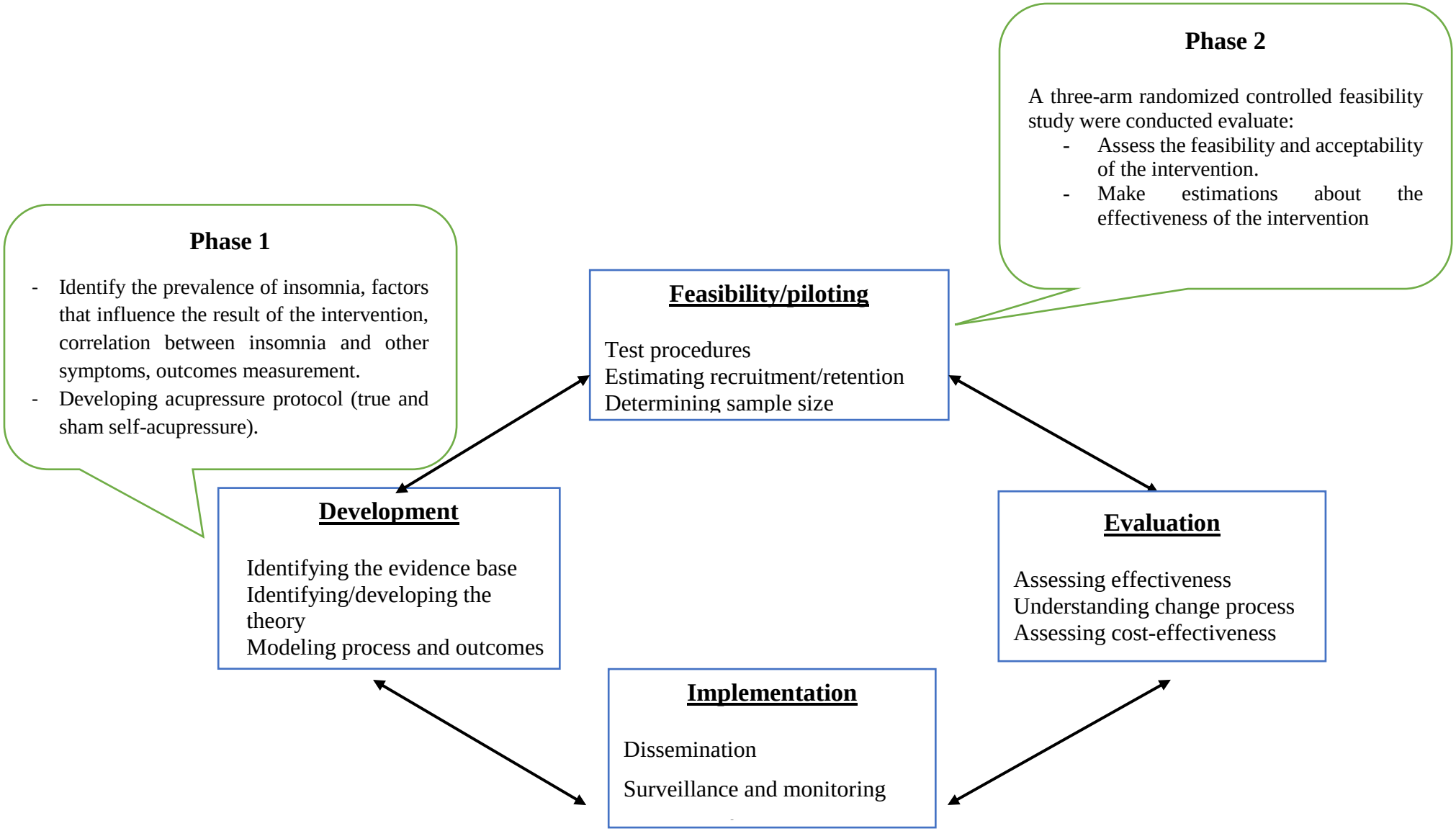

Figure 2. Process of study design following the MRC framework for Developing and Evaluating Complex Interventions

3.3. The development of the self-administered acupressure intervention

3.3.1. The theoretical framework of the cross-sectional survey and the feasibility trial

The first phase of the MRC framework is identifying the evidence base and developing theory for the self-acupressure intervention. Before the development of the self-acupressure treatment protocol, a survey must be done to serve as a preparatory study. We adopt the theory of unpleasant symptoms (TOUS) and findings for literature reviews to structure the theoretical framework of the cross-sectional survey. While the theoretical framework for the feasibility study was developed based on TOUS and related Traditional Chinese Medicine theory. In this section, the application of TOUS and related TCM theory in the two studies are presented.

3.3.1.1. Introduction to the Theory of Unpleasant Symptoms (TOUS)

The Theory of Unpleasant Symptoms (TOUS) guided the study (Lenz et al., 1997). The Theory of Unpleasant Symptoms described the Unpleasant symptoms in three components: Symptoms, the influencing factors which cause or affect the nature of the symptoms experienced, and performance outcomes associated with the symptom experience (Lenz & Pugh, 2003). The model proposed that symptoms can occur alone or in association with others. Every symptom four dimensions: timing (frequency, duration, and pattern of symptom's occurrence) distress (degree the symptoms bother) intensity (severity of the symptoms) and quality (nature of the symptoms). Influencing factors are determinants of symptoms. They are classified as: Psychologic, physiologic, and situational variables, and they relate to each other and influence symptoms. The third component of TOUS is Performance. Performance is the result of the symptoms experienced, which includes functional and cognitive activities. It is assumed that more

numerous or more severe symptoms, the worse the performances manifested. The model asserted that its components are related, and the correlation might be reciprocal. The influencing factor determines symptoms, symptoms alter the patient's performance, and the performance can also conversely impact symptoms and the influencing factors. The figure below depicts the TOUS

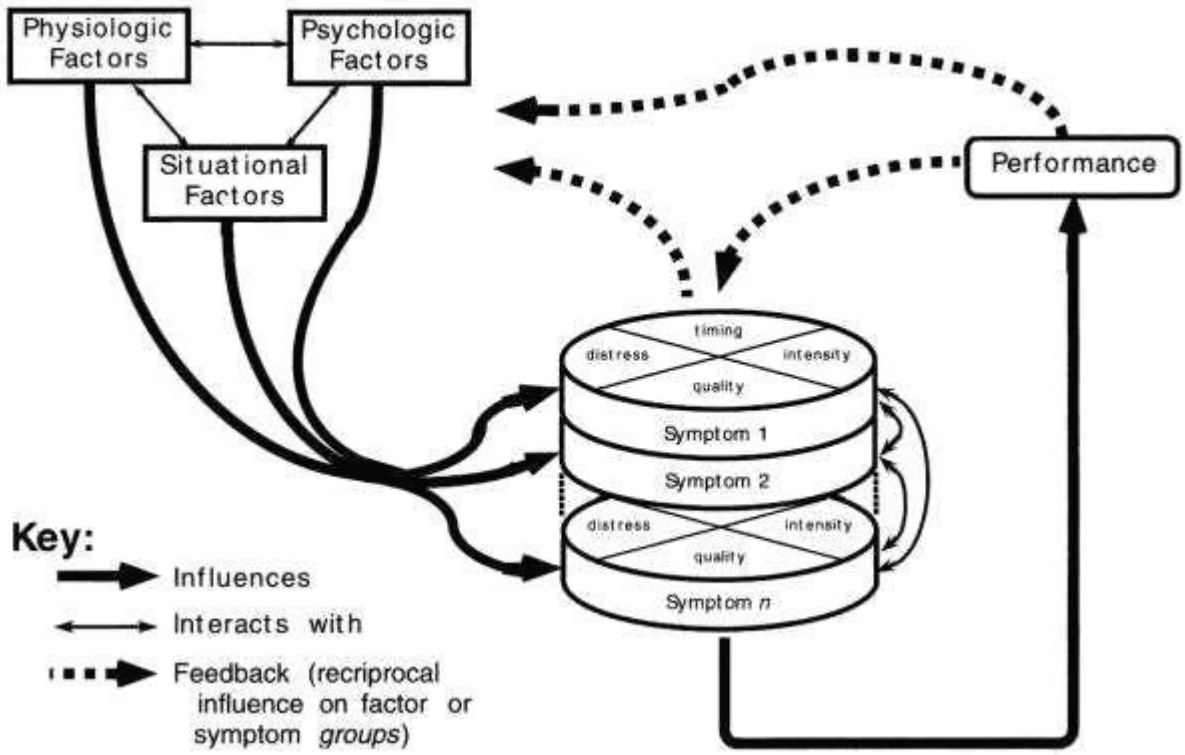

Figure 3. The Theory of Unpleasant Symptoms (Lenz & Pugh, 2003, p. 170)

3.3.1.2. Theoretical framework of the cross-sectional survey

The reason for choosing this TOUS for the survey is the assumption that insomnia can be concurrent with other symptoms, and they are interrelated to form symptom clusters. And these symptoms cluster are influenced by some factors such as gender, age, cancer

type, cancer stage. These symptom clusters also affect the patient's performance. Our assumption is fit with the concepts of the TOUS. In this study, physiologic factors that potentially influence insomnia are gender, age. Potential Psychological factors potentially influence insomnia are depression and anxiety. Potential situational factors that influence insomnia are cancer type and cancer stage, number of completed chemo-cycle. The performance was defined as the patient's quality of life. For this study, insomnia is considered the primary symptom, and other symptoms are considered as concurrent symptoms. Insomnia and other symptoms will be assessed in three aspects: timing (frequency and duration) distress (how the symptoms bother) intensity (severity). To measure insomnia, the Insomnia Severity Index (ISI) and a sleep diary were used. Other symptoms were measured by the Memorial Symptom Assessment Scale (MSAS), and quality of life was measure by the Function Assessment of Cancer Therapy (FACT-G). Detail of measurement will be detailed in the instrument part, which in chapter 4, section 4.2.5 page 126.

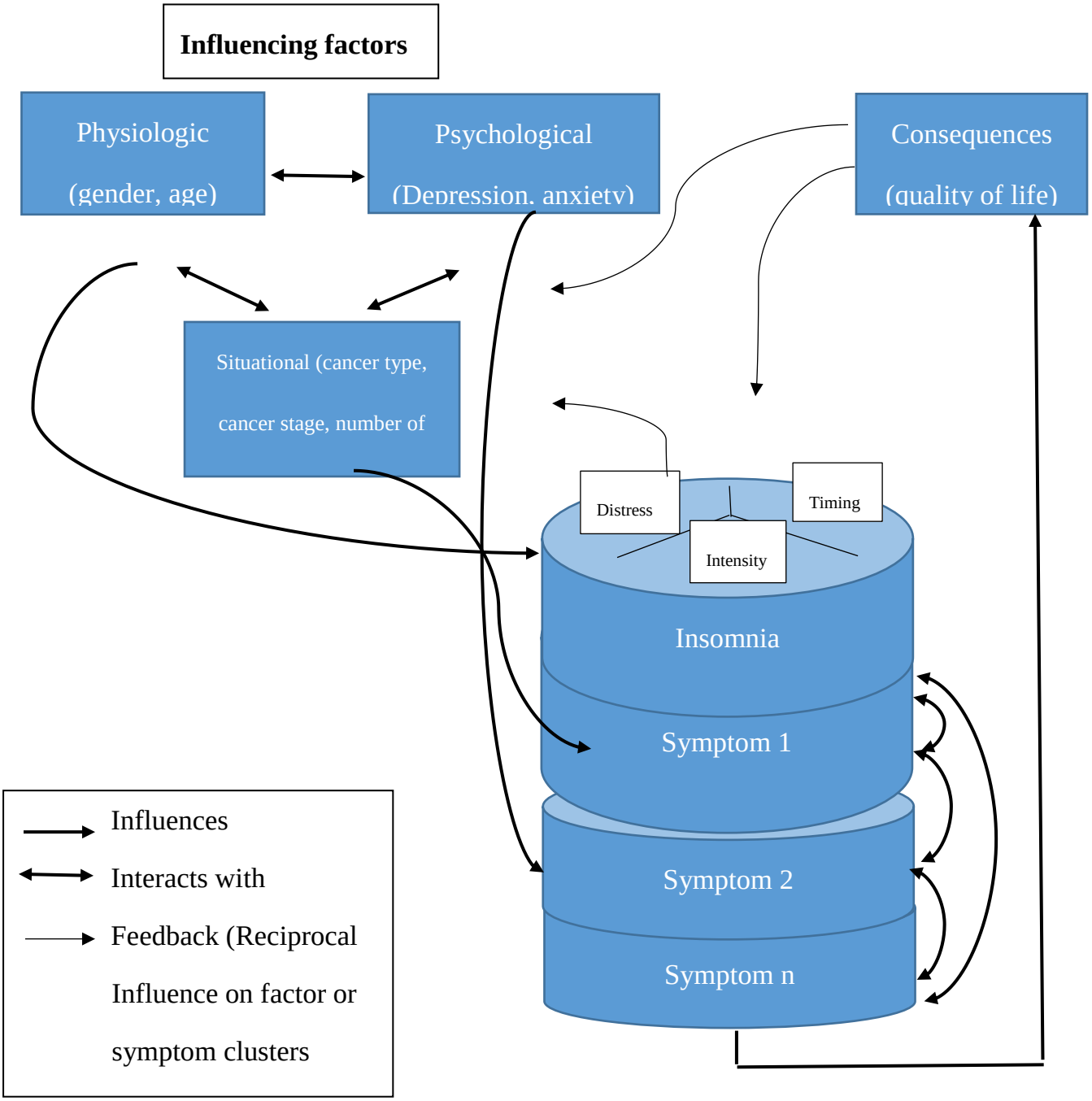

Figure 4. Conceptual Framework of the cross-sectional survey

3.3.1.3. Theoretical framework of the self-administered acupressure intervention

In this feasibility trial, the Theory of Unpleasant Symptoms (TOUS) developed by Lenz et al. (1997) and Traditional Chinese Medicine theory are used to explain how self-acupressure can help in reducing the severity of symptom cluster and model the outcome of the trial. According to the Traditional Chinese Medicine (TCM) theory, *Qi*, blood circulation to the organs, *Yin*, and *Yang* are four essential components of the human body (Kim et al., 2016). An individual's heathy status is the result of the balance between these components (Chen et al., 2010). *Qi* is a basic concept of TCM, which has no direct equivalent to western medicine (Sakagami, 2012). It represents the vital energy of the body (Hopwood, 2004). If the *Qi* of an organ is weakened or excessed results in the insufficiency of blood circulation to the organs, the function of this organ will be affected and causing symptoms (Li, 2007, p. 1023; Stux, 2003). *Yin and Yang* are two interdependent opposites in the human body (Yuan et al., 2006). The health of the human body is indicated by the balance between *Yin and Yang*. Symptoms are caused by the excess of *Yin* leads to the deficiency of *Yang* or excess of *Yang* leads to the deficiency of *Yin* (Hong, 2016). Therefore, pathogenic changes in *Qi*, the insufficiency of blood circulation to the organs, and the imbalance of *Yin* and *Yang* are the causes of the sleep-related symptom cluster and categorized as "influence factors" in the TOUS

This trial tackles the "influence factors" by using self-acupressure. Hence, acupoints that are selected in the treatment protocols must have the effect to improve the blood circulation in the organs that causes the sleep-related symptom cluster. Self-acupressure aims to harmonize the flow of *Qi* by dissolving blockages and stagnation in the organ, and balance the condition of excess or deficiency blood circulation to the organs, thus

achieve an undisturbance function (Stux, 2003). By enhancing *Qi*, the blood circulation to the organs is improved and the balancing of *Yin* and *Yang* is restored (Li, 2007, p. 1023), thus improve the sleep-related symptom cluster. Improving this symptom cluster will cause an effect on the patient's "performance." Therefore, the outcomes of the intervention are the "symptoms" and "performance" According to the TOUS, symptoms are measured in four aspects. However, measuring one aspect of symptoms is also "valid and informative for assessing the effectiveness of an intervention" (Lenz & Pugh, 2003, p. 174). Hence, in this study, we measure the intensity, which refers to the severity of the symptoms. Several specific and standardized measurements will measure the severity of individual symptoms in the cluster. Since the symptoms in the cluster co-occurred together and correlated to each other, the symptoms severity at a cluster level will also be measured. The "performance" in the TOUS model is defined as the patient's quality of life in this study. The theoretical framework of the trial is depicted in **figure 5**.

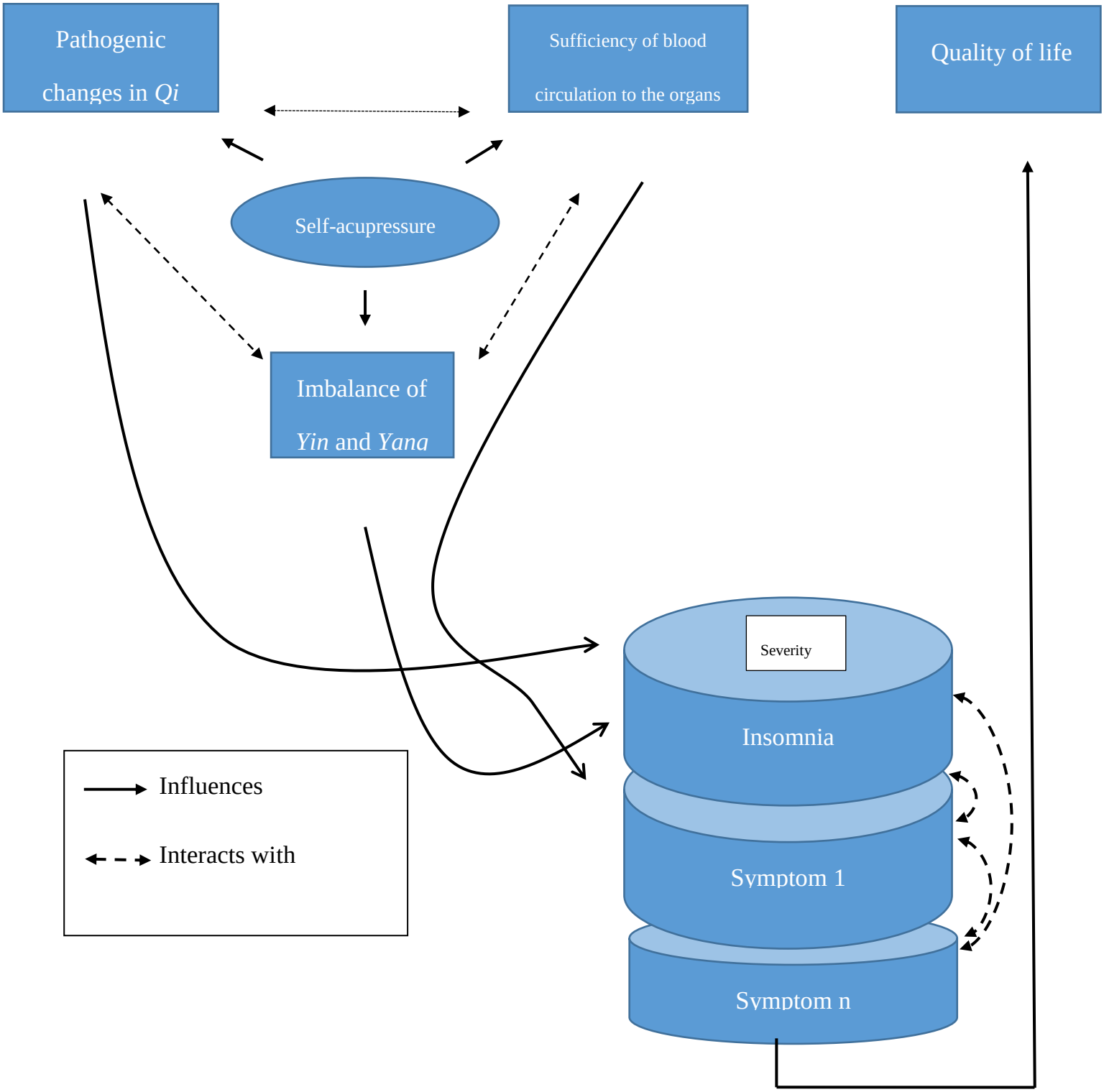

Figure 5. The theoretical framework of the intervention

3.4. The aims of the doctoral project

Based on the finding from literature, this doctoral project was carried out with the aims were:

1. To ascertain the prevalence of insomnia and to identify the risk factors and correlations between insomnia and other symptoms among cancer patients receiving chemotherapy in Vietnam (study one). Data from this study would highlight the extent of the problem and offer information that should be considered in the development of an intervention trial.
2. To develop a self-acupressure treatment protocol.
3. To test the feasibility of an intervention using self-acupressure to manage the an insomnia-related symptom cluster that will be identified from study one.

To achieve the aims of the project, two studies have been conducted. Firstly, a cross-sectional survey was conducted to explore the insomnia problem among cancer patients (including the prevalence, risk factors, and correlations with other symptoms), which will be presented in the next chapter. The development of the self-acupressure treatment protocol will be reported in chapter 5, and the feasibility trial to examine the feasibility of self-acupressure intervention will be detailed in chapter 6.

CHAPTER 4. INSOMNIA AMONG CANCER PATIENT UNDERGOING CHEMOTHERAPY IN VIETNAM: PREVALENCE, ASSOCIATIONS WITH OTHER SYMPTOMS AND IMPACT ON QUALITY OF LIFE.

4.1. Introduction

As discussed in chapter 2, publications on insomnia and sleep-related symptom cluster in cancer patients, especially those who are undergoing chemotherapy, remain limitations that need further investigation to fill the knowledge gaps. Based on search gaps were identified, and follow the MRC framework, we conducted a cross-sectional study on insomnia among cancer patient undergoing chemotherapy. Our survey is the first study conducted in Vietnam on this topic with advantages in the design such as an appropriate sample size, using a standardized tool to measure insomnia and other symptoms, or using objective measurement to measure insomnia. This survey was done to fulfill the first aim of the doctoral project. It also serves as preparatory work for the intervention to improve sleep-related symptom clusters in Vietnam, if such a cluster is identified. These objectives of the survey are to (1) determine the prevalence and the severity of insomnia among cancer patients receiving chemotherapy, (2) clarify the possible risk factors of insomnia in cancer patients, (3) identify the sleep-related symptom cluster, (4) assess the impact of insomnia on patient's quality of life, (5) evaluate the feasibility and appropriateness of objective measurement for insomnia in cancer patients. This chapter consists of four sections, which include this introduction section. The methods of the cross-sectional survey are reported in section 4.2 and 4.3. The results of the survey are presented in section 4.4. Finally, its contributions to the design of the feasibility study are considered in section 4.5.

4.2. Methods

4.2.1. Study design and settings

A cross-sectional survey was conducted in 3 large cancer hospitals in North of Vietnam: Vietnam National Cancer Institute, Bach Mai hospital, and Hanoi Oncology Hospital. All of them located in Hanoi. Vietnam National Cancer Institute: This is the largest cancer hospital in Vietnam, the hospital has 1500 beds and in charge of providing cancer treatments for patients from North and Middle of Vietnam. On average, the hospital receives about 1100 patients every day. Bach Mai hospital is one of the three largest hospitals in Vietnam, the cancer department in this hospital has 200 beds and receives about 400 patients per day on average. Hanoi Oncology Hospital is a public hospital in charge of providing cancer treatment for patients in Hanoi. The hospital has 500 beds and receives about 300 patients per day.

Participants: The participants are patients receiving chemotherapy at the chemotherapy units.

Inclusion criteria:

- Patients are currently undergoing chemotherapy.
- Age 20 – 84 years' old
- Able to understand, read and write Vietnamese
- The Karnofsky Performance Scale Index ≥ 80, which means the patients can carry on normal activity with effort (Oken et al., 1982). This indicator was chosen to ensure patients can participate in the later feasibility study.
- Have signed informed consent to the study.

- Exclusion:
    - Presence of severe cognitive impairments (e.g., Alzheimer disease, dementia, Huntington's disease) or severe psychiatric disorder (e.g., psychosis, schizophrenia, major depression, and bipolar disorder). Those patients are being excluded because they can't remember things and adherence to the study protocol.
    - Patients with a history of insomnia before the diagnosis of cancer. Those patients are being excluded since the aim of the survey is to determine cancer-related insomnia prevalence.
    - Presence of a sleep disorder other than insomnia which has no evidence of being able to treat with self-acupressure (e.g., sleep apnea, narcolepsy, restless legs syndrome, rapid eye movement sleep behavior disorder)
    - Patients have been received insomnia treatment for at least one month

4.2.1. Sample size estimation

The sample size for this study was calculated by using the Krejcie and Morgan (1970) formula. The sample size was calculated as follows:

$$n = Z^2_{(1-\propto/2)} \quad \frac{p(1-p)}{d^2}$$

When n is the required sample size, Z is the statistic corresponding to the level of confidence (95%), *p* is the expected prevalence which is 70% (obtained from a previously unpublished study on the prevalence of insomnia among cancer patients in Vietnam), and d is the degree of accuracy expressed as a proportion (0.06). Therefore, the sample size for the cross-sectional study is 224 participants.

$$1.96^2 \; x \; \frac{0.7(1-0.7)}{0.06^2} = 224$$

4.2.2. Ethical considerations

The study received ethical approval from the Human Subject Ethics Board, The Hong Kong Polytechnic University, Hong Kong SAR (Approval reference number HSEARS20170428003), and Hanoi School of Public Health (Approval reference number 2017.16.HSPH.16.RRDHN). This study has followed the ethical principles for research that involves human subjects which are: autonomy, non-maleficence, and confidentiality (Beauchamp, 2009).

Autonomy

The principle of autonomy refers to the right for participants to make their own choice of participating in the study (Beauchamp, 2009). In this study, potential subjects were given information sheet which included the purpose, objectives, and study procedures (Appendix 11). Voluntary participation was assured, and participants were assured the services that their treatment in the hospital would not be affected by their decision of participating or not participating as well as withdraw from the study. Participants were informed about the right to withdraw from the study at any time without any harm.

Non-maleficence

The non-maleficence principle indicates the study should not put subjects in any harm (Beauchamp, 2009). The nature of the cross-sectional survey its self does not cause any harm to participants since patients only require to answers questionnaire and wear Actigraphy for three days. The actigraphy used in this study received the FDA approval,

has been used in thousands of research worldwide, and cause no harm to participant's health (https://www.actigraphcorp.com/clinical-trials/)

Confidentiality

To ensure subject confidentiality, the following steps were taken:

- Personal information of the participants was replaced with research identification code - Access to master code lists for key code is limited to only Ph.D. student and research assistance.
- Contact list, recruitment records or other documents that contain personal information of the participants will be destroyed when no longer required for the research (3 years after finishing data collection)
- Files containing electronic data were password-protected and encrypted (at least when data are transferred or transported).
- Research data were stored securely in locked cabinets.
- Electronic data were stored on password-protected computers or files.
- Files containing electronic data were closed when computers will be left unattended.
- Consent forms were stored securely in locked cabinets, separately from the research data.

Ethical concerns regarding paying participants

Paying for human subjects for participating in scientific research is a common practice that has been reported for over 100 years (Levine, 1979). Several ethical concerns have been raised regarding this issue, among which, coercion is considered as the most common concern (Grady, 2005). However, in this study, the amount of 30 HKD was

not an incentive since the purpose of the payment is for express mail service to return the outcomes assessment forms to the Ph.D. student. This is a small amount, so it does not attract or motivate participants to the study.

4.2.3. Outcome Measurements

To avoid the limitation in measurement (not using standardized questionnaires and objective measurement for sleep) from previous studies as discussed in Chapter 2, in this study, we used a combination of Objective (actigraph) and Subjective (Questionnaire) to measure sleep problem in participants. We also measured other symptoms that patients may experience during their chemotherapy to identify the potential insomnia-related symptom cluster.

Insomnia

Subjective measurement

The Insomnia Severity Index was used in this study. Reason for choosing this scale because it is specially designed for insomnia and briefer in comparison with PSQI. Nevertheless, the scale can provide information regarding the severity of insomnia. The ISI can be used as a screening instrument or as a treatment-outcome measure (Buysse et al., 2006; Morin et al., 2011). According to the authors of the scale, a total score of *15 and above* indicated the patient *has insomnia*, with a total score of *15 to 21* indicated *moderate insomnia* and *22 or above* indicated *severe insomnia* (Morin, 1993). This cut-off point detects a majority of cancer patients with insomnia, and this score obtained the sensitivity of 51.3% and the specificity of 90.7% (Savard et al., 2005). This instrument had been validated and translated into Vietnamese (Long et al., 2016). In this study, the ISI had Cronbach's $\alpha = 0.92$.

To further assess sleep onset and sleep efficiency from the participants, a three days Sleep log was also included in the study. This sleep log was completed by participants, and the components of sleep log are the following

- Time the individual went to bed.

- Time the individual got out of bed.

- Time the Actigraph was removed from the participant's wrist.

- Number of night awakenings

The sleep log help in identifying misclassified sleep or wake during the recording of objective measurement (motionless activities such as watching a movie, sit in a car, etc.)

b. Objective measurement

In this study, we also used Actigraph to measure these sleep parameters objectively:

- Total sleep time (TST): The period of time measured from sleep onset during nighttime to the final awakening
- True sleep time (TuST): The period that patients actually sleep.
- Wake after sleep onset (WASO): period of time spent awake since after the sleep onset, calculated by taking TST minus TuST
- Mid-sleep awakening: The number of awakenings during a sleep period
- Sleep efficiency: calculated by dividing TuST (at night) by TST (at night) multiplied by 100%.

We used wrist Actigraph wGT3X-BT manufactured by Actigraph company. The data were collected in 1-minute epochs and scored with the ActiLife6 version 6.13.3 software using the Cole-Kripker algorithm, and the sampling rate was 30 Hz. The patient was asked to wear the Actigraph for three continuous nights. The duration of wearing an actigraph in past studies varied, but for effective time management, we decided to measure sleep parameters for 72 hours as recommended by the American Academy of Sleep Medicine (Ancoli-Israel et al., 2015).

Other symptom assessment and Quality of life

The Memorial Symptom Assessment Scale (MSAS) developed by Portenoy et al., (1994) was used to measure symptoms. The original version of the MSAS was developed for the cancer population. The MSAS measures 32 symptoms that patient experiences during the previous week. Twenty-four symptoms are evaluated in three aspects (frequency, severity, and distress), and eight symptoms are evaluated in two aspects (severity and distress). Patients were also allowed to report other symptoms by the three last open items. Patients were asked for rating how often, how severe, and distress the symptoms were during the past week. Four-point Likert-type scales were used to record the frequency and the severity of symptoms. The frequency items ranged from one (rarely) to four (almost constantly), and the severity items ranged from one (slight) to four (very severe). Another five-point Likert-type scale was used to evaluate the symptoms of distress, ranged from 0 (not at all) to four (very much). The symptom scores include the total sum of all items and four subscale scores:

- The Psychological Symptom Distress (PSYCH) subscale score is the average of the symptoms score for six symptoms: feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping, and difficulty concentrating.

- The physical symptom distress (PHYS) subscale score is the average of the symptoms score for 12 symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth. Nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness.
- The Global Distress Index (MSAS-GDI) is the average of the single dimension score for ten symptoms: The frequency score for the feeling sad, worrying, feeling irritable and feeling nervous and the distress score for lack of appetite, lack of energy, pain, feeling frowsy, constipation and dry mouth.
- The total MSAS score is the average of the symptom score for all 32 symptoms

According to an initial validation of MSAS, the total MSAS score can provide information about symptoms distress. Still, for clinical significance, the MSAS-GDI has more meaning than the total MSAS score (Portenoy et al., 1994). The scale has been validated and translated into Vietnam (Long, 2010). In this study, the internal consistency was α=0.92, and the Cronbach's α for the subscales was: α = 0.8 for PSYCH subscales, α = 0.83 for PHYS subscale, and α = 0.85 for MSAS-GDI subscale.

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) developed by was used to measure depression and anxiety that the patient is experiencing. The instrument has 14 items; each item has a Likert response scale. Scores are constructed by summation of each scale and total score for the scale. There are two subscales: depression (HADS-D, seven items) and anxiety (HADS-A, seven items). A total score of 11 and above for each of the sub-scale indicated the patients had the symptoms (Zigmond & Snaith, 1983). This is the optimal cutoff point to detect patients with depression and anxiety

with a sensitivity and specificity of 0.8 (Bjelland et al., 2002). A total score of *11 to 14* for each of the sub-scale indicates the patients had *moderate depression/anxiety* while *15 to 21* indicate *severe anxiety/depression* (Bjelland et al., 2002; Stern, 2014). This instrument has been translated into Vietnamese (Long, 2010). In this survey, the Cronbach's alpha of the scale was 0.87, for anxiety subscale 0.86 and for depression subscale 0.76.

Quality of life

The Functional Assessment of Cancer Therapy-General (FACT-G) is used in this study to assess the quality of life of participants. This scale measures four domains of quality of life: Physical well-being - PWB (7 items); Social/family well-being - SWB (7 items); Emotional well-being - EWB (6 items) and Functional well-being - FWB (7 items). The questionnaire consists of 27 items. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). The FACT-G meets or exceeds all requirements for use in cancer clinical trials, including ease of administration, brevity, reliability, validity, and responsiveness to clinical change (Cella et al., 1993). This instrument has been translated into Vietnamese by the FACIT system. In this study, the Cronbach's alpha for the scale was 0.89 and for EBW subscales was 0.78, FWB = 0.82, PWB = 0.81 and for SWB was 0.82.

4.2.4. Procedures

Data were collected by the Ph.D. student and two research assistants. After the study grants ethical approval, researchers came to each hospital to ask for permission to collect data. Before the collecting data process took place in a particular hospital, researchers worked with the hospital authorities to obtain a list of all cancer patients

who were matched with inclusion and exclusion criteria. Researchers approached eligible patients in their rooms, invited them to participate in the study, and asked them to answer the screen question to exclude patients with a history of insomnia before cancer diagnostic insomnia. The screening question for insomnia was "Did you experience any sleep problems in the past month? If the patient's response was "yes" then they were asked the second question: how about before cancer diagnosis? If the answer was "yes" which reflected a history of insomnia, then the patient was excluded from the study. If the patient was eligible for the study, the researcher invited and gave them the information sheet of the study. If the patient agreed, researchers gave them the consent form to complete. By signing the consent form, the patients agree to answer the questionnaires, as well as to allow the researchers' permission to access their medical records.

Data were collected on the last day participants stayed in the hospital. The demographic data and contact information of the participant were collected. Afterward, the investigators gave the participants the questionnaires (ISI, MSAS, FACT-G, HADS, sleep log) and explained how to complete all the questionnaires. He/she also instructed them on how to use the Actigraph and complete the sleep log. Afterward, patients were asked to wear the Actigraph for three consecutive days and return the questionnaire and the Actigraph via express mail service to the principal investigator. A small amount of 30 HKD was given to participants for the express mail service charge.

4.3. Data Analysis

Data were analyzed by SPSS 20.0. Data was clean and checked for normality before being analyzing. Detail of approaches to analysis is considered in the following sections.

4.3.1. Data cleaning

Categorical data were checked by generating frequency counts to determine the frequency of the coding as well as missing values for each variable. Continuous data were checked by generating descriptive statistics (histograms or plots) to analyze means, minimums, and maximums to ensure the range of value is appropriate. These approaches allow the researcher to identify mistakes in codes, missing data, as well as ascertain if values out if the possible ranges have been entered (Portney, 2015)

4.3.2. Assessment of data normality

Data of participant's ISI, HADS, MSAS, FACT-G scores were checked for normal distribution using the Shapiro-Wilk test, provided by SPSS software. The Shapiro-Wilk test was chosen because it is based on the correlation between data and corresponding normal score and provide better power than other tests (Peat & Barton, 2008). This test is also recommended by statisticians for a sample size of under 2000 subjects (Ghasemi & Zahediasl, 2012). The results of normality indicated the data regarding participant's ISI, HADS, MSAS, FACT-G scores are normal.

4.3.3. Missing data management

There was no missing data regarding the participant's demographic and clinical characteristics, ISI, HADS, and MSAS. Although all participants returned the FACT-G but 45 participants (21.1%) did not respond to the item FACT-G-GS 7 – "I am satisfied with my sex life." However, the missing data of this item does not affect the total score of FACT-G or subscale score (according to the *FACIT Administration and Scoring Guidelines*). Hence, no missing data handling method is needed for this item.

Data about sleep parameters of 18 patients (8.4%) were lost due to losing 01 actigraph, and 01 Actigraph did not work. The missing data for the sleep parameters is less than 10%, which is considered as inconsequential and unlikely to cause biases to the statistical analysis (Bennett, 2001; Schafer, 1999). As such, no missing data handling method is applied for this data.

4.3.4. Statistical analysis

In this survey, both descriptive statistics and inferential statistics were included. The significant level was set at $p<0.05$. The data were analyzed using different methods regarding the types of variables.

4.3.4.1. The prevalence and severity of insomnia among participants. Statistical analysis of participant's demographic, clinical characteristics and the prevalence and the severity of insomnia

The descriptive statistics were used to report the insomnia prevalence and severity (number of participants and related percentage). It was also used to analyzing the participant's demographic and clinical characteristics.

4.3.4.2. Identify risk factors for insomnia

To identify risk factors for insomnia, analysis testes were used to determine any difference between ISI score or insomnia occurrence and participant's demographic and clinical characteristics. The significant difference between ISI score and participant's gender, depression, and anxiety occurrence was determined by the T-test, which was designed to compare two means, while χ^2 test which was designed to test the relationship between insomnia occurrence and these variables (Portney, 2015). If any

significant differences were found, Pearson-correlation would be conducted to see the association between ISI score and those variables, the correlation value less than 0.39 was classified as weak, 0.4 to 0.59 was moderate, 0.6 to 0.79 was strong, and 0.8 or greater was very strong (Evans, 1996). The significant differences between ISI score and insomnia prevalence with other participant's demographic and clinical characteristics were determined by one-way ANOVA and χ^2 test (Portney, 2015).

4.3.4.3. Identify the sleep-related symptom clusters

Several analytical methods have been used to identify symptom clusters such as correlation, factor analysis, principal component analysis, cluster analysis of symptoms and subjects, latent class analysis, and structural equation modeling. Among these methods, principal component analysis (PCA) is commonly used to identify symptom clusters in cancer patients (Kim et al., 2013). In this survey, PCA was employed to identify the sleep-related symptom cluster. Due to the nature of the cross-sectional survey, we identified the sleep-related SC based on the correlation between insomnia and other symptoms. Hence, The PCA was chosen since this method can yield different symptom clusters even if the correlation levels of these symptoms were low (Kim et al., 2005). To conduct the PCA, we exclude the item "Difficulty sleeping" from MSAS (as this would be highly correlated with the independent variable of insomnia). We include the score of insomnia, anxiety, and depression (measured by ISI and HADS). As such, PCA was conducted on the 34 items with orthogonal rotation (varimax). We determined symptom cluster (SC) based on 4 aspects: symptom concurrence, symptom severity, and symptom distress, and total symptom score. The Kaise-Meyer-Olkin of the results (KMO) was greater than 0.80 which verified the sampling adequacy for the analysis,

the Barlett's test of sphericity χ^2 ranked from 2339.44 to 3358.06, $p<0.001$, indicated that correlation between symptoms was sufficiently large for PCA (Hutcheson, 1999).

4.3.4.4. Assess the impact of insomnia on patient's quality of life

The significant difference between ISI score and participants' quality of life and other sub-scales was determined by T-test, which was designed to compare two means (Portney, 2015).

4.3.4.5. Evaluate the feasibility and reliability of objective measurement for insomnia in cancer patients

The number of participants withdrawn from the study due to the actigraph and missing data related to the actigraph were recorded. The comparison of the mean of sleep parameters (measured by Actigraph and sleep log) between insomnia and non-insomnia patients regarding was determined by T-test which was designed to find the differences between two means (Portney, 2015).

4.4. Results of the study

4.4.1. Sample characteristics

Two hundred seventy-two patients were invited to the study, and 48 of them refused to participate. There were 224 patients included in the study. However, 11 patients withdrew from the survey during the time they wore the Actigraph, leaving a final sample of 213 participants. The response rate was 82.4%; the completion rate was 95%, and the attrition rate was 4.9%. Figure 6 depicts the flow of the study's participant recruitment.

The mean age of patients was 53.1 (11.3) years old (21-80), with 48.8% of them in the age group of 46 to 60 years old. Most of the participants were female (128

patients, 60%). In the survey, the majority of patients were married (198, 88.7%) and being farmers or workers (80, 37.6%). More than two-thirds of participants had the education level of high school or part of (145, 68.1%). The majority of the participant has no comorbidities (n=177, 83.1%), while for those who had, the most common comorbidity was hypertension (6.1%) followed by diabetes (3.3%). Nearly one-third of participants had breast cancer (59 patients, 27.7%). More than half of the patients had their tumor removed (121, 56.8%). The mean time from diagnosis was 13.7 (21.0) months (1 – 156). Texan based chemotherapy regimen was the most common cancer treatment regimen among participants (102, 47.9%). Detail of demographic and clinical characteristics of the sample are shown in Table 15

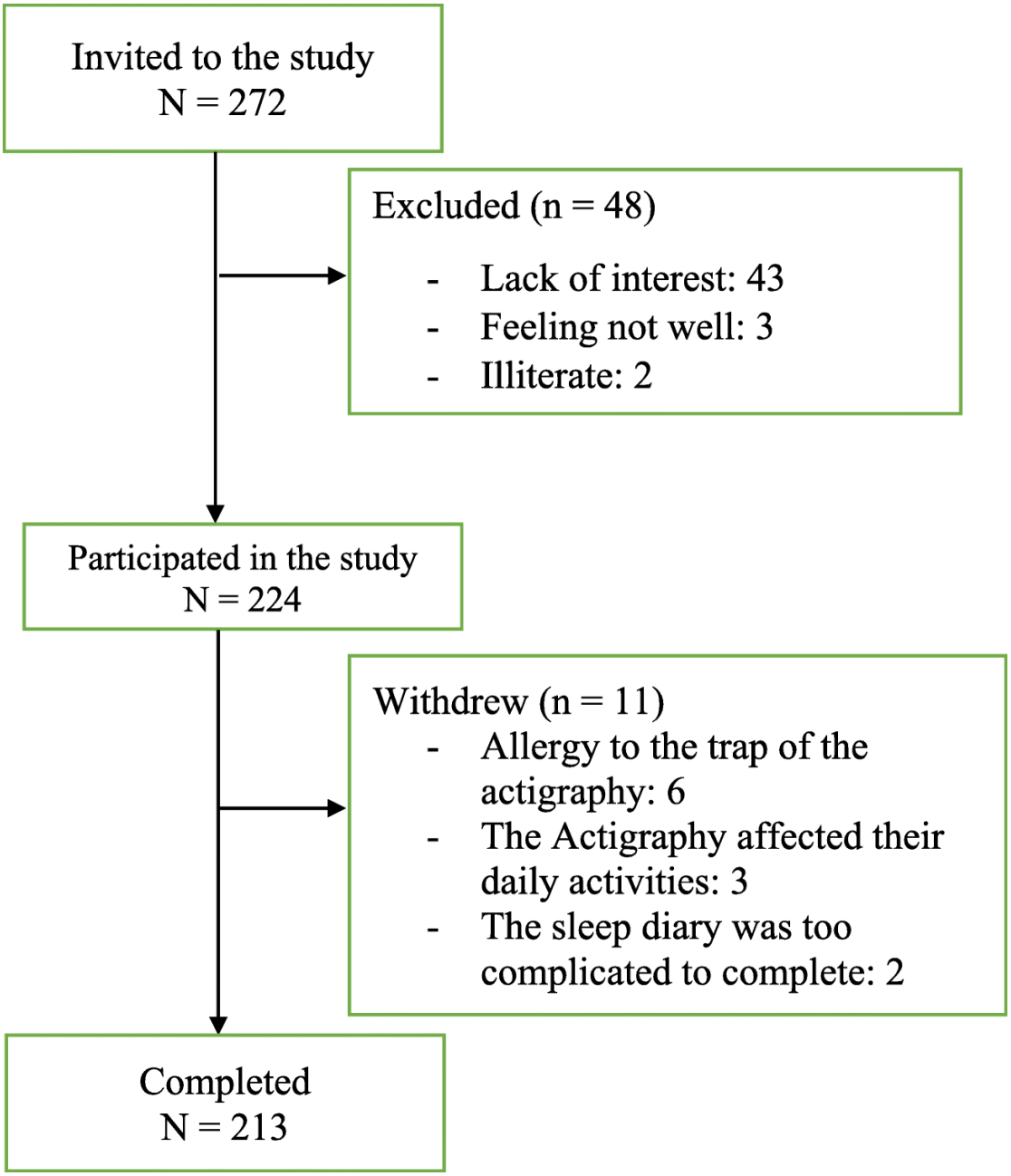

Figure 6. The flowchart of the cross-sectional survey

Table 15. Demographic and Clinical Characteristics of the patients

	Patients (n=223)	%
Age group		
≤ 45	54	25.4
46 – 60	104	48.8
> 60	55	25.8
Marital status		
Single	13	6.1
Married	189	88.7
Divorced/Widowed	11	5.1
Hospital		
Hospital A	74	34.7
Hospital B	45	21.1
Hospital C	94	44.1
Occupation		
Unemployed	30	14.1
Retired	51	23.9
Laborer	80	37.6
Officer	12	5.6
Teacher	11	5.2
Others (Medical staff, Engineer, Freelancer)	29	13.6
Education		
Primary school	18	8.5
High school or part of	145	68.1
College or part of	28	13.1
University or Higher	22	10.3
Comorbidity		
None	177	83.1
Diabetes	7	3.3
Hypertension	13	6.1
Hypertension and diabetes	3	1.4
Degenerative spine	5	2.3
Others (Adipose hepatica, Gout, Dyslipidemia)	8	3.8

Cancer diagnosis		
Breast cancer	59	27.7
Gynecologic cancer	24	11.3
Lung/Bronchial Cancer	41	19.2
Gastrointestinal Cancer	38	17.8
Non Hopkin Lymphoma	30	14.1
Others (Nasopharyngeal cancer, Brain cancer, Amygdales cancer, Laryngeal cancer, tongue cancer, Nasopharynx cancer, Urinary system cancer)	21	9.9
Cancer stage		
1	28	13.1
2	66	31.0
3	62	29.1
4	57	26.8
Surgical debulking		
Optimal	121	56.8
Suboptimal	20	9.4
None	72	33.8
Chemotherapy Regimen		
Taxane based Chemotherapy	102	47.9
Cyclophosphamide and doxorubicin based Chemotherapy	50	23.5
Oxaliptatin based Chemotherapy	23	10.8
Gemcitabine based Chemotherapy	18	8.5
Others (Vinorelbine, Rituximab, Trastuzumab)	20	9.4

4.4.2. Prevalence and Severity of insomnia

According to the results measured by ISI, almost half of the participants reported insomnia (n=91, 42.8%). Regarding insomnia severity in those who reported insomnia, 62 patients reported a total score of ISI ranged from 15 to 22 which indicated moderate insomnia (68.1%) and 29 patients (31.9%) reported severe insomnia (a total ISI score greater than 22) (Table 16).

