Management of chemotherapy-induced nausea and vomiting: A pilot randomised controlled trial using Nevasic audio programme.

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Saeed Moradian

School of Medicine

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List of Abbreviations

5-HT3	5- hydroxytryptomine
AC	Adriamycin & Cyclophosphamide
AIC	Akaike information Criterion
ANOVA	Analysis Of Variance
ANV	Anticipatory Nausea and Vomiting
AP	Area Postrema
ARMA	Auto-Regressive Moving Average
AR (1)	Auto-Regressive (1)
AMED	Allied and Complementary Medicine
BSI	Brief Symptom Inventory
CAF	Cyclophosphamide,Adriamycin (Doxorubicin), and 5-Fluouracil
CAM	Complementary and Alternative Medicine
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CINE QoL	Chemotherapy-Induced Nausea and Emesis –Quality Of Life
CINV	Chemotherapy induced Nausea and Vomiting
CMF	Cyclophosphamide,Methotrexate, and 5-Fluouracil
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CTZ	Chemoreceptor Trigger Zone
DNA	Deoxy-Ribonucleic Acid
FLIC	Functional Living Index-Cancer
FLIE	Functional Living Index-Emesis
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Organisation Research and Treatment of Cancer– Quality of Life Questionnaire

FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FACTG	Functional Assessment of Cancer Therapy – General
GI	Gastrointestinal
HEC	Highly Emetogenic Chemotherapy
HR-QoL	Health-related quality of life
ICC	Intraclass Correlation Coefficient
INVR	Index of Nausea, Vomiting, and Retching
IV	Intravenous
MANE	Morrow Assessment of Nausea and Emesis
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Anti-emesis Tool
MEC	Moderately Emetogenic Chemotherapy
MT	Music Therapy
NCCAM	National Centre for Complementary and Alternative Medicine
NCINIH	National Cancer Institute at the National Institute of Health
NHS	National Health Service
NK1	Neurokinin 1
NTS	Nucleus Tractus Solitarius
NVR	Nausea, Vomiting and Retching
PMRT	Progressive Muscle Relaxation Training
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyse
PRN	ProRre Nata (as necessary doses)
QoL	Quality of Life
RA	Receptor Antagonists
RCT	Randomised Controlled Trial

RR	Relative Risk
RS	Raw Score
SD	Standard deviation
SIP	Sickness Impact Profile
SPSS	Statistical Product and Service Solutions
VAS	Visual Analogue Scale
WHO	World Health Organisation

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Abstract

The University of Manchester

Saeed Moradian

Doctor of Philosophy

Management of chemotherapy -induced nausea and vomiting: A pilot randomised controlled trial using Nevasic audio programme

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Major advances in antiemetic therapy have been made over the past two decades. Despite these advances in antiemetic management, nausea and vomiting are still important problems in clinical practice, and approximately 50% of patients receiving chemotherapy still experience nausea and/or vomiting, highlighting the need for further developments in the field. Non-pharmacological interventions are suggested as possible adjuncts to standard anti-emetic therapy. A recently developed non-pharmacological intervention to alleviate nausea and vomiting is Nevasic, which may have potential to reduce CINV and improve management of these symptoms.

This pilot trial was run to examine the feasibility of implementing and conducting a randomised controlled trial using Nevasic programme. In addition, the study aimed to evaluate the acceptability and potential effect of Nevasic on cancer patients undergoing chemotherapy. Ninety nine adult female breast cancer patients who had been prescribed a course of moderately high emetogenic chemotherapy were randomised to usual care (standard anti-emetics) plus one of (1) intervention group (using Nevasic), (2) attention group (listening to music), and (3) control group, receiving no additional intervention. Data were collected daily using the Rhodes Index of Nausea, Vomiting and Retching (INVR) and a structured diary questionnaire. The EORTC QLQ-C30 (and BR23) were used at baseline and day 6 post chemotherapy. Data were collected from cancer centres affiliated to Mashhad University of Medical Sciences in Mashhad, Iran.

The findings from the trial highlight that conducting a non-pharmacological intervention using such an audio programme is feasible, although difficulties and limitations exist. This study did not detect any evidence for the effectiveness of Nevasic on CINV; however, the results show statistically significant less use of anti-emetics (post-chemotherapy) ($p=0.03$) and borderline non-significant ($p=0.06$) better global health status in Nevasic group. Further studies are required to investigate its implications from other perspectives such as use of anti-emetics - rather than looking only at the "level of nausea and/or vomiting" perspective.

Declaration

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Dedication

This thesis is dedicated to all cancer patients throughout the world.

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Chapter One: General Introduction

1.1. Background

Cancer is a group of more than 200 different diseases, and can generally be described as an uncontrolled growth and spread of cells, in which abnormal cells are able to invade other tissues through the lymphatic system or the bloodstream (WHO, 2012). It may be caused by internal factors (such as inherited mutation, hormones, immune deficiencies, conditions and mutations arising from metabolism) or external factors (tobacco, radiation, chemicals or infectious organisms) (American Cancer Society, 2011).

The incidence of cancer is rising, and it is estimated that by 2020, globally, more than 15 million people will experience cancer (Higginson & Costantini, 2008). The main goal of a cancer treatment programme is to cure or considerably prolong the life of patients, and to ensure the best possible quality of life to cancer survivors (WHO, 2012). The general strategies for cancer treatment include surgery, radiotherapy, and chemotherapy, or combined strategies of these. These are supplemented by more specialised therapies, such as immunotherapy or hormone therapy, which can be applied only to some types of cancer (Davies & Epstein, 2010). Transplantation involving stem cells, or bone marrow, is another method of treatment, which is usually used in haematology patients (Blazar et al., 2006).

The oldest cancer treatment is surgery. It provides the greatest chance of cure, and is generally used for solid tumours; particularly those which have not yet metastasised to other parts of the body.

Radiotherapy involves the use of high-energy particle beams or waves (radiation), such as X-rays, gamma rays, or neutrons, for treating cancer. The radioactive material transfers its energy into highly energetic electrons which ionize the matter they hit, such as water and/or proteins or other molecules of the cell cytoplasm, or Ribo Nucleic Acid (RNA) and Deoxyribo Nucleic Acid (DNA). This ionization alters the molecules and this leads to cell death, or inhibits cell division (Jin et al., 2001). Although radiation is more harmful to cancerous cells than normal cells, one of the major weaknesses of radiotherapy is that it is impossible to treat only cancerous cells, without affecting the surrounding healthy cells (Spreadbourgh & Read, 2000).

Chemotherapy uses chemicals to treat cancer, and is particularly appropriate for cancers that have metastasised and cannot be treated any longer by localised methods such as surgery and radiation. Chemotherapy has long been one of the most important parts of cancer treatment. The main goals of chemotherapy vary, and can range from intention-to-cure to provision of comfort (i.e. palliation) (Peterson & Lalla, 2010). Chemotherapeutic agents can be administered intravenously, orally or by injection, in cycles, often over a number of months. In the broad sense, chemotherapeutical agents act by creating toxic effects on dividing cells (i.e. altering the synthesis and function of DNA and impairing mitosis), effectively targeting fast-dividing cells (Castello & Erlichman, 2010). However, this frequently results in severe damage to normal tissues, leading to side effects such as bone marrow suppression, and increased susceptibility to infection, nephrotoxicity, anorexia, alopecia, diarrhoea, nausea and vomiting (Bergkvist & Wengström, 2006). The optimum goal is to find a treatment modality that specifically kills malignant cells while causing few or no side effects.

Major advances in different cancer treatment modalities (i.e. surgery, chemotherapy, radiotherapy, hormonal therapy, and biological response modifiers) have been made, and people are now living longer with cancer than they were in the past (Cella & Fallowfield, 2008; Bloechl-Daum et al., 2006). However, cancer patients suffer from a range of physical, physiological, and psychological symptoms during their cancer journey. These symptoms are either directly related to the adverse effects of cancer, or arise from the different types of treatments, and may range from mild and temporary to severe, chronic, and life threatening (Rajapakse, 2010; Abu-Saad Huijer et al., 2012).

The quality of life (QoL) and degree of suffering of patients with cancer is determined by the presence and intensity of these symptoms. Symptom prevalence and management are crucial in the clinical setting, because they enable health-care professionals to focus on the most prevalent symptoms, anticipate potential problems, and plan the type of care and symptom management accordingly (Abu-Saad Huijer et al., 2012).

As mentioned above, there are several symptoms that are common to many chemotherapeutic agents, and which can have devastating consequences for the patient. Nausea and vomiting are among the frequently experienced toxicities associated with chemotherapy. Although nausea and vomiting can result from surgery or radiotherapy, chemotherapy induced nausea and vomiting (CINV) is potentially the most severe and most distressing. This can range from mild queasiness to violent, repetitive vomiting and retching, and these remain the most distressing symptoms when receiving chemotherapy (Cohen et al., 2007; Lohr, 2008). Beyond their distressing effects, severe nausea and vomiting can lead to nutritional deficiencies, dehydration and electrolyte imbalance (Kearney et al., 2008).

Estimates regarding the incidence of CINV vary depending on the treatment administered and individual patient characteristics; however, they have been reported by approximately half of all cancer patients (Huertas-Fernández et al., 2010). The impact of CINV on QoL and daily activities is considerable. In a study conducted by Ballatori et al. (2007), for instance, the results show that more than 90% of all patients with both acute and delayed nausea or vomiting reported that it had an impact on their daily life. It has also been shown that CINV has a considerable negative impact on physical, cognitive, social, emotional and role functioning (Bergkvist & Wengström, 2006; Martin et al., 2003).

Pharmacological treatments are considered routine for CINV. Historically, antiemetic treatment was first improved in 1981 by the introduction of high-dose metoclopramide, which reduced the amount of vomiting. In the early 1990s, the development of serotonin (type three 5-hydroxytryptamine [5-HT3]) receptor antagonist (granisetron and ondansetron) supported by the concomitant use of corticosteroids, further helped to improve control of nausea and vomiting. Recently, the neurokinin NK receptor antagonist (aprepitant) was shown to have a better effect on preventing CINV for patients being treated with chemotherapy (Bergkvist & Wengström, 2006). Despite these advances in antiemetic management, approximately 50% of patients receiving chemotherapy still experience nausea and/or vomiting (Pirri et al., 2011). These side effects may lead to reducing patients' adherence to the treatment, a need to decrease the

chemotherapy dose, or even discontinuing the chemotherapy treatment (Hesketh, 2008).

Since pharmacological therapy is only partially effective in preventing or treating chemotherapy-related nausea and vomiting in many cases, the need for additional methods to reduce the symptoms has been highlighted (Tipton et al., 2007; Ezzo et al., 2009). Thus, exploring the complementary role of other, non-pharmacological, approaches that can be used in addition to pharmacological approaches is paramount. This need for additional relief has led to research interest focused not only on developing new antiemetic medications, but also on non-pharmacological adjuncts to medications.

In recent years, there has been increasing interest in the area of complementary and alternative medicine (CAM) therapies which have been shown to be effective in providing symptom relief and improving QoL (Gage et al., 2009; Lövgren et al., 2011; Egan et al., 2012). The results of a systematic review documenting the prevalence of CAM use among patients with cancer revealed that the use of CAM therapies in adult populations ranged from 7% to 64%, with the average prevalence at 31.4% (Ernst & Cassileth, 1998). It would seem that cancer patients turn to CAM to restore balance, boost their energy, improve symptom management and foster well-being (Akyol & Öz, 2011; Blaes et al., 2011). The most popular CAM therapies include mind-body approaches, dietary and food supplements, homeopathy, spiritual healing, Chinese medications and botanical preparations.

Several mind-body techniques, in addition to conventional anti-emetics, have been examined over the years for the treatment of CINV. For example, during the last decade several trials examining the efficacy of acupressure/acupuncture for alleviating CINV have been a focus of research. In addition, the impact of psychological factors on nausea and vomiting has been widely acknowledged, and the efficacy of inducing these psychosomatic aspects, e.g. by relaxation training, coping preparations, imagery, distraction techniques or hypnosis, has been demonstrated in a number of studies (Ezzo et al., 2009; Tipton et al., 2007; Schiff & Ben-Arye, 2011). Music therapy (MT), as part of a complementary medicine programme in supportive cancer care which accompanies medical treatment, can

effectively improve physical and emotional well-being in cancer inpatients, by providing benefits related to managing symptoms along the cancer journey (Lagattolla et al., 2010; Stanczyk, 2011).

Nevertheless, many patients still experience nausea and vomiting in relation to chemotherapy. The need to evaluate additional ways to reduce these symptoms is still, therefore, a priority. Combining anti-emetics with other non-pharmacological interventions may prove to be more effective in decreasing nausea than anti-emetics alone (Roffe et al., 2005).