Table 16. Prevalence and Severity of insomnia

	Patients (n = 213)	**%**
Non insomnia	122	57.2
Insomnia	91	42.8

According to the Actigraph results, insomnia patients (indicated by ISI) slept 363.75 min (approx. 6 hours) per night on average, their sleep efficiency was 89% and the average wake up time after sleep onset was 44.2 min with 1.4 wakes up times on average. According to the sleep log results, insomnia patients slept 354.82 min (approx. 6 hours) and wake up 1.8 times on average per night. The results indicated that there is no difference in sleep parameters measured by Actigraph or sleep log in terms of total night sleep, true sleep, sleep efficiency and number of nights awaken and time of wake after sleep onset between insomnia and non-insomnia patients **(table 17**)

Table 17. Measuring sleep parameters in patients with insomnia and non-insomnia

Actigraph	**N**	**Mean (min)**	***SD***	***p****
Average true sleep				0.7
Non - insomnia	111	360.01	71.14	
Insomnia	84	363.75	85.50	
Average total night sleep				0.4
Non - insomnia	111	397.63	74.89	
Insomnia	84	407.95	91.51	
Average Night awaken		Time		0.3
Non - insomnia	111	1.25	1.12	
Insomnia	84	1.40	1.1	
Sleep efficiency				0.9
Non - insomnia	111	91%	8%	
Insomnia	84	89%	5%	
Wake after sleep onset				0.7
Non - insomnia	111	37.62	27.46	
Insomnia	84	44.20	23.1	
Sleep log	**N**	**Mean (min)**	***SD***	***p****
Average total sleep time				0.2
Non - insomnia	86	376.39	86.59	
insomnia	56	354.82	120.33	
Number of nights awaken		Time		0.54
Non - insomnia	86	1.7	1.15	
insomnia	56	1.83	1.39	

*Note: *bolded "p" indicate significant differences by T-test*

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4.4.3. Feasibility of using Actigraph to measure sleep among participants

As depicted in Figure 6, there were 8 patients (3 males and 8 females) withdrawn from the study during the time they wore the actigraph due to being allergic to the trap of the actigraph: 6 patients (75%) and the Actigraph affected their daily activities: 2 patients (25%). We also lost the data of sleep parameters from 18 participants (8.4%) due to losing 01 actigraph and 01 actigraph did not work.

4.4.4. The impact of insomnia to patient's quality of life (patient's QOL)

Insomnia patients (indicated by the ISI) had significantly lowered QOL score (measured with FACT-G) in comparison with non-insomnia patients (p<0.001). They also had poorer score in term of Emotional, Functional, Physical and Social/family well-being (p<0.05) (Table 18)

Table 18. Differences in insomnia and non-insomnia patients with Quality of Life (QOL) score and QOL domains

	Insomnia patients (n=91)	**Non-insomnia patients (n=122)**	*p**
QOL score	60.16 ± 17.94	75.08 ± 16.96	**<0.001**
Emotional well-being (EWB) score	11.49 ± 6.24	9.16 ± 5.71	**0.005**
Functional well-being (FWB) score	13.57 ± 5.36	17.91 ± 6.08	**<0.001**
Physical well-being (PWB) score	15.31 ±5 .81	19.73 ± 5.69	**<0.001**
Social/family well-being (SWB) score	19.58 ± 5.81	21.29 ± 5.87	**0.043**

*Note: *bolded "p" indicate significant differences by T-test (p<0.05)*

4.4.5. Identification of risk factors for insomnia

There was no difference in the mean ISI score as well as insomnia occurrence in terms of: gender, age group, cancer diagnoses, cancer stage and chemotherapy regiments (all $p > 0.05$). A significant difference was found in the mean ISI score as well as insomnia proportion and depression or anxiety. Patients with depression (indicated by HADS) had a significantly higher ISI score and greater insomnia proportion than patients with no depression (15.4 vs 11.36; 60.4% vs 39.6% respectively, $p < 0.01$), and patients with anxiety (indicated by HADS) had a higher ISI score and greater insomnia proportion than those with no anxiety (15.24 vs 11.61; 63.7% vs 36.3% respectively, $p<0.001$) (table 19). About more than 60% insomnia patient experience depression or anxiety and 46.1% (42 patients) insomnia patient experience both anxiety and depression. Insomnia score was correlated with anxiety score ($r=0.3$; $p<0.001$) and depression score ($r=0.27$; $p<0.001$) (table 20).

Table 19. ISI score classification by demographic and clinical characteristic of patients

	n	ISI mean	SD	Insomnia proportion n = 91 (%)	*p* [a](for ISI mean score)	*p*[b] (for insomnia proportion)
Gender					0.98	0.54
Male	84	13.3	7.4	36 (39.6%)		
Female	129	13.3	6.6	55 (60.4%)		
Age groups					0.34	0.058
≤ 45	55	12.8	6.2	17 (18.7%)		
46 – 60	104	13.0	7.2	45 (49.5%)		
> 60	54	14.5	7.3	29 (31.9%)		
Cancer diagnosis					0.54	0.26
Breast cancer	59	13.14	6.7	24 (26.4%)		
Gynecologic cancer	24	13.92	6.14	11 (12.1%)		

	n	ISI mean	SD	Insomnia proportion n = 91 (%)	p^a (for ISI mean score)	p^b (for insomnia proportion)
Lung/Bronchial Cancer	41	13.54	7.4	18 (19.8%)		
Gastrointestinal Cancer	38	11.5	6.47	11 (12.1%)		
Non-Hogkins Lymphoma	30	14.27	7.82	14 (15.4%)		
Others (Nasopharyngeal cancer, Brain cancer, Laryngeal cancer, tongue cancer, Nasopharynx cancer, Urinary system cancer)	21	14.62	8.03	13 (14.2%)		
Chemotherapy Regimen					0.81	0.87
Taxane based	102	12.85	7.08	43 (47.3%)		
Cyclophosphamide and doxorubicin based	50	13.62	0.07	20 (22%)		
Oxaliplatin based	23	13.96	6.49	10 (11%)		
Gemcitabine based	18	12.83	7.39	8 (8.8%)		
Others	20	14.6	7.3	10 (11%)		
Cancer stage					0.65	0.81
1	28	12.9	6.2	12 (13.2%)		
2	66	13.0	7.2	28 (30.8%)		
3	62	14.5	7.3	29 (31.9%)		
4	57	13.3	7.0	22 (24.2%)		
Depression (HADS)					**p<0.001**	**p<0.001**
No depression	110	11.36	6.3	36 (39.6%)		
Depression	103	15.4	7.1	55 (60.4%)		
Anxiety (HADS)					**p<0.001**	**0.001**
No anxiety	113	11.61	7.07	33 (36.3%)		
Anxiety	103	15.24	6.50	58 (63.7%)		

*Note: * bolded "p" indicate significant differences (p<0.05). a=T-test, b=Chi-square test.*

*Table 20. **Correlations between insomnia score** and anxiety/depression score*

N =213	ISI score	HADS-A score	HADS-D score
ISI score	1		
HADS-A score	0.30**	1	
HADS-D score	0.27**	0.55**	1

*Note: ISI: Insomnia Severity Index, HADS-A: Anxiety score measured by Hospital anxiety and depression scale; HADS-D: Depression score measured by Hospital anxiety and depression scale** Correlation is significant at the 0.01 level (1-tailed)*

4.4.6. Identifying a sleep-related symptom cluster

The sleep-related symptom clusters (SC) was determine based on four dimensions: symptom frequency, symptom severity, symptom distress, and total symptom score (calculated by the total sum of symptom frequency, severity, and distress). The result showed that based on the symptom frequency, a symptom cluster of anxiety, depression, insomnia, worrying, and feeling sad form a sleep-related SC, the correlation between these symptoms were strong to moderate and significant (r ranged from 0.4 to 0.72, $p<0.001$). Based on symptom severity, these symptoms also for a symptom cluster, the correlation were moderate to strong and significant (r ranged from 0.4 to 0.78, $p<0.001$). Based on symptom distress, anxiety, depression, and insomnia were correlated and form a symptom cluster (r ranged from 0.6 to 0.79, $p<0.001$). And base on the total symptom score, anxiety, depression, insomnia, and worrying form a cluster, the correlation between them were moderate to strong (r ranged from 0.4 to 0.73, $p<0.001$).

Table 21. Identifying symptom clusters (SCs) by MSAS, ISI, and HADS

	Symptom frequency		**Symptom severity**		**Symptom distress**		**Total symptom score**	
	SC components	*r*	SC components	*r*	SC components	*r*	SC components	*r*
	Anxiety	0.72	Anxiety	0.7	Anxiety	0.79	Anxiety	0.64
	Depression	0.77	Depression	0.78	Depression	0.61	Depression	0.73
	Insomnia	0.63	Insomnia	0.62	Insomnia	0.61	Insomnia	0.62
	Worrying	0.45	Worrying	0.5			Worrying	0.44
	Feeling sad	0.4	Feeling sad	0.44				
KMO	0.86		0.86		0.87		0.84	
χ^2	2339.44		2413.48		2506.89		3358.06	
p value	**<0.001**		**<0.001**		**<0.001**		**<0.001**	

Note: SC: symptom cluster; MSAS: Memorial Symptom Assessment Scale, ISI: Insomnia Severity Index, HADS: Hospital Anxiety and Depression Scale MO: Kaiser-Meyer-Olkin Test; r: Pearson's r; bolded "p" indicate significant differences (p<0.05)

4.5. Contribution of the cross-sectional survey to the development of the trial's protocol

While the findings of this study will be discussed in depth in the Discussion chapter (Chapter 8), here points relevant to the development of the intervention trial are presented and discussed. The survey confirmed the high prevalence of insomnia (42.8%) and the symptom cluster of insomnia, depression, and anxiety, it also played an important role in the development of the intervention. The results from the survey were being used in different parts of the trial's development phase.

Firstly, the survey indicated that half of the insomnia burden in the targeted sample was accounted for by sleep-related SC, which includes insomnia, depression, and anxiety. This finding provides us the direction to develop a trial that targets this symptom cluster instead of individual symptoms. Based on the literature, acupressure was chosen due to its advantage of reducing multiple symptoms with safety but lack of evidence in managing this symptom cluster in cancer patients.

Nevertheless, insomnia is considered as the core symptom in the cluster of insomnia, depression, and anxiety. Taylor et al. (2005) used the diathesis-stress model (Monroe & Simons, 1991) to explain the effect of insomnia on depression and anxiety. In this model, stress caused by insomnia might worsen or stimulate the development or recurrence of depression and anxiety. Time spent awake at nighttime can make individuals think about past failures, worry about future situations, and the next day's responsibilities, thus causing depression and anxiety. On the other hand, daytime ruminations are usually associated with depression and anxiety, and these daytime ruminations spill over into bedtime, increasing mental and physiological arousal resulting in insomnia. Besides, a review article also stated the impact of sleep disturbances on the perception of anxiety and depression (Davis & Goforth, 2014). Evidence from the literature supports the role of insomnia as the sentinel symptom for the cluster. Therefore, in the trial, when the inclusion criteria were being developed, we did not have any criteria regarding gender, cancer diagnosis, cancer stage, time from diagnosis, number of completed chemotherapy cycles, and type of chemotherapy. The reasons for not including these criteria were due to the results of the survey, which

indicated age, gender, and treatment-related factors did not correlate with insomnia occurrence or severity.

Selecting suitable outcome measurement instruments for a study is a critical step in designing a trial. This decision should be based on the evidence of the quality of available outcome measurement instruments (i.e., reliability, validity, and responsiveness), as well as on aspects of feasibility. As such, the survey helped us to choose suitable outcome measurements for the trial. In the survey, the ISI, HADS, MSAS, FACT-G, sleep diary, and Actigraph were being used. The majority of the measurements were considered as suitable for cancer patients with a high response rate and Cronbach's alpha (Cronbach's alpha ranged from 0.87 to 0.92). However, the use of Actigraph was not feasible. The results also demonstrated there was no difference between sleep parameters measured by Actigraph between insomnia and non-insomnia participants.

Nevertheless, according to the study procedure, participants were required to wear the Actigraph for three consecutive days. The data were collected in the summertime so the cloth strap was very easy to get wet due to sweat, when washing hands, taking a shower or washing clothes by hand (the majority of participants lived in the countryside, so they normally do not use washing machines). The major reason for not taking part in the study was related to the Actigraph. The patients were afraid the device could cause some harm to their health, or it could have a record or locating function that can invade their privacy. Although, the researcher explained clearly that Actigraph would not cause any harm to their health as well as guarantee their privacy, 40/48 participants refused to participate.

On the other hand, with patients who agreed to participate in the study, they were more interested in other functions of the Actigraph (measuring daily taken steps, blood pressure, and heart rate) than the main function of measuring sleep. In addition, returning the Actigraph after the 3-days measurement also caused inconvenience for both the researcher and the participants. Participants who lived in rural areas may have to travel several kilometers to the post-office for returning the devices. Nevertheless, this was time-consuming since it took up to 3 days to deliver and there was the

additional risk of losing the device (one device was lost during transportation causing losing data from ten participants). Since the use of Actigraph was not feasible and reliable, in the current trial did not include this device.

In summary, the survey was a part of the development phase of the intervention. It was conducted to assess the sleep problem among cancer patients in different aspects, including examining the extent of the problem, determining possible risk factors for insomnia, confirming the relationship between insomnia, depression, and anxiety, as well as testing appropriate outcome measures in the targeted population. These findings helped us to develop the study protocol for the trial.

CHAPTER 5. DEVELOPMENT OF THE SELF-ACUPRESSURE PROTOCOLS

5.1. Introduction

The result of our cross-sectional survey reported a high prevalence of insomnia among cancer patients undergoing chemotherapy that indicates the need to develop an intervention to improve insomnia. Nevertheless, this survey identified a symptom cluster of insomnia, depression, and anxiety among participants, which indicates that to manage insomnia effectively, we must also consider managing correlated symptoms. As such, we decided to develop an intervention to manage the symptom cluster of insomnia, depression, and anxiety. Based on the literature review, self-acupressure can potentially reduce insomnia as well as other symptoms in cancer patients. However, the use of self-acupressure in managing the symptom cluster of insomnia, depression, and anxiety is unknown but worthy for further research. Finding from the literature also indicated the contribution of non-specific effects (placebo effect) of acupressure to the overall effect of this treatment. The non-specific effect is referred to the positive change in patient outcomes that not related to the therapeutic effect of the treatment (Hrobjartsson & Gotzsche, 2010). As such, the trial to assess the effect of self-acupressure should include a sham (placebo) acupressure group that serves as a control group. Hence, in our trial, two self-acupressure treatment protocols were being developed which were the true and the sham self-acupressure treatment protocol. The self-acupressure treatment protocols include a set of acupoints, the dose of the treatment, and the technique for stimulating acupoints. These treatment protocols were developed based on acupressure theories, systematic reviews, and WHO guidelines on locating acupoints. The chapter begins with the development of the true self-acupressure, follows by the sham self-acupressure treatment protocol development, and the validation of the true and sham acupressure protocols.

5.2. The development of the true self-acupressure protocol.

5.2.1. Justification of the selected acupoints

From Traditional Chinese Medicine (TCM) theory, the frequently involved organs causing insomnia, depression, and anxiety are heart, liver, stomach, and spleen (Young, 2001). Based on this point, acupoints included in the self-acupressure treatment protocol are selected based on their effect on the organs and their effect on the symptoms from the literature reviews. In a systematic review from 40 studies on the efficacy of acupressure for insomnia, Yeung et al. (2012) indicated 12 RCTs reported that acupressure was significantly improved sleep quality among participants when compared with usual care or sleep medicine or sham acupressure. In these RCTs, the most commonly used acupoints were: *Baihui (GV20), Shenmen (HT7), Taiyang (EX-HN5), Fengchi (GB20), Yintang (EX-HN3) and Sanyinnjiao (SP6). Regarding depression and anxiety, Baihui (GV20), Yintang (EX-HN3). Taichong (LR3), Hegu (LI4) and Shenmen (HT7)* were listed as commonly used acupoints from a review of 13 studies (Pilkington, 2010). In this review, studies include these acupoints reported significantly lower depression and anxiety severity among participants when compared with usual care *(Pilkington, 2010)*. From this evidence, ***Baihui (GV20), Yintang (EX-HN3), Shenmen (HT7), Fengchi (GB20) and Hegu (LI4), Taichong (LR3)*** are included in the acupressure protocol for this study.

Baihui (GV20) linked with all *Yang* channels, this acupoints response for sufficiency of blood circulation in the Heart and Spleen resulting in enhancing the "the source of generation and transformation of Qi and Blood" to improve insomnia, depression, and anxiety. The combination of *GV20* and *HT7* supplies and boosts the Heart and Spleen (Li, 2007). ***Shenmen (HT7)*** is selected to supplement, clear and settle the Heart also calm the Spirit to treat insomnia, depression, and anxiety by "depletion of Blood in the Heart and Spleen, Qi deficiency of the heart and Gall-bladder, effulgent Yin deficiency fire and disharmony of the stomach (Li, 2007). The acupoint has been demonstrated to be effective in improving sleep across studies in both cancer and non-cancer population (Cerrone et al., 2008; Sok et al., 2003; Sun et al., 2010; Yeung et al., 2012). Also, *HT 7* was proved to increase the release of Melatonin from the pineal gland resulted in better

sleep in human (Spence et al., 2004). ***Fengchi (GB20)*** has been demonstrated to be effective to clear the Brain and calm the sleep. It was commonly used to treat insomnia due to depletion of blood in the Heart and Spleen, or lack of interaction between the Heart and the Kidneys, or *Qi* deficiency in the body. Stimulation of this acupoint is related to the improvement of depression and anxiety (Li, 2007). ***Yintang (EX-HN3)*** has been demonstrated to treat insomnia, depression, and anxiety by calming the mind (Marley, 2010). ***Hegu (LI4):*** is effective in treating disorders of the spirit and mind and commonly uses in the treatment of disease patterns due to *Qi* deficiency such as insomnia, depression, and anxiety (Li, 2007). ***Taichong (LR3):*** has demonstrated to treat the symptoms related to activities of *Liver Qi* such as depression, anger by enhancing and regulates the functions of the liver and eliminates pathological symptoms and sign caused by dysfunction of the liver (Li, 2007)

5.2.2. Justification for the dose of the true self-acupressure treatment

The dose of the treatment refers to the combination of frequency, duration of each treatment session, and the duration of the whole treatment period. This section reports the justification for choosing the whole treatment duration, the frequency, and duration of each treatment section.

Duration of the whole treatment and frequency of each treatment section

An optimal acupressure treatment dose is a gap in the literature since a wide range of duration treatment was reported. Various duration for the whole acupressure treatment period was recorded from one week to 10 weeks for insomnia (Choi et al., 2016), six days to six weeks for anxiety (Pilkington, 2010), and from two weeks to 16 weeks (Pilkington, 2010; Wang et al., 2008). As the guidelines for such dose of each symptom or disease have not been established, the researcher should fine an appropriated duration treatment for their trial (Deng et al., 2015). Such duration treatment must be resulted in an improvement of the symptoms and not being too long to ensure good participant adherence (Zheng et al., 2014). Finding from systematic reviews showed that the acupressure treatment duration of four or five weeks resulted in a significant improvement of sleep (Bokmand & Flyger, 2013; Williams et al., 2013) while the shorter duration (one week) and longer duration (ten weeks) did not (Mao et al., 2015;

Song et al., 2015). In addition, other review indicated that the treatment group showed significant improvement in anxiety than the control with six days to ten days treatment duration but not with longer duration (six weeks) (Pilkington, 2010).

Regarding the duration of depression, the results from two reviews indicated the duration of four to eight weeks brought a significant improvement in the intervention group compared with control groups (Pilkington, 2010; Wang et al., 2008). Yeung et al. (2012) reviewed 40 RCTs and indicated the effects of acupressure on improving symptoms were observed after four weeks of treatment. A treatment duration of four weeks is also considered a short-term treatment, which is likely to ensure good adherence to a TCM trial (Zheng et al., 2014). Therefore, an acupressure duration of four weeks with the frequency of once a day seems to be optimal for improving insomnia, depression, and anxiety.

Previous systematic reviews also revealed several numbers of acupressure session needed to see the effects of the intervention (Choi et al., 2016; Mao et al., 2015; Pilkington, 2010; Song et al., 2015; Waits et al., 2016; Wang et al., 2008; Yeung et al., 2012). A total of 28 sessions was proved to have a significant positive impact on the sleep quality among participants (Mao et al., 2015; Song et al., 2015; Waits et al., 2016; Yeung et al., 2012). However, a smaller number of acupressure sessions were required for testing the effectiveness of acupressure on depression and anxiety. Only six to ten sessions were needed to see the improvement of anxiety between participants in the intervention groups compared with the control group (Pilkington, 2010). After 12 acupressure sessions, a significant improvement in depression severity was found in the intervention group compared with control groups (Pilkington, 2010; Wang et al., 2008). Therefore, in this trial, 28 acupressure treatment sessions were included in the treatment protocol to ensure the effectiveness of the intervention on the targeted symptom cluster. As such, our intervention has a duration of 28 days with the frequency of once a day (equal to 28 self-acupressure sessions)

Duration of each treatment section

Systematic reviews indicated that to ensure the acupressure treatment has effects in improving symptoms, the time to stimulate an acupoint must rank from one to three

minute which made the length of each treatment section ranged from 15 to 45 minutes (Choi et al., 2016; Pilkington, 2010; Pilkington et al., 2007; Waits et al., 2016; Wang et al., 2008; Yeung et al., 2012). Other recent studies also showed that practicing acupressure three minutes per acupoint significantly reduced the burden of the symptoms (Abedian et al., 2015; Lu et al., 2013; Tsay & Chen, 2003; Zheng et al., 2014). However, some TCM textbooks indicated that an acupoint must be stimulated in two minutes to release the stuck *Qi*, relax muscles, and calm the internal organs (Sollars, 2000; Stux, 2003). Therefore, to achieve the maximum effects of acupressure, a three-minute stimulation is applied for each of acupoints in our treatment protocol. There are six acupoints with four of them located on both sides of the body, giving a total of ten acupoints to stimulate. Among these acupoints located on both sides of the body, *Fengchi* and *Taichong* can be pressed bilaterally at the same time. Hence, the duration of each true self-acupressure treatment session is set at 24 minutes.

Intensity and technique for true self-acupressure

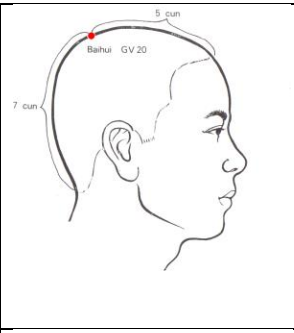
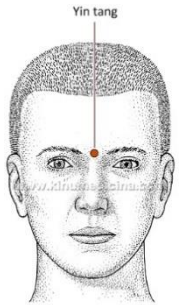
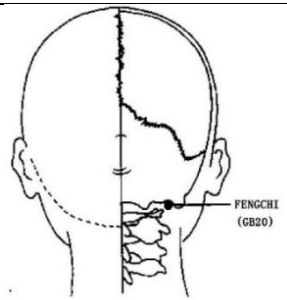
According to the TCM theory, acupressure only shows its effects on symptoms when patients experience *deqi* sensation (Yang et al., 2013). The *deqi* sensation is described as the feeling of sore, numb, heavy, distended, and warm at the acupoints and is felt by patients (Tsay & Chen, 2003; Yeung et al., 2017). Therefore, the technique for acupressure using in this study will be using the thumb pad to massage the surrounding area of the specific acupoint firmly, and the participant must feel the *deqi* sensation during performing self-acupressure (Yeung et al., 2017). However, the pressure techniques for *Baihua* and *Fengchi* are different from other acupoints due to their specific locations (on the scalp). For *Baihua*, participants use four finger pads to tap gently the area of this acupoint on the scalp (Yeung et al., 2017). For *Fengchi*, participants using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally (Tsay & Chen, 2003) . The true self-acupressure protocol is depicted in **Table 22**.

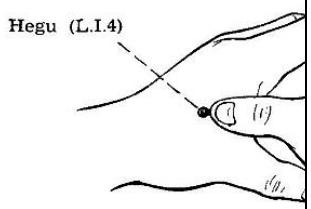
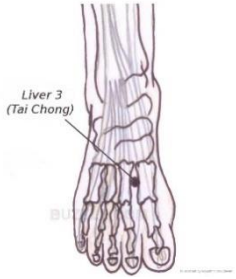
Time for practicing acupressure

To archive the therapeutic effects of acupressure in reducing symptoms, patients must practice self-acupressure in a comfortable, low light, and private environment that can

conduct a deep relaxation, and avoid practicing on a full stomach or right after long hours of working (Dale, 2019). Acupressure should be practiced when patients feel the presence of the symptoms (Stux, 2003). Our intervention targeted on the symptom cluster of insomnia, depression, and anxiety. While depression and anxiety may present at any time during the day, insomnia only present at night time. Thus, practicing at bedtime is recommended. Nevertheless, *HT 7,* an acupoint included in the treatment protocol, has been demonstrated to increase the production and release of melatonin (Spence et al., 2004). Melatonin is a hormone in the body that the brain produced in response to darkness and helps with sleep (Andersen et al., 2016). Hence, to avoid practicing self-acupressure can interfere with the participant's daily activities, participants will be asked to perform self-acupressure one hour before going to bed.

Table 22. The proposed true self-acupressure treatment protocol for insomnia, depression, and anxiety

Sequence/acupoint	Location (*)		Pressing technique	Frequency, duration
1. Baihui (GV20)	On the head, 5 B-cun superior to the anterior hairline on the anterior median line (5 B-cun is equal to the distance from the center of the umbilicus to the superior border of the pubic symphysis)		using four finger pads, gently tap the area of this acupoint on the scalp	3 minutes Once a day for four weeks
2. Yintang (EN-HN3)	The midpoint between the eyebrows		using thumb pad, firmly massage the surrounding area of this acupoint	*3 minutes* Once a day for four weeks
3. Fengchi (GB20)	In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of sternocleidomastoid and the trapezius muscle		using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally	*3 minutes for each side (total 3 minutes, both side at the same time)* Once a day for four weeks

Sequence/acupoint	Location (*)		Pressing technique	Frequency, duration
4. Hegu (LI 4)	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone.		Using thumb pad, firmly massage the surrounding area of this acupoints and press on the acupoints with rotation movements	*3 minutes for each side (total 6 minutes)* Once a day for four weeks
5. Shenmen (HT7)	On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease.		Using thumb pad, firmly massage the surrounding area of this acupoint on the ulnar side of the wrist	*3 minutes for each side (total 6 minutes)* Once a day for four weeks
6. Taichong (LR3)	On the dorsum of the foot in the depression distal to the junction of the first and second metatarsal bones.		Using thumb pad, firmly massage the surrounding area of this acupoints and press on the acupoints with rotation movements	*3 minutes for each side (total 3 minutes, both side at the same time)* Once a day for four weeks

* directly quote from World Health Organization (2009)

5.3. Development of the protocol for the sham self-acupressure

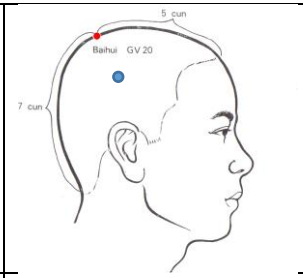
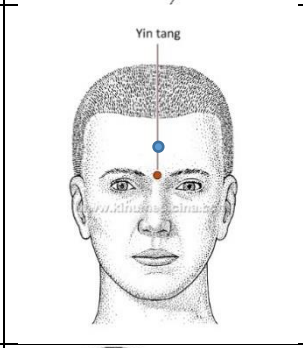
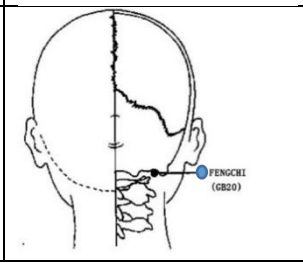
5.3.1. Justification for choosing a sham acupressure approach

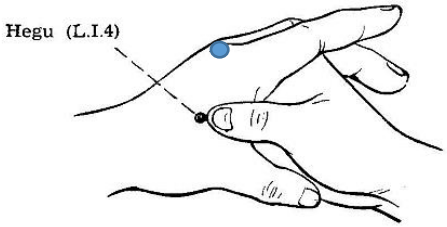
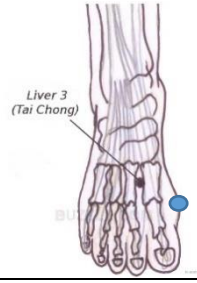
In a recent systematic review on the application of sham acupressure in 66 randomized controlled trials, Tan et al. (2015) listed out three approaches of using sham acupressure: using irrelevant acupoints, using non-acupoints, and using the same acupoints as true treatment with light touching. The approach of using the same acupoints as true treatment with light touching/no stimulation is believed not to create any therapeutic effect (Tan et al., 2015). However, Vietnamese people are familiar with the acupressure technique, so the light stimulation may not be adequate to maintain blinding participants. Using irrelevant acupoints refers to the use of acupoints to relieve different symptoms (Zhang et al., 2010). This approach is also not appropriated as the "holism concept" of acupuncture theory indicated that every stimulation on any acupoints could create responses of the body and generate specific or non-specific effects (as cited in Tan et al., 2015). As such, it should not be included in the research design to investigate the specific effect of acupressure. Therefore, we decide to choose the using of non-acupoints approach for the protocol of sham-acupressure since pressing non-acupoints cannot produce any therapeutic effects and maintain blinding participants.

5.3.2. Sham self-acupressure protocol

Sham acupoints are located 2 to 5 cm away from the true acupoints. The base or head of some bonds located near the true acupoint were chosen to be the sham acupoint. If the nearby area of the true acupoint does not have any base or head of a bond, then a random point was chosen as the sham acupoint. The location of sham acupoints was checked to ensure their location is actually non-acupoint to ensure no therapeutic can be generated (World Health Organization, 2009). The location and pressing technique of sham acupoints are described in **table 23**. The treatment dose in the sham self-acupressure protocol is the same as in the self-acupressure protocol.

Table 23. The proposed sham self-acupressure protocol

Sequence/acupoint	Location		Pressing technique	Frequency, duration
SA 1	3 cm from GV20		using four finger pads, gently tap the area of this acupoint on the scalp	3 minutes Once a day for four weeks
SA 2	3 cm away from Ying Tang		using thumb pad, firmly massage the surrounding area of this acupoint	*3 minutes* Once a day for four weeks
SA 3	The mastoid bone		using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally	*3 minutes* Once a day for four weeks

SA 4	The head of ulnar styloid		Using thumb pad, firmly massage the surrounding area of this acupoints and press on the acupoints with rotation movements	*3 minutes for each side (total 6 minutes)* Once a day for four weeks
SA 5	The base of metacarpal bone of the index finger		Using thumb pad, firmly massage the surrounding area of this acupoints and press on the acupoints with rotation movements	*3 minutes for each side (total 6 minutes)* Once a day for four weeks
SA 6	3 cm away from Tai Chong		Using thumb pad, firmly massage the surrounding area of this acupoints and press on the acupoints with rotation movements	*3 minutes for each side (total 3 minutes, both side at the same time)* Once a day for four weeks

5.4. Validation of the true self-acupressure and sham self-acupressure protocol

A panel of TCM experts was invited to validate the suitability of the true and sham self-acupressure protocol before the implementation of the feasibility study. To provide a sufficient level of control for chance agreement, a panel of six experts was recommended by Lynn (1986). Six TCM experts who specialized in TCM from Hong Kong and Vietnam were invited to validate treatment protocol. The six experts work in a university. All had at least ten years of working experience related to TCM and acupuncture/acupressure. Among six experts, two were appointed as an associate professor, two held the positions of assistant professor, one held the position of senior lecturer, and one held the position of clinical associate. The Characteristics of the six experts are presented in the table below.

Table 24. Characteristics of experts in the panel for validating acupressure treatment protocols

Characteristics of the Experts (n=6)	Number (%)
TCM registration location	
Hong Kong	4 (67%)
Vietnam	2 (33%)
Highest academic qualifications	
Doctorate	5 (83.3%)
Master's degree	1 (16.7%)
Academic and professional rank	
Associate Professor	2 (33.3%)
Assistance Professor	2 (33.3%)
Senior Lecturer	1 (16.7%)
Clinical Associate	1 (16.7%)

After identifying potential members of the panel, an invitation email was sent to each member. The experts had one week to respond to the invitation. Afterwards, a cover letter and an assessment form were sent to the experts who agreed to participate in the study. The cover letter briefly introduced the study purposes, the criteria for selecting experts, intervention protocol, and scoring method. The acupressure protocols were made to assessment form. There were 13 items for each of the acupressure treatment protocol. Thirteen items indicated the locations and pressing technique for each of the acupoint or sham acupoint, as well as the duration of each self-acupressure treatment session, the duration of the whole treatment period, the frequency, and the time for practice self-acupressure. Each expert rated each item on the acupressure protocols by using a 4-point Likert scale, where four = very appropriate, 3 = appropriate, 2 = inappropriate, and 1 = very inappropriate. Comments or suggestions for each item were encouraged (Please see appendix 10). Experts were required to return their feedback by email within one week of receiving the assessment form. If the expert did not reply, a reminder would send two days later.

The validity index for each item (I-VI) was calculated using the number of the expert rate the acupoints either "very appropriate" or "appropriate" divided by the total number of experts (6). The item was rated as valid when at least five out of six experts agree as "very appropriate" or "appropriate" (Lynn, 1986). As such, the I-VI should be at least 0.83 (5/6); if an item had I-VI less than 0.83 it was revised based on comments and suggestions of experts. The validity index for the whole acupressure protocol (P-VI) was calculated based on the average I-VI (Lynn, 1986; Rubio et al., 2003). An P-VI of 0.83 was considered valid.

Two rounds of validation were conducted in this doctoral research project. In the first round of validation, the majority of items in the true and sham acupressure were rated as valid. However, there were two items in the self-acupressure protocol, and three in the sham self-acupressure protocol had the validity index lower than 0.83, which was considered as not valid (**Table 25**). In the true self-acupressure protocol, *Hegu* was rated as inappropriate by two experts. One expert did not provide the reason for his decision but suggest to use *Neiguan (PC6)* because of its ability to support *Shenmen (HT 7)* to

promote sleep better. Another expert rated *Hegu* as inappropriate due to the unpleasantness when stimulating this acupoint. *Hegu* must be press until the patients feel sore, which is not pleasant. Thus, the patients may not press *Hegu* hard enough throughout the entire of the self-acupressure session. The pressing technique of *Baihua* was also rated as inappropriate by two experts because they indicated the proposed pressing technique was wrong. In the proposed sham acupressure protocol, the locations of SA1, SA2, and SA6 were rated inappropriate because their locations were in the meridian and touched another acupoint (3 experts). Besides, the pressing technique for SA1 was rated as inappropriate by three experts. Among them, two experts indicated this pressing technique is wrong, and one expert indicated it is easy to stimulate *Sishencong (another acupoint)* if using this technique. However, none of the experts who rated "inappropriate" provides a reference for their decisions.

Based on the results, *Hegu* was replaced by *Neiguan* (PC6). *Neiguan* regulates the circulation of chi, strengthens the spleen and stomach, which resulted in calming the mind, restoring clarity to the brain, and improving anxiety, irritability, depression, and anxiety (Cross, 2010; Stein, 2009; Young, 2001). The pressing technique for *Baihui* was also revised (using a finger pad and firmly massage the acupoint instead of four finger pads and tap). The location of SA1 was changed to the base of the metacarpal bone of the left index finger as there is no acupoint in the area (World Health Organization, 2009). Hence, its pressing technique was also revised. The location of SA 2 was relocated to 2cm superior to the end of the right eyebrow. The location of SA 6 was relocated to the medial malleolus. **Table 28** retails the final true and sham self-acupressure treatment protocols.

In the second round of the acupressure protocols validation, all the components of the self-acupressure and sham self-acupressure protocols were determined to be valid, with the validity index for each item (I-VI) ranging from 0.83 to 1.00. The validity index for the true self-acupressure and sham self-acupressure (P-VI) also valid with P-VI was 0.92 and 0.89, respectively (**table 26 and table 27**). Although a satisfactory agreement for the true acupressure was achieved among the panel, one expert held a different opinion in terms of pressing technique for *Baihui*. However, the expert did not suggest

any pressing technique for this acupoint. Four experts suggested the pressing technique for Baihui as “using middle or index finger pad firmly massage the surrounding area of the acupoints with moderate pressure at rhythm of one second per cycle” and for other acupoints (except for *Fengchi)* as “using thumb pad firmly massage the surrounding area of the acupoints with rotation movements at rhythm of one second per cycle”. After discussing with the chief supervisor, a TCM expert, who works in the acupuncture/acupressure research area, the pressing technique for these acupoints was revised according to the experts. The process of validation acupressure protocols was therefore complete. The final true and sham self-acupressure protocols are described in **table 28.**

Table 25. Components of the proposed acupressure protocols that did not meet the agreement level in the first round of the validation study

Components	Validation Assessment of the content			Reason for rating as inappropriate	I-IV
	"very appropriate"	"appropriate"	"inappropriate"		
Section of the true acupoints					
Hegu	**1**	**3**	**2**	- In order to trigger effect, this point should be pressed until it is sore. And this is not pleasant and the subject sure will not be pressing hard enough throughout the entire course of the treatment - Do not provide any reason but suggest to using *Neiquan* instead of this acupoint	**0.67**
Location of the sham acupoints					
SA1 (3cm away from Baihui)	**0**	**3**	**3**	Touches other acupoints	**0.5**
SA2 (3cm away from Yintang)	**0**	**4**	**2**	Touches other acupoints	**0.67**
SA6 (3 cm away from Taichong)	**0**	**4**	**2**	Touches other acupoints	**0.67**
Pressing technique					
For Baihui (*using four finger pads, gently tap the area of this acupoint on the scalp) (Yeung et al., 2017)*	**3**	**1**	**2**	Wrong technique	**0.67**
For SA1 (*using four finger pads, gently tap the area of this acupoint on the scalp)*	**2**	**1**	**3**	Wrong technique. There is a high chance of stimulating *Sishencong* if using this pressing technique	**0.5**

Table 26. Results of the true self-acupressure protocol validation

Components	Validation Assessment of the components			I-VI
	Number of experts rating "very appropriate"	Number of experts rating "appropriate"	Number of experts rating valid	
True acupressure protocol				
Selection of the acupoints				
Baihui	3	2	5	0.83
Yintang	2	4	6	1
Fengchi	2	4	6	1
Neiguan	3	3	6	1
Shenmen	5	1	6	1
Taichong	1	5	6	1
Pressing technique				
Baihui	3	2	5	0.83
Fengchi	5	1	6	1
Other acupoints	4	2	6	1
Duration of each section	1	4	5	0.83
Duration of whole treatment	3	2	5	0.83
Frequency	4	1	5	0.83
Time for practice self-acupressure	4	1	5	0.83
P-VI				**0.92**

Table 27. Results of the sham self-acupressure protocol validation

Components	**Validation Assessment of the components**			**I-VI**
	Number of experts rating "very appropriate"	Number of experts rating "appropriate"	Number of experts rating valid	
Selection of the sham acupoints				
SA 1	2	3	5	0.83
SA 2	2	4	6	1
SA 3	3	2	5	0.83
SA 4	2	3	5	0.83
SA 5	2	3	5	0.83
SA 6	2	4	6	1
Pressing technique				
SA 3	3	3	6	1
Other acupoints	4	2	6	1
Duration of each section	2	3	5	0.83
Duration of whole treatment	4	1	5	0.83
Frequency	4	1	5	0.83
Time for practice self-acupressure	4	1	5	0.83
P-VI				**0.89**

Table 28. The final true and sham self-acupressure protocols

Sequence acupoint	Location	Pressing technique	Frequency, duration
True acupressure protocol			
Baihui (GV20)	On the head, 5 B-cun superior to the anterior hairline on the anterior median line	using middle or index finger pad firmly massage the surrounding area of the acupoints with moderate pressure at rhythm of one second per cycle	3 min
Yintang (EX-HN3)	The midpoint between the eyebrows	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements.	3 min
Fengchi (GB20)	In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of sternocleidomastoid and the trapezius muscle	using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally	3 min both size at the same time
Neiguan (PC6)	On the anterior aspect of the forearm, between the tendons of the palmaris longus and the flexor carpi radials, 2 B-cun proximal to the palmar wrist crease.	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements.	3 minutes for each side
Shenmen (HT7)	On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease.	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements.	3 minutes for each side
Taichong (LR3)	On the dorsum of the foot in the depression distal to the junction of the first and second metatarsal bones.	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements.	3 minutes both size at the same time
Sham acupressure protocol			
SA 1	Base of metacarpal bone of the right middle finger	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements	3 minutes
SA 2	2 cm superior to the end of the right eyebrow		3 minutes
SA 3	Mastoid bone	using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally	3 minutes both size at the same time
SA 4	Head of ulnar styloid	using thumb pad, firmly massage the surrounding area of this acupoint with rotation movements	3 minutes for each side
SA 5	Base of metacarpal bone of the index finger		3 minutes for each side
SA 6	Medial malleolus		3 minutes both size at the same time
Duration of each section: 24 minutes			
Duration of whole treatment: 4 weeks (28 days)			
Time for practice self-acupressure: Before bedtime (final activities of the day, after practicing acupressure the participants should attempt to sleep)			

CHAPTER 6. THE METHODOLOGY OF THE INTERVENTION FEASIBILITY TRIAL

6.1. Introduction

A Randomized Control Trial (RCT) is the golden standard for evaluating the efficacy of intervention since this is the most rigorous method to examine the effectiveness of the treatment (Schulz et al., 2010). This method aims to minimize certain sources of bias and control confounding or prognostic factors that can affect the results of the study by including proper control groups, randomization, and blinding (Viera & Bangdiwala, 2007). However, before running a large-scale trial, there is a need to assess the feasibility of the study procedure. Feasibility study generally is used to identify possible issues and resolving problems related to the implementation of the trial (Hertzog, 2008). For this reason, we decide to conduct this feasibility study with the objectives are:

(1) To assess the feasibility of the recruitment process.