1.2. Thesis organisation

The overall structure of the thesis takes the form of seven chapters, including this introductory chapter. Chapter two is background and begins by laying out the theoretical dimensions related to the research topic. The three identifiable phases within the development of CINV are explained, and the incidence of CINV and related factors (treatment and patient) which may affect it are reviewed and discussed. Understanding such factors is important, as the identification of high-risk patients allows for better treatment planning. The impact of CINV on patients' QoL is then explored.

To control nausea and vomiting, two treatment modalities are generally used; these can be categorised as pharmacological and non-pharmacological therapy. Pharmacological therapy uses antiemetic medications to prevent, control and treat nausea and vomiting, while non-pharmacological interventions, which are usually combined with and support pharmacological therapies, do not involve the use of any pharmacological medicine. Therefore, the current status of pharmacological CINV management will be explored in chapter two, and an overview will then be given of non-pharmacological interventions (mind-body medicine) in controlling nausea and vomiting in cancer patients receiving chemotherapy in chapter three which is literature review. In this chapter (chapter three) a description and discussion is provided of previous studies focusing on CAM (such as acupuncture/acupressure, progressive muscle relaxation, guided imagery, hypnosis, virtual reality, and music therapy), in addition to anti-emetics, to ameliorate CINV. A description of the search strategy used and the quality issues relating to the reviewed studies is then provided.

The fourth chapter explains the research methods used, and is divided into two sections. The first explores potential different study designs to evaluate the effectiveness of interventions. The relationship between the research question(s) and design and components of this clinical study are explored and discussed. The methods of the feasibility study are then presented, along with the rationale for any decisions made. Details of the process of protocol development are described, including the processes of sampling, data collection, and procedure, and a detailed examination of the validated measurement tools appropriated for use in the study is conducted.

As the setting of research was cancer centres in Iran, and one of the measurement tools used in this study (the Rhodes INVR) has not previously been translated into Persian, it was necessary to translate this for use in this study. The process of translation and the psychometric tests used are also explained in chapter five.

The sixth chapter presents the findings of the research and an analysis of the results. The results are presented in four sections. The first explores the acceptability of the study, and describes issues such as adherence, acceptability, reasons for attrition and participant burden. Descriptive data relating to the feasibility of running a full trial are then presented. Following this, the intervention's effect on nausea and vomiting are explored, and finally, data about the effect of nausea and vomiting on health-related QoL are presented.

Chapter seven provides a discussion of the study and focuses on issues related to efficacy in non-pharmacological interventions, and also different aspects of study feasibility. This is followed by an examination of the study's strengths and limitations, and recommendations for further research.

Chapter Two: Background

2.1. Introduction

This chapter begins by presenting definitions of nausea, vomiting and retching, and explains the different phases of CINV. Then, the mechanisms of nausea and vomiting are reviewed. The incidence and factors associated with CINV, and its impact on patients' QoL, are explored. The current status of pharmacological management of CINV is explored.

2.2. Definitions of nausea, vomiting and retching

2.2.1. Nausea

The word "nausea" originally referred to seasickness, and is derived from the Greek word "naus", meaning ship (Horn, 2008). Nausea is a separate but related symptom to vomiting and retching. Nausea has been defined as "an unpleasant feeling of the need to vomit, often accompanied by autonomic sensations" (Tadman & Roberts, 2007). Rhodes et al. (1995, p. 257) define nausea as "a subjective and unobservable phenomenon that may or may not culminate in vomiting". It is synonymously described as feeling "sick to the stomach". It is a disagreeable feeling experienced in the back of the throat, the epigastrium, and may be accompanied by pallor, cold clammy skin, increased salivation, faintness, tachycardia, and diarrhoea. It is often associated with decreased gastric functioning, such as hypotonicity, hypoperistalsis, and hyposecretion (Grant, 1987; Naylor, 2002; Harbord, 2009). Nausea is a subjective and unpleasant sensation that can only be measured or quantified by patients themselves, rather than objectively by clinical staff. Nausea has a higher incidence, and also a greater effect on patient QoL, than vomiting does (Naylor, 2002; Foubert & Vaessen, 2005).

2.2.2. Vomiting

Vomiting is defined by Rhodes et al. (1995, p.257) as "a forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity". Vomiting can be objectively quantified by frequency of occurrence and by the volume.

Vomiting can be classified according to three phases: the first phase (pre- ejection or prodromal phase) is usually accompanied by nausea, and sometimes retching, as the gastrointestinal tract prepares itself for an emetic episode. Actual expulsion

of stomach contents occurs in the second phase (ejection phase). The third phase is the post-ejection phase, when vomiting has stopped, nausea dissipated, and the person usually feels better (Baker et al., 2005).

2.2.3. Retching

"Retching is the attempt to vomit without bringing anything up" (Rhodes & McDaniel 2001, p.234). It can be described by such terms as "gagging", "dry heaves", and "attempting to vomit without results". Retching occurs with a rhythmic contraction of the diaphragm, the rectus abdominis, and the external intercostal muscles (Baker et al., 2005).

2.3. Chemotherapy- induced nausea and vomiting

CINV can be defined as nausea and vomiting that occurs in patients receiving chemotherapy. It can be classified according to three phases (acute, delayed and anticipatory) (Cohen et al., 2007; Middleton & Lennan, 2011).

2.3.1. Acute CINV

Acute CINV is typically defined as nausea and/or vomiting within the first 24 hours after chemotherapy administration (Grunberg, 2004; Schwartzberg, 2007). Vomiting, in the absence of effective antiemetic prophylaxis, most commonly begins within one to two hours of chemotherapy, and typically peaks in the first four to six hours (Dewan et al., 2010).The actual period of acute nausea and vomiting is affected by many factors (including specific patient risk factors, which are explored in the following section), but are mainly influenced by the chemotherapy agent's emetogenicity, and prescribed antiemetic drugs.

2.3.2. Delayed CINV

Delayed CINV is usually defined as nausea or vomiting that begins after the first 24 hours of chemotherapy administration. Although the duration of the delayed phase has not been fully defined, it may last for 5-7 days (Dupuis & Nathan, 2003; Grunberg, 2004). Regardless of the regimen used, the frequency and the number of episodes of nausea and vomiting may be less in the delayed phase, compared with acute CINV. However, control and treatment of the delayed CINV, particularly

delayed nausea, with current antiemetic medications is more difficult to manage than acute nausea and vomiting (Grunberg, 2004; Dewan et al., 2010).

2.3.3. Anticipatory CINV

Anticipatory nausea and vomiting (ANV) often occurs prior to the second or subsequent administration of chemotherapy (Dupuis & Nathan, 2003). It occurs almost exclusively in patients who have experienced poorly controlled nausea and vomiting during previous courses of chemotherapy (Schwartzberg, 2007). Although several studies (Dupuis & Nathan, 2003; Grunberg, 2004; Schwartzberg, 2007) consider ANV as a conditioned response, it is not only a learned response and can occur without prior exposure to chemotherapy, depending on patients' emotional distress and expectations (Aapro et al., 2005).

2.3.4. Breakthrough and refractory CINV

Breakthrough and refractory CINV are two other terms that may be used with reference to chemotherapy. Breakthrough CINV can be defined as nausea and vomiting during any phase of the chemotherapy cycle, despite antiemetic prophylaxis. Breakthrough CINV is defined as nausea and vomiting that occurs despite standard preventative therapy (antiemetic prophylaxis), either in the acute or delayed phase. Refractory CINV is also described as a failure to respond to prevention and/or intervention during a previous cycle of treatment (Middleton & Lennan, 2011). For clinical purposes, if a patient vomits and/or retches twice, or experiences 4 hours of moderate to severe nausea, within 24 hours, it is considered significant breakthrough CINV, which requires intervention (Dupuis & Nathan, 2003).

2.4. Mechanisms of CINV

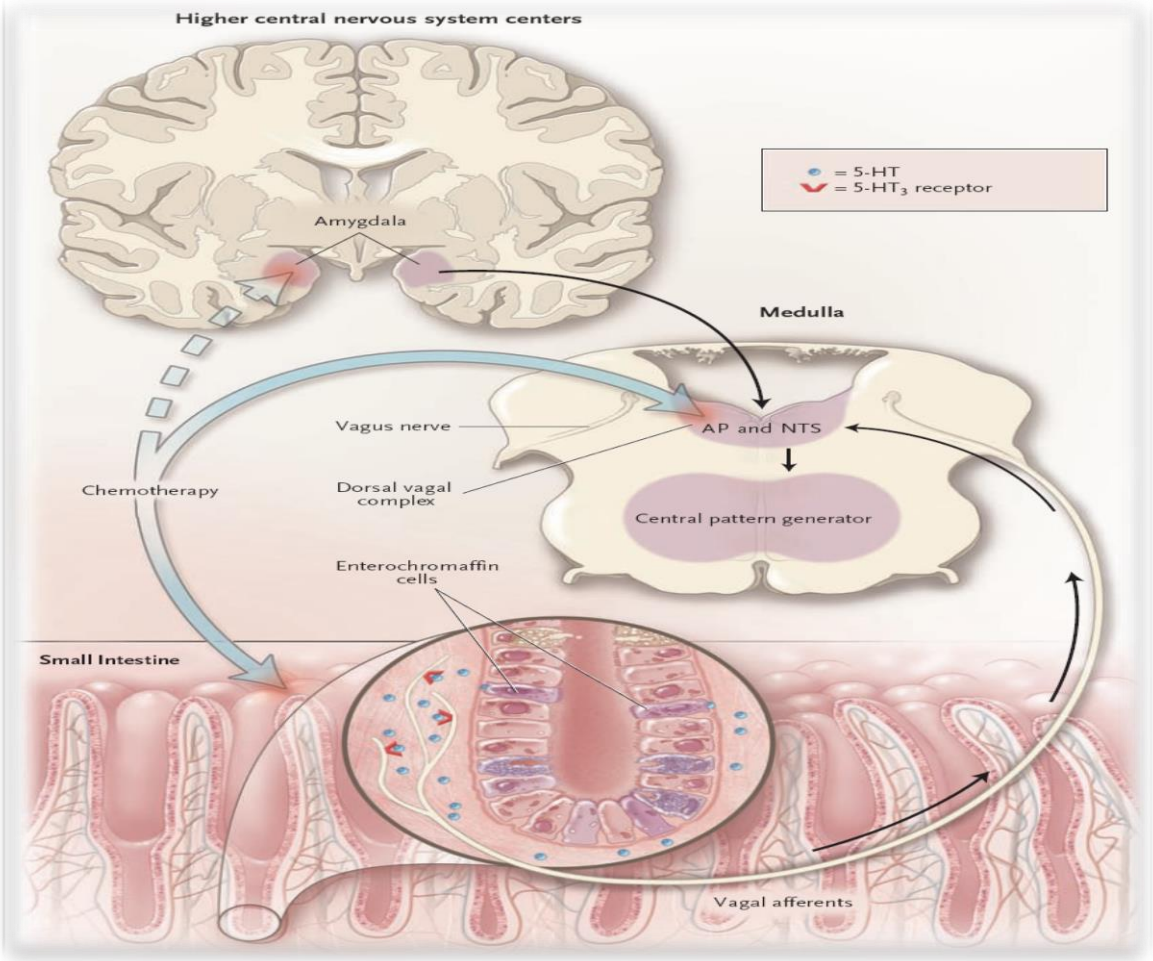
In order to understand the approach to CINV and modern antiemetic treatment, it is crucial to obtain an understanding of the pathophysiology underpinning the emetic response (Middleton & Lennan, 2011). The pathophysiology of CINV is very complex, and not yet completely understood (Hesketh, 2008). This (the lack of understanding) might be related to different mechanisms being responsible for nausea and vomiting in the different phases. Furthermore, the mechanism within one chemotherapy agent may be different in another.

2.4.1. Summary of pathways by which chemotherapeutic agents may produce an emetic response

Administering chemotherapy drugs is considered one of the stimuli of nausea and vomiting through effects at a number of sites. The mechanism that is best supported by research involves an effect on the upper small intestine (Figure 2-1) (Hesketh, 2008).

After the administration of chemotherapy, the enterochromaffin cells (in the gut) are stimulated, leading to localised exocytotic release of serotonin (5-hydroxytryptomine), which then interact with the chemoreceptor 5-hydroxytryptomine 3, which are located on the vagus nerve in the wall of the intestine (Baker et al., 2005). Subsequently, an impulse will be transmitted primarily to the nucleus tractus solitarius (NTS), and then the chemoreceptor trigger zone (CTZ) in the brain. Receptors (neurokinin-1, 5-HT3, and dopamine-2) are present in the dorsal vagal complex, and bind to neurotransmitters (substance P, 5HT and dopamine, respectively). Efferent fibres project from the dorsal vagal complex to the final effecter of the emetic reflex in the brain stem (Naylor, 2002; Baker et al., 2005). Antineoplasic agents may also induce nausea and vomiting through interaction with the area postrema (AP) within the dorsal vagal complex. Other potential sources of efferent include a number of structures in the temporal lobe, such as the amygdala (Hesketh, 2008).

Figure 2-1: The main inputs into the vomiting centre that lead to vomiting



(Hesketh 2008, pp. 2485. Permission granted)

Most anti-emetic medications, such as NK1 receptor antagonists, that are able to prevent or control many types of emesis (induced by drugs, motion, vagal stimulation, etc.) work by blocking afferent inputs (cerebral, vestibular, area postrema, and gut) for nausea and vomiting that converge on the nucleus of the solitary tract (NTS) in the caudal hindbrain (Horn, 2008).

The sensory pathways for nausea and vomiting are well understood (e.g. vagal and vestibular inputs); however, the critical problem of defining the convergent neural circuitry that generates nausea and vomiting is still largely unexplained (Horn, 2008). This might one of the main reasons that make designing effective treatments to control nausea and vomiting complicated.

2.5. Incidence of chemotherapy-induced nausea and vomiting

The incidence of acute and delayed CINV varies, according to the emetogenicity of chemotherapeutic agents, as well as patient-related risk factors (Glaus et al., 2004). Table 2-1 shows recent studies investigating the incidence of CINV in cancer patients mainly receiving 5-HT3 receptor antagonists.

Emetogenicity of chemotherapeutic drugs is classified according to several schemes. Most schemes categorise agents according to intrinsic emetogenicity (proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis) as follows: high emetic risk (>90% incidence), moderate (30–90%), low (10–30%), and minimal (<10%) (Kris et al., 2006).

Table 2-1: Incidence of CINV with the current prophylactic antiemetic treatments						
Reference/country	**Research Methods/ Sample**	**CINV different phases (%)**				**Appraisal of the study**
		Acute phase		**Delayed phase**		
		Nausea (%)	**Vomiting(%)**	**Nausea (%)**	**Vomiting(%)**	
(Ihbe-Heffinger et al., 2004) Germany	Prospective, multi-centre (6 centres), 244 cancer patients who scheduled to receive HEC and MEC. Patients were in different chemotherapy cycles.	32.3	13.8	58.7	23.9	Heterogeneous patient populations. No information regarding the validity and reliability of nausea and vomiting measurement tools.
(Liau et al., 2005) Taiwan	Prospective, observational study – 2 centres/ 107 adult patients scheduled to receive HEC and MEC for the first time.	43 HEC * 55 MEC**	21 HEC 8 MEC	64 HEC 74 MEC	60 HEC 55 MEC	Risk of selection bias. Study enrolled predominantly female patients (3/4). Heterogeneous patient populations. Sample size and power calculations were irrelevant as they were based on treatment group differences.
(Valle et al., 2006) Mexico	Prospective, observational study , nine oncology centres, 73 cancer patients scheduled to receive chemotherapy for the first time. (57 received HEC, 16 received MEC)	57.9 HEC 31.3MEC	52.6 HEC 18.8 MEC	75.4 HEC 68.8 MEC	63.2 HEC 43.8 MEC	Risk of selection bias (differences in antiemetic prophylaxis and rescue anti-emetics at each centre. Lack of a systematic approach to the antiemetic treatments employed by each centre. Study enrolled predominantly female patients (92%).

Table 2-1: Incidence of CINV with the current prophylactic antiemetic treatments				
(Bloechl-Daum et al., 2006) European countries & US	Prospective, observational study- 14 centres (Denmark, France, Italy, Germany, UK and US). 322 cancer patients scheduled to receive HEC for the first time.	33.3HEC 11.9 HEC 36.6MEC 13.2MEC	60.3HCE 50.0 HEC 52.4MCE 27.9 MEC	Risk of selection bias (213 were female compare to 85 male; 67 (22.5%) patients received HEC; 232 patients (77.5%) received MEC; breast (49.3%) and lung (17.8%) cancers).
(Molassiotis et al., 2008) UK	Prospective ,observational Study (over four cycles of chemotherapy) 102 cancer patients scheduled to receive chemotherapy for the first time	59.9HEC 11.8HEC 41.2MEC 21.6MEC (in cycle 1)	58.8HCE 17.6HCE 56.9MCE 19.6MEC (in cycle 1)	Risk of selection bias (female: 58.8%; breast cancer: 29.4%; moderate emetic potential: 50%).

*HEC= Highly Emetogenic Chemotherapy,

**MEC= Moderately Emetogenic Chemotherapy

The current data in the literature shows that vomiting is relatively well controlled (with the exception of MEC, where antiemetic management needs improvement). However, nausea, both acute and delayed, is a major problem in more than half of the patients receiving HEC or MEC (Molassiotis et al., 2008).

2.6. Factors associated with chemotherapy-induced nausea and vomiting

The identification of factors which increase a patient's risk of developing CINV is beneficial for use in both clinical practice and research. Patients most at risk of developing CINV can be identified before chemotherapy administration and early interventions are employed. Such factors can also be used to stratify patients in clinical trials in order to balance the treatment arms, and such factors can be controlled for in *post hoc* analyses. A large number of factors which contribute to the development of nausea and vomiting have been identified. These factors can be categorised into two major groups: treatment-related risk factors and patient-related risk factors (Figure 2-3) (Hesketh, 2008; Jakobsen & Herrstedt, 2009).

2.6.1. Treatment-related factors

The emetogenic potential of the chemotherapeutic agents used is the main risk factor for the degree of CINV. Table 2-2 shows the emetogenic risk of some current chemotherapeutic agents (the figures in parentheses represent the percentage of patients having emetic episode(s) when no prophylactic antiemetic protection is provided).

Table 2-2: Emetogenic risk of chemotherapeutic agents

Intravenous (IV)		per oral (PO)	
High (emesis risk, >90% without anti-emetics)			
Carmustine, BCNU	Lomustine	Hexamethylmelamine	
Mechlorethamine	Cisplatin	Procarbazine	
Streptozotocin	Dactinomycin		
Dacarbazine, DTIC ,	Actinomycin D		
Cyclophosphamide (>1,500 mg/m²)	Pentostatin		
Moderate (emesis risk, 30%–90% without anti-emetics)			
Altretamine	Ifosfamide	Cyclophosphamide	
Carboplatin	Irinotecan	Temozolomide	
Melphalan	Oxaliplatin	Etoposide	
Idarubicin	Cytarabine (>1 g/m²)	Vinorelbine	
Daunorubicin	Doxorubicin	Imatinib	
Temozolomide	Epirubicin		
Treosulfan			
Mitoxantrone (>12mg/m²)			
Cyclophosphamide (<1,500 mg/m²)	Trabectedin		
Low (emesis risk, 10%–30% without anti-emetics)			
Asparaginase	Paclitaxel	Capecitabine	
Mitoxantrone (<12 mg/m²)	Cetuximab	Fludarabine	
Bortezomib	Trastuzumab	Tegafur Uracil	
Pegasparaginase	Gemcitabine	Etoposide	
Cytarabine (<1g/m²)	Pemetrexed	Sunitinib	
Docetaxel	Teniposide	Everolimus	
Etoposide	Thiopeta	Lapatinib	
5-Fluorouracil	Topotecan	Lenalidomide	
Methotrexate (>100 mg/m²)		Thalidomide	
Minimal (emesis risk, <10% without anti-emetics)			
Bleomycin	Busulfan	Chlorambucil	Melphalan
Alfa-, Beta- interferon	Bevacizumab	Erlotinib	Methotrexate
Mercaptopurine	Chlorambucil	Gefitinib	Sorafenib
Methotrexate (<100 mg/m²)	Cladribine	Hydroxyurea	Sunitinib
Thioguanine	Vinblastine	L-Phenylalanine mustard	
Cytarabine (<100 mg/m²)	Fludarabine	6-Thioguanine	
Vincristine	Vinorelbine		

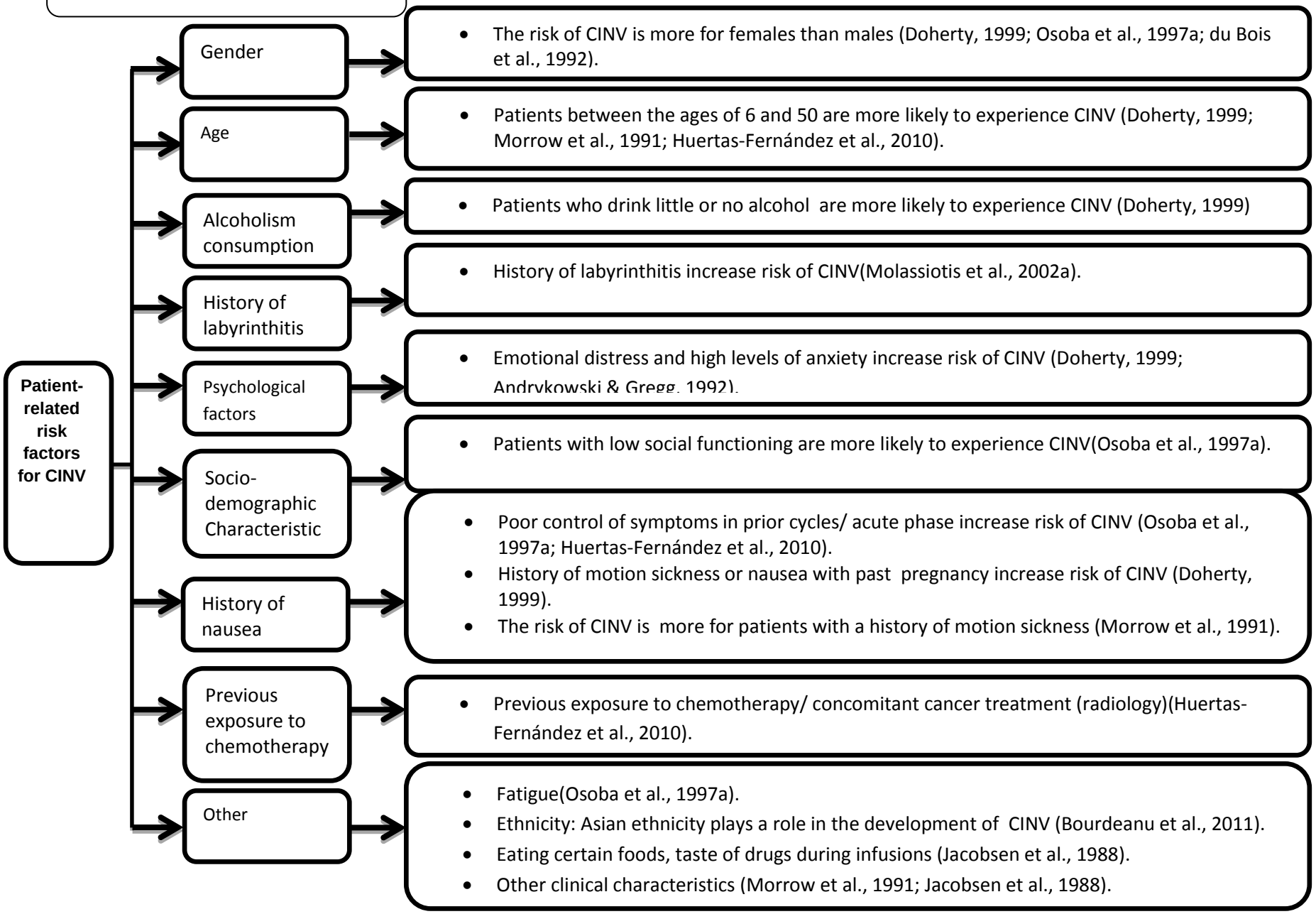
Adapted from:(Jordan et al., 2007); (Herrstedt and Roila, 2009); (Roila et al., 2010)

Combined chemotherapy regimens also affect the nausea and vomiting experienced. Consequently, combining different types of chemotherapy agents increases the emetic incidence, and perhaps the duration of nausea and vomiting. Generally, compared with all other predictive factors, the intrinsic emetogenicity of an administered chemotherapeutic agent is considered the predominant factor in developing nausea and vomiting after chemotherapy (Hesketh, 2008).

2.6.2. Patient-related factors

Even when individual patients receive a similar chemotherapy regimen, the degree of nausea and vomiting they experience differs. It has been found that some characteristics influence the risk of developing CINV (Figure 2-2) (ASHP, 1999; Jakobsen & Herrstedt, 2009).