(2) To determine the attrition rate and reason for attrition during the follow-up process.

(3) To determine the feasibility of the study measurements.

(4) To evaluate the participant's acceptability of the intervention.

(5) To assess the fidelity of the trial.

(6) To identify potential adverse events associated with self-acupressure.

(7) To preliminary evaluate the effects of self-acupressure on the severity of the symptom cluster, individual symptoms, and participants' quality of life.

(8) To determine the sample size for the future full-scaled randomized controlled trial.

(9) To refine the study protocol for a future full-scale randomized controlled trial.

This chapter presents the design of the feasibility study to evaluate the trial process, which includes eight sections. The chapter begins with the introduction (section 6.1) followed by the study design (section 6.2) and the description of the settings and study

participants (section 6.3). Afterward, the sample size estimation was reported (section 6.4). The details of the intervention and control arms were located in section 6.5, while section 6.6 described the study process and data collection. The data analysis includes detail of outcome measurements were reported in section 6.7. Finally, ethical consideration is presented in section 6.8.

6.2. The study design

The design of the study was a three-arm randomized sham-controlled trial in a 1:1:1 allocation ratio, allocation concealment, and single-blind. The three trial arms were the true self-acupressure group, the sham self-acupressure group, and the enhanced standard care group. Managing the non-specific effect was found to improve the reliability of acupuncture/acupressure treatment (Hrobjartsson & Gotzsche, 2010). The non-specific effect is referred to positive change in patient outcomes that are associated with patient's desire for symptom relief (Tough et al., 2009), or patient's perceptions of the treatment (Dowrick & Bhandari, 2012), or the communication between the therapists and participants (Paterson & Dieppe, 2005). As such, the sham acupressure group must be included to serves as a control group to test the specific effect of self-acupressure. In this study, participants in the sham self-acupressure group stimulated a non-acupoint without eliciting *deqi* sensation. As such, the sham treatment was believed to create no therapeutic effect (Xiang et al., 2018). Therefore, the sham treatment helps to distinguish between the specific effect and the non-specific effect of self-acupressure, which cannot be managed in the waiting-list control or standard care control group. The "enhanced standard care" control group must also be included. An enhanced standard care control group refers to a group that receives no intervention, but standard care provided by the hospitals and some tips to manage insomnia, depression, and anxiety from the researcher. The enhanced standard care control group serves as a benchmark, allowing researchers to compare the intervention group to the control group to see the changes in the outcomes of the study. It allows researchers to assess the effect of the intervention against not receiving treatment during that same period. This group also helps to test the size of the non-specific effects of the self-acupressure treatment by comparing the effect of the intervention between the sham self-acupressure group and the "enhanced standard care" group (Tan et al., 2015).

The design of the feasibility study followed the Standards for Reporting Intervention in Controlled Trials of Acupuncture 2010 version (STRICTA), which is an official extension of the Consolidated Standards of Reporting Trials statements (CONSORT) (Svenkerud & MacPherson, 2018). Participants from two oncology hospitals in Hanoi, Vietnam, were recruited and randomized to 4-week self-acupressure intervention or the 4-week sham self-acupressure or 4-week enhanced standard care control groups. The outcome measurement of the feasibility study including the numerical rating scale (NRS) to measure the severity of insomnia, depression, and anxiety separately, the ISI, HADS, FACT-G, sleep diary, Intervention Rating Profile-15 (IRP-15). Specific effects of self-acupressure were measured by comparing the patient's outcomes between the true self-acupressure group and the sham self-acupressure group. The non-specific effect of the treatment was measured by comparing the patient's outcomes between the sham self-acupressure group and the enhanced standard care group. The true and sham self-acupressure treatment protocols used in the feasibility study had been validated. All outcomes were measured at baseline (T1, before the randomization), at the end of the 4th week (T2, at the end of the intervention), and at the end of the 8th week (T3, after 4-week follow-up period). Participants in the true and sham self-acupressure group were blinded to the group assignments.

6.3. Setting and study participants

6.3.1. Settings

The feasibility study was conducted in two large oncology hospitals in Vietnam, which are the Vietnam National Cancer Institute, and Hanoi Oncology Hospital. They were hospitals where the cross-sectional survey was conducted. All of them are located in Hanoi, the capital of Vietnam.

(1) **Vietnam National Cancer Institute (Hospital A)**: This is the largest cancer hospital in Vietnam, the hospital has 1500 beds and is in charge of providing cancer treatments for patients from North and Middle of Vietnam. On average, the hospital receives about 1100 patients every day. The hospital has three branches, data were collected in the largest branch of the hospital which has two chemotherapy units. The A1 chemotherapy unit provides chemotherapy

treatment for patients diagnosed with breast cancer or gynecologic cancer. The A2 chemotherapy unit provides chemotherapy treatment for patients with various cancer diagnoses (such as lung cancer, gastrointestinal cancer, Non-Hopkin lymphoma). These units have 24 wards, 130 beds in total. There are 22 doctors and 40 nurses. Every day these units received about 160 patients.

(2) **Hanoi Oncology Hospital (Hospital B)** is a public hospital that is in charge of providing cancer treatment for patients in Hanoi. The hospital has 500 beds and receives about 300 patients per day. There are two chemotherapy units in this hospital. The C1 unit provides chemotherapy treatment for breast cancer patients and gynecologic cancer patients. The C2 unit provides the treatment for patients with various cancer diagnoses (such as lung cancer, gastrointestinal cancer, Non-Hopkin lymphoma). There are 120 beds in these units with eight doctors and 24 nurses. The chemotherapy units provide treatment for approximately 80 patients per day.

The average nurse to patient ratio is quite equal in these settings (approximately from 1:3 to 1:4). These hospitals are public institutions. Thus, the standard care for cancer patients undergoing chemotherapy has followed the standards of the Vietnam Ministry of Health. The quality of staff and health care services among those settings are equal. So it can be said that the treatment environment in potential settings is similar.

6.3.2. Participants

The participants were patients receiving chemotherapy at the Vietnam National Cancer Institute and Hanoi Oncology Hospital, commencing from December 2018 to June 2019. Eligibility criteria for participation of the study are reported below.

Inclusion criteria:

To be included in the trial, patients have to be:

- Undergoing chemotherapy currently.
- Age 20 – 84 years' old
- Able to read and write Vietnamese (to complete the questionnaires and provide informed consent).

- Report all three symptoms (insomnia, depression, and anxiety) in the previous week and ranked the severity of each of the symptoms as four or more on a Numerical Rating Scale (from 0 to 10) at the time of recruitment.
- Have Karnofsky score ≥ 80 (to be able to practice self-acupressure).
- Have Insomnia Severity Index score ≥ 11 (as an optimal cutoff point to detect a majority of patients with insomnia and this score has obtained a sensitivity of 97.2% and specificity of 100% in the study by Savard et al. (2005)
- Have Anxiety score measured by HADS ≥ 8 and Depression score measured by HADS ≥ 8 (as an optimal cutoff point to detect cases with the sensitivity and specificity of 90% for both anxiety and depression as shown in the study by Bjelland et al. (2002).

Exclusion criteria:

Patients are excluded from the trial if they:

- Are unable to understand or cooperate with study procedures.
- Are receiving other cancer treatments (e.g., radiotherapy, hormonal therapy) at the same time as receiving chemotherapy and during the period of their involvement in the trial (to avoid the selection bias by ensuring all participants were under the same treatment condition)
- Are participating in other research studies which may have interacted with the current trial or affect insomnia, depression, anxiety perception.
- Are receiving insomnia or depression/anxiety treatment currently.

6.4. Sample size estimation

According to the rule of thumb, 30 subjects must be recruited for each study group as the requirement for a feasibility study involving between-groups comparisons and effect size estimation (Hertzog, 2008; Lancaster et al., 2004). The potential attrition rate of 20% is used to calculate the total sample size for the feasibility study. This is the attrition rate of previous similar RCTs using three-group designs to evaluate the efficacy of self-acupressure to reduce symptoms in cancer patients (Chung et al., 2015; Zick et al.,

2016). Therefore, the total sample size was set at 114 patients, with 38 patients per group.

6.5. Trial arms: Intervention and control arms

There are one group receiving the intervention (the true self-acupressure group) and two control groups (the sham self-acupressure and enhanced standard care group) in this study. Detail of how the three study groups were operated are presented below, while the summary is presented in **table 29.**

6.5.1. Enhanced standard care group (ESC)

The ESC group received the usual care provided by the hospital and an education session on "10 recommendations to manage insomnia, depression, and anxiety." These recommendations include some basic sleep hygiene rules (Posner & Gehrman, 2011) and recommendations for managing anxiety and depression adapted from the Anxiety and Depression Association of American's website at http://www.apa.org/topics/anxiety/index.aspx. (Anxiety and Depression Association of America, 2018). A leaflet with ten recommendations was used and given to participants during the education session. Below is the detail of these recommendations:

(1) Take a time-out. Going out, listen to music, or do whatever you like to help clear your head.
(2) Eat well-balanced meals. Avoid consuming coffee, alcohol, and nicotine.
(3) Exercise daily to help you feel good and maintain your health.
(4) When you feel anxiety, take deep breaths. Inhale and exhale slowly. Count to 10 slowly. Repeat, and count to 20 if necessary.
(5) Accept that you cannot control everything. Put your stress in perspective: Is it really as bad as you think?
(6) Welcome humor. A good laugh goes a long way.
(7) Maintain a positive attitude. Make an effort to replace negative thoughts with positive ones.
(8) Get involved. Volunteer or find another way to be active in your community, which creates a support network and gives you a break from everyday stress.

(9) Talk to someone. Tell friends and family you're feeling overwhelmed and let them know how they can help you. Talk to a physician or therapist for professional help.

(10) Try to get good sleep by applying the following rules:

- Regular bedtime, arising time or both
- Avoid naps if possible
- Avoid frequent use of bed for non-sleep related activities (e.g. watching TV, reading, studying, snacking)
- Avoid mental activities such as thinking, planning, reminiscing, etc. to occur in bed.
- Curtail time in bed. If you cannot sleep, you are advised to leave the bed, do some other activities such as: reading a book, listening to soft music and only come back to bed when you feel sleepy.
- Eliminate the noise from the bedroom.
- Have a comfortable pre-bedtime routine (light snack before bedtime, comfortable bed mattress, appropriated temperature for bedroom, comfortable sleep clothes)

The standard care hospital for cancer patients undergoing chemotherapy includes health assessment, regular health advice regarding symptoms that patients report and nutrition advice while taking chemotherapy treatment. On the first day admitted to the hospital, the patients will receive a health assessment session by doctor and nurses. If the result of the health assessment reflects that patients can receive chemotherapy treatment, the patients will be scheduled to start their chemo-cycles in the following days. During receiving chemotherapy treatment, patients stay in the hospital. However, patients who already completed several chemo-cycles can choose to stay in the hospital or only come to the hospital to receive the treatment then come back home/guess house in the nighttime. The doctors and nurses also monitor them during the treatment. After receiving chemotherapy treatment (from one to three days), patients receive another health assessment session by doctors or nurses. In this session, health education

regarding symptoms that patients report, nutrition advice, and schedule for the next chemo-cycle are included. Afterward, patients are being discharged from the hospital and then come back for the next chemo-cycles, which are delivered three or four weeks apart. There is no standard care for depression and anxiety since patients normally do not report these symptoms during the health assessment, and also these symptoms are not assessed by a healthcare professional when the patients admitted to the hospital. Unless the symptoms become so severe that patients give up on treatment or attempt suicide, the doctor refers patients to psychological counseling services. The standard care for patients with insomnia in the hospitals includes giving hypnotics to patients (Diazepam 5mg) for 1 to 3 days and some tips to help the patient improve their sleep. However, since the duration of using hypnotics was short (3 days maximum), the use of this drug did not influence the results of the trial. Besides, in this trial, all participants were requested to report the use of any drugs or supplements to manage insomnia, depression, and anxiety during the time they participated. If the number of participants using drugs or supplements to manage the targeted symptoms was higher than 5, their use of these drugs would become a covariant to control in the statistical model. Although standard care guidelines are available in the hospitals where the study took place, they are not being followed properly. Based on the Ph.D. student's observation, the health educations regarding insomnia is provided verbally to the patient in a few minutes by nurses. Many participants do not receive this education. This fact can be explained by the hospital overcrowding and shortages of nurses in Vietnamese cancer hospitals.

In this study, apart from the standard care provided by the hospitals, by providing participants in the ESC this education session, we slightly enhance the standard care but do not contaminate the effective of the intervention since these recommendations are basic and participants can easily read about them on the internet or newspaper. In addition, to minimize the bias caused by contact between researchers and participants, the education session was conducted at the same length with the acupressure training session (30 minutes). After being discharged, participants were told to apply these commendations as much as possible to their daily life. During the first four weeks of the study, weekly telephone reminder was made (same as participants in the true and

sham acupressure group). It was a neutral conversation between the Ph.D. student and the participant in three to five minutes. The Ph.D. student asked some questions such as how the participant was, does the participant take any kind of medication to manage their symptom, and reminded the participant to come back to the hospital for the next chemo-cycle on time. During the call, the main research avoided discussing any kind of management for insomnia, depression, and anxiety.

6.5.2. True self-acupressure group [Enhanced standard care + true self-acupressure group]

Participants in this group received a true self-acupressure training session in a group of two to three patients in 30 minutes in the consultation room, as a previous study showed that it took 15 minutes on average for participants to learn the self-acupressure technique (Zick et al., 2012). In the acupressure training session, we instructed the participants on how to locate and stimulate acupoint following the self-acupressure protocols. After giving instruction and time for participants to practice, we checked the patient's mastery of self-acupressure technique by using the Self-Acupressure Skill Check form A for participants (Please see Appendix 8). The self-acupressure skill check allowed the interventionists to check the accuracy of the acupoint's location and stimulation technique. If the participant failed to identify the acupoint or stimulate the acupoint wrongly, the interventionist then corrected them. By the end of the training session, a handout with step by step guide with the images-illustrating true self-acupressure protocol were given to participants together with the ten recommendations (as presented in page 152) on how to improve insomnia, depression, and anxiety (same as participants in ESC group). Participants were requested to practice acupressure and apply ten recommendations at home for four weeks. During the four weeks of treatment, they received a weekly phone call from researchers for encouraging to practice acupressure and answer queries that they may have.

6.5.3. Sham self-acupressure group [Enhanced standard care + sham self-acupressure group]

Participants in this group also received a sham self-acupressure training session with the same length and manner as the true self-acupressure group. By the end of the sham

self-acupressure training session, participants were checked for the mastery of the sham acupressure technique by using the Self-Acupressure Skill Check form B (Please see Appendix 8). A handout with step by step guide with the images-illustrating sham self-acupressure protocol was given to participants together with the ten recommendations on how to improve insomnia, depression, and anxiety (as presented in page 152). Participants were requested to practice self-acupressure and apply ten recommendations at home for four weeks. During the four weeks of treatment, they received a weekly phone call from researchers for encouraging them to practice self-acupressure and answer inquiries may have.

Table 29. Summary of the study arms and intervention

Study arms	**Intervention components**		
	Acupressure training True-self acupressure follow the protocol 4 Weekly follow – up phone call	Acupressure training Sham-self acupressure follow the protocol 4 Weekly follow – up phone call	Heath assessment Nutrition advice Hypnotics (when necessary) Patient Leaflet 4 Weekly follow-up phone calls
True self-acupressure group	✓		✓
Sham self-acupressure		✓	✓
Enhanced standard care			✓

✓ Components of the intervention are included in each of the study arm

6.6. Study process and data collection

6.6.1. Study procedures

The Ph.D. student met the representative of the two hospitals (in Hanoi, Vietnam) one month before the commencement of the feasibility study to asking for permission to collect the data. Ethical approval memos, a study packet that contained the study proposal, information sheet, invitation letter, and consent form were given to the representatives of the hospitals. After receiving approval for data collection, the Ph.D.

student worked with hospital authorities to recruit interventionists and research assistance to help in screening. Four nurses were trained to become interventionists for the study (2 nurses/hospital). Nurses who worked in hospitals with at least two years' experience in caring for cancer patients were recruited as interventionists of the study. All of them were the head nurses of chemotherapy units. Moreover, four other nurses (2 nurses/hospital) were trained to be researcher assistance helping in screening and recruiting participants. A TCM professional was in charge of training the interventionists for the feasibility study. She was a senior lecturer of the Traditional Medicine Department, Hanoi Medical University, with seven years of experience in teaching, practicing, and conducting research on acupuncture/acupressure. The Ph.D. student was in charge of training research assistance in helping to screen and recruit participants.

Training of the interventionists and subject recruitment

Four nurses were trained to become interventionists for the study (2 nurses/hospital). A one-hour interventionist and subject recruitment training session was delivered by the Ph.D. student and the TCM professional. It consisted of three parts. In the first part of the interventionist and subject recruitment training session, the Ph.D. student briefly introduced the main study proposal include the rationale for conducting this study, the study aim and objectives, study protocol, and outcomes measurement. In the second part, the TCM professional instructed the participants on how to locate and stimulate acupoints following the true and sham self-acupressure protocols. By the end of the training session, the TCM professional checked the mastery of the interventionist's acupressure technique by using Interventionist Skill Checklist for self-acupressure (Please see Appendix 7). If the wrong location or technique was given, further instructions were made until all of the participants know how to locate and stimulate acupoint as indicated in the acupressure protocol. In the last part, the Ph.D. student introduced the self-acupressure and enhanced standard care training protocol to the interventionist and asked them to strictly follow these protocols when they deliver the training sessions to participants (Please see appendix 6 and 9). By the end of the training session, a copy of all slides and self-acupressure protocols, the ten recommendations on

how to manage insomnia reported in section xxx, depression, and anxiety, the self-acupressure and enhanced standard care training protocol were given to participants.

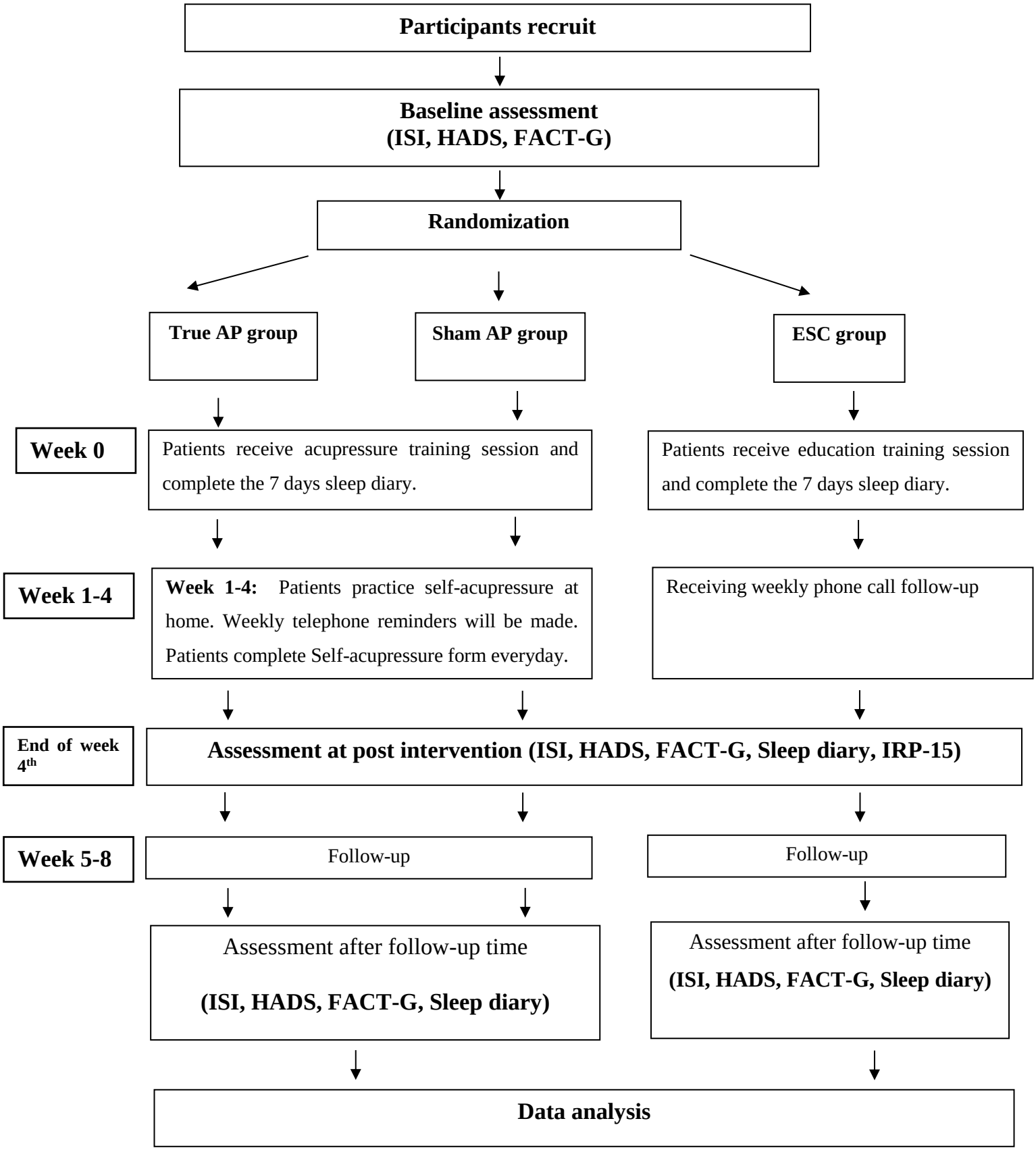
Subject recruitment and data collection

Participants from four chemotherapy units were recruited to the study (two chemotherapy units in hospital A, and two from hospital B). On the first day patients admitted to the hospital, during the health assessment, nurses asked the patients to rate the severity of insomnia, depression, and anxiety that they experience during the previous month on three separate Numerical Rating Scales (NRS). If the patients rated 4 or above for their insomnia, depression, and anxiety, nurses informed the Ph.D. student. The Ph.D. student met and introduced the study in detail to participants and gave them the information sheet. The information sheet provided brief and clear information on the essential elements of the study: the aim of the study, the study procedure, the voluntary involvement, participant rights, and potential risks, and contact information (Please see Appendix 1). The Ph.D. student gave participants time to read the information sheet and decided whether the study was interested them and whether they wanted to discuss it further. Participants could ask the Ph.D. student any questions related to the study. If the potential participants agreed to participate in the study, they were given the informed consent form to sign. After signing the consent form, the Ph.D. student collected the demographic data of the participants and instructed them to complete the ISI, HADS, and FACT-G. Afterward, the Ph.D. student summarized the results. If the participant was not eligible for the trial, he/she was informed that their symptoms were not severe enough to participate in the study. As such, their baseline data including demographic, clinical characteristics, ISI, HADS, and FACT-G were subsequently destroyed.

On the other hand, if the participant was eligible for the trial, he/she was instructed how to complete the seven days sleep diary after being discharged from the hospital. Then the participant was randomly assigned to one of the following groups: the true self-acupressure group (True AP), the sham self-acupressure group (Sham AP) and enhanced standard care group (ESC). Subject recruitment, baseline assessment, and

randomization were completed on the first or the second-day participants admit to the hospital. Sleep diary was completed in the first week after the participants discharged from the hospital. Training sessions were scheduled on the same day or one day after participants finish baseline assessments based on the availability of the participants and interventionist. Details of the training session for participants in the true/sham self-acupressure group and the enhanced standard care group were described in session 6.5. After the self-acupressure training session, participants in the true/sham acupressure group were requested to practice acupressure and apply ten recommendations on how to improve insomnia, depression, and anxiety at home for four weeks. Participants in the ESC were asked to apply ten recommendations on how to improve insomnia, depression, and anxiety at home for four weeks.

After four weeks treatment, all participants were asked to complete and send back all the post-intervention assessing questionnaire to the Ph.D. student by express service (Numerical Rating Scale [NRS], Insomnia Severity Index [ISI], Hospital Anxiety and Depression Scale [HADS], FACT-G, Sleep Diary [SD], Self-acupressure Record Form, and Intervention Rating Profile 15 [IRP-15]). A short-term follow-up was then carried out in four weeks to assess the persistence effect of acupressure on the symptom's outcome. During this time, the patients in the true/sham acupressure groups were asked to stop practicing self-acupressure at home. By the end of follow-up time, the Ph.D. student called the participants and asked them to complete and send back all the post follow-up assessment questionnaires by express service (ISI, HADS, FACT-G, sleep diary). The time points for collecting data is presented in **table 30**. Two hundred thousand Vietnam Dong (equal to 70 HKD) were given to participants to cover the express mail service charge by the end of the follow-up time. The procedure of the feasibility study is depicted in **Figure 6** depicts the feasibility study procedures.



Note: True AP: True self-acupressure, sham AP: Sham acupressure, ESC: Standard care

Figure 7. The flowchart of the feasibility trial

Table 30. Time points for data collection during each participant's involment in the feasibility trial

	Screening	**Week 0 Baseline**	**Daily (from week 1-4)**	**Week 4**	**Week 8**
Number of eligible participants	X				
Number of eligible participants sign the informed consent form	X				
Reason for ineligibility, refusal	X				
ISI		X		X	X
HADS		X		X	X
NRS for each symptom		X		X	X
Sleep diary		X		X	X
FACT-G		X		X	X
Karnofsky performance status scale		X			
Self-Acupressure Record Form			X		
Assessment treatment fidelity		X		X	
Adverse Events				X	X
IRP-15				X	
Concomitant medication and Supplement	X	X		X	X

6.6.2. Randomization, allocation concealment

Randomization refers to a method based on chance only by which participants are assigned to a trial group. Randomization also helps to ensure the allocation concealment, which refers to preventing researcher, clinicians, and participants from being known the next group assignment and thus influencing group assigning process (Altman et al., 2001). Randomization is an important component of trial design to evaluate the true benefits of a treatment since a trial with inadequate and unclear

concealment of allocation sequence is believed to produce 40% larger estimation of the effectiveness of a treatment (Jüni et al., 2001).

In this feasibility study, block randomization was applied to keep the equal size of each trial arm. After being recruited in the trial, 114 participants were randomized into three study groups in a block of six participants. The block size must be the multiplier of the sum of the treatment ratio (1:1:1). Therefore the block size must be 3, 6, 9, etc. As such, six is the size of the block since 114 is divisible by six. A randomization table was computer-generated by using the online randomizer at https://www.sealedenvelope.com/simple-randomiser/v1/lists . The randomization table was prepared and kept by a researcher at Phenikaa University, Hanoi, Vietnam, who did not involve in any research process. After recruiting enough participants for a block, the Ph.D. student sent the list of participants' names to the researcher who kept the randomization table. The randomization table keeper then randomly assigned participants into trial groups based on the prepared randomization table and emailed or texted the group assignments to the Ph.D. student. By using this strategy, the trial ensures the allocation concealment since researchers were unable to predict and change the group allocation after randomization (Vickers, 2006).

6.6.3. Blinding

Blinding refers to ensure that participants or personnel within a trial are unaware of treatment allocation. There are several levels of blinding include single-blind which refers to one party of the trial (participants or researchers) is blinded to the treatment allocation, double-blind refers to two parties (participants and researchers) are blinded to the treatment allocation, and triple-blind refers to three parties of the trial (participant, researchers and other staff involved in the trial) are blinded to the treatment allocation (Friedman et al., 2015). Blinding design is applied to reduce detection bias and performance bias (Probst et al., 2016). In this study, due to the nature of the intervention, a single-blinded design was employed. Participants randomized in ESC group knew their group assignment, but participants randomized to true and sham self-acupressure groups did not know whether they receive true or sham self-acupressure treatment. To ensure the successful blinding design, the Ph.D. student also worked with

the head-nurse of the departments to arrange patients in the true and the sham acupressure group into different wards.

6.6.4. Fideltity of the study

Fidelity of the intervention referred to strategies to ensure the intervention is implemented as planned (Bellg et al., 2004). Basic aspects of treatment fidelity are intervention design, intervention training, and receipt of intervention (Murphy & Gutman, 2012). The current study involves a self-administered intervention. As such, we used the behavioral change components, which was outlined by the Treatment Fidelity Workgroup of the Behavior change Consortium at the National Institutes for Health (NIH-BCC workgroup) to report and develop strategies to ensure the fidelity of the study. The NIH-BCC workgroup components to assure fidelity for intervention include study design, training interventionists, participants training, participant's self-delivery of the intervention, and enactment of the intervention skill (Bellg et al., 2004). Strategies to ensure the fidelity of this study are listed in each of the above components.

6.6.4.1. Fidelity of the feasibility design

Strategies for enhancing treatment fidelity regarding study design are aimed to ensure the same treatment dose with conditions, ensure equivalent dose across conditions, address potential setbacks. For this aspect, the true and sham self-acupressure protocol has been developed and validated. The detailed self-acupressure intervention was described including the location of acupoints, acupressure technique, dose of the intervention. To ensure the equal number of contacts for each intervention arms to minimizer potential bias, patients in control groups also received the training in the same length and enthusiasm as in the intervention group. Potential setbacks and solutions were identified and are listed below:

- Provider drop-out: four nurses were trained to be interventionists to deliver acupressure training sessions. Two of them were the main interventionist and others were the extra interventionists. Therefore, the intervention had three main interventionists (including the Ph.D. student). The main interventionists were in

charge of delivering the participants training sessions when they were not available the extra instructor replaced them.

- Lost to follow-up due to not available phone number: In order to keep contact with participants during the study period, the participant's mobile phone, the participant's fixed-line numbers were recorded. Participants were given the name card of the Ph.D. student.

- To ensure the fidelity of outcome measurements, participants were instructed on how to complete the questionnaires and sleep diary. Telephone reminders were also be made to remind participants to complete and send back the follow-up questionnaire to the Ph.D. student. Envelopes with the address of the Ph.D. student were provided to participants. If there was no reply from participants after the first telephone reminder, the second one was made five days later.

6.6.4.2. Training of the interventionists

The interventionists must be trained to ensure they have been satisfactory to deliver the intervention to participants. The training must be evaluated and monitored. Strategies for this aspect included standardize training, ensure interventionist skill acquisition, and minimize "drift" in interventionist skills (Bellg et al., 2004). Strategies to ensure fidelity of training interventionist are reported as below:

(1) Standardize training: to ensure the training was conducted similarly for different provider, a training session was conducted by the Ph.D. student and a TCM doctor. Four nurses were trained to become interventionists for the study (2 nurses/hospital).

(2) To ensure interventionist skill acquisition between interventionist, by the end of the training sessions, the ***TCM professional checked the mastery of participant'***s acupressure technique by using the "Interventionist Skill Checklist for Self-acupressure" and "Interventionist Skill check for Sham self-acupressure". Interventionists were checked for the location and stimulation technique of true and sham-acupoint (Please see appendix 7). If the wrong location or technique were given, further instructions would be made until all of

the participants know how to locate and stimulate acupoint as indicated in the self-acupressure protocol**.**

(3) Minimize "drift" in interventionist skills: to ensure the interventionist skills did not decay over time, by the end of training session, a copy of all slides and an images-illustrating self-acupressure protocol was given to participants for references. Besides, during the training session, the Ph.D. student recorded the training session and sent it to the interventionists. They could play the video back to enhance the acupressure mastery before delivering the intervention to participants.

(4) To ensure the self-acupressure training session run smoothly, the researcher provided a comfortable environment. The rooms were convenient to reach, keep quiet and clean, equipped with necessary furniture, such as comfortable chairs, tables, air-condition, refreshment.

6.6.4.3. Participants training

The aim of this aspect is to ensure participants understand the information provided in the training sessions and able to use and perform knowledge taught in the intervention (Bellg et al., 2004). Strategies to ensure fidelity of training participants are reported as below:

Maintaining consistency of delivering intervention among four interventionists: To ensure consistency of delivering intervention among interventionists, the following plans were implemented. ***The protocol for self-acupressure training sessions and enhanced standard care education sessions*** (for participants) were also developed, and interventionists were requested to follow this protocol when delivering the training to participants (Please see Appendix 6 and Appendix 9). To ensure the training sessions are implemented in the same manner, ***the Ph.D. student monitored at least 80% of training sessions.*** If there are any problems occur, the researcher discussed with the interventionist.

Participants training

The self-acupressure training session was conducted in a small group (two to three participants). Participants were given training on how to perform the acupressure specific to the protocol for their group assignment. After the training session, interventionists used the "Acupressure Skill Check Form" to check the mastery of the participants. The location and stimulation technique of the true and sham acupoints were checked (Please see appendix 8). If the wrong location or stimulation technique were given, the interventionist would correct and further instruct until participants know how to locate the acupoint and stimulation technique. By the end of the training session, an images-illustrating acupressure protocol was given to participants for references. To ensure the training sessions run smoothly, the researcher provided a comfortable environment and facilities. The rooms were convenient to reach, keep quiet and clean, equipped with necessary furniture, such as comfortable chairs, tables, air-condition, refreshments.

6.6.4.4. Participants' self-delivery of the intervention

The aim of treatment fidelity strategies is to ensure participants practice acupressure follow the acupressure treatment protocol provided in the intervention. Participants were expected to perform self-acupressure daily following the treatment protocol. To enhance and monitor the participant's adherence to the treatment as well as to answer any question during the study period, weekly telephone reminders were made, and contact information was also provided to participants. Participants were requested to record their self-acupressure session on the intervention log during the treatment period. Participants also had a follow-up visit with interventionists when they admit to the hospital for their next chemo-cycles (approximately 3 to 4 weeks after the training session). During the visit, the interventionist checked the patient's mastery of the self-acupressure technique by using the Self-Acupressure Skill Check Form. The ability of participants to perform the intervention was evaluated with the goal of maintaining at least 80% accuracy on the Self-Acupressure Skill Check Form.

6.7. Data analysis

6.7.1. Outcome measurements

The aim of this feasibility study is to assess the potential for the success of the implementation of an RCT to test the effectiveness of self-acupressure in improving the symptom cluster of insomnia, depression, and anxiety. Therefore, it does not necessarily need to have a primary outcome and secondary outcomes (National Institutes of Health, 2012; Tickle-Degnen, 2013), as one of the reasons for carrying out a feasibility trial is also to explore appropriate primary outcomes for a future trial. As such, the outcomes are regarding the objectives of the studies. Details of the study's outcome measurements are presented below.

Objective 1: To evaluate the feasibility of the recruitment process

- The recruitment rate, the eligible rate, and refusal rate during the recruitment process were calculated based on the number of screened patients, the eligible patients, the number of eligible patients who finally agree to participate in the study, reason for ineligibility, refusal, and time to recruit participant were recorded.

Objective 2: To determine the attrition rate and reason for attrition during the follow-up process

- The attrition rate was calculated by the number of participants who left the study. Reasons for attrition were recorded.

Objective 3: To determine the feasibility of the study measurements

- Missing data for all measurements were recorded to estimate the feasibility of the outcome measurements used in this trial.

Objective 4: To evaluate participant's acceptability of the intervention

- The adherence rate was calculated based on the number of participants correctly following the treatment protocol, which will be measured by the "Self-Acupressure Record Form." (adherence rate= number of participants practice acupressure in 28 days/total number of participants in the group at post-

intervention). Self-Acupressure Record Form required participants to record their self-acupressure session in 14 days, the number of acupoints, treatment time was recorded in this form. The reason for not practicing self-acupressure and related adverse events were also recorded. Participants were also requested to report any self-care methods or drugs/supplements to manage insomnia, depression, and anxiety in this form (Please see Appendix 4).

- The acceptability score of the intervention will be measured by The Intervention Rating Profile – 15 (Martens et al., 1985). The Intervention Rating Profile – 15 (IRP-15) consists of 15 items. Each item is rated on a six-point Likert scale ranging from one (Strongly disagree) to six (Strongly agree). The higher score indicated higher acceptability of the intervention. A total score of 70 would represent a moderate level of acceptability, while 71 and above indicates a high level of acceptability (Carter, 2010). The scale had been validated, translated into Vietnamese with high reliability (Cronbach's $\alpha = 0.89$) (Nguyen et al., 2018). In this feasibility study, its Cronbach's alpha value was 0.93.

Objective 5: To assess the fidelity of the study

Based on different aspects of the fidelity of the study, the following information was recorded

Fidelity of the feasibility design:

- Number of interventionists dropped out during the study period
- Number of participants lost to follow up due to not available phone number
- Number of participants had a fixed-line telephone number

Fidelity of training interventionist

- Result of checking master of interventionist after the acupressure training session

Fidelity of participants training

- Time to instruct each participant in the true and sham acupressure group were recorded

- Number of training session supervised by the Ph.D. student
- Number of a training session conducted by interventionist that not follow the training protocol
- Result of the first round of checking acupressure mastery of participants

Fidelity of the participants self-delivery of the intervention

- Number of participants completed the true and sham acupressure treatment period
- Result of the second round of checking acupressure mastery of participants

Objective 6: To identify adverse events associated with self-acupressure

- Participants were requested to report adverse events related to acupressure in the "Self-Acupressure Record Form" (Please see Appendix 4).

Objective 7: To preliminary evaluate the effects of self-acupressure on the severity of the symptom cluster, individual symptoms, and participants' quality of life.

Using Numerical Rating Scale (NRS)

The intervention aims to manage a symptom cluster of insomnia, anxiety, and depression. As such, the severity of the whole cluster, as well as individual symptoms must be measured. Most of publications in symptom cluster management hasn't included a method to measure symptom cluster severity (Kwekkeboom, 2016; Su-Chen et al., 2015; Yeh et al., 2016; Zick et al., 2018). However, some authors proposed using separate NRS on their trial to measure the severity of each symptom in the cluster and calculate the severity of the whole cluster by averaging the individual symptom summary scores (Kwekkeboom et al., 2012; Nguyen et al., 2018). This method of composite outcome measurements has been applied to calculated multiple symptom severity and to detect the combined effect of the trial (Cleeland et al., 2013; Kuo et al., 2018). Therefore, in this trial, we use three NRS to measure insomnia, depression, and anxiety separately. The NRS is an 11-point scale with 0 means "not present," and 10 means "as bad as it could be." Symptom severity at the cluster level was evaluated by

the averaging symptom severity score of each symptom in the cluster. The symptom cluster severity is calculated by the following formula.

$$\boldsymbol{Symtom\ cluster\ severity} = \frac{\text{Anxiety score +Depression score +Insomnia score (measured by NRS)}}{3}$$

Besides using NRS, standardized tools such as the Insomnia Severity Index and the Hospital Anxiety and Depression Scales were used to measure insomnia, depression, and anxiety were also used.

Insomnia severity and participant's sleep parameters

The Insomnia Severity Index (ISI) was used to measure insomnia severity among participants. The higher ISI score indicates the more severe insomnia. The cut-off point for insomnia used in this trial was presented at inclusion criteria section (page 151). This instrument had been validated translated into Vietnamese previously (Long et al., 2016) and was being used in the cross-sectional study with high reliability (Please see section 4.2.3, page 104). The Cronbach's alpha coefficient of this scale in the feasibility study was 0.86. As discussed in Chapter 2, subjective (questionnaire) and objective measurements (actigraph) are required to measure sleep. However, the results of the cross-sectional survey in Chapter 4 (that will be discussed in chapter 8 in detail) indicated that the participants' insomnia severity is not associated with objective sleep measures, and using objective measurement causes difficulty in subject recruitment. Therefore, in this intervention, no objective measurement was used to measure sleep parameters among participants. A sleep diary was used to measure sleep parameters. The sleep diary is used to measure these sleep parameters: Total Sleep time (minute), total time in bed (minute), the number of nights awaken after sleep onset, and sleep efficiency. Participants were requested to complete the sleep diary when they wake up the next morning. A sleep diary is a useful tool for evaluating and tracking insomnia treatment effects (Buysse et al., 2006). In this study, the sleep diary (SD), which has been developed, standardized, and validated by 25 insomnia experts, is used to measure participants' sleep parameters (Carney et al., 2012). The following sleep parameters were measured:

- Sleep onset latency (SOL): the length of time that participant takes to accomplish the transition from full wakefulness to sleep,
- Total time spend in bed (TSB): is the length of time that participant spend in bed
- Wakefulness after sleep onset (tWASO): the period of wakefulness occurring after sleep onset.
- The number of nights awake after sleep onset (nWASO)
- Total sleep time (TST): is the length of time that the participant spent actually sleeping.
- TST (min) = TSB (min) – SOL (min) – tWASO (min)
- Sleep efficiency (SE): the ratio of total sleep time to the total time spent in bed.

$$SE\ (\%) = \frac{\text{TST (min) x 100}}{\text{TSB (min)}}$$

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith (1983) to measure depression and anxiety among participants. The higher HADS score indicates the more severe of depression and anxiety. A total score of *8 to 10* indicates participants had *mild depression/anxiety*; *11 to 14* for each of the sub-scale indicate the patients had *moderate depression/anxiety,* while *15 to 21* indicate the *severe anxiety/depression* (Bjelland et al., 2002; Stern, 2014). The cut-off point for depression and axiety used in this trial was presented at inclusion criteria section (page 151). This instrument had been translated into Vietnamese previously (Long et al., 2016). It was used in the cross-sectional study with the Cronbach's alpha for the scale was 0.87, and for anxiety subscale was 0.86, and for depression subscale was 0.76 (Please see section 4.2.5). In this feasibility study, its Cronbach's alpha values were 0.75 and 0.82 for the subscales of anxiety and depression, respectively.

Participants 'quality of life.

The Functional Assessment of Cancer Therapy-General (FACT-G) is used in this study to assess the quality of life in participants. This scale measure four domains of quality of life: Physical well-being (PWB) the severity of pain also being measured in this domain of the questionnaire; Social/family well-being (SWB); Emotional well-being

(EWB) and Functional well-being (FWB). The higher score indicates a better quality of life. This instrument has been translated into Vietnamese by FACIT system and had been used in the previous study with the Cronbach's alpha for the scale was 0.89, and for Emotional well-being, subscales were 0.78, FWB = 0.82, PWB = 0.81 and for SWB was 0.82 (Please see section 4.2.3). The Cronbach's alpha values were 0.77 in this feasibility trial.

6.7.2. Data analysis

IBM SPSS 20.0 was used for data analysis. Data cleaning was conducted before being analyzing. Intention-to-treat (ITT) principle is adapted for analyzing the result of the feasibility study. Missing data were managing using linear mix model analysis. Detail of approaches to analyze the data will be discussed in this section.

6.7.2.1. Data cleaning

Categorical data were checked by generating frequency counts to determine the frequency of the coding as well as missing values for each variable. Continuous data were checked by generating descriptive statistics (histograms or plots) to analyze means, minimums, and maximums to ensure the range of value is appropriate. These approaches allow the researcher to identify mistakes in codes, missing data, as well as ascertain if values out if the possible ranges have been entered (Portney & Watkins, 2015).

6.7.2.2. Intention-To-Treat (ITT) principle

Two common principles can be applied to analyze the data of an RCT including Intention-To-Treat (ITT) and Per-protocol (PP). The principal of ITT is that every participant randomized to the trial should enter the primary analysis. Accordingly, patients who drop out, dead, or non-compliant to the study treatment are included in the analysis within the respective treatment groups that they have been assigned to at randomization (McCoy, 2017). In contrast, PP analysis refers to include only those patients who adhered to the treatment protocol in the analysis (Ranganathan et al., 2016). Both approaches are valid but have different roles in the analysis of clinical

studies. An analysis according to the ITT analyze the study population is as complete as possible, and potential bias due to the exclusion of patients is avoided. While the aim of PP analysis is to identify a treatment effect which would occur under optimal conditions and create bias of inclusion only participant who strictly adherence to the treatment. Therefore, the ITT approach seems to under-estimate the effect of the intervention, while PP seems to over-estimate the effect. For instance, a recent RCT conducted to evaluate the protectiveness of early introduction of allergenic food in the diet to the development of food allergy in breast-fed infants in England (Perkin et al., 2016). The main outcome of the intervention is the development of food allergy between 1 and 3 years of age. The ITT analysis (1162 participants) indicated no difference between-group for the primary outcome while PP analysis (732 participants) showed a significant lower frequency of food allergy between the intervention group and the control group. In our study, while the ITT analysis (114 participants) reported significant difference between groups for two outcomes at post intervention (symptom cluster severity at T2, insomnia severity at T2), the PP analysis (74 participants) reported significant difference between groups for three outcomes at both post intervention and post follow-up (symptom cluster severity at T2, insomnia severity index at T2 and T3, depression severity at T3)

Consider the above issue, ITT principle is adopted to analyze the data in this current trial. This strategy has been widely used in analysis RCTs. Furthermore, it is proved that measuring the effectiveness of a trial may be biased without performing an ITT analysis (Hollis & Campbell, 1999).

6.7.2.3. Missing data management

Missing data due to attrition is a major problem in the analysis since this issue lead to bias in treatment comparisons and impact the overall statistical power of the trial. In an overview of handling missing data, the author listed basic strategies for analysis when missing data present which include complete-case analysis, weighting methods, imputation methods, analyzing data as incomplete (Myers, 2000). The complete-case analysis only includes those patients with complete data (similar to PP analysis). The weighting methods referred to construct weighs for complete cases in order to reduce or remove bias which allow generalized estimating equation analyses to be used. The

imputation methods referred to fill the missing data with plausible estimated. The last observation carried forwards methods is a commonly used imputation procedure—the analyzing data as incomplete which typically performed in longitudinal studies. Due to the high attrition rate in the trial (35.1%), none of these above methods can be applied in analyzing since all of the drop-out participants left the trial before completing the intervention. However, using a model to predict the missing value is a way of handling the issue of high missing data proportion (Harrison et al., 2018). The linear mix effects model analysis was used to analyzing data regarding individual symptoms, symptom cluster severity (measured by NRS), ISI score, depression and anxiety score (measured by HADS), and quality of life (measured by FACT-G). The reason for choosing this model is because of its advantage in using available data to manage missing data for outcome variables directly related to the effectiveness of the intervention (Friedman et al., 2015).

6.7.2.4. Statistical analysis

In this feasibility trial, both descriptive statistics and inferential statistics were included. The significant level was set at $p<0.05$ for a two-tailed test. The data were analyzed using different methods regarding the types of variables and the numbers of participants in the study groups.

Statistical analysis of the feasibility outcomes.

(1) Feasibility of subject recruitment and follow-up process the recruitment rate, the consent rate, refusal rate, attrition rate, and reason for attrition were analyzed using descriptive statistics (number of patients and related percentage). Differences in the proportions of subject recruitments at different study sites were examined using the Chi-square test.

(2) Missing data for the outcome measurements

Descriptive analysis was used to examine the completion rate of the study outcome measurements. The percentage of missing values for each item in a questionnaire and the whole questionnaire was computed to demonstrate the feasibility of the questionnaire.

(3) Participant's acceptability of the intervention

Descriptive analysis was conducted to present the averaging number of days of acupressure treatment as well as the averaging time of self-acupressure sessions in the true AP and sham AP group. Fisher's exact test was used to determine the difference in the averaging number of days of self-acupressure and averaging time of self-acupressure sessions between two groups. The participants' acceptability of the intervention in the true AP group was present as mean and standard deviation.

(4) Adverse events of self-acupressure

Descriptive statistics (number of adverse events and related percentage) were used to demonstrate adverse events associated with acupressure in both true AP and sham AP group.

(5) Fidelity of the study

Descriptive statistics (number and related percentage) were used to demonstrate information regarding the fidelity of the study.

Statistical analysis related to participants' characteristics

Categorical data of participant's demographic and clinical characteristic, including gender, occupation, education, marital status, cancer diagnosis, cancer stage, surgical debunking, chronic disease (Yes/no) were analyzed using Chi-square test or Fisher's exact test to conduct baseline comparisons between-groups and between participants who completed the study and who withdraw. Continuous data from demographic and clinical characteristic, including age, time from diagnosis, number of completed chemo-cycles, baseline symptom cluster score, ISI, HADS, FACT-G and its subscale score were firstly checked for normality using Shapiro-Wilk test, and the assumption of homogeneity of variance was measured by Levene's test. For normal distribution data, a one-way ANOVA was conducted while Kruskal-Wallis test was utilized for non-normal distribution data.

Statistical analysis related clinical outcomes of the feasibility study

The preliminary effect of the intervention is determined by the change of scores for outcomes. Two methods were used to measure symptom severity in this study. The first

method is using Numerical Rating Scale (NRS) from 0 to ten to measure the severity of each symptom and the symptom cluster (by averaging score of three symptoms). The second method is using standardized tools to measure the severity of each symptom (Insomnia was measured by ISI, depression, and anxiety were measured by HADS). Quality of life was measured by FACT-G. The lower in symptom score, Insomnia Severity Index (ISI), depression score, and anxiety score (measured by HASD) indicated improvement while the higher Quality of Life score indicates a better quality of life. Linear mixed-effect model analysis used to evaluate the effect of the intervention in changing the score of each outcome between and within three study groups over time. In the model, the fixed effect is group, time, and group-time interaction, the ID of participants was put as the random effect. Bonferroni test was using as post-hoc comparison when there was any significant effect.

The impact of the intervention on participant's sleep parameters was investigated using one-way ANOVA and repeated measure.

Effect size estimations

The effect size was calculated by Cohen *d* based on the estimated means and standard deviations (results from the linear mixed effect model test) between the treatment group and control groups at post-intervention. The effect size was calculated for the differences between means of the symptom cluster and individual symptom score between study groups. An online tool developed by The Hong Kong Polytechnic University was used to calculate the effect size (at https://www.polyu.edu.hk/mm/effectsizefaqs/calculator/calculator.html)

6.8. Ethical considerations

Research ethical approval for the study was obtained from The Hong Kong Polytechnic University (HSEARS20180604004) and Hanoi Medical University (2518/HMUIRB). The study was registered in ClinicalTrials.gov (ID: NCT03823456). This study has followed the ethical principles for research that involves human subjects which are: autonomy, beneficence, non-maleficence, and confidentiality (Beauchamp, 2009). The strategies to ensure autonomy and confidentiality for participants in this feasibility study were the same as in the cross-sectional survey. Participants were given the information

sheet with detail of purpose, objectives, study procedures, and potential harms of acupressure (Appendix 1) and sign the consent form if they decided to participate. The data of feasibility were kept in a safe place, and only the Ph.D. student had access to the data to ensure confidentiality for participants. The strategies to ensure beneficence and non-maleficence are reported below.

Beneficence

The principle of beneficence refers to a concept in research ethics which indicates that researcher should have the welfare of the subject as a goal of the clinical trial (Beauchamp, 2009). In this study, we used acupressure to manage symptom cluster in participants. This treatment is a non-pharmacological, non-invasive treatment with evident its safety and effectiveness in managing different symptoms (Lee et al., 2011; Song et al., 2015; Waits et al., 2016; Yeung et al., 2012).

Non-maleficence

The non-maleficence principle indicates the intervention should not put subjects in any harm (Beauchamp, 2009). In this study, we used a sham acupressure group as a control group. The purpose of having this sham group is to test the placebo effect of the intervention which is acceptable to determine the efficacy of an intervention (World Medical Association, 2018). We decide to choose the using of non-acupoints approach for sham-acupressure. Pressing non-acupoints cannot produce any therapeutic effects. Therefore, this approach creates no harm for participants.

Ethical concern regarding paying participants

Paying for human subjects for participating in scientific research is a common practice that has been reported for over 100 years (Levine, 1979). Several ethical concerns have been raised regarding this issue, among which, coercion is considered as the most common concern (Grady, 2005). However, in this study, the amount of 70 HKD was given to participants cannot be considered as “paying for participation” since the purpose of the payment is for express mail service to return the outcomes assessment forms to the Ph.D. student. As such, this payment does not attract or motivate

participants to the study. Therefore, it is acceptable to give 70 HKD to participants in this study.

Ethical concerns regarding not informing participants about their group allocation

In this study, we did not inform participants in the true acupressure group and sham acupressure about their group allocation. They were informed that the study is conducted to compare the effectiveness of two acupoint sets. One set is similar to the acupressure treatment of Chinese Traditional Medicine, and the other set does not follow the theory of TCM but has been associated with improvement of insomnia, depression, and anxiety. This explanation helps to maintain the blinding design of the study. However, by informing participants in this way, the researcher did not tell the truth to participants which is unethical in some aspects. However, in a research on participant's view of not informing group allocation, Hughes et al. (2014) indicated that participants perceive this approach as being acceptable. Nevertheless, testing the placebo effect is acceptable, and the sham acupressure method used in this study does not create any harm to the participant's health. As such, we believe it is acceptable to not informing participants about their group allocation.

CHAPTER 7. RESULTS OF THE FEASIBILITY TRIAL

7.1. Introduction

This chapter presents the results of the feasibility RCT study. The results are presented in 11 sections including this introduction section. The participant's demographic and clinical characteristics and baseline outcomes data are reported in section 7.2. The feasibility of the recruitment process including the total time to recruit participants, the recruitment rate, the eligible rate, and refusal rate during the recruitment, reason for ineligibility and refusal are reported in section 7.3. Afterward, section 7.4 presents the attrition rate and reason for attrition. The differences in the characteristics between participants who withdrew and those who completed the study are reported in this section. The feasibility of the study measurements is presented in section 7.5 while section 7.6 reports the participant's acceptability of the intervention. Section 7.7 reports the fidelity of the trial and section 7.8 presents the adverse events associated with self-acupressure. The preliminary effects of the intervention on individual symptoms and the symptom cluster severity as well as on participants' quality of life are reported in section 7.9. The effect size and the sample size calculation for the future full-scale RCT are also presented in section 7.10. Finally, summary of the results of the feasibility study are reported in section 7.11.

7.2. Participants' characteristic and baseline outcomes data

7.2.1. Participants' demographic characteristics

Table 31 depicts the demographic information of participants. The mean age of the participants was 54.95 ± 9.1 years. The majority of the participants were female (82/114, 71.9%). Eighty participants were farmers (70.18%), only a few were employed (12/114, 10.5%) or unemployed/freelancer (9/114, 7.8%). Most of them received junior high school or high school (95/114, 83.3%) education and only a small number received university/college education (11/114, 9.6%). The majority of participant were married (100/114, 87.7%), the rest were single or divorced/widowed. No significant difference was found regarding demographic variables of participants between-groups .

Table 31. Baseline demographic information of the participants (n=114)

	Group assignment			Total	p*
Variable	**True AP** **N= 38**	**Sham AP** **N = 38**	**ESC** **N = 38**	**N = 114**	
Age	54.58 ±10.92	53.48 ± 7.13	56.58 ±9.04	54.95 ± 9.1	> 0.05[a]
Gender					
Male	9 (23.7%)	8 (21.1%)	15 (39.5%)	32 (28.1%)	> 0.05[b]
Female	29 (76.3%)	30 (78.9%)	23 (60.5%)	82 (71.9%)	
Occupation					
Unemployed	2 (5.3%)	1 (2.6%)	3 (7.9%)	6 (5.26%)	> 0.05[b]
Officer	3 (7.9%)	1 (2.6%)	2 (5.3%)	6 (5.26%)	
Retired	3 (7.9%)	3 (7.9%)	4 10.5%)	10 (8.77%)	
Farmer	26 (68.4%)	26 (68.4%)	28 (73.7%)	80 (70.18%)	
Engineer	0	2 (5.3%)	0	2 (1.75%)	
Worker	2 (5.3%)	1 (2.6%)	1 (2.6%)	4 (3.51%)	
Freelance	2 (5.3%)	1 (2.6%)	0	3 (2.63%)	
Education					
Primary School	2 (5.3%)	2 (5.3%)	4 (10.5%)	8 (7.2%)	> 0.05[b]
Junior high school	14 (36.8%)	22 (57.9%)	25 (41%)	61 (53.51%)	
High school	18 (47.4%)	9 (23.7%)	7 (20.6%)	34 (29.82%)	
University/College	4 (10.5%)	5 (13.2%)	2 (5.3%)	11 (9.65%)	
Marital status					
Single	1 (2.6%)	1 (2.6%)	1 (2.6%)	3 (2.63%)	> 0.05[b]
Married	34 (89.5%)	32 (84.2%)	34 (89.5%)	100 (87.7%)	
Divorced	2 (5.3%)	1 (2.6%)	2 (5.3%)	5 (4.38%)	
Widowed	1 (2.6%)	4 (10.5%)	1 (2.6%)	6 (5.26%)	

*Note: True AP: true self-acupressure group, sham AP: Sham self-acupressure group, ESC: enhanced standard care group. *Significant level of p-value was set at ≤ 0.05; a=one-way ANOVA; b= Fisher's exact test*

7.2.2. Participants' clinical characteristics

Table 32 describes the clinical characteristics of participants. The most common cancer diagnosis was breast cancer (51 patients, 44.7%), followed by lung cancer and cancer of digestive system (12.28% and 9.65% respectively). Almost half of the participants were in stage 4 of their disease (49.98%), and the proportion of participants with stage 2 and 3 was almost equal (24.6% and 17.54% respectively). The majority of participants had not had an operation (46.49%), one-third of them had operation to remove the tumor completely (33.3%), and the rest receive suboptimal surgery (14.9%). On average, the time since participants diagnosed with cancer was 10.13 ± 8.26 months and this was higher in the sham AP group (more than 11 months). The average number of completed chemotherapy cycles was 6.96 ± 5.54. Most of the participants did not have any chronic diseases. There was no significant difference regarding the clinical characteristics of the participants between study groups.

Table 32. Baseline clinical characteristics of the participants (n=114)

Variable	Group assignment			Total	p*
	True AP N= 38	Sham AP N = 38	ESC N = 38	**N = 114**	
Cancer Diagnosis					> 0.05[b]
Breast Cancer	14 (37.8%)	22 (57.9%)	15 (45.1%)	51 (44.7%)	
Lung Cancer	6 (16.2%)	4 (10.5%)	4 (10.5%)	14 (12.28%)	
Cancer of digestive system	4 (10.5%)	2 (5.4%)	5 (12.7%)	11 (9.65%)	
Cervical Cancer	2 (5.4%)	4 (10.5%)	3 (7.9%)	9 (7.89%)	
Non-Hodgkin Lymphoma	2 (5.4%)	2 (5.4%)	4 (10.5%)	9 (7.89%)	
Hodgkin Lymphoma	3 (8.1%)	2 (5.3%)	4 (10.5%)	9 (7.89%)	
Others cancer	6 (16.2%)	2 (5.3%)	3 (7.9%)	11 (9.64%)	
Cancer stage					> 0.05[b]
Stage 1	6 (16.2%)	9 (23.7%)	2 (5.3%)	17 (14.91%)	
Stage 2	7 (18.9%)	11 (28.9%)	10 (26.3%)	28 (24.56%)	
Stage 3	5 (13.5%)	7 (18.4%)	8 (21%)	20 (17.54%)	
Stage 4	19 (51.4%)	12 (28.9%)	18 (47.4%)	49 (42.98%)	
Time from diagnosis (Months)	9.4 ± 6.68 (1 – 24)	11.89 ± 11.21 (1-48)	9.1 ± 6.1 (1-28)	10.13 ± 8.26	> 0.05[a]
Completed Chemotherapy Cycles	7.2 ± 5.4 (1-21)	7.02 ± 7.1 (1-36)	6.5 ± 3.8 (2-16)	6.96 ± 5.54	> 0.05[a]
Surgical debunking					
None	18 (47.4%)	16 (42.1%)	19 (50%)	53 (46.49%)	> 0.05[b]
Optimal	14 (37.8%)	14 (37.8%)	10 (26.3%)	38 (33.33%)	
Sup-Optimal	5 (13.5%)	6 (16.2%)	6 (16.2%)	17 (14.9%)	
Chronic Disease					
None	30 (81.1%)	33 (86.8%)	34 (89.5%)	97 (85.1%)	> 0.05[b]
Diabetes	0	2 (5.3%)	2 (5.3%)	4 (3.5%)	
Hypertension	4 (10.8%)	1 (2.6%)	2 (5.3%)	7 (6.14)	
Adiposis Hepatica	2 (5.3%)	1 (2.6%)	0	3 (2.63%)	
Others (Gout, COPD)	1 (2.6%)	2 (5.3%)	0	3 (2.63%)	

*Note: COPD: Chronic obstructive pulmonary disease. *Significant level of p-value was set at ≤ 0.05; a=one-way ANOVA; b= Fisher's exact test.*

7.2.3. Participants' baseline outcomes data

Table 33 reports the result of the subject's baseline assessment. The average severity of the symptom cluster score was moderate (6.4 ± 1.67). Specifically, the average ISI score was 19.95 ± 3.85 (moderate), the average anxiety and depression score also indicated a moderate severity in the sample (11.74 ± 3.54 and 10.35 ± 2.62, respectively). The mean quality of life score of the participants was 59.06 with the score ranging from 7 to 92.7. There was no significant difference in most of baseline measurements between-groups regarding ISI and HADS score. The ANOVA test indicated that the total quality of life score and the functional well-being subscale score were significantly lower in the self-acupressure group than two control groups. The participants took more than an hour to fall asleep on average (71.67 ± 49.85 min). The sleep efficiency of the participants was low (62.89%). Participants waked up 3.57 times per night on average and the mean time for wakefulness after sleep on set was 113.35 minutes.

Table 33. Participants' baseline outcomes data

Variables (Range)	**Group assignment**			**Total N = 114**	**p***
	True AP N= 38	**Sham AP N = 38**	**ESC N = 38**		
Symptom Cluster Score (0-10)	6.69 ± 1.65 (3.67 - 9.67)	6.21 ± 1.58 (3 – 9.33)	6.4 ± 1.7 (3.33 – 10)	6.4 ± 1.67	> 0.05
ISI Score (0-28)	20.2 ± 3.87 (13 – 28)	19.31 ± 4.37 (13 – 28)	20.6 ± 3.14 (16 – 28)	19.95 ± 3.85	> 0.05
Anxiety Score (0-28)	12.15 ± 3.73 (8 – 21)	11.18 ± 3.11 (8 – 20)	11.97 ± 3.5 (8 – 21)	11.74 ± 3.54	> 0.05
Depression Score (0-28)	11.07 ± 2.89 (8 – 21)	9.89 ± 1.9 (8 – 14)	10.31 ± 2.62 (8 – 21)	10.35 ± 2.62	> 0.05
Quality of life (0-108)	52.64 ± 15.3* (7-81)	62.32 ± 13.8 (24 – 92.7)	62.2 ± 12.21 (37 – 84)	59.06 ± 14.5	**< 0.05**
EWB (0-24)	11.13 ± 4.58 (4-20)	12.55 ± 4.61 (4-20)	11.76 ± 5.1 (4-20)	11.81 ± 4.77	> 0.05
FWB (0-28)	11.26 ± 4.55* (0 - 20)	16.05 ± 5.4 (6 – 28)	15.26 ± 5.07 (5 – 25)	14.19 ± 5.4	**< 0.05**
PWB (0-28)	13.05 ± 5.16 (1 – 22)	13.52 ± 4.47 (4 – 25)	14.31 ± 4.89 (7 – 26)	13.63 ± 4.92	> 0.05
SWB (0-28)	17.19 ± 7.64 (1 – 28)	20.19 ± 6.6 (7-28)	20.86 ± 6.7 (2 – 42)	19.42 ± 7.13	> 0.05
Sleep parameters	**True AP (N = 25)**	**Sham AP (N = 15)**	**ESC (N = 19)**	**Total (N = 59)**	
SOL (min)	61.7 ± 44.01 (14.29 – 192)	56.47 ± 27.5 (25 -100)	96.7 ± 61.9 (19.29 – 270)	71.67 ± 49.85	> 0.05
nWASO* (n)	2.05 ± 1.49 (0.57-6)	2.07 ± 1.02 (0.57 – 4)	2.79 ± 0.74 (1.71 – 4)	3.57 ± 7.54	> 0.05
tWASO** (min)	89.69 ± 59.29 (3.43 – 240)	145.22 ± 107.8 (10 – 330)	124.43 ± 62.9 (26 – 240)	113.35 ± 97.28	> 0.05
Total Sleep time (min)	314.98 ± 89.38 (120 – 525)	313.85 ± 102.76 (120 – 441.43)	269.65 ± 88.81 (145.71 – 439.29)	300.1 ± 97.03	> 0.05
Total time in bed (min)	515.9 ± 73.15 (420 – 687.5)	518.16 ± 65.4 (430 – 675)	478.79 ± 124.87 (157.14 – 687.50)	504.52 ± 91.69	> 0.05
Sleep efficiency (%)	62.05 ± 20.10 (22.86 – 95)	61.35 ± 20.02 (22.22 – 93.74)	65.49 ± 53.88 (23.67 – 95.2)	62.89 ± 34.17	> 0.05

*Note: * Significantly lower than Sham AP and ESC.* ISI; Insomnia severity index, EWB: Emotional well-being subscale, FWB; Functional well-being subscale; PWB: Physical well-being subscale; SWB; Social well-being subscale *SOL: Sleep onset latency; nWASO: the number of nights awaken after sleep onset; tWASO: time of wakefulness after sleep onset. *:bolded 'p' indicates significant difference by One-way ANOVA (p<0.05)*

7.3. Feasibility of the recruitment process

7.3.1. Time to recruit participants

The participants' recruitment started in December 2018 and ended in April 2019. The total time for recruitment was 20 weeks, about six patients were recruited to the study per week. One hundred and fourteen participants were recruited from enrolled to the study with sixty-one participants were recruited from study hospital A and fifty-three participants were from hospital B. There was no significant difference regarding participant group allocation in different study sites (as shown in **Table 34).**

7.3.2. The recruitment rate, eligible rate, and refusal rate

During the recruitment period, 902 participants from two hospitals were assessed for eligibility, and 87.5% of them (788/902) were excluded. Reason for exclusion were participants: did not meet the inclusion criteria (439 patients, 55.7%); lack of interested to participate in the study (281 patients, 35.7%); scheduled to received or currently undergoing radiotherapy (43/788, 5.5%); and had Karnofsky Performance Status Index lower than 80 (25/788, 3.2%). Nearly half of the patients who refused to participate were eligible for the study (120/281, 42.7%). Therefore, the eligible rate of the feasibility study was 25.9% ([120+114]/902); the recruitment rate for eligible participant was 12.6% (114/902) and the refusal rate was 31.5% (281/902). The recruitment process is summarized in **Figure 8.**

Table 34. Subject recruitment at different study sites

Variables	Group assignment			Total N = 114	p[a]
	True AP* N= 38	Sham AP* N = 38	ESC* N = 38		
Site 1					
No of participants	20	21	20	61	
Within-group	52.6%	55.3%	52.6%	53.5%	> 0.05
Within study site (%)	32.8%	34.4%	32.8%	100%	> 0.05
Site 2					
No of participants	18	17	18	53	
Within-group	47.4%	44.7%	47.4%	46.5%	> 0.05
Within study site (%)	34%	32%	34%	100%	> 0.05

Note: True AP: True self-acupressure group, Sham AP: Sham self-acupressure group, ESC: Enhanced standard care group. Significant level of p-value was set at ≤ 0.05; a=Chi-square test

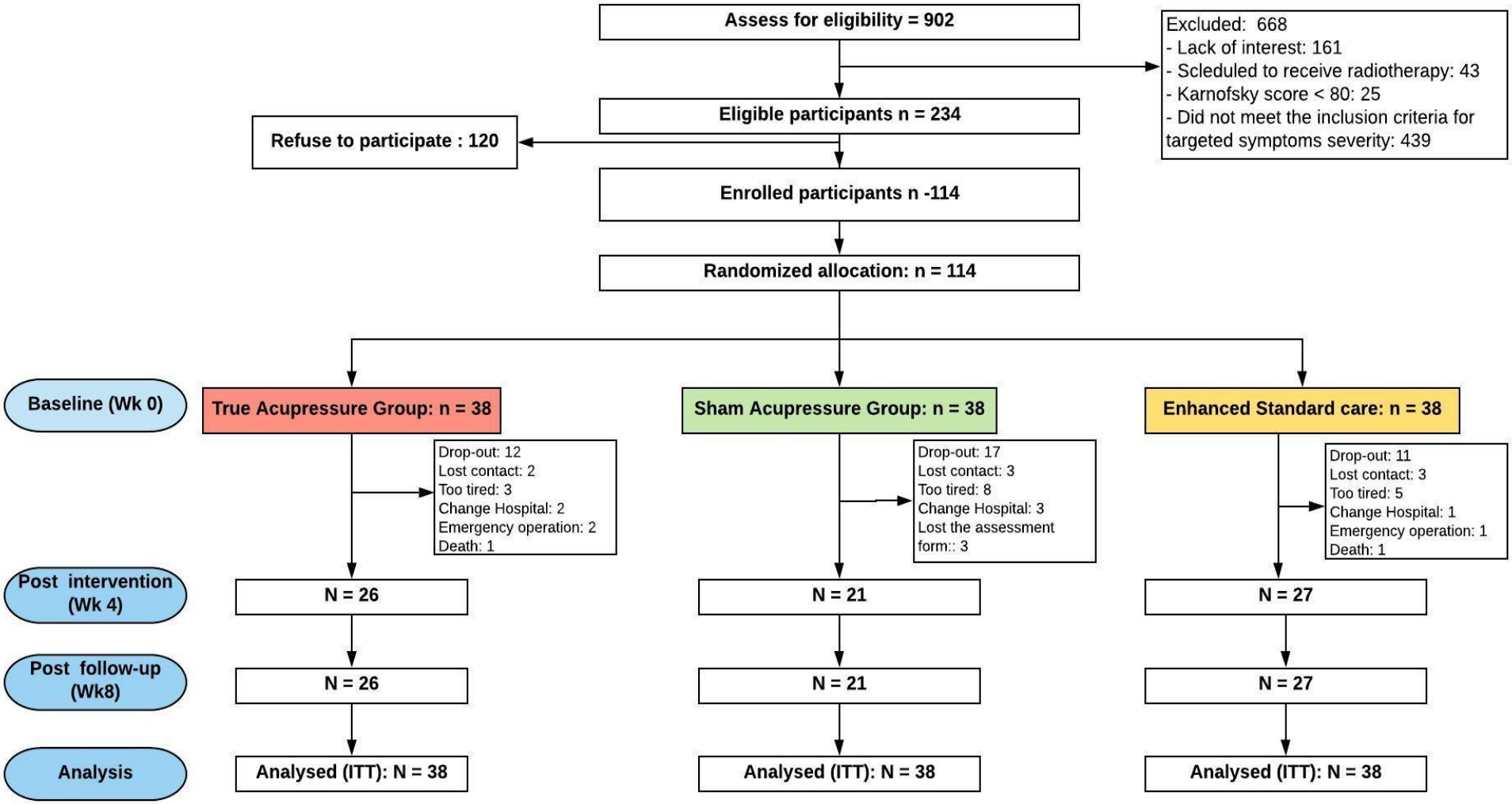


Figure 8. The CONSORT diagram of the feasibility trial

7.4. Attrition rate and differences in characteristic between withdrawn participants and participants who completed the feasibility study

7.4.1. Attrition rate and reason for attrition

During the four weeks of intervention, there were 40 participants drop out the intervention which indicated a high attrition rate in the study (40/114, 35.1%). No participants dropped out during the follow-up time. Among the withdrawn participants, 12 of them were located in the true acupressure group, 17 were in the sham acupressure group, and 11 were located in the enhanced standard care group. The attrition rates were not significantly different between-groups. The most common reason for discontinuing was feeling too tired to participate in the trial (40%). Details of attrition rate and reasons for it are listed in the **table 35**.

Table 35. Reasons for attrition

	Group assignment			**Total**
	True AP **N = 12**	**Sham AP** **N =17**	**ESC** **N = 11**	
Drop-out rate	31.6%	44.7%	29.9%	35.1%
Lost contact	2 (16.7%)	3 (17.6%)	3 (27.3%)	**8 (20%)**
Too tired	3 (25%)	8 (47.1%)	5 (45.5%)	**16 (40%)**
Change hospital	2 (16.7%)	2 (11.8%)	1 (9.1%)	5 (12.5%)
Emergency operation	1 (8.3%)	0	1 (9.1%)	2 (5%)
Too busy	1 (8.3%)	0	0	1 (2.5%)
Death	1 (8.3%)	0	1 (9.1%)	2 (5%)
Lost assessment form	0	3 (17.6%)	0	3 (7.5%)
Do not follow the study protocol	2 (16.7%)	1 (5.9%)	0	3 (7.5%)
Total	12	17	11	40

Note: True AP: True self-acupressure group, Sham AP: Sham self-acupressure group, ESC: Enhanced standard care group

7.4.2. Differences in the characteristics between participants who withdrew and participants who completed the study

Table 36 demonstrates the demographic, clinical characteristics, and baseline assessment of those participants who withdrew. This table also indicates similarities in demographics, clinical characteristics, and almost of baseline assessments between participants who completed the study and who withdrew. Significant differences were found only in the physical well-being score (PWB). Withdrawn participants had a mean PWB score significantly lower than those completed participants (PWB is a subscale of FACT-G).

Table 36. Demographic, clinical characteristic, and baseline assessment different between participants who withdrew and who stayed in the feasibility trial

Variables	**Group**		**p***
	Participants who completed N = 74	**Participants who withdraw N = 40**	
Demographic characteristics			
Age	55.05 ± 9.05	54.55 ± 9.13	> 0.05[a]
Male	22 (29.7%)	10 (25%)	> 0.05[b]
Female	52 (70.3%)	30 (75%)	
Occupation			
Unemployed	3 (4.1%)	3 (7.5%)	> 0.05[b]
Officer	4 (5.4%)	2 (5%)	
Retired	7 (9.5)	3 (7.5%)	
Farmer	51 (68.9%)	32 (80%)	
Others	9 (12.3%)	0	
Education			
Primary School	4 (5.4%)	4 (10%)	> 0.05[b]
Junior high school	37 (50%)	24 (60%)	
High school	24 (32.3%)	10 (25%)	
University/College	9 (12.3%)	2 (5%)	
Marital status			
Single/Divorced/Widowed	7 (9.5)	7 (17.5%)	> 0.05[b]
Married	67 (90.5%)	33 (82.5%)	
Clinical Characteristics			
Cancer Diagnosis			
Breast Cancer	33 (44.6%)	18 (45%)	> 0.05[b]
Lung Cancer	10 (13.5%)	5 (12.5%)	
Digestive system cancer	8 (10.8%)	3 (7.5%)	
Others	23 (31%)	14 (35%)	

Variables	Group		p*
	Participants who completed N = 74	**Participants who withdraw N = 40**	
Cancer stage			
Stage 1	12 (16.2%)	5 (12.5%)	> 0.05[b]
Stage 2	21 (28.4%)	7 (17.5%)	
Stage 3	13 (17.6%)	7 (17.5%)	
Stage 4	28 (37.8%)	21 (52.5%)	
Time from diagnosis (Months)	10.74 ± 8.85	9.0 ± 7.01	0.05[a]
Completed Chemo-Cycle	7.2 ± 5.96	6.5 ± 4.7	0.05[a]
Surgical debunking			
None	30 (40.5%)	25 (62.5%)	> 0.05[b]
Optimal	28 (37.8%)	10 (25%)	
Sup-Optimal	16 (21.6%)	5 (12.5%)	
Chronic Disease			
Yes	61 (82.4%)	37 (92.5%)	> 0.05[b]
No	13 (17.6%)	3 (7.5%)	
Baseline assessments			
Symptom Cluster Score	6.3 ± 1.66	6.5 ± 1.71	0.05[a]
ISI Score	19.9 ± 3.87	20.0 ± 3.87	0.05[a]
Anxiety Score	11.44 ± 3.29	12.3 ± 3.96	0.05[a]
Depression Score	10.31 ± 2.8	10.42 ± 2.28	0.05[a]
Quality of life	59.9 ± 14.1	57.4 ± 10.05	0.05[a]
EWB	11.77 ± 4.78	11.99 ± 4.82	0.05[a]
FWB	14.12 ± 5.21	14.35 ± 5.81	0.05[a]
PWB	**14.44 ± 4.7**	**12.12 ± 4.99**	**< 0.05[a]**
SWB	19.57 ± 6.99	19.12 ± 7.46	0.05[a]

*Note: True AP: True self-acupressure group, Sham AP: Sham self-acupressure group, ESC: Enhanced standard care group; ISI; Insomnia severity index, EWB: Emotional well-being subscale, FWB; Functional well-being subscale; PWB: Physical well-being subscale; SWB; Social well-being subscale; * bolded "p" indicated significant difference (p<0.05); a: one-way ANOVA; b= Fisher's exact test.*

7.5. The feasibility of the study measurements

The number of participants who did not complete questionnaires was used to estimate the feasibility of the measurements used in the study. At baseline assessment, there was no missing data for the NRS, ISI, HADS (n=114). Although all participants returned the FACT-G but 42.1% of them (48 patients) refused to respond to one item of the scale (FACT-G-GS7 - "I am satisfied with my sex life"). Similarity, 48.2% of participants (55 patients) did not return the sleep diary.

At post intervention assessment, NRS, ISI, HADS, and FACT-G were completed by participants. However, nearly one-third of them (23 participants) did not complete the sleep

diary. About nearly half of them did not respond to item FACT-G-GS7 of the FACT-G (32 participants, 43.2%).

At post follow-up assessment, completed participants complete all the study measurement. However, 47.3% of them (37 participants) did not return the sleep diary and half of them (49 participants, 47.3%) did not respond to item FACT-G-GS7 of FACT-G. **Table 37** reports missing data for the FACT-G-GS7 item and Sleep diary.

Table 37. Missing data for the FACT-G-GS7 and Sleep Diary at different time points of data collection

Items	**Baseline (n=114)**		**Post intervention (n=74)**		**Post follow-up (n=74)**	
	No. of responded participants	Missing	No. of responded participants	Missing	No. of responded participants	Missing
FACT-G-GS7	66	48 (42.1%)	42	32 (43.2%)	37	37 (50%)
Sleep diary	59	55 (48.2%)	51	23 (31.1%)	49	35 (47.3%)

7.6. Participants' acceptability of the intervention

7.6.1. Participants' adherence to the self-acupressure treatment protocol

The self-acupressure protocol used in the true and sham AP group required participants to stimulate six acupoints (four of them located at both side of the body) once per day for 28 days, and each acupoint to be stimulated for 3 minutes. Taking into account that there was a total of 10 acupoints, 24 minutes was the standard duration for each acupressure session. Data from the acupressure diary indicates good adherence to the acupressure treatment protocol among participants who completed the study. The average number of completed treatment days in the true and sham acupressure group was high (27.03±1.56 and 26.85 ± 1.38, respectively). The average time of acupressure session in both groups is close to the standard time with 23.6 ± 5.9 minutes in the true AP group and 24.2 ± 4.9 in the sham AP groups ($p<0.05$). During the treatment period, besides using self-acupressure, there were 3 participants (7.8%) in the true AP group using the herbal Gingko Biloba extract (150mg/day) as supplement to reduce insomnia.

Overall, participants had a 66% adherence rate for daily acupressure practice through the 4-weeks acupressure for both the true and sham AP group (adherence rate was 73% in the true AP group and 57.1% in sham AP group). There were seven participants in the true AP group and nine participants in the sham AP group who did not complete the 28 days of the treatment with the main reason for that being that they were too busy to practice acupressure at home. Reasons for not completing acupressure treatments are listed in **table 38.**

Table 38. Reasons for not completing 28 days of treatment in true and sham acupressure groups

Reasons for not complete treatment	**Group assignment**		Total N = 47	p*
	True AP N = 26	**Sham AP N = 21**		
Hospitalization	3 (11.5%)	1 (4.7%)	4 (8.5%)	> 0.05
Too tired	2 (7.7%)	3 (14.3%)	5 (10.6%)	
Too busy	2 (7.7%)	5 (23.8%)	7 (15%)	

*Note: True AP: True self-acupressure group, Sham AP: Sham self-acupressure group, * Significant level of p-value was set at ≤ 0.05 by Fisher's exact test.*

7.6.2. Participants' perception of the intervention

The study results indicated high acceptability of the intervention by the participants who completed the study. The mean total score of the Intervention Rating Scale (IRS-15) was 76.73 ± 6.99, ranging from 60 to 90. Most of the participants gave positive feedback about the intervention. However, there were 2 participants (7.6%) disagreed that the intervention would be appropriate for patients with difference cancer diagnosis and 1 participant (3.8%) did not like the procedures used in this intervention **(table 39)**

Table 39. Participants' perception of the acceptability of the intervention

	Strongly disagree n (%)	**Disagree n (%)**	**Slightly disagree n (%)**	**Slightly agree n (%)**	**Agree n (%)**	**Strongly agree n (%)**	**Mean**	**SD**
1. This was an acceptable intervention to care for symptoms related to my cancer	0	0	0	3 (11.5)	19 (73.1)	4 (15.4)	5.03	0.5
2. Most of the cancer patient with similar symptoms would find this intervention appropriate for them.	0	0	0	2 (7.7)	20 (76.9)	4 (15.4)	5.07	0.48
3. This program supports me to self-care symptom effectively	0	0	0	7 (26.9)	14 (53.8)	5 (19.2)	4.92	0.52
4. I would introduce this intervention to other patients	0	0	0	0	22 (84.6)	4 (15.4)	5.15	0.48
5. My symptoms burden was severe enough to suitable with the use of this intervention	0	0	0	5 (19.2)	14 (53.8)	7 (26.9)	5.07	0.68
6. Most patients would find the information provided in the program easy to understand	0	0	0	3 (11.5)	17 (65.4)	6 (5.3)	5.11	0.59
7. I would be willing to use this self-care treatment at home and hospital	0	0	0	1 (3.8)	16 (61.5)	9 (34.6)	5.31	0.55
8. This intervention did not result in negative side-effect	0	0	0	1 (3.8)	14 (53.8)	11 (42.3)	5.38	0.57
9. This treatment would be appropriate for patients with difference cancer diagnosis	0	2 (7.6)	0	1 (3.8)	15 (57.7)	8 (30.8)	5.03	1.07
10. This intervention was consistent with those I have used	0	0	0	1 (3.8)	18 (69.2)	6 (23.1)	5.15	0.54
11. The intervention was an effective to handle my needs	0	0	0	2 (7.7)	17 (65.4)	7 (26.9)	5.19	0.56
12. The length of the intervention is reasonable for my needs	0	0	0	1 (3.8)	3 (11.5)	14 (53.8)	5.11	0.76
13. I like the procedures used in this intervention.	0	1 (3.8)	0	3 (11.5)	16 (61.5)	6 (23.1)	5.03	0.72
14. This intervention was a good way to handle symptoms burden	0	0	0	5 (19.2)	16 (61.5)	5 (19.3)	5.00	0.63
15. Overall, this intervention would be beneficial for me	0	0	0	3 (11.5)	17 (65.4)	6 (23.1)	5.11	0.58
Total							**76.73**	**6.99**

7.7. Fidelity of the trial

7.7.1. Fidelity of the feasibility study design

- No interventionist dropped out during the study period
- Eight participants were lost to follow-up due to not available phone numbers.
- Only 4.6% of participants had a fixed line telephone number (10/214)

7.7.2. Fidelity of the training of the interventionists

Result of checking the self-acupressure mastery of the interventionists indicated that the location of *Baihua* and *Shenmen* were identified wrongly by two interventionists. After further instruction, all interventionist clearly knew how to locate and stimulate the acupoints as indicated in the true self-acupressure protocols. On the other hand, the location and pressing technique of the sham acupoints were identified correctly by all the interventionists.

7.7.3. Fidelity of the participants' training

There were 64 training sessions for participants (40 self-acupressure training sessions and 24 training sessions for participants in the ESC). On average, it took 20 minutes to instruct each participant in the true self-acupressure group how to locate and press the acupoints while it was shorter in the sham self-acupressure group (15 minutes). The PhD student supervised all the training sessions. All of the participant training sessions were conducted by strictly following the true/sham self-acupressure training protocol or the enhanced standard care training protocol.

After each of self-acupressure training session (for both true AP and sham AP group) the interventionist checked the acupressure mastery of the participants. None of the sham acupoints were wrongly located by the participants in the sham AP group. In contrast, 3 true acupoints were located wrongly by six participants including *Baihua*, *Shenmen*, and

Fengchi. However, after further instruction, all of them identified those acupoints correctly. **Table 40** describes the wrong location of acupoint identified by the participants.

Table 40. Wrong acupoints identified by the participants after the true self-acupressure training sessions

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Baihua	x	x	x		x	
Shenmen	x			x	x	
Fengchi	x		x			x

7.7.4. Fidelity of the participants' self-delivery of the intervention

There were 47 participants (26 participants in the true AP group and 21 participants in the sham AP group) completed the mandatory self-acupressure treatment period. The second round of checking for the acupressure mastery of the participants was carried out in the next hospital visit which was two or three weeks after the first acupressure session. In this follow-up visit, participants demonstrated the acupressure protocols while the main instructors observed them and corrected them if necessary. In this second round of checking acupressure mastery, the location of *Baihua* and *Fengchi* were incorrectly identified by two participants in the true AP group, while none of the participants in the sham acupressure group identified wrongly the location of sham acupoints. The participant's retention of the skills and ability to perform the acupressure protocol was good with 98.6% and 100% of accuracy on the acupressure skill check form in the true AP and sham AP group, respectively.

7.8. Adverse events associated with self-acupressure

During the 28 days treatment period, four participants reported adverse events related to acupressure at mild severity. Two participants in the true AP group reported feeling hurt at the acupoint after stimulating it (7.6%). Two participants in the sham AP group reported that their finger was tired while stimulating the acupoint (9.5%).

7.9. Evaluating the preliminary effects of the intervention on the severity of the symptom cluster, individual symptoms, and participants' quality of life

The preliminary effects of the intervention on targeted symptoms were evaluated by three separate Numerical Rating Scales (NRS) and standardized scales (Insomnia Severity Index and Hospital Anxiety and Depression Scale). This section reports the preliminary results of the feasibility trial on the targeted symptoms measured by these scales as well as participants' quality of life (measured by the Function Assessment of Cancer Therapy – General).

7.9.1. Preliminary effects of the intervention on individual symptoms and the symptom cluster score (measured by NRS)

7.9.1.1. Preliminary effects of the intervention on the insomnia score (measured by NRS)

As shown in **Figure 9**, the insomnia score (by NRS) reduced for all groups over time. However, within-group comparisons indicated the insomnia score was significantly lower from T1 to T2 in the true AP group. The insomnia score in this group reduced from T2 to T3 but not significantly. The decline of insomnia score in the sham AP group and ESC groups appeared to be nonsignificant at T2 and T3 (**table 41**).

At T2 and T3, between-group comparisons indicated the insomnia score in the true AP group was significantly lower than those in the sham AP and ESC. In contrast, the mean

difference of insomnia score between sham AP and ESC did not reach significant level (**table 42**).