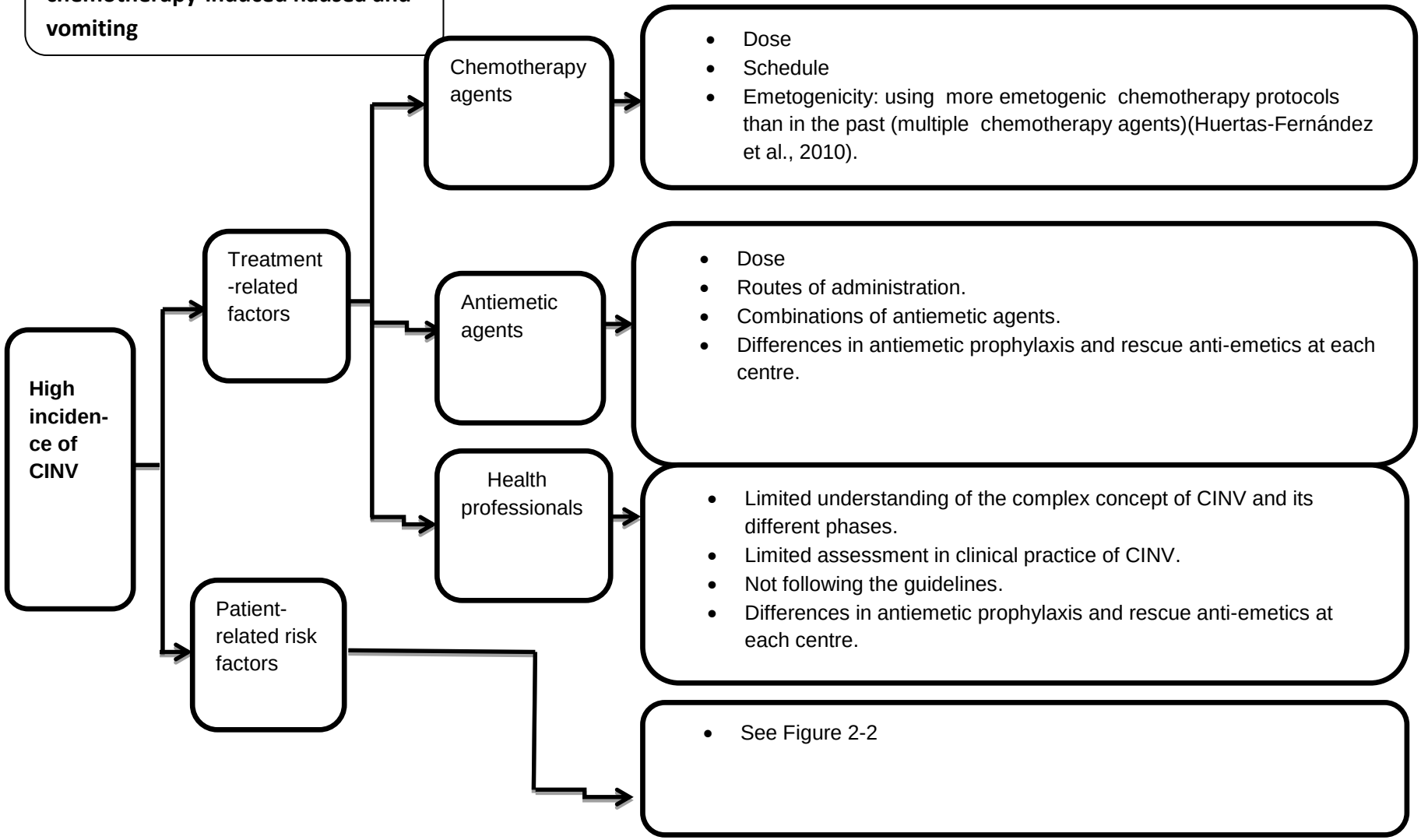
Figure 2-2: Patient-related risk factors for CINV



It has been shown that females have more severe episodes and longer durations of nausea and vomiting than males; however, no explanation for this has been found. Generally, women of menstrual age experience more severe nausea and vomiting (du Bois et al., 1992; Levin et al., 2009). However, one study (Roscoe et al., 2010) shows that although the average nausea for breast cancer patients receiving doxorubicin was considerably greater than for other patients receiving doxorubicin or cisplatin, there is no evidence that gender is a significant predictor of nausea in patients with gender-neutral cancers. Despite this, Molassiotis et al (2008) found that female gender and younger age were associated with more acute and/or delayed nausea and/or vomiting over the most of the four cycles of chemotherapy that they observed in their study. It is also found that previous life events of nausea and vomiting with specific diseases such as motion sickness, severe vomiting with previous chemotherapy, history of labyrinthitis and hyper emesis gravidarum are associated with increased post-chemotherapy nausea and vomiting. In addition, psychological aspects such as anxiety and the presence of certain socio-demographic characteristics are contributory factors to the development of CINV (Molassiotis et al., 2002a; Foubert & Vaessen, 2005).

Furthermore, in previous studies, several other risk factors, such as susceptibility to eating certain foods, taste of drugs during infusions, feelings of generalised weakness following treatment, feeling warm or hot all over after treatment, sweating after chemotherapy, and desire for control and choice of anti-emetics, are implicated as minor risk factors (Shelke et al., 2008; Jacobsen et al., 1988; Morrow et al., 1991).

Figure 2-3: Factors associated with chemotherapy-induced nausea and vomiting

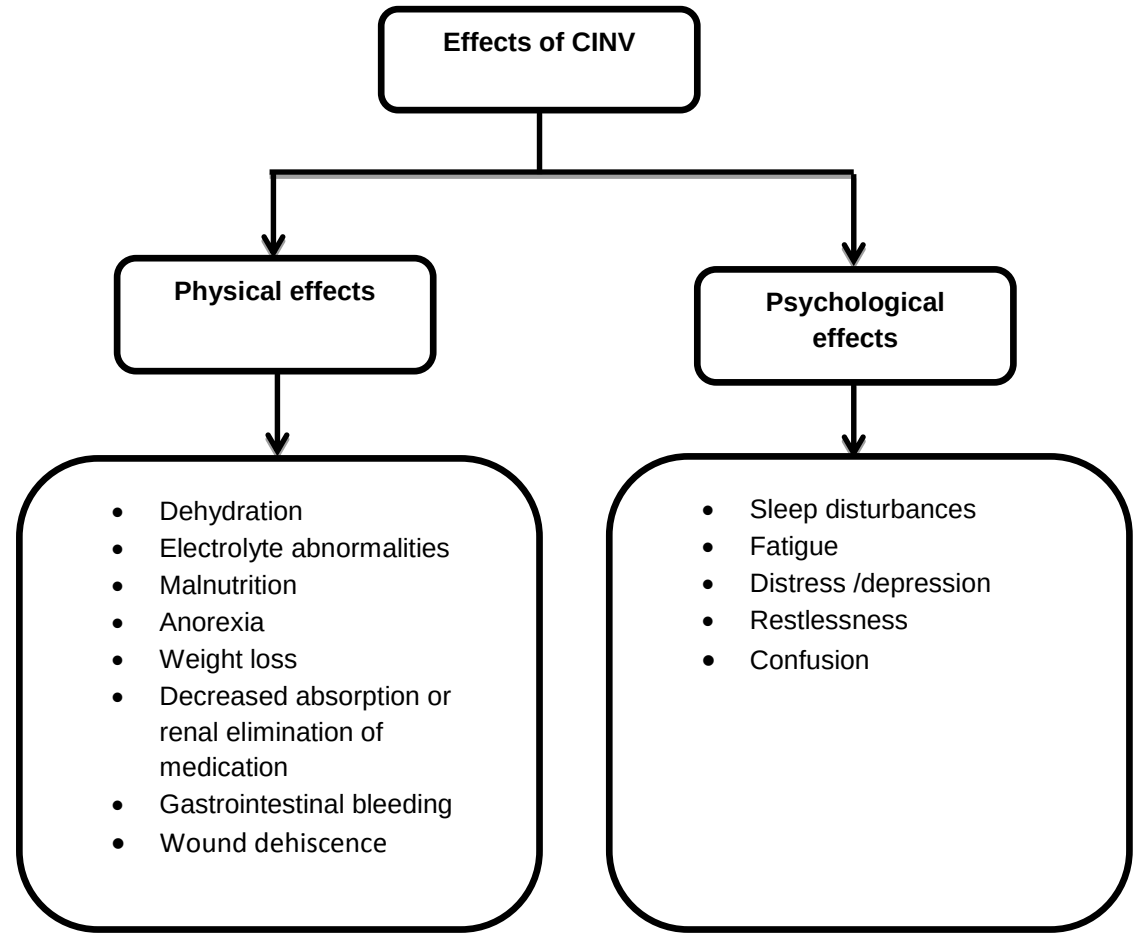


Although nausea- and vomiting-associated factors have been recognised, this problem is still considered intolerable for many patients. As a result, complications could occur which can affect the patients' QoL. The consequences of CINV are explored below.

2.7. Consequences of CINV

Uncontrolled or poorly controlled CINV can adversely affect the patients' overall health and wellbeing in different dimensions: physical, psychological and emotional (Figure 2-4) (Wiser & Berger, 2005; Schwartzberg, 2007).

Figure 2-4: Physical, emotional and psychological effects of nausea and vomiting



Adapted from: (Lohr, 2008); (Bloechl-Daum et al., 2006)

It has been revealed that dyspnoea and constipation are associated with CINV, although the reasons for these symptoms are not clear. Anorexia (loss of appetite) may also develop when patients feel no desire to eat anything as a consequence of nausea and vomiting (Rhodes & McDaniel, 2001; Wiser & Berger, 2005).

In addition to metabolic imbalances, CINV is associated with depression, insomnia and fatigue. The reasons for this are unclear, but one component of this phenomenon is likely to be the psychological stress of constant nausea and vomiting (Wiser & Berger, 2005; Schwartzberg, 2007).

These adverse effects can negatively impact patients' QoL, performance status, and daily functioning. Poor compliance with scheduled chemotherapy due to nausea and vomiting can result in treatment interruptions or discontinuation, leading to poor outcomes (Lindley et al., 1992; Lohr, 2008).

2.7.1. Impact of chemotherapy-induced nausea and vomiting on patients' quality of life

Health-related QoL (HR-QoL) has emerged as an important parameter for evaluating the quality and outcome of health care (Moons et al., 2006). However there is no consensus on the definition and measurement of QoL, and it is often used as a generic label to describe a mixture of physical and psychosocial variables (Moons et al., 2006). HR-QoL is a multidimensional construct; however, most agree that it consists of a variety of domains of general health, physical symptoms, and emotional and social well-being (Moons, 2004). HR-QoL measures and determines disabilities related to specific diseases and effectiveness of treatment. CINV adversely affects HR- QoL; therefore, HR-QoL is considered as an outcome in intervention(s) to prevent and/or control CINV in clinical research (Enzo & Fausto, 2003; Moons, 2004).

Among cancer patients, the same level of nausea and/or vomiting may vary in the degree to which it affects patients' HR-QoL. Some of the studies regarding the impact of CINV on HR-QoL are shown in Table 2-3 (Lindley et al., 1992; Osoba et al., 1997b; Rusthoven et al., 1998).