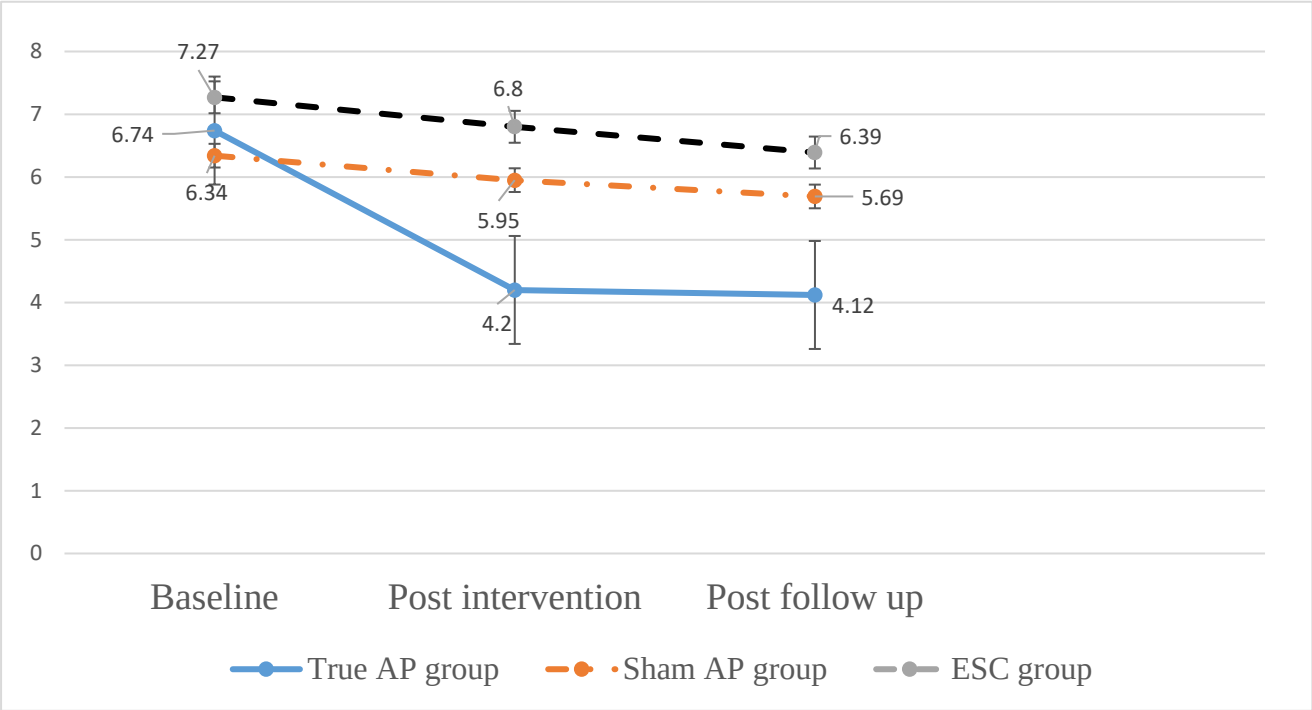


Figure 9. Changing of insomnia score (measured by the NRS) over time in study groups

*Table 41. Pairwise comparison of insomnia score (measured by the NRS) **within-group** over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value	Contrast estimated	Adjusted p-value	Contrast estimated	Adjusted p-value
True AP	2.54	**p< 0.001***	2.62	**p< 0.001***	0.079	0.72
Sham AP	0.39	0.7	0.64	0.63	0.26	0.7
ESC	0.51	0.22	0.89	0.21	0.37	0.23

Note: bolded 'p' indicates statistically significant as p < 0.05

*Table 42. Pairwise comparison of insomnia score (measured by the NRS) **between-group** over time (Post-hoc test adjustment)*

Time points	Post-hoc Analysis (sequential Bonferroni test)					
	True AP vs Sham AP		True AP vs ESC		Sham AP vs ESC	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
Baseline	0.39	0.36	-0.53	0.4	-0.92	0.065
Post intervention	-1.75	**0.009**	-2.56	**p<0.001**	-0.8	0.14
Post follow-up	-1.57	**0.04**	-2.26	**0.002**	-0.67	0.27

Note: bolded 'p' indicates statistically significant as p < 0.05

7.9.1.2. Preliminary effects of the intervention on the depression severity (measured by NRS)

Similar to the trend in the insomnia score, **figure 10** shows that the depression score (measured by NRS) reduced in all study groups over time. However, within-group comparison indicates only in the true AP group the depression score was significantly lower in T2 and T3 (compared with baseline). No significant reduction was found in true AP group from T2 to T3. Within-group comparison also reported no significant reduction of depression score from T1 to T2, and from T2 to T3 in the sham AP and ESC group (**table 43**). Between-group comparison did not show any significant differences among the three study groups at T2 and T3 (**table 44**).

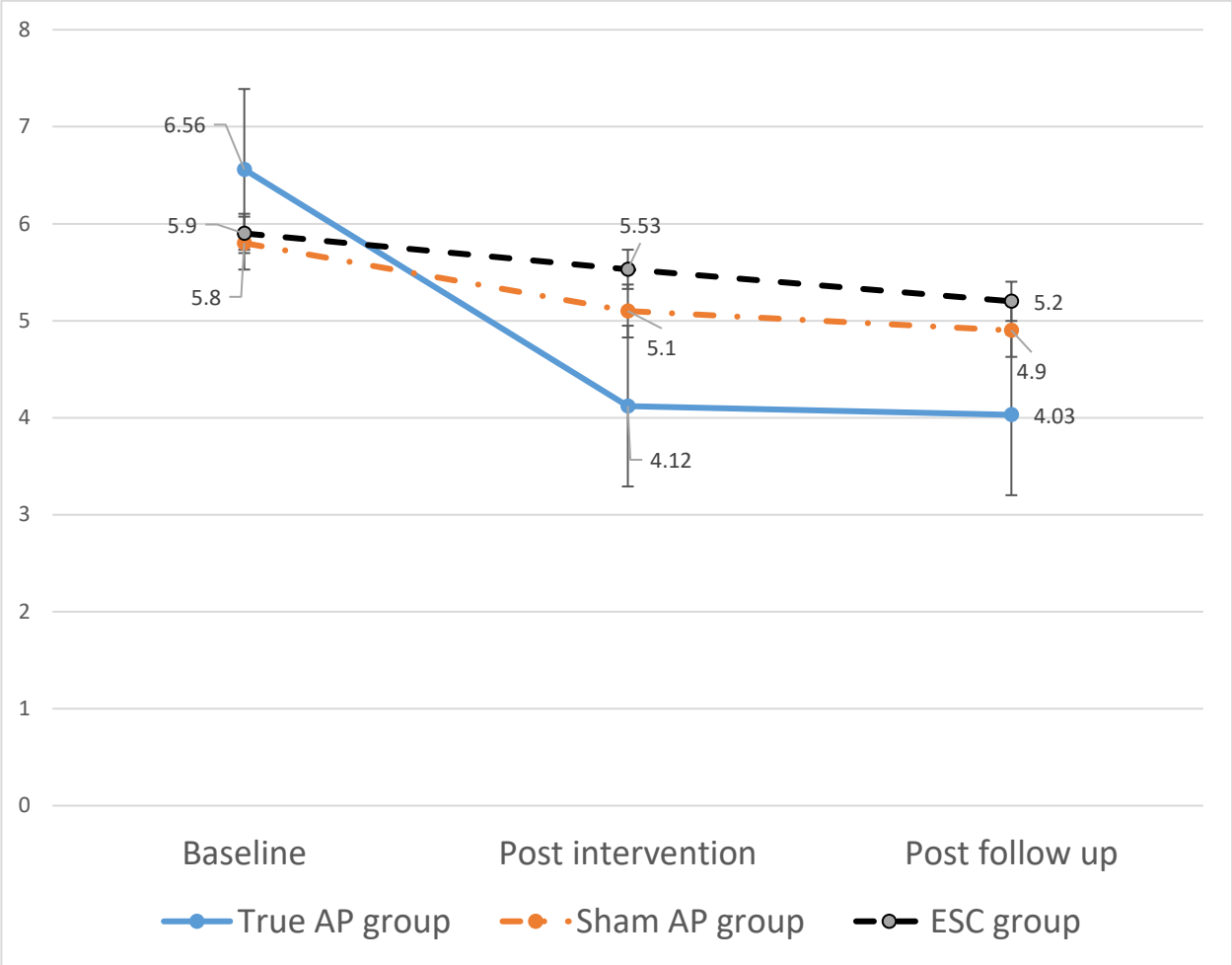


Figure 10. Changing of depression score (measured by the NRS) over time in study groups

Table 43. Pairwise comparison of depression score (measured by the NRS) ***within-group*** *over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	2.4	**p<0.001**	2.5	**p<0.001**	0.09	0.8
Sham AP	0.77	0.4	0.94	0.4	0.16	0.6
ESC	0.4	0.7	0.75	0.5	0.34	0.68

Note: bolded 'p' indicates statistically significant as p < 0.05

Table 44. Pairwise comparison of depression score (measured by the NRS) ***between-group*** *over time (Post-hoc test adjustment)*

Time points	Post-hoc Analysis (sequential Bonferroni test)					
	True AP vs Sham AP		True AP vs ESC		Sham AP vs ESC	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
Baseline	0.68	0.4	0.61	0.4	-0.08	0.9
Post intervention	-0.96	0.37	-1.41	0.15	-0.46	0.5
Post follow-up	-0.89	0.59	-1.15	0.4	-0.29	0.7

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates statistically significant as p < 0.05

7.9.1.3. Preliminary effects of the intervention on the anxiety severity (measured by NRS)

Similar to the patterns of the depression score, the linear mixed model indicated the mean anxiety score (measured by NRS)in all study group decreased from baseline to post intervention assessment (**figure 11**). However, within-group comparisons indicate that only in the true AP group the anxiety score was significantly lower in T2 and T3 (compared with baseline). However, no significant reduction was found in true AP group from T2 to T3. The reduction of anxiety score in sham AP and ESC group appeared to be non-significant **(table 45).** Between-groups comparison did not report any significant differences among three study groups at T2 and T3 (**table 46**).

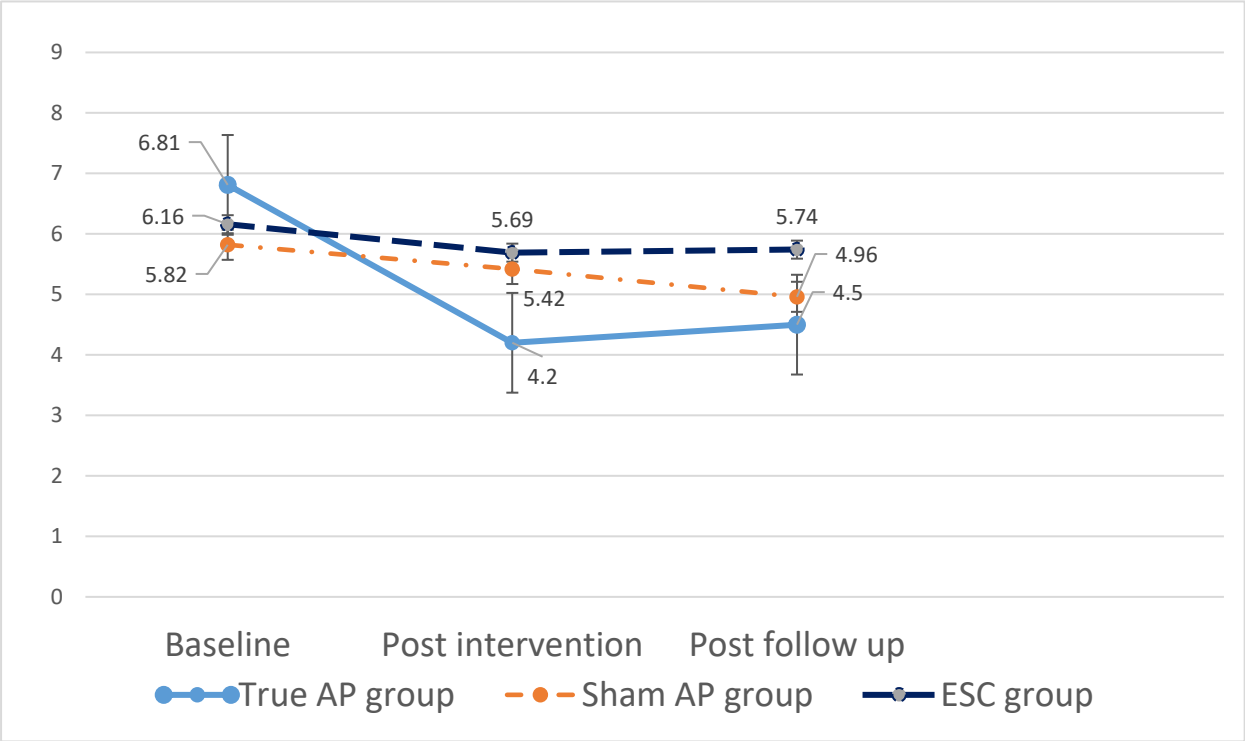


Figure 11. Changing of anxiety score (measured by the NRS) over time in study groups

Table 45. Pairwise comparison of anxiety score (measured by the NRS) ***within-group*** *over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	2.62	**p<0.001**	2.3	**p<0.001**	-0.32	0.3
Sham AP	0.39	0.6	0.85	0.53	0.5	0.57
ESC	0.46	1	0.41	1	-0.05	1

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates statistically significant as p < 0.05

*Table 46. Pairwise comparison of anxiety score (measured by the NRS) **between-group** over time (Post-hoc test adjustment)*

Time points	Post-hoc Analysis (sequential Bonferroni test)					
	True AP vs Sham AP		True AP vs ESC		Sham AP vs ESC	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
Baseline	1	0.1	0.66	0.35	-0.34	0.5
Post intervention	-1.22	0.2	-1.5	0.12	-0.27	0.7
Post follow-up	-0.45	0.66	-1.23	0.36	-0.78	0.66

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates statistically significant as $p < 0.05$

7.9.1.4. Preliminary effects of the intervention on the symptom cluster severity measured by NRS

Similar to the patterns of the individual symptoms, the linear mix effect model analysis indicated that the severity of the SC decreased in the three groups over time (**Figure 12**). However, comparisons of mean differences in SC score within-groups revealed only a significant reduction between T2 and T3 compared with T1 in the true AP group. However, no significant reduction was found in true AP group from T2 to T3. The reduction of SC score in sham AP group and ESC were non-significant (**Table 47**)

Between-groups comparisons only reported significant differences in SC score between true AP and ESC group at post intervention. No significant difference was observed regarding SC score between the true AP group and the sham AP group as well as between the sham AP and ESC at T2 and T3 (**Table 48**).

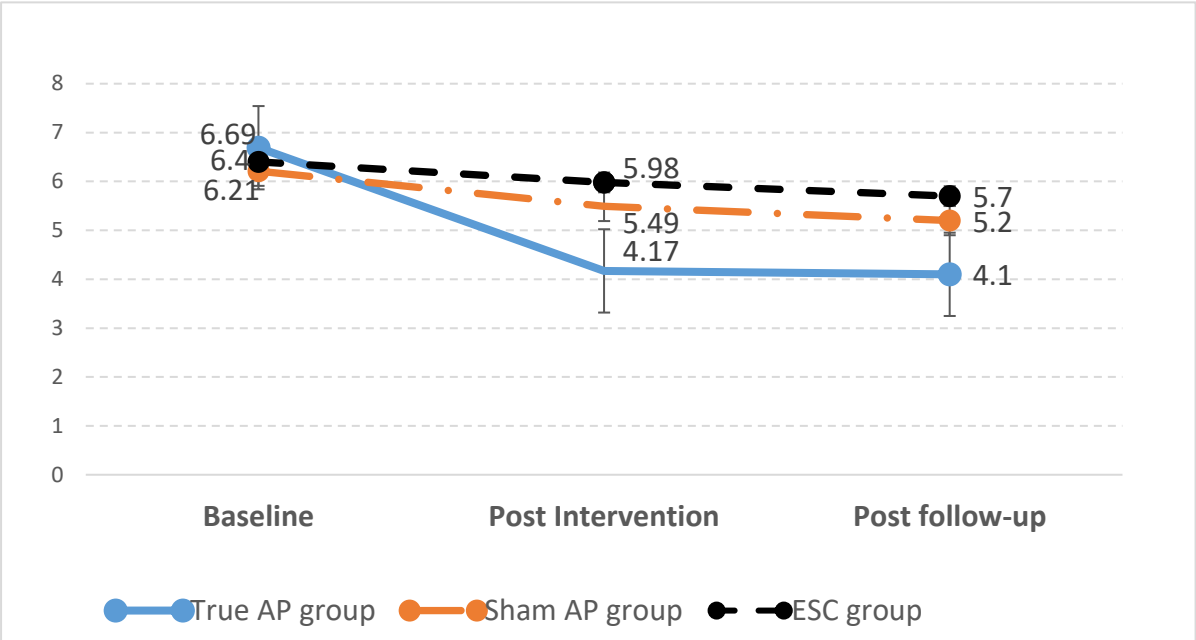


Figure 12. Reduction of symptom cluster severity (measured by the NRS) in study groups over time.

Table 47. Pairwise comparison of symptom severity (measured by the NRS) ***within-group*** *over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	2.53	< **0.0001**	2.6	< **0.0001**	0.76	0.725
Sham AP	0.505	0.535	0.79	0.406	0.292	0.535
ESC	0.47	0.42	0.69	0.42	0.22	0.427

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; * bolded 'p' indicates significant different as p < 0.05*

*Table 48. Pairwise comparison of symptom cluster severity (measured by the NRS) **between-groups** over time (Post-hoc test adjustment)*

Time points	Post-hoc Analysis (sequential Bonferroni test)					
	True AP vs Sham AP		True AP vs ESC		Sham AP vs ESC	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
Baseline	0.693	0.18	0.25	0.53	-0.45	0.49
Post intervention	-1.32	0.061	-1.808	**0.009**	-0.486	0.403
Post follow-up	-1.1	0.27	-1.66	0.059	-0.56	0.43

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; * bolded 'p' indicates significant different as p < 0.05*

7.9.2. Preliminary effects of the intervention on the individual symptoms in the cluster (measured by ISI, sleep diary, and HADS)

7.9.2.1. Preliminary effects of the intervention on the ISI and sleep parameter

Effect of the intervention on Iinsomnia Severity Index (ISI)

The analysis showed that the insomnia severity indicated by ISI was reduced in the three study groups over time (**Figure 13**). However, within-group comparison showed a significant reduction of ISI from T1 to T2 and T3 the true AP and sham AP group. However, no significant reduction of ISI was found in true AP and sham AP group from T2 to T3. The reduction of ISI score overtime was not statistic significant in the ESC group (**Table 49**). Between-group comparison indicated that the mean of ISI score was significantly lower in the true AP and Sham AP group in comparison with the ESC group at post intervention and post follow-up. No significant difference regarding ISI was found between the true AP and sham AP at any time point of assessment (**Table 50**).

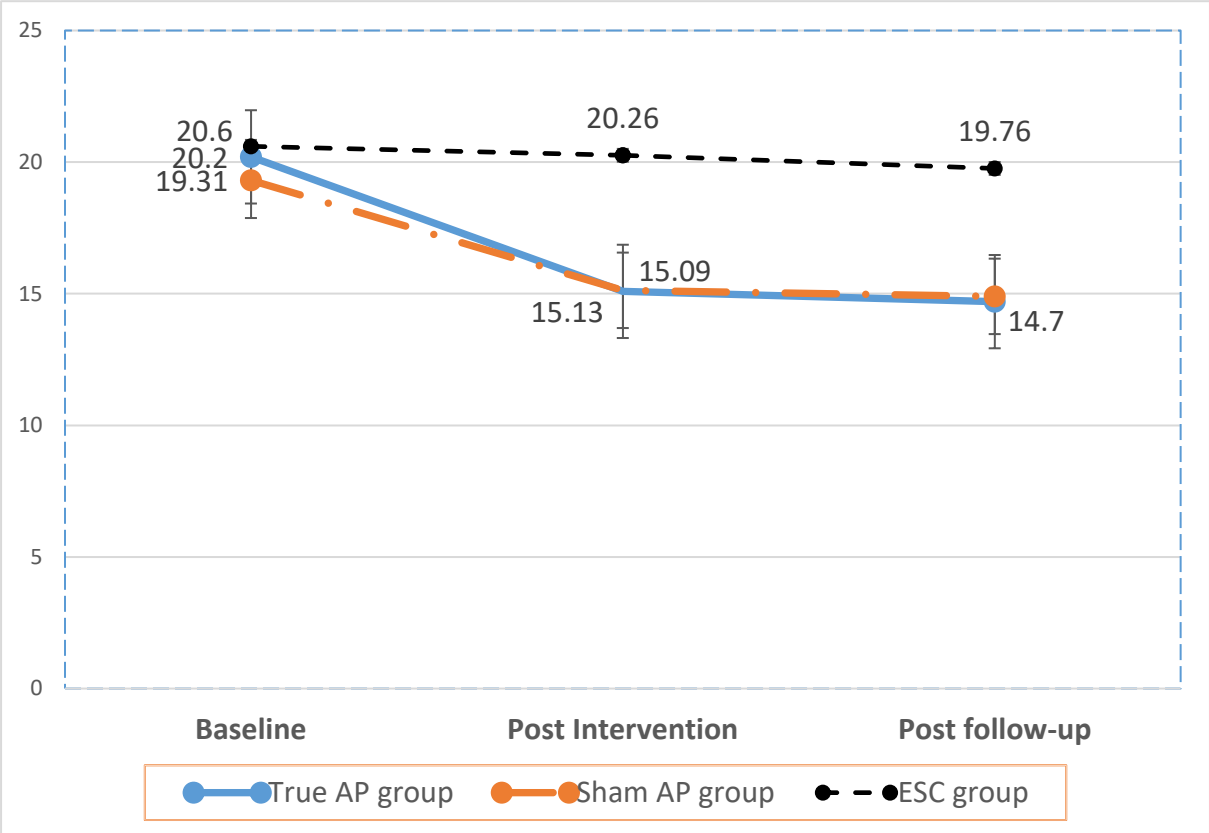


Figure 13. Reduction of insomnia severity (measured by ISI) in study groups over time.

*Table 49. Pairwise comparison of insomnia severity (measured by ISI) **within-group** over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	5.13	**<0.0001**	5.49	**<0.0001**	0.37	0.5
Sham AP	3.89	**< 0.0001**	4.08	**0.001**	0.195	0.73
ESC	0.13	1	0.63	1	0.5	1

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; * bolded 'p' indicates significant different as p < 0.05*

*Table 50. Pairwise comparison of insomnia severity (measured by ISI**) between-group** over time (Post-hoc test adjustment)*

Time points	Post-hoc Analysis (sequential Bonferroni test)					
	True AP vs Sham AP		True AP vs ESC		Sham AP vs ESC	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
Baseline	1.18	0.39	-0.18	0.82	-1.37	0.32
Post intervention	-0.49	0.96	-5.18	**0.002**	-5.13	**0.001**
Post follow-up	-0.23	0.89	-5.05	**0.006**	-4.82	**0.006**

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates significant different as p < 0.05*

Effect of the intervention on sleep parameters

One way-ANOVA analysis and repeated measures analysis were used to investigate the effect of acupressure on participant's sleep parameters in the three study groups. **Table 51** describes the desciptive analysis of sleep parameters of the participants in each study group at post intervention (T2) and post follow-up (T3). While **table 52 and 53** indicate the differences within-groups and between-groups over time.

In the true AP group, the within-group comparison indicated a significant effect on reducing the time of wakefulness after sleep onset (tWASO) as well as increasing the total sleep time and sleep efficiency in the true AP group at T2 and T3 (compared with T1). However, the reduction of tWASO as well as increase of total sleep time and sleep

efficiency in the true AP group from T2 to T3 was found to be non-significant. In the sham AP group, the within-group analysis had not found any differences regarding sleep parameters from T1 to T3. However, in the ESC group, within-group analysis reported a the decrease of nWASO between T2 and T3 and the longer total sleep time between T1 and T3 were found to be significant. No changes regarding other sleep parameters in the ESC group were found significant over time **(Table 52).**

At T2, one way ANOVA analysis indicated no significant difference in most of the sleep parameter between study groups. However, the total sleep time in the true AP and sham AP group was found significant higher than the ESC group ($p = 0.002$ and 0.019, respectively). Also, the sleep efficiency was found to be significant better in true AP and sham AP group than the ESC group ($p=0.002$ and 0.03, respectively). At post follow-up, no significant difference in any sleep parameter was found between the study groups except for the tWASO between the true AP and ESC group ($p<0.05$)

Table 51. Descriptive analysis of participant's sleep parameters

Variables	True AP group Mean ± SD			Sham AP group Mean ± SD			ESC Mean ± SD		
	T1 N=25	**T2 N =24**	**T3 N = 22**	**T1 N = 15**	**T2 N = 13**	**T3 N = 12**	**T1 N = 19**	**T2 N=14**	**T3 N= 15**
SOL(min)	61.7 ± 44.01	59.11 ± 50.09	64.15±59.2	56.47 ± 27.5	49.74 ± 32.23	45.11±30.4	96.7 ± 61.9	92.78 ± 70.9	76.68±65.02
nWASO (n)	2.05 ± 1.49	3.16±5.78	3.25±6.06	2.07 ± 1.02	1.8±1.06	1.34±0.79	2.79 ± 0.74	2.75 ± 1.0	2.3±1.07
tWASO (min)	89.69 ± 59.29	48.22±49.26	47.79±41.36	145.22 ± 107.8	80.25 ± 68.57	59.14±63.09	124.43 ± 62.9	133.03 ± 68.7	105.08±74.8
Total sleep time (min)	314.98 ± 89.38	382±85.9	362.08±72.9	313.85 ± 102.76	372.23±130.78	363.19±126.09	269.65 ± 88.81	266.04±74.4	301.57±94.63
Total time in bed (min)	515.9 ± 73.15	511.68±81.1	519.63±60.79	518.16 ± 65.4	517.25±64.08	528.61±30.36	478.79 ± 124.87	511.63±76.8	539.14±117.28
Sleep efficiency (%)	62.05 ± 20.10	75.68± 17.35	70.17±14.09	61.35 ± 20.02	71.9±23.19	68.42±22.84	65.49 ± 53.88	52.71±23.19	57.96±18.95

Note: AP: self-acupressure, ESC: Enhanced Standard Care; SOL: Sleep onset latency; nWASO: the number of nights awaken after sleep onset; tWASO: time of wakefulness after sleep onset

Table 52. Changes of sleep parameters in each study group over time

Variables	**Groups**	**Post-hoc Analysis (sequential Bonferroni test)**					
		T1 vs T2		**T1 vs T3**		**T2 vs T3**	
		Mean difference	**p***	**Mean difference**	**p***	**Mean difference**	**p***
SOL (min)	True AP	5.2	1	0.98	1	-4.21	1
	Sham AP	7.35	1	13.49	0.7	6.1	0.8
	ESC	-0.14	1	6.12	1	6.26	1
nWASO (n)	True AP	2.06	0.42	2.0	0.46	-0.06	1
	Sham AP	0.26	1	0.83	0.09	0.56	1
	ESC	0.05	1	0.37	0.38	0.42	**0.02**
tWASO (min)	True AP	42.5	**0.002**	45.44	**0.003**	2.85	1
	Sham AP	61.7	0.06	77.85	0.09	16.14	0.75
	ESC	-4.57	1	16.03	0.98	20.87	0.6
Total sleep time (min)	True AP	-65.2	**0.004**	-53.55	**0.03**	11.65	0.9
	Sham AP	-59.33	0.2	-49.12	0.2	10.20	1
	ESC	-29.36	0.2	-41.54	**0.03**	-12.17	1
Total time in bed (min)	True AP	10.84	1	0.99	1	-9.8	0.7
	Sham AP	-3.15	1	-4.09	1	-0.9	1
	ESC	-29.53	0.56	-52.72	0.9	-23.19	1
Sleep efficiency (%)	True AP	-14.08	**0.02**	-9.72	0.06	4.35	0.18
	Sham AP	-9.3	0.13	-7.5	0.39	1.85	1
	ESC	-1.8	1	-3.38	1	-1.5	1

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; SOL: Sleep onset latency; nWASO: the number of nights awaken after sleep onset; tWASO: time of wakefulness after sleep onset. * bolded "p" indicates significant difference as $p < 0.05$.*

Table 53. Changes in sleep parameters of participants at post intervention (T2) and post follow-up (T3)

Time	**Variable**	**Post-hoc Analysis (Bonferroni test)**					
		True AP vs Sham AP		**True AP vs ESC**		**Sham AP vs ESC**	
		Mean difference	**p***	**Mean difference**	**p***	**Mean difference**	**p***
T2	SOL (min)	9.36	1	-33.67	.2	-43.03	0.13
	nWASO (n)	1.33	1	0.4	1	-.91	1
	tWASO (min)	-5.57	1	0.04	1	5.6	1
	Total sleep time (min)	9.8	1	116.0	**0.002**	106.19	**0.019**
	Total time in bed (min)	-5.57	1	0.04	1	-5.61	1
	Sleep efficiency (%)	3.7	1	22.97	**0.002**	19.19	**0.03**
T3	SOL (min)	19.03	1	-12.53	1	-31.56	0.45
	nWASO (n)	1.9	0.6	0.9	1	-0.95	1
	tWASO (min)	-11.34	1	-57.27	**0.03**	-45.92	0.22
	Total sleep time (min)	-1.1	1	60.51	0.2	61.6	0.3
	Total time in bed (min)	-8.9	1	-19.5	1	-10.5	1
	Sleep efficiency (%)	1.7	1	12.4	0.1	10.6	0.4

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; SOL: Sleep onset latency; nWASO: the number of nights awaken after sleep onset; tWASO: time of wakefulness after sleep onset. * bolded "p" indicates significant difference as $p < 0.05$.*

7.9.2.2. Preliminary effects of the intervention on the depression severity (measured by HADS

Unlike the patterns of insomnia severity, linear mixed models indicated the mean depression score (measured by depression subscale of HADS) reduced in the True AP and sham AP group while increased in the ESC group (**Figure 13**). However, no significant statistical difference was found regarding the mean depression score within study groups over time (**table 54**). Similarly, no significant difference on the depression score was found between study groups at post intervention. However, at post follow-up, the mean depression score of the sham AP group was significantly lower than the ESC group ($p<0.05$) (**Table 55**).

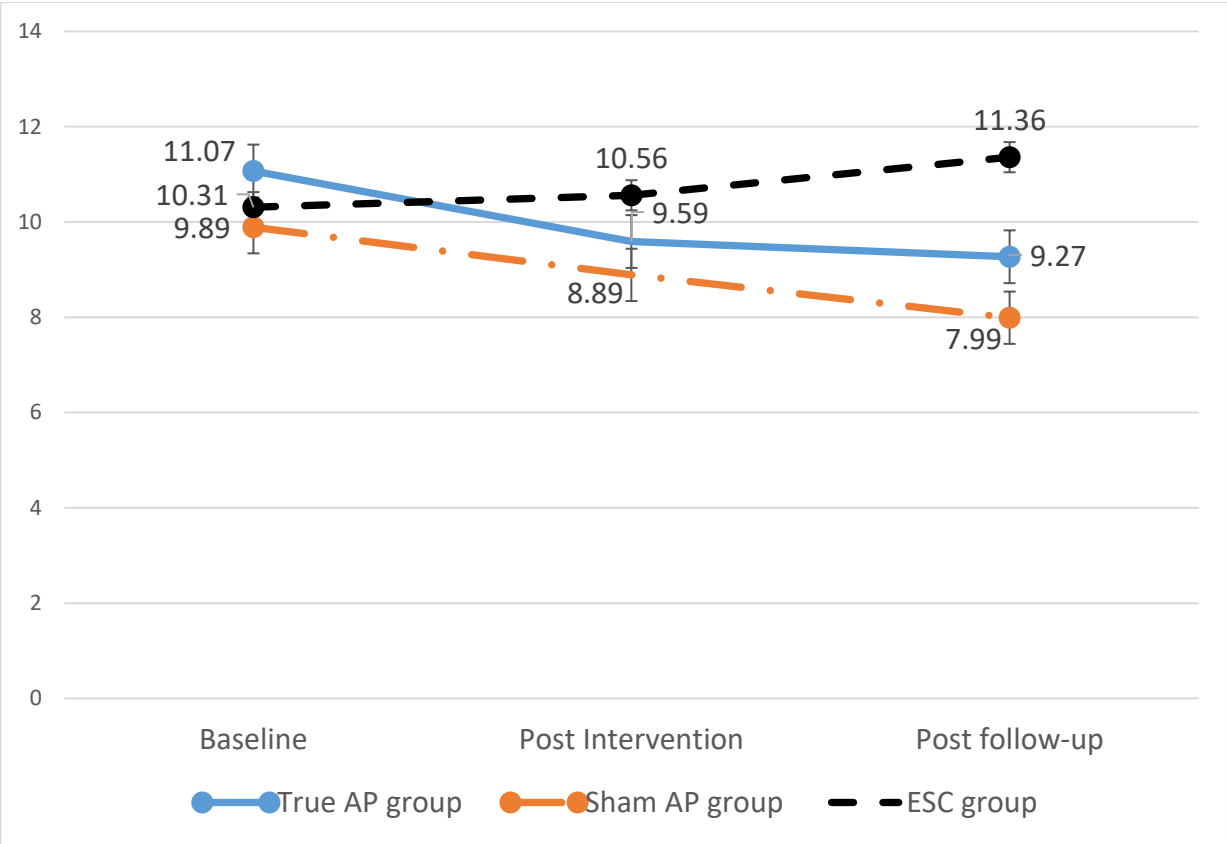


Figure 14. Changing of depression severity (measured by HADS) in study groups over time

*Table 54. Pairwise comparison of depression score (measured by HADS) **within-group** over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	1.41	0.09	1.61	0.05	0.20	0.6
Sham AP	0.92	0.36	1.82	0.17	0.9	0.33
ESC	-0.32	0.72	-1.12	0.61	-0.8	0.61

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; * Significant level of p-value was set at ≤ 0.05*

*Table 55. Pairwise comparison of depression score (measured by HADS) **between-group** over time (Post-hoc test adjustment)*

Time points	**Post-hoc Analysis (sequential Bonferroni test)**					
	True AP vs Sham AP		**True AP vs ESC**		**Sham AP vs ESC**	
	Contrast estimated	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***
Baseline	1.19	0.12	0.76	0.48	-0.41	0.48
Post intervention	0.69	0.82	-0.97	0.8	-1.67	0.63
Post follow-up	1.39	0.26	-1.97	0.2	-3.37	**0.03**

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates significant different as p < 0.05*

7.9.2.3. Preliminary effects of the intervention on anxiety

The linear mixed effect model analysis revealed a reduction in the anxiety severity (measured by anxiety subscale of HADS) in the study groups at post intervention. However, at post follow up, while the score was still reduced in the true AP and ESC group, it slightly increased in the sham AP group (**Figure 14**).

Within-groups comparisons shown a significant decreased anxiety score from T1 to T2 in the true and sham AP group but not in the ESC group. However, significantly lower anxiety score between T1 and T3 was only found in the true AP group. Between T2 and T3, no significant differences were found within study groups (**Table 56**).

Between-group comparisons only indicated a significantly lower in anxiety score at T2 between sham AP and ESC groups. No other significant differences regarding anxiety score between study groups was found (**Table 57**).

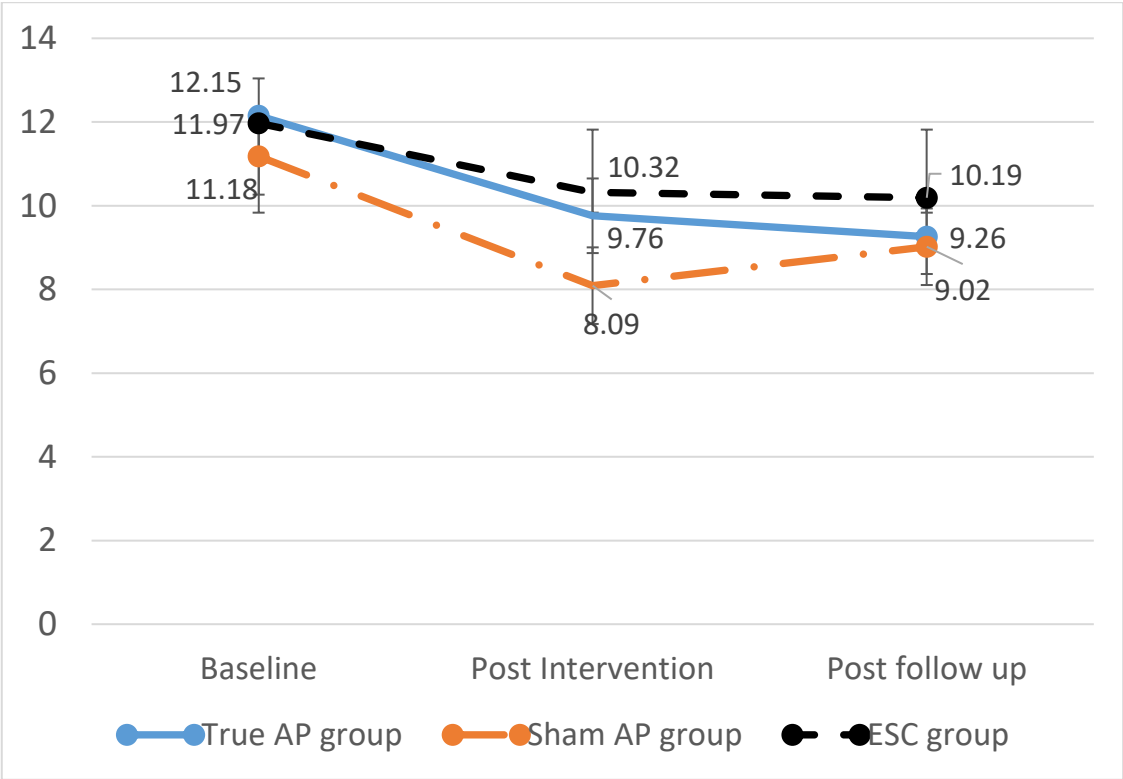


Figure 15. Changing of anxiety severity (measured by HADS) in study groups over time

*Table 56. Pairwise comparison of anxiety score (measured by HADS) **within-group** over time (Post-hoc test adjustment)*

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	2.37	**0.001**	2.87	**0.001**	0.49	0.28
Sham AP	2.75	**0.002**	1.83	0.071	-0.92	0.15
ESC	1.55	0.21	1.67	0.16	0.12	0.8

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates significant different as p < 0.05*

*Table 57. Pairwise comparison of anxiety severity (measured by HADS) **between-groups** over time (Post-hoc test adjustment)*

Time points	**Post-hoc Analysis (sequential Bonferroni test)**					
	True AP vs Sham AP		**True AP vs ESC**		**Sham AP vs ESC**	
	Contrast estimated	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***
Baseline	1.29	0.29	0.26	0.09	-1.03	0.29
Post intervention	1.67	0.45	-0.55	0.58	-2.23	**<0.0001**
Post follow-up	0.25	0.79	-0.93	0.05	-1.19	0.08

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates significant different as p < 0.05.*

7.9.3. Preliminary effects of the intervention on the patients' quality of life (QOL)

Analyses identified an improvement in patient's quality of life (indicated by FACT-G) during the study period in the true AP and sham AP group while the adverse was found in the ESC group (**Figure 15**). Pairwise comparisons within study groups over time only showed a significant improvement in QOL between T1 and T2 as well as between T1 and T3 in the true AP group. Although the QOL also increased over time in the sham AP group it was not significant change. Similarly, the decrease in QOL over time in the ESC group was also nonsignificant (**Table 58**). Comparisons between-groups indicated a significant lower QOL between the true AP group and the control groups (Sham AP and ESC) at baseline. Other differences between-groups at T2 and T3 assessment were found to be nonsignificant (**Table 59**).

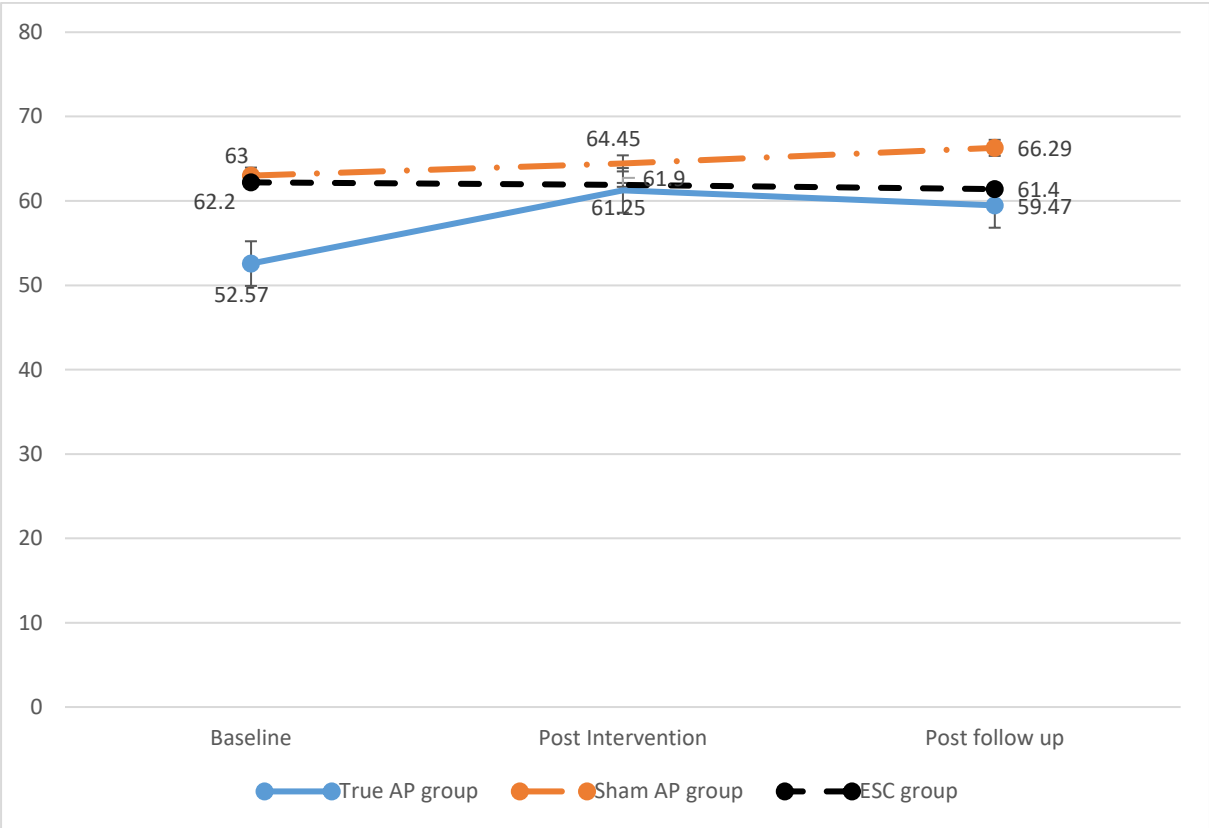


Figure 16. Changing of Quality of Life score in study groups over time

Table 58. Pairwise comparison of quality of life (measured by FACT-G) within study group over time (Post-hoc test adjustment)

Groups	Post-hoc Analysis (sequential Bonferroni test)					
	T1 vs T2		T1 vs T3		T2 vs T3	
	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*	Contrast estimated	Adjusted p-value*
True AP	-8.69	**0.008**	-6.9	**0.008**	1.78	0.37
Sham AP	-1.38	0.53	-3.22	0.52	-1.84	0.53
ESC	0.63	1	0.57	1	0.51	1

Note: AP: self-acupressure, ESC: Enhanced Standard Care; bolded 'p' indicates significant different as p < 0.05*

Table 59. Pairwise comparison of quality of life index (measured by FACT-G) between study groups over time (Post-hoc test adjustment)

Time points	**Post-hoc Analysis (sequential Bonferroni test)**					
	True AP vs Sham AP		**True AP vs ESC**		**Sham AP vs ESC**	
	Contrast estimated	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***	**Contrast estimated**	**Adjusted p-value***
Baseline	-10.51	**0.003**	-9.43	**0.005**	1.07	0.69
Post intervention	-3.2	1	-0.68	1	2.6	1
Post follow-up	-6.82	0.255	-1.96	0.67	4.86	0.47

*Note: AP: self-acupressure, ESC: Enhanced Standard Care; * bolded 'p' indicates significant different as p < 0.05*

7.10. Effect size and sample size calculation

The effect size was calculated based on estimated means and standard deviations between the treatment group and control groups at post intervention assessment. **Table 60** shows the post intervention estimated means and standard deviations in the study groups at post intervention assessment. Effect sizes were identified as small to medium between the true self-acupressure group and ESC (*d* ranged from -0.1 to 0.77). The sample size for a future RCT is calculated based on the Cohen's *d* of the symptom cluster score between the true AP group and ESC group (*d*=0.65). Considering a power of 0.8 and α of 0.05, the total sample size is calculated as 156 (52 subjects per group). Talking into account a potential attrition rate of 35%, the final sample size for a future main study was determined to be 240 participants (80 patients per group).