Table2-3: The impact of nausea and vomiting on HR-QoL							
Author (s)/ country	Research Methods/ Participants	Cancer (type)	Chemother-apy(emetogenicity	HRQL assessment (times)	Finding	Comments#	**Levels of Evidence ##**
(Lindley et al., 1992) USA	Cross-sectional survey /122 cancer patients scheduled to receive bolus combination chemotherapy regimens.	Various	Various	FLIC* and FLIE** (before and after 3 days), plus a patient maintained diary	FLIC: decreased significantly from 121 before to 110 three days after chemotherapy ($p < 0.01$). FLIE: decreased significantly from 118 immediately before chemotherapy treatment to 101 three days after treatment ($p < 0.001$). Score decrease for patients who experienced vomiting was from115 to 85. Lower scores indicating a more negative impact on quality of life.	Emesis was defined as one or more episodes of vomiting and/or a nausea-severity rating of 2.0 or more on a 10 cm VAS ranging from 1 (no nausea) to 10 (nausea as bad as could be). The period of study (3 days) was too short to detect the impact of delayed CINV appropriately.	**+**
(Osoba et al., 1997a) Canada	Prospective study/ 832 chemotherapy naive patients	Various	Moderately and highly	EORTC QLQ-C30 *** (before chemotherapy (baseline) and day 8 and 2–4 weeks after chemotherapy)	The group with both nausea and vomiting showed statistically significantly worse physical, cognitive and social functioning, global quality of life, fatigue, anorexia, insomnia and dyspnoea as compared to the group with neither nausea nor vomiting ($0.0001<P<0.05$).	Risk of selection bias at HR-QoL evaluated before 2nd cycle chemotherapy (only 70% participants completed the questionnaires)	**+**

Table2-3: The impact of nausea and vomiting on HR-QoL							
(Rusthoven et al., 1998) Canada	Prospective, observational study/119 patients	Various	Moderately	EORTC QLQ-C30 (before and after 2 and 6 days	N&V associated with a decrease in HR-QoL from pre chemotherapy levels on six functioning and five symptom scales at day 2, and on four functioning and four symptom scales on day 6.	As the QLQ-C30 questions were modified for this study, the validity and reliability of the instrument might be affected.	+
(Bloechl-Daum et al., 2006) European countries & US	Prospective, observational study/ 298 patients (chemotherapy naı¨ve)	Various	(67 received HEC, 231 received MEC)	FLIE (before chemotherapy (baseline) and day 6)	HEC patients reported significantly lower mean FLIE total score than MEC patients (95.5 v 107.8 respectively; P =.0049).Among all patients the nausea score was significantly lower than the vomiting score (50.0 and 55.3, respectively; P= .0097). Lower scores indicating a more negative impact on quality of life.	Nausea had a stronger negative impact on quality of life than vomiting (on contrary of previous studies). Only 85 were male compare to 213 female	++

* The Functional Living Index-Cancer: It consists of 22 questions (Scales & Rubenfeld) which represent five factors related to a cancer patient's quality of life (physical well-being and ability, emotional state, sociability, family situation and nausea).
** Functional Living Index-Emesis: It is a 7-point Likert scale of 22 items, addressing the impact of CINV on physical activities, social and emotional function, and ability to enjoy meals (it focus on the impact of CINV on some aspects of daily functioning).
*** EORTC QLQ-C30: It is a short core measure for general use with cancer patients. It is designed to measure physical, psychological, and social functioning of patients and contains 30 items.
# The Cochrane Consumers and Communication Review Group. Study Quality Guide (Ryan et al., 2007) was used to assess the quality of the studies.
The GRADE approach, adopted by The Cochrane Collaboration was used to assess the levels of the studies that specify four levels of quality (high [++++], moderate [+++], low [++] and very low [+]).

Lindley et al. (1992) acknowledge that several variables affect QoL; however, they show that nausea and vomiting are among the major factors in decreasing QoL. Furthermore, the Functional Living Index-Emesis (FLIE) tool, which exclusively measures the level to which QoL changes could be attributed to nausea and vomiting, illustrated the relationship between the incidence and severity of nausea and vomiting and the reduction in QoL (Lindley et al., 1992). However, it is argued that the use of the FLIE and its interpretation might be limited by its use of an aggregate score, its strong focus on physical functioning, and the absence of some relevant domains of QoL in the instrument (Rusthoven et al., 1998). Although the result of Lindley et al.'s study indicates that QoL was no different following chemotherapy in the group who did not report vomiting, this finding suggests that the instruments [the FLIE instrument was based on Functional Living Index-Cancer (FLIC)] used for the study might not be appropriate. In fact, although FLIE is a validated nausea- and-vomiting specific tool, it focuses on the impact of CINV on only some aspects of daily functioning, and not on all dimensions of QoL.

Osoba et al. (1997) also shown that post-chemotherapy nausea and vomiting adversely affects several quality-of-life domains. However, their results indicated that 2–4 weeks after chemotherapy, all QoL scores returned to their baseline levels, or even better than baseline. It should be noted that in this study 94.8% of the patients completed the questionnaire one week after the baseline (on day 8). However, only about 70% of the patients filled out the questionnaire on the day of second cycle of chemotherapy (2–4 weeks after the first cycle of chemotherapy). This might have increased the possibility of selection bias at HR-QoL evaluated before the second cycle chemotherapy (Enzo & Fausto, 2003). It is obvious that the proportion of the respondents who were followed up was not appropriate, and this might have negatively affected the quality of the study and its results.

Rusthoven (1998), by conducting a comparison of mean scores between the unmodified EORTC QLQC-30 and the nausea and vomiting versions, showed that the HR-QoL rating attributed to nausea and vomiting accounted for much (though not all) of the deterioration in HR-QoL scores in patients who experienced these symptoms. Nevertheless, some of the decrease in health-related QoL might be related to other factors which were unrecognised (Rusthoven et al., 1998).

In summary, although the results of the above studies are not robust, they display that CINV adversely affects HR-QoL. Nausea and vomiting affect cancer patients in different ways: physically, psychologically and emotionally. This consequently affects patients' overall health, well-being and HR-QoL. Nausea has a stronger negative impact on QoL than vomiting. Therefore, preventing, controlling, and minimising CINV, particularly chemotherapy-related nausea, can help to maintain patients' HR-QoL during chemotherapy treatment. Based on the need, as established by this review, for interventions to prevent and control nausea and vomiting in patients with cancer undergoing chemotherapy, the next section will explore the current pharmacological treatments for CINV. Published reports of non-pharmacological interventions for the prevention of CINV will then be reviewed.

2.8. Pharmacological management of nausea and vomiting

Pharmacological management of CINV is the most commonly used treatment to control nausea and vomiting. The basis for antiemetic treatment is the neurochemical control of vomiting. While the mechanism is not fully understood, peripheral neuroreceptors and the CTZ are recognised to have receptors for serotonin, histamine (H1 and H2), dopamine, acetylcholine, opioids, and many other endogenous neurotransmitters (Miller & Leslie, 1994). Many anti-emetics act by competitively blocking receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the CTZ, and possibly at the vomiting centre. Table 2-4 lists the primary classes and mechanisms of action of anti-emetics according to the targeted receptors, as well as the specific agents in each class, their side effects and indications for use.

Table 2-4: Major antiemetic agents and their characteristics				
Drug Class	**Specific agents**	**Mechanism of Action**	**Indication**	**Adverse Effects**
Serotonin (5-HT3) antagonists	Dolasetron, Ondansetron Granisetron, Azasetron Ramosetron, Tropisetron Palonosetron	Blocks serotonin (5-HT3), gut receptors to prevent, peripheral stimulation of the, CTZ by afferent neurons	Acute nausea Delayed nausea Acute vomiting Delayed vomiting	Headache, diarrhoea constipation, hypertension or hypotension, dizziness.
Dopamine receptor antagonists	Phenothiazines (prochlorperazine or promethazine) Butyrophenones Substituted benzamides	Minimize the effect of dopamine at the dopamine (D2) receptor in the CTZ, thereby limiting emetic input to the medulla VC	Acute nausea /Delayed nausea	Extrapyramidal syndromes sedation, akathisia, dizziness, postural hypotension, tachycardia, agranulocytosis.
Dopamine/ 5-HT3 receptor antagonists	Metoclopramide	Dopamine (D2) receptor antagonist and a 5-HT3 receptor antagonist at high doses.	Acute nausea /Delayed vomiting	Extrapyramidal syndromes sedation, akathisia, dizziness, postural hypotension, tachycardia, agranulocytosis.
Substance P antagonists (Neurokinin -1 receptor antagonists)	Aprepitant, Fosaprepitant Casopitant, Vofopitant CP-122 721 CJ-11 794	Inhibit the action of neurokinin 1 receptors in the small bowel, vagus nerve, and CTZ. Thisaction decreases afferent visceral and CTZ stimulation of the VC	Acute nausea Delayed nausea Acute vomiting Delayed vomiting	Diarrhoea or constipation, loss of appetite, dizziness, headache, insomnia.
Corticosteroids	Dexamethasone (Decadron) Methylprednisolone sodium succinate	Unknown; may modify capillary permeability in CTZ, decrease gut inflammation, reduced sensitivity of the 5-HT3 receptor, or stabilize intracellular membranes	Acute nausea Delayed nausea Acute vomiting Delayed vomiting	Insomnia, agitation, Immunosuppression, Proximal muscle weakness (especially involving the thighs and upper arms) psychosis, GI irritation, hyperglycaemia, hypokalaemia, perineal burning with rapid infusion, increased appetite, Aseptic necrosis of the long bone, Cataract formation, Hyperglycemia and exacerbation of pre-existing diabetes or escalation of subclinical diabetes to clinical pathology, Adrenal suppression with hypocortisolism, etc.

2.8.1. Dopamine and dopamine receptors

The main area of activity of dopamine antagonists is the CTZ, where dopamine receptors are known to exist (Navari, 2009). D2-receptor antagonists can be divided into phenothiazines (chlorpromazine, prochlorperazine and metopimazine), butyrophenones (haloperidol and the derivative domperidone) and substituted benzamides (metoclopramide and alizapride). D2-receptor antagonists are effective when administered in conventional doses; however, they can cause considerable adverse effects, such as acute dystonic reactions, akathisia, and sedation (Herrstedt & Dombernowsky, 2007; Dewan et al., 2010).

2.8.2. Corticosteroids

The mechanism of action of the antiemetic effects of corticosteroids is unknown. However, it is suggested that dexamethasone, which is the most commonly used corticosteroid antiemetic, takes action by reducing inflammatory effects on intestinal mucosa, blocking 5-HT3 release, and decreasing the permeability of the blood-brain barrier (Dewan et al., 2010). In a meta-analysis, it was concluded that dexamethasone considerably reduces acute and delayed nausea and vomiting (Herrstedt & Dombernowsky, 2007; Herrstedt, 2008; Dewan et al., 2010). Nevertheless, they are sometimes used as single agents against mildly to moderately emetogenic chemotherapy. It is notable that in combination with high-dose metoclopramide, corticosteroids may alleviate adverse effects such as the frequency of diarrheal episodes (Winokur et al., 1981).

Dexamethasone is commonly used orally to treat delayed nausea and vomiting. However, long-term corticosteroid use is unsuitable, and may cause extensive side effects (Table 3-1).

2.8.3. Serotonin (5-HT3) antagonists

5-HT3 antagonists are one of the most efficient antiemetic drugs, and their use is widespread (Stieler et al., 2003). The introduction of ondansetron (the first-discovered compound in this group) into routine oncology practice in 1991 was one of the most important advances in supportive care (Wiser & Berger, 2005). The effectiveness of these agents is due to their ability to block serotonin receptors in the brain stem (CTZ) and inhibit serotonin release from

enterochromaffin cells in the GI tract for approximately 24 hours (DiVall & Cersosimo, 2007). Serotonin receptors, specifically 5-HT3 receptors, exist in the central nervous system (CNS) and in the GI tract. The 5-HT3 receptor antagonists act through both the CNS and the GI tract via the vagus and splanchnic nerves (Navari, 2009). The serotonin antagonists have a response rate of 60–80% when used as single antiemetic drug; nevertheless, this rate is higher when these agents are used with corticosteroids. These drugs are more effective in preventing vomiting than in preventing nausea (Rubenstein et al., 2006; Lohr, 2008). The first-generation 5-HT3 receptor antagonists have not been as effective against delayed nausea and vomiting as they are against acute CINV; however, some studies suggest second-generation 5-HT3 receptor antagonists (Palonosetron) may have some efficacy in controlling delayed CINV (Navari, 2009).

Some studies have shown that ondansetron produces an antiemetic response that equals or is superior to high doses of metoclopramide; however, ondansetron has a superior toxicity profile compared with dopaminergic antagonist agents (De Mulder et al., 1990). Ondansetron may cause some adverse effects, such as headache, constipation or diarrhoea, fatigue, and dry mouth.

Palonosetron has antiemetic activity at both central and gastrointestinal sites. In comparison to the first generation of 5-HT_3 receptor antagonists, it has a higher binding affinity to the 5-HT_3 receptors, a higher potency, a considerably longer half-life (approximately 40 hours, which is four to five times longer than that of dolasetron, granisetron, or ondansetron), and a better safety profile (Eisenberg et al., 2004). However, despite the use of both first-generation and second-generation 5-HT_3 receptor antagonists, acute CINV, and especially delayed post-chemotherapy nausea and vomiting, is not appropriately controlled (Hickok et al., 2003).

2.8.4. Neurokinin 1 (NK 1) receptor antagonists

Substance P induces vomiting and binds to neurokinin-1 (NK-1) receptors in the abdominal vagus and the area postrema. It is documented that NK-1 receptor antagonists may exert their main antiemetic action by depressing the neural activity of the NTS neurons, with some possible antiemetic effects from peripheral

sites through a blockade of the NK-1 receptors located on the vagal terminals in the gut (Navari, 2009).