Table 60. Effect size of the intervention calculated based on post-intervention assessment results

Outcomes	**Estimated Mean (SD)**			**Effect Size (Cohen's *d*)**		
	True AP	**Sham AP**	**ESC**	**Sham AP vs True AP**	**ESC vs True AP**	**ESC vs Sham AP**
Symptom Cluster Score	4.17 (2.77)	5.49 (2.52)	5.98 (2.84)	0.5	0.65	0.18
ISI	15.09 (7.58)	15.13 (6.1)	20.26 (5.79)	0.006	0.77	0.86
Depression (HADS)	9.59 (4.87)	8.89 (6.29)	10.56 (5.24)	-0.12	0.19	0.29
Anxiety (HADS)	9.76 (5.49)	8.09 (5.36)	10.32 (5.61)	-0.31	0.1	0.4

Note: AP: self-acupressure, ESC: Enhanced Standard Care; ISI: Insomnia Severity Index, HADS: Hospital Anxiety and Depression Scale

7.11. Summary of the results of the feasibility trial

There were 114 cancer patients with various cancer diagnoses recruited during a twenty-week period participating in the study, and 74 of them completed the outcome assessment at all time-points. The attrition rate was high in this feasibility trial (35.08%). Regarding the study outcome measurements, the sleep diary was determined as inadequate with a high proportion of missing data (48.2%, 31.1%, 47.3% at T1, T2, and T3, respectively). Other measurements were found to be acceptable for use with missing values identified in only one item of FACT-G (the FACT-G- GS7). The self-acupressure treatment was identified to be acceptable for use in cancer patients undergoing chemotherapy as the majority of those completing trial participation from the true AP and sham AP group followed the full treatment protocol (31/47, 65.9%). In addition, self-acupressure was determined as highly acceptable as the mean score of the IRP was 76.73/90. Adverse events associated with self-acupressure such as mild pain at the acupoint after stimulation and finger being tired when stimulating the acupoints were reported by a few participants, but the reactions were mild, tolerable, and transient.

Two methods were used to measure severity of individual symptoms in this trial. Surprisingly, each of method reported different results. The within-group comparisons indicated insomnia, depression, anxiety, and the symptom severity scores (measured by NRS) were found to be significantly reduced at T2 and T3 compared with T1 in the true AP group ($p<0.001$), while the reduction of thoes scores in the sham AP and ESC group were nonsignificant. However, between-group comparisions found insomnia score measured by NRS (NRS-I) was significantly lower than that in the sham AP and ESC group at T2 and T3 ($p<0.05$). In addition, symptom scores were significantly lower in the true AP group than those in the ESC ($p<0.05$) at post intervention assessment (T2).

On the other hand, the preliminary anlysis of individual symptoms using standardized measurements indicated a different result. The within-group comparisons reported a significant reduction of insomnia and anxiety at T2 and T3 in the true AP group and at T2 in the sham AP group while no significance was found at any time point in ESC. The analysis also indicated a significant difference in the ISI score between the true and sham AP group compared with ESC at T2 and T3. However, a significant difference in anxiety score measured by HADS (HADS-A) was only found between the sham AP and ESC group at post intervention. Regarding depression severity measured by HADS, time main effect and group by time interaction were found to be non-significant ($p>0.05$). However, significance was found between the sham AP and ESC group at T3 ($p<0.05$).

Within-group analysis on sleep parameters indicated a significant differences in tWASO, total sleep time, and sleep efficienct in the true AP group at T2 and T3 (compared with T3). However, in the ESC group, within-group analysis also reported a significant decrease of nWASO only between T2 and T3 and significantly longer total sleep time only between T1 and T3. Between-group analysis indicated the total sleep time in the true AP and sham AP group was found significant higher than the ESC group ($p = 0.002$ and 0.019, respectively). Also, the sleep efficiency was found to be significant better in true AP and sham AP group than the ESC group ($p=0.002$ and 0.03, respectively). At post follow-up, no significant difference in any sleep parameter was found between the study groups except for the tWASO between the true AP and ESC group ($p<0.05$).

For the quality of life assessment, within-group comparisons indicated a significant increase QoL score in the true AP group at T2 and T3 compared with T1, but showed no difference in the sham AP and ESC groups ($p<0.05$). However, between-group comparisons did not found any significant differences in QOL status among study groups.

The intervention was shown to be feasible and acceptable by the study population. The next chapter will discuss these results in the context of evidence from the literatures. Strengths, limitations, and the contribution of the study will also be considered. The possibility of future research based on the study findings will also by discussed.

CHAPTER 8. DISCUSSION AND CONCLUSIONS

8.1. Introduction

The purpose of this project was to ascertain the prevalence of insomnia, identify its risk factors and explore the existence of a sleep-related symptom cluster as well as develop a self-acupressure treatment protocol and examine the feasibility, effectiveness, and acceptability of self-acupressure to reduce the identified symptom cluster, including insomnia, depression, and anxiety, among cancer patients undergoing chemotherapy in Vietnam. This chapter is the final chapter of the doctoral research project, which will consider the results of the cross-sectional survey and the feasibility trial (which were reported in chapter 4 and chapter 7). The chapter consists of 13 sections. Sections 8.2 to 8.5 discuss the results of the cross-sectional survey, including the insomnia prevalence and its risk factor, the symptom cluster of insomnia, depression, and anxiety as well as the impact of insomnia and insomnia related-symptom cluster to participants' quality of life, and the appropriateness of subjective measurement in measuring insomnia. Sections 8.6 to 8.9 discuss the results of the feasibility study including the feasibility of the intervention, its fidelity and effectiveness on study outcomes. The selection of control groups is also discussed in section 8.8. The strengths and limitations of the doctoral project are considered in section 8.10. Afterward, the changes for the future study and the doctoral project implications are discussed in section 8.11 and 8.12, respectively. Lastly, the conclusion of the project is presented in section 8.13. The purpose of the discussion is to expand upon the findings in an effort to provide further understanding of the intervention implementation within the Vietnamese healthcare context.

8.2. Insomnia prevalence and its risk factors

8.2.1. Insomnia prevalence

The findings of this study showed a high prevalence of new onset complaints of insomnia among cancer patients undergoing chemotherapy (42.8%) which is double than that of the general population (Buysse, 2013; Neubauer et al., 2018). This prevalence is higher than previous studies which also used the ISI to measure insomnia in cancer patients (Davis et al., 2014; Morris et al., 2015; Savard et al., 2005). The difference can be explained by the characteristics of the samples used. More specifically, Morris et al. (2015) recruited out-participants who contacted a cancer care helpline, and this could create selection bias. Davis et al. (2014) recruited advanced cancer patients who participated in a palliative medicine program and did not report the type of cancer treatment the participants received. However, two studies conducted in breast cancer patients and prostate cancer patients indicated that the chemotherapy period was associated with more insomnia severity than other times, which is in line with our findings (Savard et al., 2013; Savard et al., 2015). Our sample was drawn from Vietnamese hospitals, where patients are often treated in overcrowded clinics, and patients often have to travel long distances from other regions to attend for treatment in Hanoi. Hence, we can conclude that the peri-chemotherapy time is a stressful time that is strongly linked with the development of insomnia complaints in cancer patients as a relatively high percentage of chemotherapy patients have moderate to severe insomnia complaints.

8.2.2. Risk factors of insomnia

Analyses failed to find a significant difference in insomnia frequency and severity rates between male and female participants, participants at different age groups, and with different cancer diagnoses or cancer stages. These findings are different from some of the existing literatures. Gender and age were identified as predisposing factors for insomnia in cancer

patients as well as in the general population (Lowery, 2015; Ohayon & Roth 2001). Nevertheless, these findings are in line with some recent studies in cancer patients, whereby there was no significant difference in insomnia rates between males and females, and participants in different age groups (Akman et al., 2015; Miaskowski et al., 2011; Morris et al., 2015; Phillips et al., 2012; Romito et al., 2014). Several large-scale studies, however, found significant differences in insomnia prevalence between lung/breast cancer patients compared to other cancer diagnoses (Palesh et al., 2010; Savard et al., 2001). Some potential reasons for the differences may include the antiemetic drugs used (i.e., dexamethasone) that may influence the patients' sleep pattern, tumor biology and side effects from chemotherapy (i.e., induced menopause) (Palesh et al., 2010; Savard et al., 2001). In addition, we found participants reporting depression and/or anxiety had significantly higher insomnia rates than those with no depression and anxiety. Studies in the literature also showed consistently that patients with depression experience insomnia, and insomnia is also a risk factor for developing depression and anxiety (Perlis et al., 1997). Anxiety brings more difficulty in falling asleep resulting in less restorative sleep and nightmares, while depression has been linked to difficulties maintaining sleep and unwanted early waking up in the morning as well as nightmares (Berk, 2009; Mercadante et al., 2004). Therefore, the rate and severity of insomnia may be related to the participants' distressing symptoms, but not to the participant's characteristics and cancer diagnosis or treatment variables.

8.3. The symptom cluster of insomnia, depression, and anxiety

This survey also identified insomnia, anxiety, depression and depressive symptoms (worrying and feeling sad) all forming a symptom cluster (SC). Since worrying and feeling sad are symptoms of depression (The National Institutes of Mental Health, 2018), we conclude that insomnia, anxiety, and depression form a clear and concrete SC. Previous studies in different cancer populations also reported similar findings (Redeker et al., 2000; Walsh & Rybicki,

2006). Results from a systematic review further suggested a bidirectional relationship between insomnia, depression, and anxiety (Alvaro et al., 2013). However, previous studies used non-specific scales to measure symptoms (Redeker et al., 2000) or identified symptom clusters on one dimension of the symptom experience only (severity) (Alvaro et al., 2013; Walsh & Rybicki, 2006). It is interesting to see that the correlations between the three symptoms were low in the correlational analysis, suggesting that other factors, not examined in this study, may be part of this relation. However, the strength of this relationship became moderate-to-strong in the SC analysis. Hence, anxiety and depression are clearly part of insomnia, but perhaps not the only parts. This supports the use of selective serotonin reuptake inhibitors (SSRIs) as an option to improve sleep in this population when anxiety and/or depression are present, balancing well the possible beneficial effect over side effects and polypharmacy. However, as SSRIs have multiple side effects, can be addictive and there are other factors contributing to insomnia in cancer patients who often experience a high symptom burden, these have a place in the management of insomnia in select patients but should not be considered as the drug of choice in this population. To our knowledge, our study is the first study to date using standardized measurements to assess insomnia, depression, and anxiety and identify SCs based on different dimensions of the symptom experience that give more concrete evidence that insomnia, anxiety, and depression form a SC.

8.4. The impact of insomnia and the insomnia related-symptom cluster on participants' quality of life

In the survey, participants with insomnia or the sleep-related SC had a significantly worse global QOL score as well as other subscale scores (except for the SWB) than those without insomnia. The sleep-related SC seemed to contribute to lower physical and functional well-being, and poorer emotional well-being of the patients. The consistent results from previous studies also support our findings of how insomnia impact on patients' quality of life

(Davidson et al., 2002; O'Donnell, 2004; Phillips et al., 2012; Trudel-Fitzgerald et al., 2014; Vargas et al., 2010). Insomnia may cause cancer patients to be less able to cope with stress and carry on with their daily activities and had greater difficulty dealing with emotional problems (Phillips et al., 2012; Vargas et al., 2010), which impaired them physically and emotionally (Clevenger et al., 2013; Trudel-Fitzgerald et al., 2014).

8.5. The appropriateness of subjective measurement for insomnia in cancer patients

The results also demonstrated there was no difference between sleep parameters measured by Actigraph between insomnia and non-insomnia participants. The average true sleep time for both insomnia and non-insomnia participants was greater than six hours per night, and the sleep efficiently was nearly 90%. Interestingly, we found that insomnia participants slept (numerically) more than non-insomnia participants (although the difference was not statistically significant) but they seemed to have lower sleep efficiency and tended to wake up more often. Using both objective and subjective measurements are being recommended to evaluate multiple sleep parameters of insomnia (Ancoli-Israel et al., 2015; Ruivo Marques et al., 2018). However, our study indicates the sleep parameters between insomnia and non-insomnia participants are related to patients' experience of insomnia, and how their perceived sleep quality impacts on their lives rather than objective quantifiable sleep parameters, that cannot incorporate patient perceptions. A study also found insomnia frequency is related to patients' perception about sleep, but not the result from objective measurements (Zorick, 1994).

Studies also further reported a difference between the participant's perception of sleep quality and objective measurements (Grandner et al., 2006; Landry et al., 2015). A study by Siberfarb et al. indicated that perceptions of "poor" or "good" sleep were associated with the amount of delta sleep (the deepest form of sleep) but not with other objective sleep parameters in cancer

patients (Silberfarb et al., 1985). This condition may also be explained by “the sleep discrepancy” referring to underestimation of the total sleep time and overestimation of the sleep latency, and wakening after sleep onset in insomnia patients (Kay et al., 2017). Sleep experts define this sleep discrepancy as “paradoxical insomnia”, experienced by up to 50% of insomnia patients (Manconi et al., 2010). Considering the above evidence, Actigraphy can measure sleep parameters but it does not measure the sleep quality as perceived by the patients, and the latter informs the patient’s satisfaction with sleep, as part of the experience of insomnia. Furthermore, patients’ satisfaction with sleep may impact on their psychological states (anxiety/depression) and their lives quality, relating to the co-occurrence of sleep-related symptoms. However, the results from Actigraph should be interpreted with caution since daytime napping was not measured in the current study. Changes in sleep architecture and maladaptive sleep behavior include prolonged bedtime and daytime napping that are considered as perpetuating factors contributing to the maintenance of insomnia. Cancer patients, in an attempt to cope with sleeplessness, might try the above sleep behaviors, but as these become habits, insomnia persists for long-term (Lowery, 2015). In addition, individuals with persistent insomnia, possibly including those with cancer, tend to engage in sleep-interfering activities in their bedroom for staying awake rather than inducing sleep (e.g., watching TV, listening to music, eating, working or reading in the bed or the bedroom). These behaviors tend to weaken the association between certain normally sleep-inducing stimuli (bed, bedtime, and bedroom) and sleep (Morin et al., 2011). Furthermore, sleep efficiency in our study may be misrepresented, as there are inherent weaknesses in its measurement when there is no standardized time in bed.

In summary, the results of the study confirm the high prevalence of insomnia among cancer patients undergoing chemotherapy. In addition, insomnia and the sleep-related SC significantly reduced the patient’s quality of life. Approximately half of the insomnia burden

in the sample was accounted for by the sleep-related SC while the other half experienced only insomnia. This finding suggests that insomnia is driven both by shared and unique mechanisms. The results from this study also indicate that insomnia is a subjective symptom, and the patients' perception of insomnia or quality of sleep may differ from the actual objectively-measured insomnia severity they experience. The results highlight a high unmet need in this population requiring interventions to help patients manage these symptoms.

To meet the need identified in the survey, the intervention of self-acupressure was selected for testing. Finding from previous systematic reviews indicated the promising results of self-acupressure in managing multiple symptoms including insomnia among cancer population (Lee et al., 2011; Ling et al., 2014; Song et al., 2015). However, its effectiveness in managing symptom cluster of insomnia, depression, and anxiety is unknown. As this intervention has not been tested before in cancer population, and in accordance with the MRC framework, we conducted a study to test the feasibility and preliminary effectiveness of self-acupressure in manage symptom cluster of insomnia, depression, and anxiety in cancer patient undergoing chemotherapy.

8.6. The feasibility of the intervention

8.6.1. The feasibility of the recruitment process

Overall, findings of the trial regarding recruitment support the feasibility of the design of this trial for use in future research. The recruitment rate was 12.6 % which is lower than the recruitment rate (around 22%) reported by other studies of nurse-delivered interventions for symptom clusters among cancer patients undergoing chemotherapy (Kurtz et al., 2007; Ly Thuy et al., 2016). Compared to other self-acupressure interventions for cancer-related symptoms, the recruitment rate was higher than 8.5% in a study of general cancer patients (Zick et al., 2011) and lower than those (ranging from 45.3% to 68%) in studies with renal

cancer (Tsay & Chen, 2003), or lung cancer (Tang et al., 2014). The differences in the recruitment rate in this trial are most likely due to the restrictive inclusion criteria for the present study, whereby participants needed to have the symptom cluster of insomnia, depression, and anxiety at least at moderate severity (4/10) and an ISI score of 11 or above, as well as signs of depression and anxiety (a HADS score of 16 or above with at least 8 for each subscales). While other studies just required participants to report one of those targeted symptoms (Zick et al., 2018) or all symptoms but ranking the severity of at least two of three symptoms as 3 or above on 0-10 numeric scale (Yeh et al., 2016). While the restrictive inclusion criteria resulted in excluding 439/902 participants (48.6%), the total time for recruitment was 20 weeks. The time for recruitment in this study is much shorter than that with similar sample size studies in cancer patients (less than 150 patients). A pilot study conducted using auricular self-acupressure to manage the symptom cluster of nausea and vomiting in breast cancer patients took 15 months for the recruitment (Tan, 2018). Others symptom cluster interventions in Vietnam also took 12 months for recruitment (Ly Thuy, 2018; Vu, 2019). The ability of recruiting enough participants in a short time (by half) compared with other studies confirmed that the more restrictive approach was nonetheless acceptable and feasible for a multisite randomized controlled trial.

Moreover, the refusal rate of the trial was 31.5% which is similar to other self-acupressure interventions in cancer patients (Tang et al., 2014; Yeh et al., 2016; Zick et al., 2011). Other studies reported lower refusal rates, ranging from 4.9% to 12.9% (Su-Chen et al., 2015; Yeh et al., 2019; Zick et al., 2016). In previous studies, the researcher provided limited information concerning reasons for non-participation. Where such information was reported, lack of interest was often the key factor for cancer patient's decision not to participate (Yeh et al., 2016; Zick et al., 2011; Zick et al., 2016). In line with these previous studies, in this trial, the main reason for refusal was lack of interest (31.2%).

8.6.2. Attrition rate and reasons for attrition

The attrition rate of the study was 35.1% which is higher than other symptom cluster intervention studies using self-acupressure for cancer patients (ranging from 15% to 25.5%) (Su-Chen et al., 2015; Yeh et al., 2016; Zick et al., 2018). The major reason for withdrawal was that participants were too tired during the time of their participation in the trial (40%). Studies indicated the attrition rate is influenced by sociocultural beliefs, practices, and research burden (Grill et al., 2015; Ly Thuy et al., 2016). Acupressure is a modality of Traditional Chinese Medicine which is quite popular in the Vietnamese context. Therefore, participants were likely to accept the treatment easier compared to other self-treatments. However, the total time required for each subject to participate was eight weeks with a period of four weeks of self-acupressure, with three repeated measurements at baseline, post-intervention, and post-follow-up. Moreover, no significant difference was found regarding attrition rates between the intervention group and control groups. Nevertheless, the demographic and clinical characteristics of the participants who withdrew and those who stayed in the trial were also comparable. However, withdrawn participants had significantly lower physical well-being index (measured by FACT-G). Therefore, the reasons for withdrawal were not directly related to the nature of the intervention but is contextually relevant to the nature of oncological disease itself.

8.6.3. Feasibility of the study measurements

Participants' responses to the study questionnaires were assessed in this feasibility study. Findings for this trial indicated that there were no missing data at scale-level at all assessments for the NRS for each symptom in the clusters, ISI, HADS, and FACT-G. However, at item-level, the FACT-G-GS 7 ("I am satisfied with my sex life") was found missing in a high proportion (42.1% at baseline, 43.2% at post intervention, and 50% at post follow-up).

Furthermore, missing data at scale-level was found in the sleep diary at high rate (48.2% at baseline, 31.1% at post intervention, and 47.3% at post follow-up). Missing data for the FACT-G and sleep diary is discussed in this section.

All of the measurements used in this trial were already used in the cross-sectional survey except for the sleep diary. The sleep diary was used to record sleep parameters, and participants were required to complete a seven-day sleep diary at baseline, post intervention, and post follow up. Sleep diaries are most often used as a quantitative measure to assess the impact of the intervention (Buysse et al., 2006). In this trial, nearly half of the participants did not return the baseline sleep diaries. The reason for this can be explained due to the long period of measurement. In addition, participants filled the sleep diaries in the seven days after completing their chemotherapy cycle when many side effects from the treatment are present such as fatigue, nausea, and vomiting that make them exhausted and limit the ability to complete the diaries. Given all above concerns, the feasibility of the sleep diary was determined to be low, and a future RCT should consider excluding the sleep diary or using sleep diary but for a shorter period. However, due to characteristic of Vietnamese cancer patient (majority are farmer with the education lever of junior high school) future study has better to reduce the respond burden to minimum the missing data. Hence, the future RCT should exclude the sleep diary.

FACT-G, a tool to assess the quality of life of general cancer patients was adopted in this trial to measure the subject's quality of life. The scale contains 21 items to measure four dimensions of QOL which are physical, social/family, emotional, and functional well-being. While most of the items in the scales were completed by the participants, considerable missing values were identified in item FACT-G-GS7 ("I am satisfied with my sex life"). At the baseline assessment, 42.1% of participants refused to answer this item. Similar result was found in the post-intervention assessment with 43.2% of the participants not responding to

this item. At post follow-up, half of the participants did not answer the FACT-G-GS7. In a trial among Chinese breast cancer patients, 59.36% of participants also refused to answer this item (Tan, 2018). Perhaps, this result is no surprising. Vietnamese are more conservative than Western people when talking about sex. Whenever sex is mentioned, Vietnamese people usually consider it as being sensitive and avoid answering or giving their opinion. Other reason for having a large missing proportion for this item is related to the structure of the questionnaire. The order of the scale in the study questionnaire was personal information, NRS, ISI, HADS, and FACT-G. While the previous scale was short (7 items or less per scale), the FACT-G contained 21 items. As observed during the data collection process, after completing some scales participants felt tired with the last scale. Nevertheless, it was the scale's instruction that suggested participants to choose whether they want to answer this item by indicating "If you prefer not to answer it, please mark this box). In addition, participants may have been distracted by other nearby patients that observed them while they marked their answer. As a result, they may have decided to skip this sensitive question. As this is a common occurrence in many studies, based on the *FACIT Administration and Scoring Guidelines*, the missing data of GS7 does not affect the FACT-G total score or subscale scores, the score for each subscale is calculated by averaging the score of answered items. Although there are missing data, the FACT-G score and its subscale were valid in reflecting subject's quality of life. As such, a future RCT should consider including FACT-G. However, in order to avoiding feeling tired with long questionnaires, the researcher may ask the participant to complete the ISI and HADS first. After being identified as eligible to the study, the researcher can summarize the results for the participants then ask them to complete the FACT-G. By giving a short break, participants may consider to better complete the questionnaire. Other solution can be mixing up the order of the questionnaires by placing FACT-G before ISI and HADS.

8.6.4. Adverse events from self-acupressure

Adverse events associated with self-acupressure were recorded by the participant's self-acupressure daily record form. During 28 days of self-acupressure treatment, only four participants (two from true AP and two from sham AP group) reported discomfort related to self-acupressure at mild severity and transient. Two participants in the true AP group reported feeling pain at the acupoint after stimulating it. This discomfort is related to the *deqi* sensation. The *deqi* sensation is described as the feeling of soreness, numbness, heaviness, distention, and warmth at the acupoints and is felt by patients (Tsay & Chen, 2003; Yeung et al., 2017). According to the TCM theories, acupressure only shows its effects on symptoms when patients experience *deqi* sensation (Yang et al., 2013). However, the *deqi* sensation dissipated quickly after the acupressure session. Two participants in the sham AP group reported their finger to be a little tired when stimulating the acupoint. This discomfort related to the duration of self-acupressure session. Each participant required to stimulate six acupoints for 24 minutes. Therefore, it is expected that some patients may experience this adverse reaction. No serious adverse events were reported and all participants who reported discomfort had completed the study. This supports the safety of self-acupressure. Most of the trials using self-acupressure in cancer patients do not report adverse event (Benedicto, 2016; Cerrone et al., 2008; Haddad & Palesh, 2014; Harris, 2014; Harris & Zick, 2010; Shin et al., 2004; Tang et al., 2014; Tsay & Chen, 2003). Others reported mild discomfort including bruising, skin break, muscle spasm, or headache (Murphy et al., 2019; Zick et al., 2018). All of them are related to applying too much pressure to acupoints. As such, our pressing technic used in this trial requiring the finger to firmly massage the area of the acupoint with rotation movements with the pressure that achieve *deqi* sensation was tolerable with participants. In line with our findings, a systematic review from 11 studies using acupoint stimulation for anxiety and depression in cancer patients also reported no serious adverse events (Wang et al., 2016). Two

other reviews also supported the safety of self-acupressure (Song et al., 2015; Waits et al., 2016). The findings support the safety of self-acupressure as reported adverse reactions were mild, tolerable, and transient.

8.6.5. Acceptability of the intervention

Exploring the intervention's acceptability is an important aspect of a trial. In this present study, acceptability was assessed using several indicators, including treatment completeness and acceptability of the intervention using the Intervention Rating Profile (IRP-15). Taken overall, findings in relation to each of these indicators support the acceptability of the intervention for trial in future studies.

8.6.5.1. Self-acupressure treatment completeness

The study results indicate a good intervention adherence (66%) which is higher than previous self-acupressure studies in cancer patients who already completed cancer treatments (Zick et al., 2011) but lower than studies conducted in breast cancer patients using auricular self-acupressure (Yeh et al., 2016; Yeh et al., 2017). Several factors can influence the participant's adherence to an intervention, including the perception of relevance, convenience, and beliefs in the intervention (Ellis et al., 2012). In this trial, participants underwent chemotherapy as a treatment for their cancer, therefore, adopting self-acupressure to manage insomnia, depression, and anxiety was relevant to them as the side effects of chemotherapy treatment were also their concern (Chua et al., 2018).

Beliefs of patient can influence their engagement to the treatment (Benedetti et al., 2011). A study conducted with breast cancer patients taking tamoxifen revealed the non-adherers thought taking tamoxifen did not have any effect, while the reverse was stated by adherers (Grunberg, 2004). A meta-analysis of 94 studies also indicated a significant relationship between participant's beliefs and adherence (OR=1.7, $p<0.0001$) (Horne et al., 2013).

Nevertheless, supporting practical abilities and resources can optimize the adherence to the study of the participants (Horne, 2003). Our trial is the first intervention in the literature focusing on managing insomnia, depression, and anxiety in cancer patients during chemotherapy. Since acupressure is a well-known traditional non-pharmacological treatment in Vietnam, participants had beliefs in the treatment. In addition, since they can practice self-acupressure at home with no equipment, the intervention had the advantage of being fully intergraded into the participant's daily life. This can explain the high average number of completed treatment days in the true and sham self-acupressure groups (27.03±1.56 and 26.85 ± 1.38 days, respectively). Also, the average time of self-acupressure sessions in both groups was close to the standard time required (24 minutes) with 23.6 ± 5.9 minutes in the true AP group and 24.2 ± 4.9 in the sham AP groups. Belief of participants or expectation about the success of a treatment also influences the treatment outcomes. A study conducted by Devilly and Borkovec (2000) pointed out that the participant's belief on the efficacy of the intervention was a strong predictor of the treatment outcomes. Goossens et al. (2005) also indicated patients' beliefs about the success of a treatment were shown to influence the treatment outcomes. A review also reported patient's expectation could affect the results of clinical trials and indicated the placebo effect is related to expectancy (Rutherford et al., 2010). However, the current trial did not measure patient's beliefs. A future full-scaled RCT can consider measuring this issue.

Low level of education of the participants suggests poor health literacy among the study population. This is not a surprising result since it is in line with previous studies that illustrate the low health literacy in Vietnamese patients (Duong et al., 2015; Laverack, 2003). Being aware of the impact of the health literacy, several strategies were employed to ensure that participants of all literacy levels benefitted from the study and to increase the adherence rate with the intervention. For instance, a patient booklet with colored image-guide pictures was

presented to participants during the self-acupressure education session. Participants were requested to keep the booklet. Weekly phone calls were also made to encourage patients to practice self-acupressure at home. As a result, although some patients withdrew from the study, those who completed the study showed a high adherence to the intervention.

8.6.5.2. Participants' acceptability of the intervention

The intervention was highly-accepted by the participants in the intervention group. They found self-acupressure appropriate and beneficial in helping them to manage insomnia, depression, and anxiety. Participants gave positive feedback to most of the items in the Intervention Rating Profile (IRP-15). Regarding the appropriateness of the intervention, 80.7% of the participants agreed or strongly agreed their symptoms were severe enough to require the use of self-acupressure. Importantly, almost all participants would recommend other patients to use self-acupressure as 92.3% of them agreed or strongly agreed that self-acupressure is an appropriate treatment for insomnia, depression, and anxiety in cancer patients. In addition, most of them were willing to use the intervention at home or hospital. Participant's opinion about the effectiveness of self-acupressure was also positive as 73% agreed on its effectiveness, 92.3% were satisfied with self-acupressure, and 88.5% of them agreed on the beneficial effect of the intervention. 25/26 participants reported that the self-acupressure did not have any negative side-effects on them which further supports the safety of the self-acupressure. The positive feedback from participants explained the high adherence to the intervention as discussed above.

The results also showed that discomfort among participants was not considered negative as 96.2% of the responders agreed or strongly agreed that self-acupressure did not result in any negative side-effect. In contrast to the positive feedback for most of the items in the scale, there were only few negative responses regarding the appropriateness of self-acupressure to

various cancer diagnoses (2/26). Also, one patient slightly disliked the procedures of the intervention.

The participant's acceptance of self-acupressure was deemed good in this study. However, the result should be interpreted with caution. The data reflected opinions from patients who completed the study (68.4% participants in the true AP group). If data were also collected from patients who withdrew from the study, better insights would be gained about which aspects of the intervention could be improve or modified.

8.7. Fidelity of the intervention

Fidelity of the intervention refers to strategies used to ensure the intervention is implemented as planned by the trial protocol (Bellg et al., 2004). Fidelity should be implemented at all stages of research, however, it is often emphasized in the development and piloting stage (Rounsaville et al., 2001). Nevertheless, it could be problematic to assess the effect or replicate an intervention if the internal and external validity of a certain study is in doubt (Bellg et al., 2004). However, reporting the components of intervention fidelity for studies is not widely done (Wyatt et al., 2015). In this trial, several strategies to ensure fidelity of the intervention were implemented to maintain the rigor of the self-acupressure intervention.

8.7.1. Intervention design

A key aspect of an intervention design includes the content and dose of the intervention which should be the same across study groups and potential setbacks regarding this might occur during the study implementation (Bellg et al., 2004; Borrelli, 2011). In this feasibility trial, the dose of the intervention was the same for both true and sham self-acupressure group. In addition, some solutions to prevent provider dropout and lost to follow-up due to lost contact were drafted in the intervention proposal and were implemented during the study (section 4.5.9.1). We had three main interventionists (the main reseacher and two nurses) and two

extra main interventionists (one nurse per study site) and no interventionist dropped out during the study period. All interventionists were trained and checked for accuracy of locating the acupoints and the pressing technique after an self-acupressure training session.

Regarding preventing lost to contact during the trial, only a few patients had a fixed line telephone number (10/214) although all of them had moblie phone numbers. Obtaining the phone number of the participant's family member appeared to be a better solution. However, not many patients were willing to give this information (60/214) due to privacy issues, and in some cases the patients and their partners were using the same phone number for communication. Withdrawing due to losing contact was the second main reason for attrition in this study. Among the eight patients lost to contact, two of them were living alone, three were living with their childrent instead of partner, and three were living with their family. 4/8 of them provided the researcher with their partner's phone number. However, the partner hang off and blocked the phone of the researcher after she introduced herself. Taken the above issue, the future RCT should consider to obtain the second phone number of the participant's family member. However, in oder to keep a good comunication with the patients and their family member, the research should invite the patient's family member to the training session or asking for permission to obtain their phone number.

8.7.2. Intervention training and monitoring of the intervention delivery

The component of intervention training involved a step to ensure that the intervention protocol can be implemented as designed. Since the study involved multiple instructors, the training should be standardized. As such, prior to the commencement of the study, all of the instructors attended a training session (as described in section 4.5.9.2). In our study, the interventionists were scored by the TCM doctor on their demonstration and achieved 100% of accuracy to begin training participants. This requirement is higher than in another study which required

95% of accuracy in interventionists to begin and continue training the participants (Zick et al., 2012).

There were 40 self-acupressure instruction sessions and 24 enhanced standard care sessions conducted. Most of the true self-acupressure training sessions were delivered by the Ph.D. student/interventionist (35/40), other sessions were done by an extra interventionist. The Ph.D. student supervised all the training sessions to ensure the training were implemented in the same manner across study groups. All of the participant training sessions were conducted by strictly following the true/sham self-acupressure training protocol or the enhanced standard care training protocol.

On average, it took 20 minutes to instruct each participant in the true self-acupressure group how to locate and press the acupoints while it was shorter in the sham self-acupressure group (15 minutes). Another study also indicated participants can be taught to perform self-acupressure within 15 minutes (Zick et al., 2012). That result supported the advantage of self-acupressure being a treatment which is easy to be learned by participants. To ensure that the participants clearly knew how to locate and press the acupoints, by the end of each self-acupressure session the instructors checked the self-acupressure mastery of the participant. None of the sham acupoints were wrongly located by the participants in the sham group. This result supported the use of the sham self-acupressure approach used in this trial as it was easy to understand the points and hence ensure the blinding in the design. In contrast, several true acupoints were located wrongly by the participants in the first round of checking their self-acupressure mastery. *Baihua, Shenmen,* and *Fengchi* were identified incorrectly by six participants. However, after further instruction, all of them identified those acupoints correctly.

8.7.3. Monitoring of patients receiving the intervention

In this second round of checking self-acupressure mastery (two or three weeks after the first self-acupressure session) the location of *Baihua* and *Fengchi* were incorrectly identified by two participants in the true AP group, while none of the participants in the sham self-acupressure group identified wrongly the location of sham acupoints. The participant's retention of the skills and ability to perform the self-acupressure protocol was good with 98.6% and 100% of accuracy on the self-acupressure skill check form in the true AP and sham AP group, respectively. This proportion is higher than the proposed 80% and comparable to the goal of maintaining 95% accuracy on self-acupressure among participants in the trial protocol in a study of (Zick et al., 2012).

To monitor the self-acupressure practice at home, participants were requested to record their daily self-acupressure practice on the self-acupressure form. Moreover, weekly telephone reminders were also made to encourage participants to practice self-acupressure at home. The result from analyzing the self-acupressure form revealed a good adherence to the study among participants who completed the trial (as discussed previously). Using a log book to monitor the receipt of the intervention was used in several self-acupressure interventions (Molassiotis et al., 2007; Wyatt et al., 2015). Perhaps a better solution to monitor participants at home should be considered in the future since the attrition rate for the feasibility study was high. Involvement of family is essential for optimal treatment of cancer patients in ensuring treatment compliance, continuity of care, and social support (Glajchen, 2004). Therefore, the future RCT should consider asking a family member of caregiver to help in monitoring and encouraging participants to practice self-acupressure at home in order to decrease the attrition rate and increase the adherence of the participants to the protocol.

Overall, the intervention fidelity of the self-acupressure protocols was well maintained in this feasibility trial, although some drawbacks in the follow-up process were still observed given the high attrition rate which affected the validity and reliability of the study findings. Family involvement is a potential strategy to improve the attrition rate that can be utilized in further enhancing the fidelity of self-acupressure treatment in a future trial.

8.8. Selection of control groups

Selection of control groups is a significant criterion for conducting a study in evidence-based medical research. Yet, it can be difficult task to do it for a non-pharmacological intervention since the mechanism of intervention is not fully comprehensive. Therefore, it is crucial for a trial to apply the control groups to distinguish the therapeutic effect from the effect of other factors.

Placebo effects in acupressure/acupuncture treatment have been well documented in the literature. A meta-analysis of almost 18,000 participants from 23 high-quality RCTs have shown that the effects of acupressure/acupuncture consist of therapeutic effect and placebo effects related to participant's belief and expectation in the effectiveness of the treatment (Vickers et al., 2012). As such, it is important to determine the therapeutic effect of acupressure/acupuncture by controlling for any placebo effect by having a sham control group as an intervention group and remain blind the participants to their group allocation (Lin et al., 2012). Nevertheless, a review concluded that the communication and interaction between the healthcare providers and the patients also produced placebo effects in an RCT (Bensing & Verheul, 2010). Thus, in this current trial, two types of control groups were used: (1) the sham acupressure to control the placebo effects related to the participant's belief and expectation in the effectiveness of acupressure; (2) the enhanced standard care to control the placebo effects

related to the communication or interaction between the health workers/researchers and the participants.

A high-quality systematic review on sham acupressure had identified three types of sham acupressure: using non-acupoint approach, using irrelevant acupoints approach, and using the same acupoints as in the true AP arms with light touch or no pressure approach (Tan et al., 2015). The approach of using the same acupoints with light touch was believed not to activate the *deqi* sensation, thus avoid creating any therapeutic effects (Pan et al., 2014). However, the participants of the current study are Vietnamese who are familiar with acupressure, this choice of sham control arm is deemed to be inadequate to maintain blinding of the subjects as they may easily assume that they did not receive the true treatment. Yet, when participants practiced acupressure at home, there was no guarantee that the participants would stimulate the acupoint with light touch, thus the *deqi* sensation can be achieved, causing failure of the sham control. The approach of using irrelevant acupoints referred to using the acupoints which have no effect on the targeted symptom(s). According to the acupuncture theories, every acupoint stimulation can also exert a certain degree of therapeutic effect (Zhang et al., 2010). As such, the approach was inappropriate to use as sham control for an intervention.

Considering the above findings, only the approach of using non-acupoints, the most common choice for the sham control arm (Tan et al., 2015) deemed to be appropriate for our trial. A review also indicated that using non-acupoints outside the channel of meridian was a better choice (compared with the other sham acupressure approaches) for sham control arm in studying the acupoints therapeutic effect (Zhang et al., 2010) although it is challenging to locate a non-acupoint outside the channel of meridian. Previous studies located the sham acupoint as being as close as 0.5 to 1 cun (ca. 1.5cm) to the true acupoints (Li et al., 2015; Tan et al., 2015). However, this distance seems to be not far enough since a study pointed out the point size of an acupoint (acupuncture field) range from 2.7 to 41.4 cm (Molsberger et al.,

2012). As such, it is not easy to select a truly non-acupoint. Therefore, our sham acupoints used in the trial were located in different areas of the body, some located near the true acupoint but we had used the findings from the literature to ensure they are truly the non-acupoints, and not located in the acupuncture field of any true acupoints (Kim & Kang, 2014; Molsberger et al., 2012; World Health Organization, 2009). In addition, sham acupoint locations were also validated by a panel of six TCM experts before implementation of the trial. Therefore, the non-acupoints were selected as the most appropriate placebo for this study.

Another factor needed to be controlled for placebo effect in this trial is the communication and interaction between the health workers/researchers and the participants. To control for this factor, we had also included the ESC group. Participants in this trial arm received the same amount of interaction as in the other study groups. An education session on 10 recommendations of how to manage insomnia, depression, and anxiety was provided to participants allocated in this group. This education session was conducted in the same length as the acupressure education session in the other study groups. In addition, participants in the ESC group also received weekly follow-up phone call for four weeks (same as participants in the true and sham acupressure group). However, in order to avoiding creating any other placebo effects, the researcher avoided discussing any kind of management for insomnia, depression, and anxiety other than those recommendations discussed initially. Hence, the ESC provided in this trial is an appropriate approach to control for the placebo effect related to the interaction between health workers/researchers and participants.

8.9. Preliminary effectiveness of the intervention

8.9.1. Effectiveness of the intervention on the symptom cluster severity

Several trials have been conducted targeting cancer-related symptom clusters as reported in Chapter 2. Our trial is the first study targeting the cancer-related symptom cluster of insomnia,

depression, and anxiety. The preliminary effectiveness of the intervention was evaluated at both symptom cluster and individual symptom level. As a standardized measurement for symptom cluster severity is not available, a composite score for the symptom cluster was calculated by averaging the score of each symptom using three separate numbered rating scales. This is an advantage of this study, as targeted symptoms were combined into a single composite variable of a symptom cluster.

This method of combining outcome measurements provides an opportunity to better detect intervention effects than measuring single outcomes and reduce the risk of type I error (Freemantle et al., 2003). Combining individual symptom scores to measure the symptom cluster score has been used in several trials that used CBT to manage the SC of pain, fatigue, and sleep disturbance among cancer patients. Kwekkeboom et al. (2012) used subsets of items from the Brief Pain Inventory (four pain severity items), the Brief Fatigue Inventory (four fatigue severity items), and the Pittsburgh Sleep Quality Index (two sleep quality items) to measure individual symptom scores. In their recent RCT, the latter author also used NRS (0-10) for each symptom in the cluster and calculated the SC score by averaging the individual symptom scores (Kwekkeboom et al., 2018). Similarly, in the trial conducted by Nguyen et al. (2018) the NRS was also used to measure the severity of individual symptoms and the SC score was calculated by averaging the individual symptom scores. In addition, this method was supported by the bi-directional relationship of the insomnia, depression, and anxiety from the literature. Two prospective studies found depression and anxiety were related to the development of insomnia (Jansson-Fröjmark & Lindblom, 2008; Morphy et al., 2007), other studies indicate insomnia is a risk factor for depression and anxiety (Cole & Dendukuri, 2003; Neckelmann et al., 2007; Taylor et al., 2005). Alvaro et al. (2013) conducted a systematic review from nine studies that explored the relationship between these three symptoms and suggested a bidirectional relationship between these symptoms where insomnia predicts and

is predicted by anxiety and depression. Moreover, the use of this method was also supported by the correlation of the three symptoms over time in this study. Pearson correlation tests revealed a significant weak to moderate positive correlation among the three symptoms at baseline (T1), and significant, moderate to strong at post intervention and post follow-up (T2 and T3). This result not only confirmed that the three symptoms were clustered during different time points in the study but also indicate the reduction of any one symptom can lead to the decrease in the others too.

The result from this study demonstrates a significant reduction of the symptom cluster score in the true AP group after the self-acupressure treatment period (T2) and follow-up (T3) compared with baseline (T1). Although the SC score in the sham AP and ESC group slightly reduced overtime, no statistically significant differences were found. Between groups comparisons indicated that participants in the true AP group had a significant improvement of the symptom cluster severity compared to the ESC group with relevant effect size of medium (near large). In addition, a borderline non-significance was also found between the true and the sham AP group regarding SC score at post intervention ($p=0.06$) with small effect size. The results have shown that the reduction in the SC score was supported further by the reduction of insomnia, depression, and anxiety scores measured by the NRS. However, it is worthy to notice the reduction of depression and anxiety in the true AP group was not significant compared with the control groups. In contrast, the reduction of insomnia was significant in the true AP group compared with others. This result supported the assumption of insomnia being the core symptom in the cluster and improving the core symptom in the cluster can also somewhat improve the others. However, the results also indicate a potential bias in the method of measuring the SC score by averaging the score of three symptoms. The result clearly indicates the reduction of the SC was mainly affected by the reduction of the insomnia.

Overall, the results demonstrate the significant positive therapeutic effect of self-acupressure on improving the targeted symptom cluster severity. However, the result should be interpreted with caution due to the small sample of a feasibility study. In addition, the significant reduction in the symptom score measured by averaging individual symptoms is the result of the reduction of one symptom (insomnia) instead of all individual symptoms.

8.9.2. Effects of the intervention on individual symptoms

Individual symptoms in the cluster were measured by the NRS and specific questionnaires Reporting of both severity of the SC and individual symptoms allows researchers to investigate the effect of intervention on multiple symptoms in a more in-depth way.

8.9.2.1. Effects of the intervention on insomnia

Insomnia was both measured by the NRS, the Insomnia Severity Index, and a sleep diary. Among the three symptoms in the cluster, only the improvement of insomnia can be quantified by investigating changes in sleep parameters. As such, a seven-day sleep diary was also used to measure sleep parameters among participants.

Results of the study demonstrated a significant improvement of ISI among participants in both the true and sham AP groups at T2 and T3 compared with baseline. However, no improvement of ISI was reported in the ESC group. In addition, the findings of the study revealed a significant better ISI from participants in both true AP and sham AP group than those in the ESC group after the intervention. The relevant effect sizes were medium and large, respectively. The data from the sleep diaries supported the measurement by ISI since it indicated a higher sleep efficiency that reached statistical significance in the true and sham AP group. A significantly higher total sleep time also was found between the true and ESC group at post-intervention. Within-group comparisons also detected some significant

improvements in sleep parameters in the true AP group which were the reduction in time awaken after sleep onset, increasing total sleep time, and sleep efficiency.

Taken together, self-acupressure seemed to have positive effect on reduction of ISI, insomnia score, and some sleep parameters. However, it was noted that the sham AP group also showed a significant lower score of ISI with a larger effect which indicated the possibility of a placebo effect of the self-acupressure treatment.

A comparison of the current study findings with other well-designed self-acupressure trials on insomnia in cancer patient is impossible due to lack of rigorous study of this kind in the current literature. A recent systematic review indicated the number of trials evaluating the efficacy of self-acupressure on sleep in cancer were limited with low-quality designs (two RCTs with small sample size and two quasi-experimental studies) (Garland et al., 2019). Nevertheless, most of those studies were conducted in a specific cancer population (breast cancer, lung cancer) and using auricular self-acupressure (another form of self-acupressure which requires participants to stimulate acupoints located in the ear instead of body as in the current trial). The most recent RCT was conducted in Korea (n=41) evaluating the effect of self-acupressure in breast cancer patients (Yoon & Park, 2019). The study evaluated the quality of sleep using the PSQI and Fitbit (a smartwatch with tracking function for physical activities and sleep) between the true auricular self-acupressure and sham auricular self-acupressure. The results indicated a significant improvement in PSQI score in the intervention group compared with the sham control group. In contrast, no significant improvement in sleep parameters were found. We only found one study conducted almost ten years ago evaluating the efficacy of self-acupressure in the treament of insomnia in general cancer patients (Cerrone et al., 2008). In this one-group design study, 25 cancer patients with various cancer treatments were requested to stimulate *Shenmen* once a day for two weeks. An improvement of 60% in sleep quality after the intervention was reported. Although all of the results from

previous studies indicated a potential benefit in improving insomnia in cancer patients, the limitations in their design (absence of control group, randomization, and allocation concealment) are more likely to overestimate the effect of self-acupressure. Current literature reviews on the efficacy of self-acupressure in managing insomnia in non-cancer populations also support our statement. A systematic review from eight RCTs using self-acupressure to manage insomnia indicated most of the included studies have methodological limitations and unclear risk of bias (Hmwe et al., 2016). Other literature reviews had concluded that the poor methodological quality of the reviewed RCTs made it difficult to determine the efficacy of self-acupressure (Song et al., 2015; Yeung et al., 2012).

Our trial is unique in its rigorous design (randomization, blinding, including proper control groups) that helps to enhance the power to evaluate the effect of self-acupressure. However, due to the nature of the study being a feasibility study, the efficacy of self-acupressure is not properly evaluated. Therefore, a future main RCT with sufficient sample size is necessary to further evaluate the effect of self-acupressure on insomnia in cancer patients.

Given the concerns above, this feasibility study reported evidence on the significant effect of self-acupressure in improving insomnia which is not fully confirmed. Moreover, it was noted that the sham AP group also had a significant improvement in insomnia compared to the ESC group, which also suggested the existence of non-specific effects of self-acupressure. Futher discussion regarding the placebo effects of self-acupressure will be presented later in section 8.9.5.

8.9.2.2. Effects of the intervention on depression

Depression was measured by HADS with the lower score meaning lower severity. Unlike the patterns of insomnia, results indicated that depression was reduced in the true AP and sham AP groups while it was increased in the ESC group. However, no significant difference

between groups was found after the intervention (T2) and the relevant effect sizes were small. In contrast, after the follow up time, depression was significantly lower in the sham AP group compared with the ESC group at post follow up (T3). The significant difference regarding depression score between the sham AP and ESC group at post follow-up was related to the increase of depression score in the ESC group. During the follow-up time participants did not stimulate self-acupressure points. Nevertheless, participants in the sham AP group stimulated the non-acupoints, so no therapeutic effect was achieved. The finding also demonstrated the reduction of depression in the true AP group was higher than in the sham AP group although it was not significant. Therefore, self-acupressure had a potential positive effect in improving depression. However, since depression also was reduced in the sham AP group, we consider the therapeutic effect of AP in improving depression is not greater than the placebo effect.

The findings of our study suggested both true and sham acupoints stimulation can improve depression in cancer patients. Findings from the literature also support our results. In an experimental pilot study conduct among 57 lung cancer patients during chemotherapy in Taiwan, authors reported an improvement in depression but non-significant in the true AP and sham AP group compared with usual care (Tang et al., 2014). Furthermore, a review of 11 trials with 1073 cancer patients also indicated acupoints stimulation is a promising approach in reducing depression and anxiety in oncology patients but the placebo effects may contribute to the benefit (Wang et al., 2016).

Taken together, results from the study indicate that self-acupressure has the potential to manage depression in cancer patients. However, the benefit of improving depression for this treatment was affected by a placebo effect.

8.9.2.3. Effects of the intervention on anxiety

Anxiety was also measured by HADS with the lower score meaning lower severity. Findings of the current study supported the beneficial effect of 4 weeks self-acupressure treatment in cancer patients to improve anxiety within-group over time. The mean anxiety score in the true AP group decreased by 2.37 points between baseline and post intervention (p=0.001) and continued to decrease by 0.49 points until the end of follow-up time. This shows that self-acupressure improved anxiety. However, results also indicated a significant reduction of anxiety in the sham AP group between baseline and post intervention, while no improvement was reported in the ESC group. Findings from the study also indicated a reduction in anxiety severity among study groups over time. However, a lower anxiety score that reached statistical significance was found between the sham AP and ESC group at post intervention (T2) with a small effect size (close to medium). In addition, a borderline statistical significance in lower anxiety score was found between the true AP and ESC group at T3 (p=0.05).

The effect of self-acupressure on anxiety was evident in the literature. However, in line with our findings, most RCTs with rigorous designs (i.e. those which included a sham control group) also reported the presence of placebo effect in relieving anxiety in the self-acupressure treatment. For instance, a recent RCT conducted among 288 cancer survivors, the authors found both the true and sham self-acupressure were better than the usual care at improving anxiety (Harris, 2018). Another RCT with double-blinded design reported a significant improvement in anxiety among participants in the true and sham self-acupressure group compared with the control group (Sharifi Rizi et al., 2017). In addition, a review also found both true and sham acupoints stimulation can reduce anxiety more effectively than the usual care (Wang et al., 2016).

Taken together, the results from the study support the potential of using self-acupressure to manage anxiety in cancer patients. However, the effectiveness of self-acupressure on improving anxiety was affected by a placebo effect.

8.9.3. Effects of the intervention on participants' Quality of life (QoL)

Participants' QoL was measured by the FACT-G at baseline, post-intervention, and post follow up. Although a significant improvement within-group was found in the true AP group from baseline to post-intervention, there were no statistically significant differences in QoL status among the three groups over time. The results demonstrated that self-acupressure seemed to have no effects on the participant's QoL. In line with our findings, other pilot self-acupressure interventions for symptom cluster management have also not reported any enhancement in the functional status and health-related quality of life (Yeh et al., 2016; Yeh et al., 2017; Yeh et al., 2019). There are several explanations for this finding. Firstly, the small sample size of a feasibility/pilot study places limitations on the statistical power (Jarden et al., 2009; Purcell et al., 2011). The second explanation was the insignificant improvement in two over three symptoms in the cluster as discussed previously. Although the symptom cluster severity was significantly improved in the true AP group, this was mostly related to improvements in insomnia symptom only. Therefore, participants still suffered from depression and anxiety which may be linked with insignificant QoL changes among the groups given the close relationship between depressive symptoms and QoL in cancer patients (Huang & Hsu, 2013; Lin et al., 2012). The third explanation was related to the concept of QoL. The FACT-G comprehensively measures different dimensions, from functional, emotional, physical, to social well-being. However, the self-acupressure intervention protocol designed in this research project was mainly focused on physical and emotional symptom relief. As such, the selection of acupoints did not take into account functional support. The component for social well-being was also not included to the study protocol. These could be

potential reasons for insignificant results in terms of self-acupressure on participants' QoL in this feasibility study. Furthermore, the time for QoL assessment can also affect the results. Findings from studies indicate that a significant improvement in health-related quality of life was not found right after the intervention (week four), but at week eight to 12 (six to eight weeks after completing the treatment) (Chan et al., 2011; Yeh et al., 2016; Yeh et al., 2017; Yeh et al., 2019; Yorke et al., 2015; Zick et al., 2016), which means that we may need to assess QoL after a longer period of time than in this study to more accurately evaluate any such changes.

The above three sections have discussed the results of the feasibility trial evaluating the effects of self-acupressure on the symptom cluster and on the individual symptom level for insomnia, depression, and anxiety as well as participants' quality of life. According to the statistical analyses, self-acupressure is an effective self-administered non-pharmacological approach to manage the symptom cluster of insomnia, depression, and anxiety. Self-acupressure has significantly improved insomnia severity among participants. However, its effect in improving depression and anxiety were not greater than the placebo effect or enhanced standard care or both. Improvement in QoL was not evident in this study. The small sample size with underpowered statistical analysis and non-adherence to the treatment protocol may be the reasons for these findings. Additionally, in some between-group and within-group comparisons, no statistical significance was found, but a clinically significant change may exist which could further demonstrate the potential value of self-acupressure in the practice. Nevertheless, the presence of a placebo effect was also found in the study's findings. Thus, the issue of the therapeutic effect (true) and non-therapeutic effect (placebo) of self-acupressure on targeted symptoms should be further discussed. Therefore, in the following section, statistical significance and clinical significance, as well as the therapeutic and non-therapeutic value of self-acupressure will be discussed.

8.9.4. Clinical significance of the intervention on insomnia, depression, anxiety severity, and quality of life

Clinical significance is the terms which indicate whether the results of a study are meaningful or not for the healthcare provider and the patients (Copay et al., 2007). It also refers to change of study outcomes that provide clinical insight into important variables such as the treatment effect size, magnitude of change, or direction of the outcome (Page, 2014). Therefore, it is important to include the clinical significance in the discussion of a study's result in order to explore comprehensively the impact of an intervention. Clinical significance is identified (sometimes interchangeably) by several similar terms including "minimal important differences (MID)", "clinically meaningful differences (CMD)", and "minimally important changes (MIC)" (Page, 2014). The variation in approaches to determine it make it difficult to calculate accurately the clinical significance (Wells et al., 2001). Researchers have divided those methods into two categories which are distribution-based and anchor-based approaches (Lydick & Epstein, 1993). The anchor-based method compares the change in a patient reported outcome with a second external measure of change, which serves as the anchor (Jaeschke et al., 1989). The distribution-based interpretation are based on statistical characteristics of the obtained samples which include the standard error of measurement, the standard deviation, the effect size, the minimal detectable change, or the reliable change index (de Vet et al., 2006; Page, 2014). In addition, all approaches have not been standardised and no consensus could be found as to the optimal method to measure the clinical significance of an intervention (Man-Son-Hing et al., 2002; Rai et al., 2015). In this feasibility study, we used the MID recommended by previous studies to interpret the clinical meaning of self-acupressure on insomnia, depression, anxiety, and participants' quality of life. The MID refers

to the minimal changes in the score that reflects the clinical change after treatment (Morin et al., 2011).

We only found a few studies indicating the MCID of ISI, HADS, and FACT-G. In a study conducted by Morin et al. (2011) aiming to evaluate insomnia treatment response using ISI among insomnia patients, authors indicated that a reduction of 4.65 points from baseline to post treatment was associated with slight improvement. Another study found a reduction of 6 points is recommend to represent a clinically meaningful improvement with insomnia patients (Yang et al., 2009). In our study, after the treatment, participants in the true AP group reduced insomnia 5.13 points, while the sham AP reduced 3.89 points, and participants in ESC only reduced 0.13 points. The results indicated self-acupressure has a slight clinical improvement with insomnia which also reached statistical significance.

Regarding the clinically significant changes in depression and anxiety, three RCTs conducted in patients with psychological distress (Arvidsdotter et al., 2013), patients with chronic obstructive pulmonary disease (Puhan et al., 2008), and in the general population (Lisspers et al., 1997) recommended a reduction from baseline to post treatment of 1.5 points or more can show a minimal clinical significance of HADS anxiety and depression mean change scores. Applying the above recommendations, results from our trial showed no clinical or statistical significance after the self-acupressure treatment. However, at the end of the follow-up time, a clinical reduction of depression compared with baseline was found in both the true and sham AP groups (reduced 1.6 points in the true AP and 1.8 points in the sham AP compared with baseline). Although the improvement of depression reached clinical significance in both the true and sham AP groups, it only reached statistical significance in the sham AP group.

The results also indicated the anxiety score was reduced among participants in the three study groups at T2 and T3 and reached clinically significant changes. However, only the improvement of anxiety score in the sham AP reached both clinical and statistical significance. This is an interesting finding because it showed that the ESC can also clinically improve anxiety. Perhaps, the ten recommendations provided to participants have some benefit in reducing anxiety. In those recommendations, we advised participants to practice deep breathing when they felt anxious. This deep breathing technique can lower blood pressure, reducing the work of the heart and muscle tension, hence, promote physical comfort that helps to reduce anxiety (Ariga, 2019).

Regarding the changes in quality of life status, Yost and Eton (2005) have demonstrated a method that combines the distribution- and anchor – based approaches to determine minimally important differences of FACT-G. They reviewed results from previous studies in which minimal important difference was calculated to be 4-7 points from baseline to post-treatment. Other authors used results from 71 cross-sectional and longitudinal studies to develop evidence-based interpretation guidelines for the clinical significance for the FACT-G and showed that increases of 4-14 points indicate a clinical significance, where 4-8 was medium and 8.1-14 points was large clinical significance (King et al., 2010). Ringash et al. (2007) indicated an improvement of greater than 5% of the maximal FACT-G score (equal to 5.4 points) show a positive minimal importance clinical change among cancer patients. Based on the above recommendations, the results of our study indicated the improvement of the QoL score in the true AP group reached a large clinically significant change (reduced 8.96 points at T2), while the improvement among participants in the other two groups failed to show any clinically significant change.

Taken together, this section discussed the clinical significance of the intervention based on findings from previous studies. The findings of the study demonstrated that self-acupressure

treatment showed a statistical significance and a slight clinical significance in reducing insomnia. The changes in depression and anxiety score in the sham AP group reached both clinical and statistical significance while the improvement of these in the true AP group only reached clinical significance. Participants in the enhanced standard care group also reported an improvement in anxiety that reached clinical significance. Regarding the improvement in quality of life status, the AP group shown a large clinically significant change, while the other groups failing to do so. Considering the self-acupressure effect had clinical significance in reducing all the symptoms in the cluster and improving QoL with low cost and minimal adverse events (as discussed before), therefore, we concluded self-acupressure is an effective treatment in clinical practice for the management of insomnia, depression, and anxiety in general cancer patients undergoing chemotherapy.

However, the effect of self-acupressure in improving the targeted symptom cluster has included placebo effects which refer to non-therapeutic effects. In the next section, placebo effects of the intervention will be discussed. Its advantages and disadvantages will also be demonstrated.

8.9.5. Placebo effects of Self-acupressure

The contribution of the placebo effect to the overall effect of acupoints stimulation has been documented in research and practice (Tan et al., 2015; Vincent & Lewith, 1995). The placebo effect refers to an effect that is produced by the symbolic dimensions which consists of an alteration toward a positive meaning attached to the illness, an expectancy, and the stimulation of specific neurochemical processes (Brody, 2018). Controlling the non-specific effect was found to improve the reliability of acupuncture/self-acupressure treatments (Hrobjartsson & Gotzsche, 2010). To distinguish the therapeutic (true) effect of an intervention from non-therapeutic (placebo) effects, a placebo controlled trial should be included in an intervention design (Dincer & Linde, 2003). The magnitude of the placebo effect in a trial can be measured

by the comparison between the placebo control group and the usual care group (Tan et al., 2015). However, to ensure separate therapeutic effects of an intervention from placebo effects, the placebo design should eliminate or minimize its potential specific therapeutic effects, which has been found to be challenging in self-acupressure research (Dincer & Linde, 2003; Tan et al., 2015).

The appoach of using non-acupoints for the sham self-acupressure was chosen since pressing non-acupoints cannot produce any therapeutic effects thus maintaining blinding of the intervention for participants (as demonstrated in section 6.2.5). Therefore, the sham self-acupressure design in this study ensured that the effect generated from this feasibility study was purely non-therapeutic effect. As a result, pairwise comparisons between study groups could accurately indicate the therapeutic effect and placebo effect of self-acupressure.

Findings from our feasibility study indicated that both the true and sham AP intervention improved the study outcomes compared to ESC. At the symptom cluster level, the therapeutic effect of self-acupressure was found superior to placebo and ESC in reducing the targeted symptom cluster's severity. At the single symptom level, while the therapeutic effect of self-acupressure had a significant positive impact on insomnia, the placebo effect of self-acupressure was found to be statistically significant in reducing all three symptoms at T2 or T3. No statistical significance between the true AP and sham AP group was identified. Based on the findings, it was concluded that the effects of self-acupressure treatment mostly consisted of both therapeutic and placebo treatment effects. The placebo effects of self-acupressure can be judged as clinically important to cancer patients undergoing chemotherapy and clinicians.

The presence of a placebo effect in self-acupressure studies is highlighted in the literature. A review indicated both the true and sham effect of self-acupressure were greater than standard

care (Tan et al., 2015). A meta-analysis from seven trials with 385 participants reported an improvement of 13%-19% in the PSQI score, sleep latency, and sleep duration in the sham AP group (Waits et al., 2016). In addition, a recent RCTs using self-acupressure in elderly people also indicated a significant reduction in the mean score of depression in the sham AP group (Molassiotis et al., 2019). Nevertheless, a review has shown that placebo effects of self-acupressure partially contributed to the overall benefits of improving anxiety and depression in cancer patients (Wang et al., 2016).

However, detecting placebo effects in a treatment does not mean failure of the treatment. It means a non-therapeutic mechanism may be present. The mechanism of placebo effect is explained by the complex neurobiological mechanisms involving neurotransmitters (e.g., endorphins, cannabinoids, and dopamine) and activation of specific areas of the brain (Finniss et al., 2010). Studies also found that the placebo effect is associated with patient's desire for symptom relief (Tough et al., 2009), or patient's perceptions of the treatment (Dowrick & Bhandari, 2012), or the communication between the therapists and participants (Benedetti, 2013; Paterson & Dieppe, 2005). In this feasibility study, in order to maintain the blinding, the interaction between interventionist/researcher and patients was the same in the true and sham AP group. The short time of recruitment reflects their positive opinion towards self-acupressure. Based on our observation, participants in the true and sham self-acupressure were quite satisfied when they were being assigned into their groups. Therefore, the cause of placebo effect in this study may come from the patient's desire for symptom relief and perception of self-acupressure.

Although our findings did not support the TCM theories that only stimulating a true acupoint can create therapeutic treatment effects to reduce insomnia, depression, and anxiety, but in the literature, placebo effect also has been observed in pharmacological trials (Kaptchuk & Miller, 2015; Kirsch, 2019). The result also confirmed the treatment effects of self-

acupressure not only generated from specific acupoint stimulation but from a combination of specific therapeutic effects and placebo effect. In this study, the placebo effect reached both the statistical and clinical significance in some study outcomes.

8.10. Strengths and limitations

8.10.1.Study's strengths

The strengths of this doctoral project include the research design and its implementation. The project was designed following the MRC framework. In the literature, limited number of studies on symptom cluster management in cancer patients were conducted. The first two phases of the MRC framework were utilized in the study. In the first phase of MRC framework, a cross-sectional survey with a large sample, multi-site data collection, and measuring insomnia both subjectively and objectively was conducted. Not many studies on insomnia in cancer patients are conducted with these advantages to data generation before an intervention. Therefore, the cross-sessional survey served as a valued evidence base to develop the feasibility study. In addition, also in this phase, the evidence-based approach utilized to develop the self-acupressure protocols is one of the strengths of the project which ensured the treatment protocols were scientifically reasonable and practically acceptable.

In the second phase of the MRC framework, a feasibility study with the rigorous design which includes a sham control group to estimate possible placebo effects was used. In addition, the randomization and allocation concealment procedure possibly helped to reduce the chance of overestimating the effect of the intervention (Jüni et al., 2001) as well as reduce detection and performace biases (Probst et al., 2016). Most of self-acupressure studies in the literature do not include blinding in their design. The rigorous design is another strength of the trial to ensure the findings of the trial.

Collecting medication or non-pharmacological treatments used for the targeted symptom cluster during the time patients participated in the trial was also the strength of the study. This information was collected via the self-reported diary and participant's medical record. The results indicated that during the time of participating in the trial, only three patients in the true AP group used Gingko Biloba extract as supplement to improve their sleep (150mg/day). However, Gingko Biloba is used to alleviate symptoms of age-related cognitive impairment (Silberstein et al., 2011) or fatigue, thus, it may not have any effect in reducing insomnia, depression, and anxiety. Therefore, the results of the trial were not influenced by other treatments as such.

In addition, checking the mastery of participant's self-acupressure skills 2-3 weeks after training session is another strength of the study. After receiving the intervention, participants were checked for the accuracy in locating and pressing the acupoint in their next visit to the hospital (two or three weeks later). This procedure helps to maintain the study fidelity and assess the effectiveness of the self-acupressure training session. Most of self-acupressure studies in the literature do not include this part in the design. Another strength of the trial includes the high recruitment rate and short time for recruitment which indicate the acceptability of self-acupressure intervention among oncology patients.

After participating in a study, patients would like to receive feedback on study outcomes. Otherwise, they may feel abandoned or being cut off (Wilson et al., 2005). As such, after the cross-sectional survey, all participants received the results of their assessment. Due to the long time required for data analysis and lengthy distance between the researcher (in Hong Kong) and the participants (in Vietnam), the result was sent eight months after the completion of the survey. However, participants expressed their gratitude and were satisfied when receiving the results. In fact, there were three patients who participated in the survey and who

also became participants of the feasibility study. They also helped the researcher in promoting the trial to other patients.

8.10.2.Study limitations

This doctoral research project encountered a number of limitations. The first limitation is the sampling method. Both of the two studies in this project relied on a convenience sample; therefore, the recruited participants might not be representative of the overall population of cancer patients undergoing chemotherapy, although the sample of the survey was large and characteristics of participants in the feasibility study were compared. Convenience sampling can bias the data gathering and hence can limit the ability to generalize results. However, due to the limitations in human resources and time, this sampling method was the best fit with our context in recruiting participants.

Using self-reported data can also be a limitation of the study. Self-reported outcomes completed by participants can have recall bias that lower the accuracy of the data, which further can affect the validity of the outcome measures (Short et al., 2009). There are also cases when respondents guess the hypothesis of the study and provide biased responses in order to confirm the researcher's conjecture or make them appear more distressed to receive the promised treatment (Heppner, 2016).

Another limitation of the two studies is the targeted population. The cross-sectional survey and the feasibility study both targeted cancer patients undergoing chemotherapy which limits the ability to generalize the results to other populations such as cancer survivors or patients undergoing other cancer treatments.

Due to the limitations inherent in cross-sectional surveys, the survey cannot point out which symptom (anxiety, depression, and insomnia) occurred first nor how they influence each other or how these symptoms change over the trajectory of the illness.

In addition, our suggestion in the survey regarding the lack of differences between sleep parameters measured objectively between insomnia and non-insomnia participants should be interpreted with caution, as participants were required to wear the Actigraph for three nights only, which is relatively short time (despite being the recommended minimum time by the American Academy of Sleep Medicine (Ancoli-Israel et al., 2015) and may easily be affected by intra-night variability among patients. A longer Actigraph measurement may potentially correlate better with subjective measurements.

In addition, due to the aim of a feasibility study, the outcomes of the trial mainly focus on the feasibility, compliance, and acceptability rather than detecting significant outcome changes between groups.

The poor adherence to the intervention resulted in high attrition rate that confound our results. The high attrition rate might be considered as a bias that influenced the results by underestimating the effect of the treatment (Bennett & Closs, 2011). Also, the high attrition may lead the trial results encountering high chance of type II error and providing inconclusive results (Molassiotis et al., 2019).

Although the self-acupressure report form and follow-up phone calls were our strategies to monitor and encourage participants to engage with the study, lacking a sufficient method to monitor patient practice of self-acupressure at home is another limitation of the study. For this reason, the feasibility study is unable to identify the extent to which participants fully followed the treatment protocol of the study.

All the limitations of the two studies included in the doctoral project reported above provide valuable information for the design of future full-scale randomized control trial. In the next section, recommendations for modifications for a future RCT will be presented.

8.11. Changes for a future trial

The potential benefits, high acceptability of the intervention, and the short time to recruiting adequate number of participants indicate that the self-acupressure treatment is practical for trialing on a full scale RCT within the context of middle-income countries. However, considering results from the study, several possible modifications for a future larger trial are suggested.

A key lesson in this study is that the failure to keep participants in the study which resulted in a high attrition rate. In this study, the physical well-being index (measured by FACT-G) among withdrawn participants was found to be significantly lower than those who completed the study. Nevertheless, statistical analysis also indicated that the most common reason for attrition was being too tired to continue the study (40%). According to the inclusion criteria, participants must have a Karnofsky score ≥ 80 which means that a person is able to carry out normal activities and work with no special care needed but with some signs or symptoms of disease (Schag et al., 1984). Perhaps a higher Karnosky score at ≥ 90 which refers to a patient who can be able to do normal activity with minor sign or symptoms of disease may decrease the attrition rate.

In addition, family involvement is also important. Past studies pointed out that family caregivers can play a key role for patients in symptom self-management interventions by encouraging patients to undertake the intervention (Ellis et al., 2017). In addition, the Vietnamese health care system is lacking community support for outpatients. Hence, patients in Vietnam rely heavily on the support of their family, friends, or paid caregivers. Therefore, strategies to engage and prepare family members to facilitate self-management support for cancer patients may also reduce the attrition rate. Nevertheless, family members/caregivers can help to monitor the self-acupressure practice at home of the participants at home. Thus,

future research should consider inviting patient's family members/caregivers to the education session (if they are available) and requesting their support to the patients during the intervention (encouraging and monitoring participants during the treatment time).

Reducing the response burden may also increase study adherence. The sleep diary was found to be not feasible as the response rate was very low compared with other measurements. In addition, the intervention aimed to reduce a symptom cluster and, by having more measurements on one symptom may make the patient pay more attention to that symptom causing bias in the assessment. In addition, results from the cross-sectional survey indicate that insomnia is a subjective symptom which its severity may differ from the result of objective sleep parameters. Insomnia frequency is related to patients' perception about sleep rather than those measurements. Therefore, a future study can consider to not using sleep diary in the outcome measurements.

Nurses' involvement to the study was proposed at two aspects: recruiting and delivering the intervention. Their role in recruiting participants was important. The short recruiting time was the result of a good cooperation between nurses and the researcher. However, due to their high workload, nurses cannot deliver the intervention as planned. 60% of the training sessions were done by the Ph.D. student. Nevertheless, in each of the study sites, there were TCM departments with TCM nurses whose workload is relative less compared to the nurses in clinical departments. Future studies can consider cooperating with nurses in the TCM department, where available, to deliver the education sessions.

Regarding to the recruitment strategy, the proposed plan was appropriate as the recruitment time was short. However, it was a great effort to invite participants one by one and face to face. A previous study pointed out that advertising the study on newspapers can improve the recruitment (Molassiotis et al., 2007). However, this method is not in our favor considering

the study limited budget. In a review from 14 RCTs on recruitment methods, Watson and Torgerson (2006) indicated that contacting patients by mailing them, then a follow-up phone call for reminder was found to significantly increased the number of recruited participants to the trial. In line with this finding, a recent Cochrane review also reported mail and telephone reminders worked well to recruit participants (Treweek et al., 2018). Hence, to aid the recruitment, the future trial could promote the study by sending invitations with information about the study to participants then remind them again after two weeks.

In the current literature, two approaches have been used in managing the symptom cluster which were discussed in Chapter 2 of this thesis. According to our findings, self-acupressure can potentially reduce the targeted symptom cluster severity. However, the reduction of the SC severity was mostly due to the improvement of insomnia. In addition, insomnia is the core symptom of the cluster. As such, a future study could focus only on the symptom of insomnia rather than the cluster we used in this study.

8.12. Implications

8.12.1. Implications for future research

The two studies of the PhD project have sought to respond to number of research gaps related to insomnia and managing sleep-related symptom cluster in cancer patients. Our project raises several opportunities for future research. More research will in fact be necessary to further elaborate our novel findings.

First, our survey indicated insomnia correlated with depression and anxiety, however, due to the nature of the cross-sectional design, the survey cannot point out how the anxiety, depression, and anxiety influence each other. However, previous systematic review among general population suggested a bidirectional relationship between insomnia, depression, and anxiety (Alvaro et al., 2013). It is interesting to see that the correlations between the three

symptoms were low in the correlational analysis, suggesting that other factors, not examined in this study, may be part of this relation. However, the strength of this relationship became moderate-to-strong in the SC analysis. Hence, anxiety and depression are clearly part of insomnia, but perhaps not the only parts. More studies should be conducted to further explore the relationship between these symptom as well factors that influence their relatioship among cancer patients.

Second, the finding from the survey determined insomnia significant reduced participants' quality of life. However, in result from the feasibility indicated although self-acupressure improved insomnia significantly but it had not impact patient's quality of life. Previous studies also indicated significant improvement in health-related quality of life was found after six to eight weeks after completing the intervention (Chan et al., 2011; Yeh et al., 2016; Yeh et al., 2017; Yeh et al., 2019; Yorke et al., 2015; Zick et al., 2016), which means that studies aim to evaluate the impact of an intervention to participant's may need to assess QoL after a longer period of time than in the feasibility study to more accurately evaluate any such changes.

Finally, as discussed in literature review chapter, a wide range of duration for self-acupressure treatment was reported in the literature. Our four week of mandatory self-acupressure treatment period was chosen based on findings from previous systematic reviews. However, more studies are needed to validate an optimal self-acupressure treatment duration.

8.12.2. Clinical implications

The value of a research should include its contribution to clinical practice. A well-designed study with great contribution to the literature may not be adopted by the healthcare providers if its clinical implications is low. The results of this study will prompt awareness of insomnia in people with cancer as well as provide more information to assist nurses to

better understand insomnia in patients during chemotherapy treatment. Nurses play an important role in identifying and developing an intervention for these health-related issues. Studies indicated healthcare professionals in the cancer field tend to adopt treatment which is less time consuming and supported by evidence in reducing symptom burden for patients (Paterson et al., 2014; Wilson, 2008). Based on the clinical finding of the feasibility study, it is theorized that self-acupressure can reduce insomnia, depression, and anxiety. In addition, the feasibility study also raises awareness of self-management approach for cancer patient where human resources or social support are limited. Nevertheless, promising results from the feasibility study offer cancer patients a treatment to manage insomnia, depression, and anxiety at low cost, convenient, and safe with minimal discomfort. Therefore, self-acupressure can be introduced to cancer patients and be incorporated into routine nursing care.

In this study, we provide participants in the ESC group ten recommendations to manage insomnia, depression, and anxiety. Although the majority of study outcomes were found to be none improved in this group but two sleep parameters were found to be significantly improved (number of nights awaken and total sleep time at T3). In addition, the improvement of anxiety in ESC reached the clinical meaningful. Hence, the ESC provided in the feasibility shows some possible impacts to participants. From this evident, the incorporation of the study's ESC procedure into usual care in the public hospitals should be considered. However, due to the shortage of nurses in the public hospitals, it is impossible to arrange an education session for all patients, thus, a patient leaflet with these ten recommendations is a more practical way.

8.12.3.Educational implications

Up to 60% of nurses in Vietnam do not have a bachelor's degree in nursing resulting in the provision of limited support for patients. In addition, due to shortage of nurses, nurses in

hospitals are working under high workload. Therefore, nurses can only provide essential care for patients which results in poor care for patients as described in previous chapter 6, section 6.5.1. In light of this context, self-management interventions for patients with chronic diseases is preferable to the current usual care in Vietnam. However, there is currently very limited focus on self-management in Vietnam, just four interventions studies showing support for this approach among diabetics, heart failure, and lung cancer patients (Dang, 2013; Dinh et al., 2018; Ly Thuy et al., 2016; Vu, 2019). Therefore, there is a need for providing nurse-led self-administered approaches to patients in Vietnam. The successful implementation of the feasibility indicated that nurses can develop and implement a self-management program for patients.

However, to bring self-management support into routine practice requires training personnel to deliver this kind of support to patients. However, the nature of hospital context and cultural bias (deference to the authority of doctors) can limit the extent to which Vietnamese nurses are supported for preparation and delivery of self-management approaches. In addition, the current Vietnamese nurse education system inadequately prepares nurses to implement nurse-led self-administered management to patients. Based on personal experience from being an officer in a nursing department (Ministry of Health) for five years, and lecturer in a nursing school for 4 years, most of Vietnamese nurses are not well-prepared to deliver nurse-led interventions since the current education focus on nursing technical skills and the biomedical model of disease rather than nursing care science. As such, in order to enhance nursing autonomy and quality of care for patients, improving nurse education is considered an important priority (Harvey et al., 2013). Proper education for self-management, symptom assessment and management programs should be included into undergraduate curricula. Nevertheless, a similar program should also be included in continuing training programs for

nurses currently working in hospitals, as many of them do not have such program in their undergraduate studies.

8.13. Conclusions

The study results provide new knowledge to fill major gaps related to insomnia prevalence and managing the sleep-related symptom cluster which includes insomnia, depression, and anxiety in cancer patients undergoing chemotherapy. The summary of the findings is presented as follows:

(1) Insomnia is highly prevalent among cancer patients undergoing chemotherapy.

(2) Insomnia correlated with depression and anxiety to form a sleep-related symptom cluster.

(3) Insomnia is a subjective symptom, and the patient's perception of insomnia or quality of sleep may differ from the actual objective measure of insomnia severity experienced.

(4) Insomnia and the sleep-related symptom cluster significantly reduces patient's quality of life.

(5) The validated evidence-based self-acupressure treatment protocol used in the study demonstrated to be safe, convenient with initial promising effectiveness to improve the symptom cluster of insomnia, depression, and anxiety among cancer patients undergoing chemotherapy.

(6) The intervention using self-acupressure was feasible with satisfactory recruitment rate, short time for recruitment, and highly acceptability by participants.

(7) The specific effect of self-acupressure plus enhanced standard care was significant superiors to ESC alone and placebo effect of self-acupressure plus ESC in reducing symptom cluster of insomnia, depression, and anxiety.

(8) The preliminary effect of self-acupressure plus enhance standard care reached both statistical and clinically significant differences in reducing Insomnia Severity Index.

(9) The preliminary effect of self-acupressure plus enhance standard care seems to have no/borderline statistical significance but reach the clinical significance on improving depression and anxiety.

(10) The effect of self-acupressure was a mixture of therapeutic treatment effect and placebo effect. The placebo effects of self-acupressure on insomnia, depression, and anxiety were found to be large, small, and medium, respectively and even reached clinical significance (for depression and anxiety).

(11) Self-acupressure seems to have no significant effect on improving the quality of life in cancer patients undergoing chemotherapy.

(12) The feasibility study indicated that acupressure is a safe, convenient, and promising non-pharmacological self-administered intervention to reduce the symptom cluster severity of insomnia, depression, and anxiety in cancer patients undergoing chemotherapy. Future full-scale RCT is recommended to examine the promising effect of self-acupressure on symptom cluster of insomnia, depression, and anxiety as well as its effect in improving quality of life status in cancer patients undergoing chemotherapy.

The doctoral project included two studies. Results of the cross-sectional survey indicated a high insomnia prevalence among cancer patients undergoing chemotherapy in Vietnam. It also reported a symptom cluster of insomnia, depression, and anxiety which significantly reduced cancer patients' quality of life and highlighted the unmet need of a self-administered intervention to manage this symptom cluster. The feasibility trial showed high acceptability and feasibility to conduct a future full-scale RCT using self-

administered acupressure to manage insomnia, depression, and anxiety in cancer patients undergoing chemotherapy. Its preliminary results suggest the potential treatment effect of acupressure in improving the targeted SC (particularly insomnia) although the possibility of a placebo effect cannot be ruled out. Besides, considering the acupressure effect had clinical significance in improving all the targeted symptoms and QoL with low cost and minimal adverse events, therefore, a fully-powered trial is warranted. The feasibility trial also indicated that self-acupressure is a safe, convenient, and promising non-pharmacological intervention to reduce the insomnia burden for cancer patients undergoing chemotherapy. Further practice is encouraging to utilize self-acupressure as a promising complementary treatment approach to manage insomnia in cancer patients.

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Appendix 1. Information Sheet for the feasibility study (English and Vietnamese)

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

INFORMATION SHEET

Self-administered self-acupressure for cancer-related symptom cluster of insomnia, depression, and anxiety: a feasibility randomized controlled trial.

You are invited to participate in a study supervised by Prof. Alexandros MOLASIOTIS, Dr. CHAN Choi Wan and conducted by Ms. HOANG THI Xuan Huong, who is Ph.D. candidate in the School of Nursing at The Hong Kong Polytechnic University.

The study aims to evaluate the effectiveness of self-acupressure on insomnia, depression, and anxiety on cancer patients undergoing chemotherapy. In this study, two set of acupoint will be used. The voluntary participants will be randomly assigned to three groups: Acupressure 1, Acupressure 2, and enhanced standard care control group (ESC). For those who are randomized into acupressure 1 and acupressure 2 groups, they will receive a self-acupressure training session. There are two self-acupressure protocols will be used in this training session. One group using self-acupressure protocol is similar to the self-acupressure treatment in Chinese Traditional Medicine. The other does not follow the Chinese Traditional Medicine theory but has also been associated with improvement of insomnia, depression, and anxiety. After receiving the self-acupressure training session, patients will be asked to perform self-acupressure at home in 4 weeks, a telephone reminder will be made weekly to encourage patients to implement the intervention. For those who are assigned into ESC group, they will receive an education session on tips to manage insomnia, depression, and anxiety and will be requested to practice these tips in four weeks at home, a telephone reminder will be made weekly to follow up the patients. The course of intervention will be completed in two months. Participants will be given 200.000vnd for express mail service after returning all the questionnaires to the Ph.D. student.

The modality of interventions in this study will not cause any injury or harm to patient's health. It is expected that this study will provide information and data for better understanding the effectiveness of self-acupressure on insomnia, depression and anxiety.

The participants should not undergo any other interventions to manage insomnia, depression, and anxiety during the study period to avoid obscuring the real effects of the intervention.

You have entirely right to refuse to participants or withdraw from the study at any time throughout the study. Your decision will not cause any detrimental effect to your usual treatment or assume any accountability to this research. All data collected from you will be kept confidential and for this study purpose. Information is coded and coding is restricted to be accessed by the investigator only.

If you have any complaints about the conduct of this research study, please do not hesitate to contact Miss Cherrie Mok, 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 ***Ms. Hoang Thi Xuan Huong*** at telephone number 098891 or her supervisor Prof. Alexandros MOLASIOTIS telephone number +852 2766 7883.

Thank you for your interest in participating in this study.

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

GIẤY GIỚI THIỆU THÔNG TIN NGHIÊN CỨU

Can thiệp làm giảm mất ngủ, lo lắng, phiền muộn cho người bệnh ung thư đang điều trị hóa chất

Ông/bà được mời tham gia nghiên cứu được thực hiện bởi Chị Hoàng Thị Xuân Hương, hiện đang là nghiên cứu sinh tại trường Điều dưỡng thuộc Đại học Bách Khoa Hồng Kong dưới sự hướng dẫn của GS. Alexandro Molasiotis và TS. Chan Choi Wan.

Mục đích của nghiên cứu nhằm đánh giá hiệu quả của phương pháp bấm huyệt để làm giảm triệu chứng mất ngủ, lo lắng, phiền muộn cho người bệnh ung thư đang điều trị hóa chất. Người tham gia nghiên cứu sẽ được ngẫu nhiên lựa chọn vào 1 trong 3 nhóm nghiên cứu: 2 nhóm được hướng dẫn tập tự bấm huyệt và nhóm chứng. Nhóm được hướng dẫn cách bấm huyết sẽ được tham gia 1 buổi tập huấn để có thể tự thực hành bấm huyệt tại nhà. Nhóm chứng sẽ được tham gia buổi tập huấn về các cách giúp cải thiện mất ngủ, trầm cảm, lo âu.

Các phương pháp sử dụng trong nghiên cứu đã được chứng minh về độ an toàn và không gây bất kỳ tác dụng tiêu cực nào đối với sức khỏe người bệnh. Kết quả từ nghiên cứu sẽ giúp các Điều dưỡng viên chăm sóc tốt hơn các triệu chứng mất ngủ. lo lắng, phiền muộn cho người bệnh trong quá trình điều trị hóa chất và nâng cao chất lượng khám chữa bệnh trong tương lai.

Để tránh ảnh hưởng đến kết quả của can thiệp, trong quá trình tham gia nghiên cứu người bệnh không được tham gia vào bất kỳ can thiệp nào khác liên quan đến mất ngủ, lo lắng, phiền muộn.

Ông/bà có quyền rút khỏi nghiên cứu trước hoặc trong quá trình đánh giá mà không phải chịu bất kỳ thiệt hại nào. Tất cả các thông tin liên quan đến ông/bà sẽ được bảo mật và sẽ được mã hóa chỉ có nghiên cứu viên mới hiểu được.

Nếu ông/bà có bất kỳ phàn nàn nào trong quá trình tham gia nghiên cứu, xin vui lòng liên hệ với Bà Cherrie Mok, thư ký Hội đồng đạo đức thuộc trường Đại học Bách khoa Hồng, nêu rõ người và bộ phận phải chịu trách nhiệm về sai sót trong nghiên cứu này.

Nếu ông/bà muốn biết thêm về thông tin nghiên cứu, xin vui lòng liên hệ NCS. Hoàng Thị Xuân Hương, số điện thoại: 098891 hoặc người giám sát – GS. Alexandros MOLASIOTIS, số điện thoại +852 2766 7883 (Hồng Kong).

Xin trân thành cảm ơn

Đại diện nhóm nghiên cứu

Appendix 2. Consent form for the feasibility study (English and Vietnamese Version)

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

CONSENT TO PARTICIPATE IN RESEARCH

Self-administered self-acupressure for cancer-related symptom cluster of insomnia, depression, and anxiety: a feasibility randomized controlled trial.