The first NK-1 inhibitor agent, aprepitant, was introduced in 2003. Its antiemetic action occurs through inhibition of the action of substance P in the emetic pathways in both the central (area postrema) and peripheral (GI tract) nervous systems (Sanger & Andrews, 2006). The effectiveness of aprepitant in the prevention of CINV was verified in two trials with cisplatin-based chemotherapy (Lohr, 2008). Previous studies have shown that aprepitant had an effect similar to that of ondansetron on cisplatin-induced acute nausea and vomiting, although it was superior in the control of delayed nausea and vomiting (Kris et al., 1997). It is notable that the role of aprepitant in moderately emetogenic chemotherapy remains unclear (Grote et al., 2006).

2.8.5. Cannabinoids

Cannabinoid drugs can act as antiemetic agents through their effect at cannabinoid receptors in multiple parts of the CNS involved in the emetic response. Cannabinoid receptors also help to control the effect of serotonin, dopamine, and other neurotransmitters in these pathways. Cannabinoids may also have an effect at the enterochromaffin cells in the GI tract. Dronabinol and nabilone are two medications in this group which have been approved for CINV (Lohr, 2008). Considering their side effects such as dysphoria, euphoria, sedation, depression and hallucinations, which have been confirmed in previous studies, some patients even preferred nausea to the side effects (Stieler et al., 2003).

2.9. The effectiveness of pharmacological management of CINV

Since the mid-1970s, pharmacological management of CINV with antiemetic medications has progressed considerably (Ruhlmann & Herrstedt, 2010). Several new classes of anti-emetics have been identified with modest toxicity and a lack of extrapyramidal side effects, unlike the older anti-emetics. Since the advent of serotonin (5-HT3) and NK-1 receptor antagonists, major advances have been achieved in the treatment of CINV (Balu et al., 2011; Bao, 2009).

Although the incorporation of new anti-emetics has considerably altered the prevention of nausea and vomiting, in many cases it is still an unsolved problem.

Several recent trials have demonstrated that with the synergistic effect of the association of current anti-emetics (5-HT3 antagonists and corticosteroids), around 70–90% complete protection is achieved for the acute phase of nausea and vomiting induced by chemotherapy; however, the results for the delayed phase are considerably worse, at around 50% (Huertas-Fernández et al., 2010; Hesketh, 2008; Herrstedt & Dombernowsky, 2007). According to the current antiemetic guidelines, it is recommended that a three-drug combination of a 5-HT3–receptor antagonist, dexamethasone, and aprepitant be used for patients undergoing highly emetogenic chemotherapy. For moderately emetogenic chemotherapy, a two-drug combination with a 5-HT3-receptor antagonist and dexamethasone is recommended. For low emetogenic chemotherapy, dexamethasone with or without dopaminergic antagonists is recommended (Hesketh, 2008).

Another area of concern in the use of anti-emetics is the risk of drug–drug interactions. Interactions between anti-emetics and antineoplastic agents have not yet been adequately investigated (Huertas-Fernández et al., 2010). Moreover, treatment with one or more antineoplastic agents implies concomitant treatment with other supportive care medications such as analgesics, neuroleptic medications, antidepressants, anticoagulants, laxatives, corticosteroids, and antibiotics. In addition, considering the median age of cancer patients, which is 60-plus, the risk of other chronic disorders such as cardiovascular, gastrointestinal and rheumatologic diseases increase and call for additional medication. These patients are also at high risk of age-related problems which may lead to a decrease in their hepatic and renal function, and the excretion of many medications. Therefore, poly-pharmacy in the older patient raises the risk of drug interactions, and also increases the potential for toxicity (Huertas-Fernández et al., 2010; Blower et al., 2005). In addition, anti-emetics are ineffective in some patients, without any known reason (Herrstedt & Dombernowsky, 2007).

Therefore, not only is the development of new anti-emetics with other mechanisms of action awaited with interest, but non-pharmacological approaches are also being considered to develop the activity and reduce the adverse effects of chemotherapy. The next section will focus on the use of systematic reviews to

detail the results of non-pharmacological interventions (in addition to anti-emetics) which have previously been trialled for the prevention and treatment of CINV.

2.10. Non-pharmacological interventions for the control and management of CINV

Although pharmacological treatment is common for CINV, this modality is not effective for all patients in all circumstances. This unsatisfactory outcome has led some patients and health-care professionals to look for other solutions. A wide range of non-pharmacological interventions, in addition to anti-emetics, have been examined to ameliorate CINV. These include psychosocial interventions, and several types of CAM.

2.10.1. Complementary and alternative therapies

The National Centre for Complementary and Alternative Medicine (NCCAM) defines CAM as “a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine” (NCCAM, 2012). The National Cancer Institute at the National Institute of Health (NCINIH) defines CAM as any medical system, practice, or product that is not considered as standard care. Standard medical care is defined as care that is based on scientific evidence. For instance, standard care for cancer includes chemotherapy, radiation, biological therapy, and surgery (NCINIH, 2012). According to the NCINIH, **complementary medicine** is used along with standard medical treatments. For instance, acupuncture can ameliorate the side effects of cancer treatments such as nausea-related chemotherapy. However, **alternative medicine** is used in place of standard medical treatments. For example, a special diet to treat cancer as a replacement for standard treatments which a cancer specialist (oncologist) proposes. **Integrative medicine** is an approach to care that involves the patient's mind, body, and spirit. It combines standard medicine with CAM practices. For instance, some cancer patients learn to use relaxation as a way to reduce stress during chemotherapy (NCINIH, 2012).

CAM practices are classified by NCCAM into three broad categories:

- **Natural products (biologically based practices)**: Uses natural products. This includes dietary supplements and herbal products. Vitamins, herbs/herbal medicines (also known as botanicals), minerals, foods and special diets all fall into this category.

- **Mind and body medicines**: These are based on interactions among the brain, mind, body, and behaviour, with the intent to use the mind to affect physical functioning and promote health. Some examples are: music therapy, guided imagery, hypnotherapy, acupuncture, and progressive muscle relaxation.

- **Manipulative and body-based practices:** These are mainly based on the structures and systems of the body, including the bones and joints, soft tissues, and circulatory and lymphatic systems working with one or more parts of the body. For example: massage therapy (manipulation of tissues), chiropractic methods (manipulation of the joints and skeletal system), and reflexology (using pressure points in the hands or feet to affect other parts of the body).

NCINIH suggests one more category as:

- **Alternative medical systems**: These are healing systems and beliefs that have evolved over time in different cultures and parts of the world. For example: acupuncture, traditional Chinese medicine, homeopathy, and naturopathic medicine.

It is notable that some types of CAM, such as biologically based practices, which are also called pharmacologic and biologic treatments, use certain prescription drugs in a way not originally intended. This includes using vaccines, hormones, natural products (botanicals), herbs and other biologic treatments on people with cancer (NCINIH, 2012).

This study focuses only on non-pharmacological types of CAM (mind and body medicine), as music (or audio programme) interventions are categorised to mind and body medicine.

In addition, the boundaries within CAM and between CAM domains are blurred and constantly shifting (Smith et al., 2011); therefore, these categories are not formally defined, and some practices may fit into more than one category (NCCAM, 2012). For instance, acupuncture can fall into three categories: mind-body medicine, manipulative and body-based practices, and alternative medical systems.

2.10.2. Use of CAM by cancer patients

There has been a growing body of literature that demonstrates an increasing tendency in the cancer population to turn to use CAM alongside standard cancer treatments (Schiff & Ben-Arye, 2011; Harrington et al., 2012). It has been suggested that most consumers commence CAM during standard cancer treatments, and therefore tend to be complementary rather than alternative users (Beatty et al., 2012).

While it is known that cancer patients report using more CAM than the general population, the prevalence estimates for CAM use vary from 7% to 91% in different studies (Collinge et al., 2012; Beatty et al., 2012; Ernst & Cassileth, 1998). Visser et al. (2012) indicated that cancer patients are confronted with a number of emotional, social, and spiritual problems (Visser et al., 2011); therefore, they are more likely to turn to the use of CAM to raise their QoL. Moreover, it has been documented that the main reasons for CAM use include the belief that using CAM may boost the immune system, relieve disease symptoms and side effects of cancer treatment, redress emotional imbalances resulting from diagnosis and treatment, and/or enhance the efficacy of standard cancer treatments (Harrington et al., 2012; Smith et al., 2011).

CAM use during cancer treatment is a polarising and contentious issue for several reasons, including: (I) the potential for drug interactions with standard treatments, (II) the fact that patients may not always be aware of the potential risks of use, and (III) the lack of empirical evidence supporting the efficacy of many CAM therapies (Beatty et al., 2012). This therefore presents a challenge, and consequently a need for methodologically rigorous research on the efficacy of CAM therapies, as well as improved communication between health care professionals and patients about CAM use (Blaes et al., 2011; Beatty et al., 2012).

Several CAM therapies have been evaluated for controlling and managing CINV (Ezzo et al., 2005; Richardson et al., 2007; Molassiotis et al., 2007b). Recent studies suggest that CAM may have a role in cancer-supportive care. Therefore, the literature has been reviewed to assess the potential role of non-pharmacological types of CAM (mind and body medicine) on CINV.

Chapter Three: Literature Review

3.1. Introduction

This chapter is systematic reviews of studies which are relating to non-pharmacological interventions (mind-body medicine) for the control and management of CINV. Methodological quality and outcomes of the studies are reviewed, demonstrating areas of promise and those requiring additional research. Limitations of current interventions are also discussed and conclusions are summarised following the review of the literature.

3.2. Literature review research question

A review of the literature was under taken to answer the question:

“Are non-pharmacological CAM interventions (mind-body medicines) effective in controlling nausea and vomiting in cancer patients receiving chemotherapy?”

3.3. Search strategy

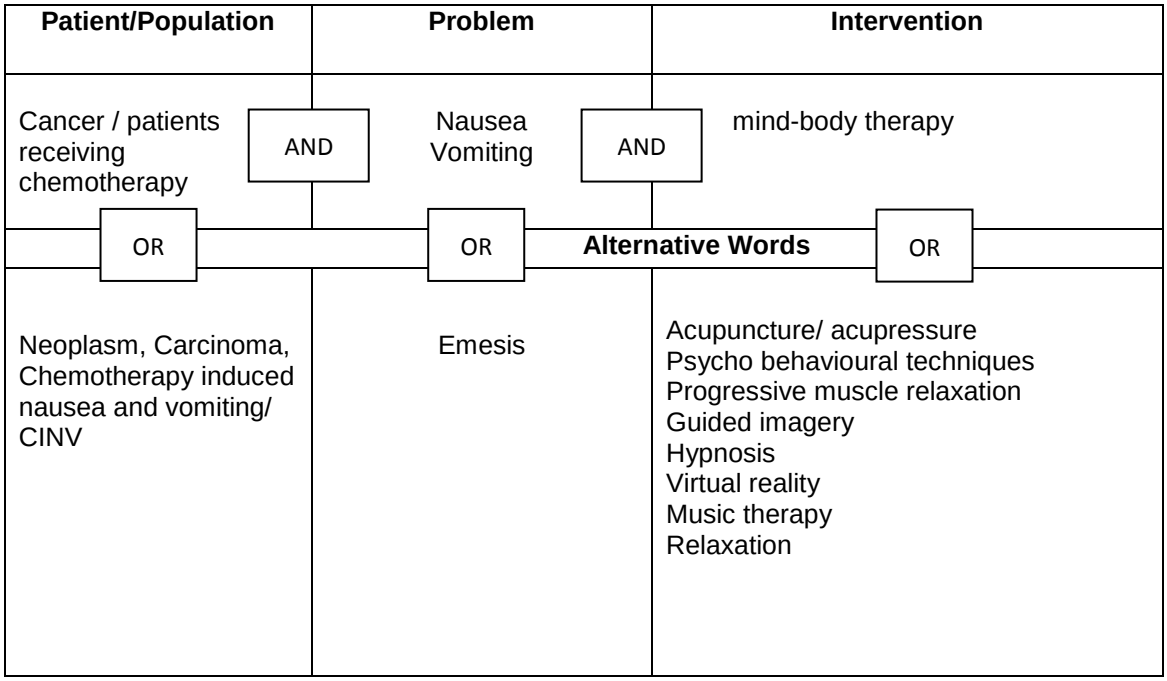
A systematic literature search was conducted (considering PRISMA guidelines) to identify studies relating to non-pharmacological CAM interventions for the control and management of CINV. The databases searched were: Cochrane Database of Systematic Reviews (CDSR); Science Direct; AMED (Allied and Complementary Medicine); EMBASE; Pubmed/Medline; and PsycINFO. In addition, Google Scholar was used to search for grey literature posted on websites.