I _____ hereby consent to participate in the captioned research supervised by Prof. Alexandros MOLASIOTIS, Dr. CHAN Choi Wan and conducted by Ms. HOANG Thi Xuan Huong

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 participants _____

Name of researcher: MS HOANG Thi Xuan Huong

Signature of researcher:_____

Date _____

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

GIẤY ĐỒNG Ý THAM GIA NGHIÊN CỨU

Can thiệp làm giảm mất ngủ, lo lắng, phiền muộn cho người bệnh ung thư đang điều trị hóa chất

Tôi _____ đồng ý tham gia nghiên cứu do GS. Alexandros MOLASIOTIS, TS. CHAN Choi Wan giám sát và được thực hiện bởi NCS. Hoàng Thị Xuân Hương

Tôi hiểu rằng các thông tin từ nghiên cứu này có thể được sử dụng cho các nghiên cứu trong tương lai và sẽ được công bố.. Tuy nhiên, tôi có quyền được đảm bảo bí mật các thông tin do mình cung cấp, ví dụ như thông tin cá nhân.

Quá trình tiến hành nghiên cứu đã được mô tả kỹ trong giấy giới thiệu nghiên cứu. Tôi hiểu các lợi ích và nguy cơ có thể xảy ra. Tôi tự nguyện tham gia nghiên cứu.

Tôi xác nhận tôi có quyền đặt câu hỏi về bất kỳ phần nào trong quá trình nghiên cứu tiến hành và có thể từ chối tham gia nghiên cứu bất kể thời điểm nào mà không phải chịu bất kỳ tổn hại nào dưới mọi hình thức.

Tên người tham gia _____

Chữ ký_____

Tên nghiên cứu viên: NCS. Hoàng Thị Xuân Hương

Chữ ký: _____

Ngày: _____

Appendix 3. Assessment and Evaluation form for the feasibility study (English and Vietnamese version)

THE HONG KONG POLYTECHNIC UNIVERSITY

SCHOOL OF NURSING

Date: _____ **Code: _____**

Hospital_____ **Department: _____**

Part 1. Demographic data

Q1: Age:.....

Q2: Gender: 1. Male 2. Female

Q3: Occupation: .....

Q4: Education: .....

Q5: Marital status: 1. Single 2. Married 3. Divorced 4. Widowed

Part 2. Health history

Q6: Diagnosis: .....

Q7: Time from diagnosis: .....

Q8: Number of cycle completed:.....

Q9: Tumor removal surgery before: 1. No 2. Yes

Q10: Type of Chemotherapy received:.....

Q11: How Chemotherapy is given.....

Q12: Given Chemotherapy Regiment: .....

.....

Part 3. Assessment the severity of the cluster of insomnia, depression, and anxiety

For each of the following symptoms, please circle the number which is best describe rate the severity of the symptom that you experienced during the previous month.

Insomnia

0	1	2	3	4	5	6	7	8	9	10
Not present										As bas as it could be

Depression

0	1	2	3	4	5	6	7	8	9	10
Not present										As bas as it could be

Anxiety

0	1	2	3	4	5	6	7	8	9	10
Not present										As bas as it could be

Part 4. Insomnia Severity Index

For each question, please CIRCLE the number that best describes your answer.

*Please rate the **CURRENT SEVERITY** of your insomnia problem(s) in the last 2 weeks.*

Insomnia Problem	**None**	**Mild**	**Moderate**	**Severe**	**Very severe**
1. Difficulty falling asleep					
2. Difficulty staying asleep					
3. Problems waking up too early					

4. How **SATISFIED/DISSATISFIED** are you with your *CURRENT* sleep pattern?

Very satisfied	Satisfied	Moderately satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How **NOTICEABLE** to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6.How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) **CURRENTLY**?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____

Total score categories:

1. No clinically significant insomnia (0-7)
2. Subthreshold insomnia (8-14)
3. Clinical insomnia (moderate severity) (15-21)
4. Clinical insomnia (severe) (22-28

Part 5. Assessment depression and Anxiety

Hospital Anxiety and Depression Scale (HADS)

Cycle beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

Section 1. Anxiety

No	Questions	Answer	Score
1	I feel tense or 'wound up':	a) Most of the time b) A lot of the time c) From time to time, occasionally d) Not at all	
2	I get a sort of frightened feeling as if something awful is about to happen	a) Very definitely and quite badly b) Yes, but not too badly c) A little, but it doesn't worry me d) Not at all	
3	Worrying thoughts go through my mind	a) A great deal of the time b) A lot of the time c) From time to time, but not too often d) Only occasionally	
4	I can sit at ease and feel relaxed	a) Definitely b) Usually c) Not Often d) Not at all	
5	I get a sort of frightened feeling like "butterflies" in the stomach	a) Not at all b) Occasionally c) Quite often d) Very often	
6	I feel restless as I have to be on the move:	a) Very much indeed b) Quite a lot c) Not very much d) Not at all	
7	I get sudden feeling of panic	a) Very often indeed b) Quite often c) Not very often d) Not at all	
Total score of Anxiety assessment			

Section 2. Depression

No	Questions	Answer	Score
1	I still enjoy the things I used to enjoy:	a) Definitely as much b) Not quite so much c) Only a little d) Hardly at all	
2	I can laugh and see the funny side of things	a) As much as I always could b) Not quite so much c) Definitely not so much now d) Not at all	
3	I feel cheerful	a) Not at all b) Not often c) Sometimes d) Most of the time	
4	I feel as if I am slowed down	a) Nearly all the time b) Very often c) Sometimes d) Not at all	
5	I have lost interest in my appearance	a) Definitely b) I don't take as much care as I should c) I may not take quite as much care d) I take just as much care as ever	
6	I look forward with enjoyment to things:	a) As much as I ever did b) Rather less than I used to c) Definitely less than I used to d) Hardly at all	
7	I can enjoy a good book or radio or TV program:	a) Often b) Sometimes c) Not often d) Very seldom	
Total Score of Depression assessment			

Part 6. Assessment Quality of Life

Functional Assessment of Cancer Therapy – General

Please circle or mark one number per line to indicate your response as it applies to the past 7 days

Code	Question	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 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
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
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 effect 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
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

Part 7. Sleep diary

Instruction: The sleep diary must be complete every day. If possible, please complete within one hour of getting out of bed in the morning. If you forget to fill in the diary or are unable to finish it, leave the diary blank on that day. If your sleep or daytime functioning is affected by some unusual events (such as illness, or an emergency) please make brief notes on your diary.

Item Instructions Use the guide below to clarify what is being asked for each item of the Sleep Diary.

Date: Write the date of the morning you are filling out the diary.

1. What time did you get into bed? Write the time that you got into bed. This may not be the time that you began “trying” to fall asleep.

2. What time did you try to go to sleep? Record the time that you began “trying” to fall asleep.

3. How long did it take you to fall asleep? Beginning at the time you wrote in question 2, how long did it take you to fall asleep.

4. How many times did you wake up, not counting your final awakening? How many times did you wake up between the time you first fell asleep and your final awakening?

5. In total, how long did these awakenings last? What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15= 70 min or 1 hr and 10 min).

6. What time was your final awakening? Record the last time you woke up in the morning.

7. What time did you get out of bed for the day? What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g. you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)

8. Comments If you have anything that you would like to say that is relevant to your sleep feel free to write it here. Also record other self-care methods using to manage in insomnia, depression, anxiety or any self-taken Chinese Herb/Western medication/supplement taken.

SLEEP DIARY

Name of participant: ……Age: …….Hospital:…….

Code: ……..

Today's date	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
1. What time did you get into bed?							
2. What time did you try to go to sleep?							
3. How long did it take you to fall asleep?							
4. How many times did you wake up, not counting your final awakening?							

5. In total, how long did these awakenings last?							
6. What time was your final awakening?							
7. What time did you get out of bed for the day?							
8. Comments							

TRƯỜNG ĐẠI HỌC BÁCH KHOA HỒNG KONG

KHOA ĐIỀU DƯỠNG

Ngày: _____ **Mã: _____**

Bệnh viện: _____ **Khoa:_____**

Phần 1. Thông tin cá nhân

Q1: Tuổi: .....

Q2: Giới: 1. Nam 2. Nữ

Q3: Nghề nghiệp: .....

Q4: Trình độ học vấn: .....

Q5: Hôn nhân: 1. Độc thân 2. Kết hôn 3. Li dị 4. Góa

Phần 2. Bệnh sử

Q6: Chẩn đoán: .....

Q7: Thời gian mắc bệnh: .....

Q8: Số chu kỳ hóa chất đã hoàn thành: .....

Q9: Đã phẫu thuật loại bỏ khối u: 1. Không 2. Có

Q10: Loại hóa chất sử dụng: .....

Q11: Đường dùng hóa chất .....

Phần 3. Đánh giá mức độ của cụm triệu chứng gồm mất ngủ, lo âu, phiền muộn

Với mỗi triệu chứng dưới đây, ông/bà vui lòng khoanh tròn vào chữ số mô tả đứng nhất mức độ của triệu chứng mà ông bà cảm nhận được trong tháng qua.

Mất ngủ

0	1	2	3	4	5	6	7	8	9	10
Không										Trầm trọng nhất

Phiền muộn

0	1	2	3	4	5	6	7	8	9	10
Không										Trầm trọng nhất

Lo âu

0	1	2	3	4	5	6	7	8	9	10
Không										Trầm trọng nhất

Phần 4. Đánh giá mức độ mất ngủ

Với mỗi câu hỏi sau đây, ông/bà vui lòng khoanh tròn vào câu trả lời đúng với câu trả lời của mình nhất.

Xin hãy đánh giá mức độ trầm trọng của chứng mất ngủ của ông/bà trong 2 tuần qua

Triệu chứng mất ngủ	**Không**	**Nhẹ**	**Vừa phải**	**Nặng**	**Rất nặng**
1. Khó khăn để chìm vào giấc ngủ					
2. Khó khăn trong việc duy trì giấc ngủ					
3. Tỉnh giấc quá sớm					

4. Ông bà cảm thấy hài lòng hoặc không hài lòng với tình trạng giấc ngủ hiện nay như thế nào?

Rất hài lòng	Hài lòng	Khá hài lòng	Không hài lòng	Rất không hài lòng
0	1	2	3	4

5. Tình trạng giấc ngủ của bạn ảnh hưởng đến chất lượng cuộc sống như thế nào?

Không ảnh hưởng	Một chút	Hơi ảnh hưởng	Nhiều	Ảnh hướng rất nhiều
0	1	2	3	4

6. Ông bà lo lắng như thế nào về tình trạng rất ngủ của mình?

Không lo lắng gì	Một chút	Hơi lo lắng	Nhiều	Rất lo lắng
0	1	2	3	4

7. Ông bà có cho rằng hiện nay tình trạng giấc ngủ của mình ảnh hưởng tới các hoạt động thường ngày không (ví dụ: gây mệt mỏi, ảnh hướng tới tâm trạng, khả năng làm việc, mức độ tập trung, trí nhớ…)

Không ảnh hương	Một chút	Hơi lo lắng	Nhiều	Rất lo lắng
0	1	2	3	4

Tổng điểm (câu hỏi 1 + 2 + 3 + 4 + 5 +6 + 7) = _____

Phần 5. Đánh giá mức độ lo lắng và phiền muộn

Hospital Anxiety and Depression Scale (HADS)

Chọn câu trả lời đúng nhất cho tâm trạng của ông/bà trong tuần vừa qua.

Vui lòng trả lời với ý đầu tiên mà ông bà cho là đúng nhất.

Phần 1. Lo lắng

No	Câu hỏi	Lựa chọn	Điểm
1	Tôi cảm thấy căng thẳng và "tổn thương"	a) Thường xuyên b) Nhiều lần c) Thỉnh thoảng d) Không hề	
2	Tôi cảm thấy sợ hãi như sắp có chuyện chẳng lành sắp xảy ra	a) Chắc chắn b) Nó sẽ xảy ra nhưng không chắc c) Nó không làm tôi lo lắng d) Không hề	
3	Tôi cảm thấy lo lắng	a) Thường xuyên b) Nhiều lần c) Thỉnh thoảng d) Không hề	
4	Tôi có thể ngồi nghỉ và cảm thấy thư giãn	a) Chắc chắn b) Thường xuyên c) Không thường xuyên d) Không hề	
5	Tôi cảm thấy nỗi lo sợ cồn cào trong bụng	a) Không hề b) Thỉnh thoảng c) Khá thường xuyên d) Rất thường xuyên	
6	Tôi cảm thấy mệt mỏi vì phải cố gắng bước tiếp:	a) Thật sự rất nhiều b) Khá nhiều c) Không nhiều lắm d) Không hề	
7	Tôi bỗng dưng thấy sợ hãi	a) Thật sự rất nhiều b) Khá nhiều c) Không nhiều lắm d) Không hề	
Tổng điểm lo lắng			

Phần 1. Phiền muộn

No	Câu hỏi	Lựa chọn	Điểm
1	Tôi vẫn có thể tận hưởng những thứ mình thích:	a) Rất nhiều b) Không nhiều c) Một chút d) Rất khó khăn	
2	Tôi có cười và nhìn vào mặt tích cực	a) Vẫn thường như tôi làm b) Không nhiều c) Không hề nhiều d) Không hề	
3	Tôi cảm thấy hài lòng	a) Không hề b) Không thường xuyên c) Thỉnh thoảng d) Phần lớn thời gian	
4	Tôi cảm thấy tôi đang chậm lại	a) Luôn luôn b) Rất thường xuyên c) Thỉnh thoảng d) Không hề	
5	Tôi không quan tâm đến ngoại hình của mình	a) Chắc chắn b) Tôi không quan tâm nhiều như lẽ ra phải quan tâm c) Tôi cũng quan tâm một chút d) Tôi vẫn luôn quan tâm đến ngoại hình	
6	Tôi tìm kiếm nguồn vui	a) Vẫn như tôi thường làm b) Ít hơn bình thường một chút c) Ít hơn rất nhiều d) Rất khó khắn	
7	Tôi có thể thưởng thức một cuốn sách hay, một chương trình phát thanh hoặc chương trình TV hay	a) Thường xuyên b) Thỉnh thoảng c) Không thường xuyên d) Rất hiếm khi	
. **Tổng điểm trầm cảm**			

Phần 6. Đánh giá chất lượng cuộc sống

Đánh giá chất lượng cuộc sống của bệnh nhân đang điều trị hóa chất

Vui lòng lựa chọn đáp án phản ánh đúng nhất câu trả lời của bạn trong 7 ngày qua

Code	**Câu hỏi**	**Không hề**	**Một chút**	**Thỉnh thoảng**	**Hơi thỉnh thoảng**	**Rất nhiều**
GE1	Tôi thấy buồn	0	1	2	3	4
GE2	Tôi hài lòng với cách mà tôi đang thích nghi với bệnh tật của mình	0	1	2	3	4
GE3	Tôi dần mất hi vọng trong việc chống chọi lại bệnh tật của mình.	0	1	2	3	4
GE4	Tôi thấy hồi hợp	0	1	2	3	4
GE5	Tô lo lắng về cái chết	0	1	2	3	4
GE6	Tôi lo lắng rằng tình trạng của tôi sẽ trầm trọng thêm	0	1	2	3	4
GF1	Tôi có khả năng làm việc (kể cả việc nhà)	0	1	2	3	4
GF2	Công việc của tôi (kể cả việc ở nhà) đem lại sự hài lòng, vui thích	0	1	2	3	4
GF3	Tôi có thể vui sống	0	1	2	3	4
GF4	Tôi đã chấp nhận bệnh tật của mình	0	1	2	3	4
GF5	Tôi ngủ tốt	0	1	2	3	4
GF6	Hiện tại tôi vui thích những gì tôi thường làm để giải trí	0	1	2	3	4
GF7	Tôi hài lòng với chất lượng cuộc sống hiện tại của tôi	0	1	2	3	4
GP1	Tôi cảm thấy thiếu năng lượng sống	0	1	2	3	4
GP2	Tôi bị buồn nôn	0	1	2	3	4
GP3	Vì tình trạng thân thể của mình, tôi khó đáp ứng các nhu cầu của gia đình của tôi	0	1	2	3	4
GP4	Tôi bị đau	0	1	2	3	4
GP5	Các phản ứng phụ của việc điều trị làm tôi bị khó chịu	0	1	2	3	4

GP6	Tôi thấy ốm yếu	0	1	2	3	4
GP7	Tôi buộc phải nằm nghỉ trên giường	0	1	2	3	4
GS1	Tôi thấy gần gũi với bạn bè mình	0	1	2	3	4
GS2	Tôi nhận được sự hỗ trợ tinh thần từ gia đình	0	1	2	3	4
GS3	Tôi được bạn bè hỗ trợ	0	1	2	3	4
GS4	Gia đình tôi chấp nhận bệnh tật của tôi	0	1	2	3	4
GS5	Tôi cảm thấy hài lòng với những giao tiếp trong gia đình về bệnh của tôi	0	1	2	3	4
GS6	Tôi rất gần gũi với bạn đời của mình (hoặc người chăm sóc chính)	0	1	2	3	4
Q1	*Bất kể mức độ hoạt động tình dục hiện nay của quý vị như thế nào* Xin vui lòng trả lời câu hỏi dưới đây về hoạt động tình dục của ông bà. Nếu ông bà không muốn trả lời vui lòng đánh dấu X vào ô bên cạnh . ☐					
GS7	Tôi hài lòng với đời sống tình dục của mình	0	1	2	3	4

Phần 7. Nhật ký giấc ngủ

Hướng dẫn: Vui lòng điền vào nhật ký giấc ngủ hàng ngày. Nếu có thể, ông bà vui lòng điền vào nhật ký giấc ngủ trong vòng 1 tiếng sau khi ngủ dậy vào sáng hôm sau. Nếu quên, ông bà có thể điền vào thời điểm khác trong ngày nhưng nếu ông bà không nhớ rõ thì có thể bỏ trống. Nếu giấc ngủ của ông bà bị ảnh hưởng bởi một vài lí do (đi du lịch, nhập viện…) vui lòng ghi rõ vào nhật ký. Vui lòng đọc các hướng dẫn tiếp theo để biết cách điền vào nhật ký giấc ngủ.

Ngày: Vui lòng ghi ngày mà ông bà điền nhật ký giấc ngủ

1. Giờ lên giường đi ngủ? Ghi thời gian ông/bà lên giường để đi ngủ.. Lưu ý đây là thời điểm ông bà lên giường để chuẩn bị đi ngủ chứ không phải là thời gian bắt đầu ngủ

2. Ông bà bắt đầu ngủ khi nào? Ghi thời gian mà ông bà bắt đầu nhắm mắt để cố gắng chìm vào giấc ngủ.

3. Mất bao lâu ông bà mới ngủ được? Tính từ thời điểm ông bà bắt đầu nhắm mắt để cố gắng chìm vào giấc ngủ, phải mất bao lâu ông bà mới ngủ được.

4. Ông/bà thức giấc giữa đêm mấy lần? Ghi số lần ông bà thức dậy lúc đang ngủ bắt đầu từ lúc cố gắng ngủ cho đến lúc thức dậy hoàn toàn.

5. Tổng thời gian tỉnh giấc giữa đêm? Tổng thời gian thức giấc giữa đêm của ông bà hôm qua là bao lâu? Ví dụ: trong lúc ngủ ông bà tỉnh giấc 3 lần, lần thứ nhất tỉnh mất 20 phút mới ngủ lại được, lần thứ 2 tỉnh mất 35 phút, lần thứ 3 tỉnh giấc mất 15 phút mới ngủ lại được, vậy tổng cộng trong khi ngủ đêm qua ông bà tỉnh giấc 20+35+15 = 70 phút..

6. Mấy giờ ông bà ngủ dậy? Ghi thời gian ông bà tỉnh giấc vào sáng hôm sau.

7. Mấy giờ thì ông bà ra khỏi giường? Ghi thời gian ông bà ra khỏi giường vào sáng hôm sau. Thời gian này có thể khác với thời gian ông bà ngủ dậy. Ví dụ ông bà ngủ dậy lúc 7h nhưng vẫn nằm trên giường (không ngủ) cho đến 7h30 mới ra khỏi giường. Thì ghi 7h vào câu số 6 và 7.30 vào câu số 7

8. Ghi chú. Nếu giấc ngủ của ông bà bị ảnh hưởng bởi một vài lí do (đi du lịch, nhập viện…) vui lòng ghi rõ vào nhật ký. Vui lòng ghi rõ các biện pháp hoặc các loại thuốc/thực phẩm chức năng ông/bà sử dụng để điều trị trầm cảm, lo âu, mất ngủ trong thời gian tham gia nghiên cứu.

NHẬT KÝ GIẤC NGỦ

Tên người bệnh: ……Tuổi: ……Bệnh viện:…….

Mã số:……..

Ngày	**Ngày thứ 1**	**Ngày thứ 2**	**Ngày thứ 3**	**Ngày thứ 4**	**Ngày thứ 5**	**Ngày thứ 6**	**Ngày thứ 7**
1. Giờ lên giường đi ngủ							
2. Mấy giờ ông bà bắt đầu chìm vào giấc ngủ							
3. Mất bao lâu ông bà mới ngủ được							
4. Trong khi ngủ ông bà tỉnh giấc mấy lần							
5. Tổng thời gian tỉnh giấc của ông bà							
6. Mấy giờ ông bà dậy hẳn							
7. Mấy giờ ông bà ra khỏi giường							
8. Ghi chú							

Appendix 5. The intervention rating profile-15 (English and Vietnamese version)

The purpose of this questionnaire is to obtain information that help to refine the study protocol for future main study. Please circle the number which best describes your agreement or disagreement with each statement.

	Strongly disagree	**Disagree**	**Slightly disagree**	**Slightly agree**	**Agree**	**Strongly agree**
1. This was an acceptable intervention for me to reduce the symptom cluster burden	1	2	3	4	5	6
2. Most of the patient with similar symptoms would find this intervention appropriate for their needs.	1	2	3	4	5	6
3. This intervention proved effective in reducing the symptom cluster burden	1	2	3	4	5	6
4. I would suggest this intervention to other patients	1	2	3	4	5	6
5. My symptoms burden was severe enough to warrant use of this intervention	1	2	3	4	5	6
6. Most patients would find this intervention suitable for their needs	1	2	3	4	5	6
7. I would be willing to use this treatment	1	2	3	4	5	6
8. This intervention did not result in negative side-effect for me	1	2	3	4	5	6
9. This treatment would be appropriate for a variety of cancer patients.	1	2	3	4	5	6
10. This intervention was consistent with those I have used	1	2	3	4	5	6
11. The intervention was a fair way to handle symptoms burden	1	2	3	4	5	6
12. This intervention is reasonable for reducing symptom burden	1	2	3	4	5	6
13. I like the procedures used in this intervention.	1	2	3	4	5	6
14. This intervention was a good way to handle symptoms burden	1	2	3	4	5	6
15. Overall, this intervention would be beneficial for me	1	2	3	4	5	6

Phụ lục 5. Đánh giá phương pháp bấm huyệt để giảm triệu chứng

Mục đích của bộ câu hỏi này nhằm giúp chúng tôi cải tiến quy trình của phương pháp điều trị bằng bấm huyệt cho nghiên cứu lớn hơn. Vui lòng khoang tròn vào số phản ánh đúng nhất mức độ đồng ý hoặc không đồng ý của ông bà với mỗi câu dưới đây..

	Rất không đồng ý	**Không đồng ý**	**Không đồng ý một chút**	**Đồng ý một chút**	**Đồng ý**	**Rất đồng ý**
1. Tôi thấy phương pháp này có thể dùng để chữa các triệu chứng của tôi	1	2	3	4	5	6
2. Phần lớn các bệnh nhân có 3 triệu chứng này sẽ thấy phương pháp này là hợp lý.	1	2	3	4	5	6
3. Phương pháp này chứng minh được tác dụng giảm các triệu chứng	1	2	3	4	5	6
4. Tôi sẽ giới thiệu phương pháp này tới người khác	1	2	3	4	5	6
5. Các triệu chứng của tôi ở mức độ đủ nặng để áp dụng phương pháp này	1	2	3	4	5	6
6. Phần lớn các bệnh nhân sẽ thấy phương pháp này đáp ứng dc nhu cầu của họ	1	2	3	4	5	6
7. Tôi rất sẵn sàng áp dụng phương pháp điều trị này	1	2	3	4	5	6
8. Bấm huyệt không gây bất kỳ tác dụng phụ nào cho tôi	1	2	3	4	5	6
9. Phương pháp này là thích hợp cho người bệnh ung thư.	1	2	3	4	5	6
10. Phương pháp này không đi ngược lại các phương pháp tôi đã áp dụng	1	2	3	4	5	6
11. The intervention was a fair way to handle symptoms burden	1	2	3	4	5	6
12. Phương pháp này là rất hợp lý để điều trị các triệu chứng	1	2	3	4	5	6
13. Tôi thích quy trình của phương pháp điều trị này	1	2	3	4	5	6
14. Phương pháp rất tốt để giúp tôi giảm khó chịu từ các triệu chứng	1	2	3	4	5	6
15. Nhìn chung, phương pháp này là hữu ích đối với tôi	1	2	3	4	5	6

Appendix 6. Protocol for the self-acupressure training session for participants

1. Purpose of the training session:
To train participants how to practice self-acupressure to manage insomnia, depression, and anxiety at home.
2. Objective of the training session
After receiving training section, participants are:
- Able to locate the acupoints
- Able to apply right pressure techniques in each acupoint
- Able to understand the dose of the treatment.

3. Location: In the consultation room of hospital.
4. Duration: 30 minutes.
5. Number of participants per session: 3 to 5 participants
6. Instructor: Trained interventionist.
7. Training materials: Patients booklet that included step by step guide with images-illustrating self-acupressure protocol.
For TSA group: Handout of Self-acupressure protocol + Self-acupressure Skill check A
For SSA group: Handout of Sham self-acupressure protocol + Self-acupressure Skill check B

8. **Detail of training session**

Step	Content	Interventionist does	Participants do
1	Introduce of the training section: Purpose and Objective	Lecture	
2	Introduce method of how to locate an acupoint and pressure techniques using the treatment protocol handout	Demonstration	
3	Practice of the method and skill to locate the selected acupoint and pressure techniques.	Supervise participants to practice. Asking participants to locate and stimulate acupoints.	Return demonstration and practice

4	Revision and correct participant if they fail to identify or stimulate acupoints	Demonstration	Return demonstration and practice
5	Checks the patient's mastery of self-acupressure technique	Using Self-acupressure Skill Check form to checks the participant's mastery.	Return demonstration
6	Summarize the training section and provide the treatment protocol to participants.	Lecture	

Appendix 7. Interventionist Skill Check of Self-acupressure and Sham Self-acupressure (English and Vietnamese version)

Interventionist Skill Check of Self-acupressure

Name of Interventionist:.....

Date:.....

Skills	**Score (*)**
Location of Acupoint	
1. Acupoint AP1	
2. Acupoint AP2	
3. Acupoint AP3	
4. Acupoint AP4	
5. Acupoint AP5	
6. Acupoint AP6	
General Stimulation techniques	
7. Applying pressure time	
8. Acupoint confirmation (identification of sore, numb, heavy, distended/warm)	
Specific stimulation techniques	
9. Acupoint AP1: Specific techniques on applying pressure	
10. Acupoint AP2: Specific techniques on applying pressure	
11. Others Acupoints: Specific techniques on applying pressure	
Total	

*Scoring instruction

0 = Incorrect, 1 = Correct

Interventionist Skill Check of Sham Self-acupressure

Name of Interventionist:.....

Date:.....

Skills	**Score (*)**
Location of Acupoint	
1. Acupoint SA1	
2. Acupoint SA2	
3. Acupoint SA3	
4. Acupoint SA4	
5. Acupoint SA5	
6. Acupoint SA6	
General Stimulation techniques	
7. Applying pressure time	
Specific stimulation techniques	
8. Acupoint SA1: Specific techniques on applying pressure	
9. Acupoint SA2: Specific techniques on applying pressure	
10. Others Sham Acupoints: Specific techniques on applying pressure	
Total	

*Scoring instruction

0 = Incorrect, 1 = Correct

Bảng kiểm kỹ thuật bấm huyệt của điều dưỡng

Tên điều dưỡng:

Ngày:

Kỹ năng	**Điểm (*)**
Xác định vị trí huyệt	
1. Huyệt AP1	
2. Huyệt AP2	
3. Huyệt AP3	
4. Huyệt AP4	
5. Huyệt AP5	
6. Huyệt AP6	
Kỹ thuật bấm huyệt chung	
7. Thời gian bấm	
8. Đắc khí	
Kỹ thuật bấm huyệt cụ thể	
9. Huyệt AP1: thực hiện đúng kỹ thuật bấm huyệt	
10. Huyệt AP2: thực hiện đúng kỹ thuật bấm huyệt	
11. Các huyệt khác: thực hiện đúng kỹ thuật bấm huyệt	
Tổng điểm	

*Hướng dẫn chấm điểm

0 = Sai, 1 = Đúng

Bảng kiểm kỹ thuật bấm huyệt giả của điều dưỡng

Tên điều dưỡng:

Ngày:

Kỹ năng	**Điểm (*)**
Xác định vị trí huyệt	
1. Huyệt SA1	
2. Huyệt SA2	
3. Huyệt SA3	
4. Huyệt SA4	
5. Huyệt SA5	
6. Huyệt SA6	
Kỹ thuật bấm huyệt chung	
7. Thời gian bấm huyệt	
Kỹ thuật bấm huyệt cụ thể	
8. Huyệt SA1: thực hiện đúng kỹ thuật bấm huyệt	
9. Huyệt SA2: thực hiện đúng kỹ thuật bấm huyệt	
10. Các giả huyệt khác: thực hiện đúng kỹ thuật bấm huyệt	
Tổng điểm	

*Hướng dẫn chấm điểm

0 = Sai, 1 = Đúng

Appendix 8. Self-acupressure Skill Check Forms for participants (English and Vietnamese version)

Noted: Self-acupressure Skill Check Form (A) is for participants in the True self-acupressure group and Self-acupressure Skill Check Form (B) is for participants in the Sham Self-acupressure group

Self-acupressure Skill Check Form (A)

Name of participant: .....

Hospital:.....

Code:.....

Date:.....

Skills	**Score (*)**
Location of Acupoint	
1. Acupoint AP1	
2. Acupoint AP2	
3. Acupoint AP3	
4. Acupoint AP4	
5. Acupoint AP5	
6. Acupoint AP6	
General Stimulation techniques	
7. Applying pressure time	
8. Acupoint confirmation (identification of sore, numb, heavy, distended/warm)	
Specific stimulation techniques	
9. Acupoint AP1: Specific techniques on applying pressure	
10. Acupoint AP2: Specific techniques on applying pressure	
11. Others Acupoints: Specific techniques on applying pressure	
Total	

*Scoring instruction

0 = Incorrect, 1 = Correct

Self-acupressure Skill Check Form (B)

Name of participant: .....

Hospital:.....

Code:.....

Date:.....

Skills	**Score (*)**
Location of Acupoint	
1. Acupoint SA1	
2. Acupoint SA2	
3. Acupoint SA3	
4. Acupoint SA4	
5. Acupoint SA5	
6. Acupoint SA6	
General Stimulation techniques	
7. Applying pressure time	
Specific stimulation techniques	
8. Acupoint SA1: Specific techniques on applying pressure	
9. Acupoint SA2: Specific techniques on applying pressure	
10. Others Acupoints: Specific techniques on applying pressure	
Total	

*Scoring instruction

0 = Incorrect, 1 = Correct

Bảng kiểm kỹ thuật bấm huyệt của người bệnh*

Ghi chú: Bảng kiễm kỹ thuật bấm huyệt (A) dành cho người bệnh trong nhóm bấm huyệt thật. Bảng kiểm kỹ thuật (B) dành cho người bệnh trong nhóm bấm huyệt giả

Bảng kiểm kỹ thuật bấm huyệt của người bệnh (A)

Tên người bệnh:

Bệnh viện:

Code:

Ngày:

Kỹ năng	**Điểm (*)**
Xác định vị trí huyệt	
1. Huyệt AP1	
2. Huyệt AP2	
3. Huyệt AP3	
4. Huyệt AP4	
5. Huyệt AP5	
6. Huyệt AP6	
Kỹ thuật bấm huyệt chung	
7. Thời gian bấm	
8. Đắc khí	
Kỹ thuật bấm huyệt cụ thể	
9. Huyệt AP1: thực hiện đúng kỹ thuật bấm huyệt	
10. Huyệt AP2: thực hiện đúng kỹ thuật bấm huyệt	
11. Các huyệt khác: thực hiện đúng kỹ thuật bấm huyệt	
Tổng điểm	

*Hướng dẫn chấm điểm

0 = Sai, 1 = Đúng

Bảng kiểm kỹ thuật bấm huyệt của người bệnh (B)

Tên người bệnh:

Bệnh viện:

Code:

Ngày:

Kỹ năng	**Điểm (*)**
Xác định vị trí huyệt	
1. Huyệt SA1	
2. Huyệt SA2	
3. Huyệt SA3	
4. Huyệt SA4	
5. Huyệt SA5	
6. Huyệt SA6	
Kỹ thuật bấm huyệt chung	
7. Thời gian bấm huyệt	
Kỹ thuật bấm huyệt cụ thể	
8. Huyệt SA1: thực hiện đúng kỹ thuật bấm huyệt	
9. Huyệt SA2: thực hiện đúng kỹ thuật bấm huyệt	
10. Các giả huyệt khác: thực hiện đúng kỹ thuật bấm huyệt	
Tổng điểm	

*Hướng dẫn chấm điểm

0 = Sai, 1 = Đúng

Appendix 9. Protocol for education session for participants in the enhanced standard care group.

1. Purpose of the training section:

To provide information about healthy lifestyle that participants can apply to their daily life to manage insomnia, depresion, and anxiety.

2. Objective of the training section

After receiving training section, participants are:

- Able to understand 10 recommendations on how to manage insomnia, depression, and anxiety.
- Able to apply these recommendations to their daily life to improve sleep

3. Location: In the consultation room of the department.

4. Duration: 30 minutes.

5. Number of participants per section: 2 to 3 participants.

6. Instructor: Ph.D. student/interventionists.

7. Training materials

Ten recommendations on managing insomnia, depression, and axiety leaflet.

8. Detail of training section

In this section, the instructor will introduce the Ten recommendations on managing insomnia, depression, and axiety to the patient and explain how this rules can improve their symptoms. The steps of this section include:

Step 1: Introduce the Ten recommendations on managing insomnia, depression, and axiety to patients.

Step 2: Let the patient read the recommendations, pausing between recommendations to explain how these recommendations works

Step 3: The instructor answers any questions related to the ten recommendations that raise from the participants.

Appendix 10. Acupresssure Protocol Validation Form (English and Vietnamese)

Self-acupressure Protocol Validation Form

Instruction: Please circle the number which best describes your agreement level with each of the items in the form. If you have comments or suggestion for any item please write down in the "comments" column. Please provide references if your comments or suggestions come from relevant studies.

1. True self-acupressure protocol

Content	Appropriateness of the content				Comments
	Very appropriate	Appropriate	Inappropriate	Very Inappropriate	
Selection of the acupoint					
Baihui (GV20)	4	3	2	1	
Yingtang (EN-HN3)	4	3	2	1	
Fengchi (GB20)	4	3	2	1	
Hegu (LI4)	4	3	2	1	
Shenmen (HT7)	4	3	2	1	
Taichong (LR3)	4	3	2	1	
Pressing technique					
Baihui: *using four finger pads, gently tap the area of this acupoint on the scalp*	4	3	2	1	
Fengchi: *using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally*	4	3	2	1	

Other acupoints: *using thumb pad, firmly massage the surrounding area of this acupoint*	4	3	2	1	
Duration of each session: 24 minute (3 minute for each acupoint; for Fengchi and Taichong, participants will press both sides of the body at the same time; for Hegu and Shenmen, participant will press the right side, followed by the left side)	4	3	2	1	
Duration of whole treatment: four weeks (28 days)	4	3	2	1	
Frequency: Once a day	4	3	2	1	
Time for practice self-acupressure: Before bedtime	4	3	2	1	

2. Sham self-acupressure protocol

Content	Appropriateness of the content				Comments
	Very appropriate	Appropriate	Inappropriate	Very Inappropriate	
Selection of the sham acupoint					
SA 1: 3cm away from Baihui	4	3	2	1	
SA 2: 3 cm away from Ying Tang	4	3	2	1	
SA 3: Mastoid bone	4	3	2	1	
SA 4: Head of ulnar styloid	4	3	2	1	
SA 5: Base of metacarpal bone of the index finger	4	3	2	1	
SA 6: 3 cm away from Taichong	4	3	2	1	
Pressing technique					
SA 1: *using four finger pads, gently tap the area of this sham acupoint on the scalp*	4	3	2	1	
SA 3: *using two thumbs, press in the acupoint bilaterally while the other four fingers should hold the back of the head naturally*	4	3	2	1	
Other acupoints: *using thumb pad, firmly massage the surrounding area of this sham acupoint*	4	3	2	1	
Duration of each session: 24 minute (3 minutes for each acupoint; for SA 3 and SA 6, participants will press both sides of the body at the same time; for SA 5 and SA 4, participants will press the right side, followed by the left side)	4	3	2	1	
Duration of whole treatment: four weeks (28 days)	4	3	2	1	
Frequency: Once a day	4	3	2	1	
Time for practice self-acupressure: Before bedtime	4	3	2	1	

Appendix 4. Self-acupressure Record Form (English and Vietnamese version)

Self-acupressure Record Form

Name of participant:……Age: ……Hospital:……

Code: ……

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number of acupoint														
Treatment time (min)														
Reason for not practicing														
Adverse events related to self-acupressure														

Other self-care methods in insomnia, depression, anxiety:

Any self-taken Chinese Herb/Western medication/supplement:

Drug/supplement name: (1) Dose:……

(2) Dose:…….

Self-acupressure Record Form

Name of participant:……Age: ……Hospital:……

Code: ……

	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Number of acupoint														
Treatment time (min)														
Reason for not practicing														
Adverse events related to self-acupressure														

Other self-care methods in insomnia, depression, anxiety:

Any self-taken Chinese Herb/Western medication/supplement:

Drug/supplement name: (1) Dose:……

(2) Dose:……

Phiếu theo dõi bấm huyệt

Tên người bệnh: ……Tuổi: ……Bệnh viện:…….

Mã số:……

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Số huyệt ông bà bấm hôm nay														
Thời gian bấm huyệt														
Nếu hôm nay ông bà không bấm huyệt, làm ơn ghi lí do														
Các khó chịu gặp phải khi bấm huyệt														

Ông bà có dùng thêm thuốc/thực phẩm chức năng gì để điều trị mất ngủ, lo âu, phiền muộn không:

Vui lòng ghi rõ tên thuốc: (1)……. Liều dùng:……

(2)……. Liều dùng:……

Phiếu theo dõi bấm huyệt

Tên người bệnh: ……Tuổi: ……Bệnh viện:…….

Mã số:……

	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Số huyệt ông bà bấm hôm nay														
Thời gian bấm huyệt														
Nếu hôm nay ông bà không bấm huyệt, làm ơn ghi lí do														
Các khó chịu gặp phải khi bấm huyệt														

Ông bà có dùng thêm thuốc/thực phẩm chức năng gì để điều trị mất ngủ, lo âu, phiền muộn không:

Vui lòng ghi rõ tên thuốc: (1)……. Liều dùng:……

(2)……. Liều dùng:……

Appendix 11. Information sheet of the cross-sectional survey

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

INFORMATION SHEET

Insomnia in Cancer patients receiving chemotherapy: Prevalence and its relationship with other symptoms

You are invited to participate in a study supervised by Prof. Alexandros MOLASIOTIS, Dr. CHAN Choi Wan and conducted by Ms. HOANG Thi Xuan Huong, who is PhD student in the School of Nursing at The Hong Kong Polytechnic University.

The aim of the study is to assess the prevalence and severity of insomnia as well as the relationship between insomnia and others symptoms and the impact of insomnia to patient's quality of life among Vietnamese cancer patients receiving chemotherapy. The finding from this study will help nurses to better manage patient's unpleasant symptoms during their treatment and increase the outcome of treatment in the future.

This is a cross-sectional study. If you agree to participate in the study, the investigator will give you the questionnaires to collect data and you will wear an actigraphy to record your sleep parameter in daily routine for 3 continuous days. The actigraphy is a device which use movement sensor to measure physical movement, it is a small device worn on the non-dominant wrist and cause no discomfort for users.

Participation is voluntary. 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 researcher. If you have any complaints about the conduct of this research study, please do not hesitate to contact Miss Cherrie Mok, Secretary of the Human Subjects Ethics SubCommittee 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 Ms. Hoang Thi Xuan Huong at telephone number 098891 or her supervisor Prof. Alexandros MOLASIOTIS telephone number +852 2766 7883. Thank you for your interest in participating in this study.

Appendix 12. Consent form for the cross-sectional survey study (English and Vietnamese Version)

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

CONSENT TO PARTICIPATE IN RESEARCH

Insomnia in Cancer patients receiving chemotherapy: Prevalence and its relationship with other symptoms

I _____ hereby consent to participate in the captioned research supervised by Prof. Alexandros MOLASIOTIS, Dr. CHAN Choi Wan and conducted by Ms. HOANG Thi Xuan Huong

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 participants _____

Name of researcher: MS HOANG Thi Xuan Huong

Signature of researcher: _____

Date _____

Appendix 13. Ethical approval memo for the cross-sectional survey

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To Molasiotis Alexandros (School of Nursing)

From CHIEN Wai Tong, Chair, Departmental Research Committee

Email hschien@_____ Date 25-May-2017

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 16-Feb-2017 to 29-Dec-2017:

Project Title: Insomnia in Cancer patients receiving chemotherapy: Prevalence and its relationship with other physical and emotional symptoms

Department: School of Nursing

Principal Investigator: Molasiotis Alexandros

Project Start Date: 16-Feb-2017

Reference Number: HSEARS20170428003

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 Human Subjects Ethics Sub-committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

CHIEN Wai Tong

Chair

Departmental Research Committee

Appendix 14. Ethical approval memo for the feasibility study

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To Molasiotis Alexandros (School of Nursing)

From Vaelimaeki Maritta Anneli, Chair, Departmental Research Committee

Email maritta.valimaki@ Date 29-Nov-2018

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-Oct-2018 to 01-Oct-2019:

Project Title: Self-administered Self-acupressure for Cancer-related Symptom Cluster of Insomnia, Depression, and Anxiety: a Feasibility Randomized Controlled Trial

Department: School of Nursing

Principal Investigator: Molasiotis Alexandros

Project Start Date: 01-Oct-2018

Reference Number: HSEARS20180604004

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 Human Subjects Ethics Sub-committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

Vaelimaeki Maritta Anneli

Chair

Departmental Research Committee

Appendix 15. Sleep log (use in the cross-sectional survey)

Instruction: The sleep log must be complete every day. If possible, please complete within one hour of getting out of bed in the morning. If you forget to fill in the sleep log or are unable to finish it, leave the diary blank on that day. If your sleep or daytime functioning is affected by some unusual events (such as illness, or an emergency) please make brief notes on your sleep log.

Item Instructions Use the guide below to clarify what is being asked for each item of the Sleep Diary.

Date: Write the date of the morning you are filling out the diary.

1. What time did you get into bed? Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.

2. How many times did you wake up, not counting your final awakening? How many times did you wake up between the time you first fell asleep and your final awakening?

3. What time was your final awakening? Record the last time you woke up in the morning.

4. What time do you remove the actigraph from your wrist? Record the time you remove the actigraph from your wrist.

5. Comments If you have anything that you would like to say that is relevant to your sleep feel free to write it here. Also record other self-care methods using to manage insomnia or any self-taken Chinese Herb/Western medication/supplement taken.

SLEEP LOG

Name of participant: ……Age……

Hospital:……

Code: ……

Today's date	**Day 1**	**Day 2**	**Day 3**
1. What time did you get into bed?			
2. How many times did you wake up, not counting your final awakening?			
3. What time did you get out of bed for the day?			
4. What time do you remove the actigraph from your wrist			
5. Comments			