No date limitations were used. The initial search occurred in 2009, and this influenced the design and conduct of the study; the search was then updated in January 2013. The search was supplemented by reviewing the reference lists of available studies. It included all papers published in English, or with English abstracts, if in other languages. The mind-body medicines interventions were included in this review if at least three studies on the management of post-chemotherapy nausea and vomiting were found. This cut-off point was selected to ensure that there were a minimum number of clinical trials focusing on the given symptom(s). Unpublished studies and abstracts were also excluded.

A search strategy was developed by considering the PICO (Patient/population and/or problem, Intervention, Comparison and Outcome) categories (Figure 3-1). The question was broken down into its components: population (cancer patients

receiving chemotherapy); intervention (acupuncture/acupressure, progressive muscle relaxation, guided imagery, hypnosis, virtual reality, and music therapy); and outcome (a measurement of the amount of nausea and/or vomiting experienced). The search strategy was run using medical subject heading terms and free text searching.

Figure 3-1: Search strategy



The inclusion criteria for considering studies for the review were:

1. Types of studies: studies using a comparison to evaluate the intervention's effectiveness in preventing and controlling acute and/or delayed nausea and/or vomiting. Studies which considered prophylactic intervention or treatment in response to post-chemotherapy nausea and vomiting.

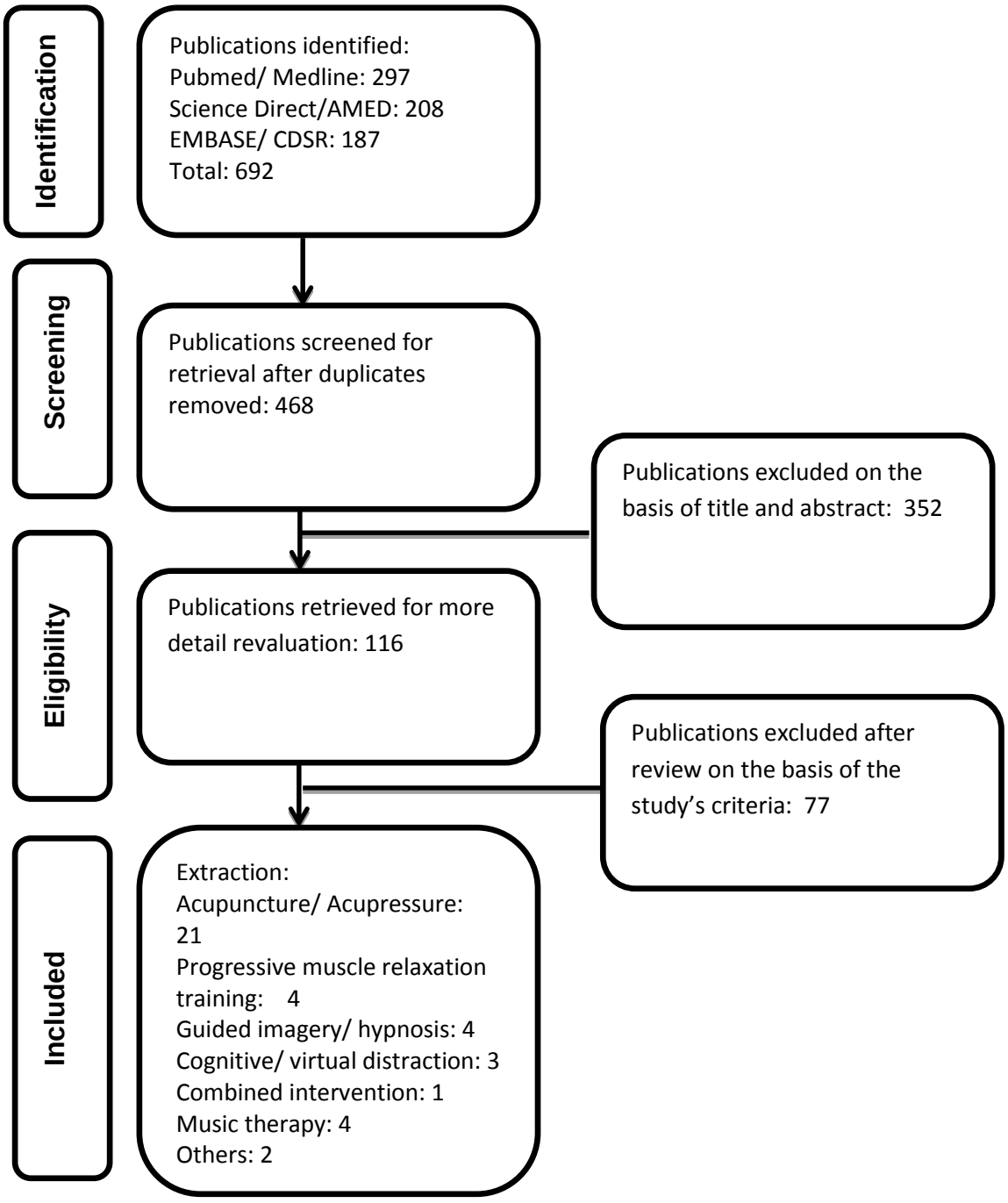
2. Types of participants: adult cancer patients receiving chemotherapy.

3. Types of interventions: non-pharmacological CAM interventions, including: acupuncture, acupressure, and psycho-behavioural techniques such as progressive muscle relaxation, guided imagery, cognitive or attentional distraction, hypnosis (passive relaxation), guided-relaxation imagery and music therapy.

4. Types of outcome measures: acute or delayed CINV, or both.

A total of 692 references were identified from all databases. Of these, 224 articles were duplicates, which left 468 articles for screening. A total of 116 references were identified as potentially relevant and were acquired for detailed consideration, of which 38 were included for data extraction (Figure 3-2). Information on study populations, procedures and data on methodological quality (such as randomisation and using sham arm) were typically extracted.

Figure 3-2: Flow diagram of the systematic review PRISMA reference



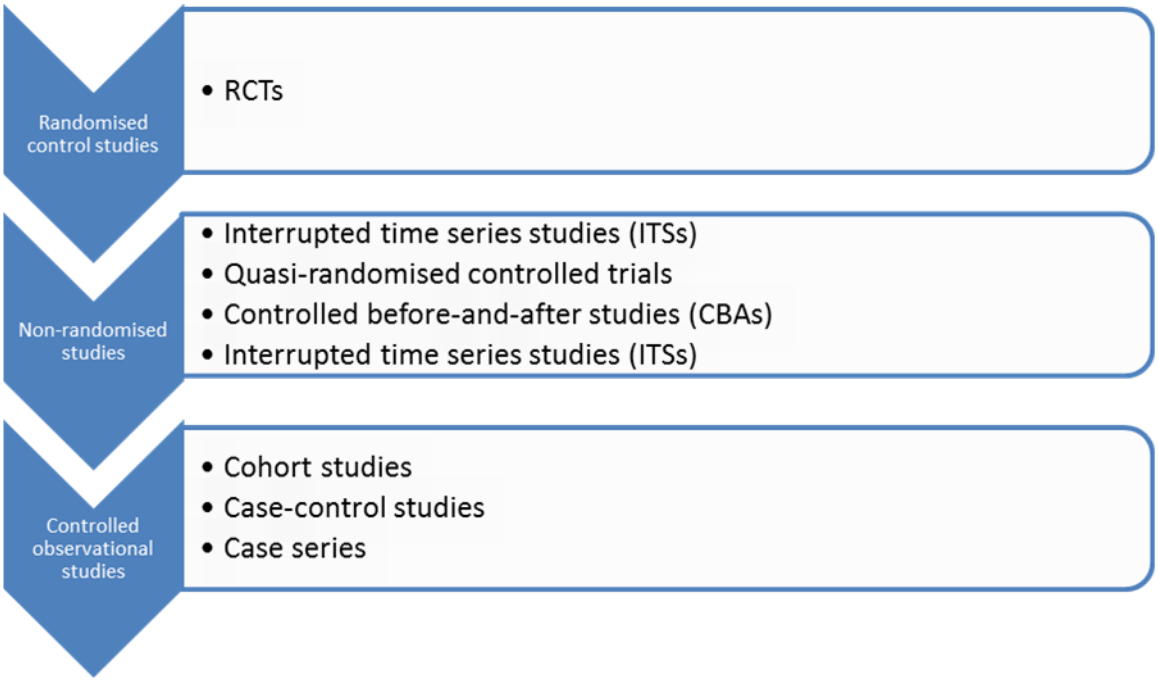
3.4. Quality issues

Several scales have been developed for quantifying the quality of studies. However, there is little agreement on the best method for scoring quality. Many quality scales have been shown to yield unreliable results, or to be limited in the information that they provide and how meaningful this information is to readers of reviews (Ryan et al., 2011). Furthermore, the reporting quality in published studies is often poor, which can increase the difficulty of assessing relevant information. In spite of these difficulties, most definitions of quality or validity used in systematic reviews involve some measure of the methodological strength of the relevant study, or how reliable it is, through its design and its conduct, to prevent systematic errors or bias (Ryan et al., 2011; Deeks et al., 2003).

3.4.1. The strength of evidence

It is known that the ranking or hierarchy of different study designs depends on the question being asked. When considering studies of effectiveness (that is, in our case, the effectiveness of non-pharmacological CAM interventions in preventing and controlling CINV), the question tends to focus on comparisons, or how an intervention compares with no intervention or with alternative intervention(s). To answer effectiveness questions, comparative studies that minimise bias will be highest in the hierarchy, or the most suitable types of studies to investigate these questions (Deeks et al., 2003; Ryan et al., 2011). Figure 3-3 shows a general classification scheme or hierarchy of studies in terms of the suitability of their design to answer questions of effectiveness.

Figure 3-3: General hierarchy of study designs to answer questions of effectiveness



In this review, assessments of study quality include systematic evaluation of validity. The methodological quality of the included studies was assessed in accordance with the guideline of the Cochrane Consumers and Communication Review Group. This is comprehensive guidance that covers both quantitative (RCTs, non-RCTs, before-and-after) and qualitative studies. The guideline has been reviewed by the Quality Advisory Group of the Cochrane Collaboration to ensure that it is up-to-date with developments in the critical appraisal of trials.

The guideline recommends the explicit reporting of the following individual quality elements for RCTs: randomisation; allocation concealment; blinding (participants, providers, outcomes assessors, data analysts); baseline comparability; follow-up; intention-to-treat analysis; validation of tools; and other sources of bias (Ryan et al., 2011). Articles were evaluated for the presence of each domain, and one point was assigned for each domain present. Scores ranged from 0 to 7, and a higher value indicated higher quality, and less risk of bias.

The process of assessing the quality of the included studies, extracting and synthesising the data, and conducting appraisals was undertaken with the aid of a checklist produced by the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010).

In this review, the data synthesis began by constructing and tabulating details about the study type, interventions, numbers of participants, a summary of participant characteristics, outcomes, outcome measures, and indications of study quality and/or risk bias. Then, a textual approach that conducted an assessment of the relationships within and between studies, and an overall assessment of the robustness of the evidence, was used. The next section of this thesis looks at the studies included in this review, and their quality.

3.5. Acupuncture and acupressure

A total of 21 studies regarding the effectiveness of acupuncture/ acupressure in CINV as a prophylactic antiemetic treatment in combination with pharmacological treatments were found (Table 3.1). All the studies have been carried out using acupuncture, electroacupuncture, acupressure, or electrostimulation wristbands as an adjunct to antiemetic pharmacotherapy.

Eight studies examined the efficacy of acupuncture for CINV. Five studies (Dundee et al., 1987; Dundee et al., 1988; Aglietti et al., 1990; Shen et al., 2000) showed protective effects on the control of acute nausea and vomiting, or delayed symptoms when using acupuncture as an adjunct to antiemetic pharmacotherapy. Three studies (McMillan & Dundee 1991; Dundee et al., 1989; Pearl et al., 1999; Streitberger et al., 2003) failed to support the effect of acupuncture in the control of CINV.

A total of 13 studies were carried out with the aim of improving control of CINV by the use of acupressure in addition to prescribed anti-emetics. Seven studies (Dibble et al., 2000; Treish et al., 2003; Shin et al., 2004; Gardani et al., 2006; Molassiotis et al., 2007b; Taspinar & Sirin, 2010; Suh, 2012) found that acupressure reduced nausea and vomiting related to chemotherapy. Six studies (Dibble et al., 2007; Genç et al., 2012; Roscoe et al., 2002; Noga et al., 2002; Roscoe et al., 2003; Roscoe et al., 2005) failed to support the effect of acupressure in the control of CINV.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Author(s)/ Country	Research aim/ theme	Research approach / Participants	Findings / outcomes	Appraisal of study	Quality assessment/ Grade		Strength of evidence
Dundee et al (1987) Northern Ireland	To assess the effect of acupuncture on post chemotherapy vomiting.	Crossover design/ 10 testicular cancer patients. Each patient had five or six treatments over three days.	There was significantly less vomiting when P6 acupuncture was done than when the dummy point was used ($p < 0.001$).	Not enough sham arm. Lack of randomisation. Small sample size. Not enough follow-up to cover delayed CINV. Reliability of used tools not determined	Random adequate: Not reported Concealment adequate: Not reported Sham control: Yes Asses'r blind stated: Not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not reported	0 0 1 0 1 1 0 Total: 3	Considering methodological issues (study design and quality), with inadequate control for confounding and small sample size, evidence seems less strong for an important effect.
Dundee et al (1988) Northern Ireland	To assess the effect of electroacupuncture on post chemotherapy vomiting.	RCT, parallel design/ 20 cancer patients having their first course of chemotherapy assigned to Anti-emetics + low frequency electroacupuncture and control group (Anti-emetics only).	The protective effects of P6 stimulation by acupuncture on chemotherapy-related vomiting last about eight hours.	Lack of sham arm. Small sample size.	Random adequate: Not reported Concealment adequate: Not reported Sham control: No Asses'r blind stated: Not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not reported	0 0 0 0 1 1 0 Total:2	Limitations in study design and its implementation might affect the study and decreased the quality level of the body of evidence.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Dundee et al (1989) Northern Ireland	To evaluate the efficacy of P6 electroacupuncture as an antiemetic in cancer patients receiving chemotherapy.	Multifaceted study (n=130) pilot study (n=15), crossover (n=10) main study(n=105). using acupuncture with electrical stimulation at the P6 point and "dummy" acupuncture	Results indicated that 97% of the patients had complete absence of nausea or had considerably reduced nausea when electroacupuncture was used. Results from crossover study indicated that the benefits were limited to the P6 point.	Small sample size (for crossover study). Not control group for the main study. Reliability of used tools not determined. Heterogeneity of sample size in terms of gender, diagnosis and treatment.	Random adequate: Not reported Concealment adequate: Not reported Sham control: No Asses'r blind stated: Not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not reported	0 0 0 0 1 1 0 Total: 2	Limitations in the design (small sample size, inadequate concealment …) and implementation of the study suggesting high likelihood of bias.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Aglietti et al (1990) Italy	To assess the addition of acupuncture to a standard antiemetic treatment in cancer patients who were at high risk of experiencing CINV despite the administration of antiemetic treatment.	Pilot study, cancer female patients divided to two groups (acupuncture+ antiemetic (n=26) and only antiemetic (n=51).	Acupuncture was shown to increase complete protection from nausea and to decrease the intensity and duration of nausea and vomiting. Complete protection from vomiting (%) :Intervention 57.7 (CI 39-77) control group 49.0 (CI 35-63) Complete protection from nausea (%): Intervention 88.5 (CI 77-I00) Control group 66.7 (C154-80).	Lack of using reliable tools for evaluation of N&V. No sham arm. Lack of randomisation.	Random adequate: Unclear Concealment adequate: Unclear Sham control: No Asses'r blind stated: Unclear Dropouts accounted: Unclear Follow-up: Yes Validation of tools: No	0 0 0 0 0 1 0 Total: 1	Limitations of given information about the study design and its implementation make it difficult to assess the strength of evidence of the study.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Mcmillan and Dundee (1991) Northern Ireland	To assess the effect of acupuncture on acute nausea and vomiting in cancer patients receiving chemotherapy.	Crossover design/ 16 patients divided to two groups, intervention: receiving anti-emetics + TENS stimulation of P6 prior to chemotherapy for five minutes followed by stimulation for five minutes every two hours when awake for five days and control group receiving anti-emetics only	stimulation of the P6 acupuncture point (Neiguan) enhances the antiemetic action of the older group of drugs such as metoclopramide, phenothiazines and cyclizine	Lack of sham arm. Small sample size. Reliability of used tools not determined. Not enough information regarding the method and data analysis	Random adequate: Not reported Concealment adequate: Not reported Sham control: No used Asses'r blind stated: Not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not reported	0 0 0 0 1 1 0 Total:2	Some methodological issues such as small sample size and lack of sham arm might affect the study. The proportion of information from the study seems to be at high risk of bias and may sufficient to affect the interpretation of results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Pearl et al (1999)	To evaluate the efficacy of a portable transcutaneous electrical nerve stimulation (TENS) unit (ReliefBand) as an adjunct to standard antiemetic therapy for controlling nausea and vomiting induced by cisplatin-based chemotherapy	RCT/ crossover design, 42 gynecologic cancer patients randomised to intervention and placebo groups. All patients received a standardised antiemetic protocol, and then wore the ReliefBand continuously for 7 days.	The incidence and severity of nausea and vomiting was similar for each group. The percentage of cycles with absent or minimal nausea was 47% overall, which was similar to that of the active (50%) and placebo (44%) cycles.	Lack of control group. Risk of selection bias. Reliability of used tools not determined. Follow-up for 7 days (cover both acute and delayed phases).	Random adequate: Yes Concealment adequate: No Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not reported	1 0 1 1 1 1 0 Total:5	Methodological issues (lack of a well-study design) might decrease the quality level of the evidence. Plausible bias raised some doubt about the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Dibble et al (2000) United States	To compare differences in nausea experience and intensity between female breast cancer patients undergoing chemotherapy receiving usual care plus acupressure training and treatment and those receiving only usual care.	Single-cycle, parallel design, randomised clinical trial, 17 patients divided to two groups.	Significant differences existed between the two groups in regard to nausea experience ($p < 0.01$) and nausea intensity ($p < 0.04$) during the first 10 days of the chemotherapy cycle, with the acupressure group reporting less intensity and experience of nausea.	Small sample size. Lack of sham arm. Risk of selection bias.	Random adequate: Yes Concealment adequate: Yes Sham control: No used Asses'r blind stated: not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 1 0 0 1 1 1 Total: 5	Some methodological issues such as small sample size and lack of sham arm might affect the study. Most information from the study is at high risk of bias. Plausible bias likely to alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Shen et al (2000) United States	To compare the effectiveness of electroacupuncture vs minimal needling and mock electrical stimulation or anti-emetics alone in controlling vomiting among patients undergoing a highly emetogenic chemotherapy.	RCT/ Parallel design, 104 breast cancer patients randomly assigned to receive low-frequency electroacupuncture at classic antiemetic acupuncture points once daily for 5 days (n=37); minimal needling at control points with mock electrostimulation on the same schedule (n=33); or no adjunct needling (n=34).	The electroacupuncture group had fewer episodes of vomiting than the other two groups (p<0.001).	Well-designed (randomised into three arms: active acupuncture, sham acupuncture, and no stimulation arm). Follow-up for 5 days (might not cover delayed phase properly).	Random adequate: Yes Concealment adequate: Yes Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Unclear	1 1 1 1 1 1 0 Total:6	Methodologically well-designed. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Noga et al (2002)	To assess the efficacy of SeaBand (acupressure band) on CINV.	RCT/ Parallel design, 120 hematologic cancer patients assigned to intervention group(Anti-emetics + acupressure band at P6 worn for 24 hours postchemotherapy) and control group (Anti-emetics + SeaBand at sham point)	No statistically significant differences in average acute vomiting and duration and frequency of nausea were observed.	Lack of control group.	Random adequate: Yes Concealment adequate: No Sham control: Yes Asses'r blind stated: No Dropouts accounted: No Follow-up: Unclear Validation of tools: Unclear	1 0 1 0 0 0 0 Total:2	No information given therefore it is impossible to evaluate the study.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Roscoe et al (2002) United States	To examine the efficacy of an acustimulation wristband for the relief of chemotherapy-induced nausea.	Randomized clinical trial using a 3-level crossover design. 42 cancer patients using active acustimulation, sham acustimulation and no acustimulation.	No statistically significant differences in average severity of nausea were observed. However, a difference close to statistical significance in the severity of delayed nausea reported during active acustimulation compared to no acustimulation (P <.06). Patients took fewer anti-emetics during the active-acustimulation cycle of this experiment compared to the no-acustimulation phase (P <.05).	Well-designed (randomised into three arms: active acustimula¬tion, sham acustimulation, and control arm).	Random adequate: Yes Concealment adequate: Yes Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Unclear	1 1 1 1 1 1 0 Total:6	Methodologically well-designed. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Roscoe et al (2003) United States	To examine the efficacy of acupressure band in relieving CINV in cancer patients.	RCT/ parallel design. 739 patients were randomly assigned to either: 1) acupressure bands, 2) an acustimulation band, or 3) a no band control condition.	Patients in the acupressure condition experienced less nausea on the day of treatment compared to controls (P< 0.05). There were no significant differences in delayed nausea or vomiting among the three treatment conditions.	Using large sample-size. Well-designed (randomised into three arms: active acustimula¬tion, sham acustimulation, and control arm).	Random adequate: Yes Concealment adequate: Yes Sham control: No Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 1 0 1 1 1 1 Total:6	Methodologically well-designed. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.
Treish et al (2003) United States	To evaluate the efficacy and tolerability of the Reliefband as an adjunct to standard anti-emetics in patients receiving moderately-high to highly emetogenic chemotherapy.	RCT, 49 cancer patients receiving chemotherapy were randomised to receive either the active Relief band (*n*=26) or an inactive device (*n*=23).	The mean number of vomiting episodes in the delayed setting was reduced more than 50% by the active Reliefband compared to the inactive device. The active Reliefband did not improve on the control rates of vomiting in the first 24 h. .	Lack of control arm. Small sample size. Reliability of used tool for measuring nausea was not determined.	Random adequate: Yes Concealment adequate: No Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 0 1 1 1 1 1 Total:6	Methodologically well-designed. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Streitber-ger et al (2003) Germany	To investigate an additional anti-emetics effect to ondansetron with needle acupuncture at P6 compared with non skin-penetrating placebo acupuncture in patients undergoing chemotherapy.	RCT/ parallel design, 80 cancer patients were randomised to receive acupuncture (*n* = 41) or non-invasive placebo acupuncture (*n*= 39) at the acupuncture point P6, 30 min before first application of chemotherapy and the day after.	No significant difference (*P* =0.82): 61% failure in the acupuncture group and 64% in the placebo acupuncture group (95% confidence interval of 3% difference: -18.1 and 24.3%).	Lack of control arm.	Random adequate: Yes Concealment adequate: No Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Unclear Validation of tools: unclear	1 0 1 1 1 0 0 Total:4	Methodologically well-designed and conducted. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Shin et al (2004) South Korea	To examine the effect of acupressure on emesis control in postoperative gastric cancer patients undergoing chemotherapy. It was designed as a prophylactic intervention.	Non-equivalent control group design/ 40 postoperative gastric cancer patients receiving the first cycle of chemotherapy with cisplatin and 5-Fluorouracil were divided into control and intervention groups (*n* = 20 each). The intervention group received acupressure at least 3 times a day, before chemotherapy and mealtimes or based on their needs.	Acupressure can reduce the frequency, duration, and severity of CINV/ Results suggests that acupressure on P6 point appears to be an effective adjunct manoeuvre in the course of emesis control.	Small sample size. No sham arm. Lack of randomisation.	Random adequate: Unclear Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	0 0 0 0 1 1 1 Total: 3	Although the study suffered from a strong study design with assessor's concealment, it can be considered as a well-conducted study with suggesting low likelihood of bias

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Roscoe et al (2005) United States	To examine the efficacy of an acustimulation wrist band for the relief of chemotherapy-induced nausea. It was designed as a prophylactic intervention.	Randomised controlled trial/ 96 women with breast cancer. Participants in intervention and sham arms wore acustimulation wrist band before chemotherapy and over 5 days.	Results do not support the hypothesis that acustimulation bands are efficacious as an adjunct to pharmacological anti-emetics for control of chemotherapy-related nausea in female breast cancer patients.	Using large sample-size. Well-designed (randomised into three arms: active acustimula¬tion, sham acustimulation, or no stimulation arm).	Random adequate: Done Concealment adequate: Adequate Sham control: Yes Asses'r blind stated: Yes Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 1 1 1 1 1 1 Total:7	Methodologically well-designed and conducted. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Gardani et al (2006) Italy	To evaluate the efficacy of acupressure in the treatment of chemotherapy - induced vomiting resistant to the standard antiemetic therapies. It was designed as a prophylactic intervention.	Experimental design /40 advanced cancer patients with untreatable chemotherapy-induced vomiting. Acupressure was made by PC6 point stimulation for at least 6 h/day at the onset of chemotherapy.	An evident improvement in the vomiting symptomatology was achieved in 28/40 (70%) patients.	Heterogeneous sample in terms of cancer site and chemotherapeutic regimens. No randomised trial (lack of control and sham groups). Not indicate the difference between early and delayed antiemetic efficacy.	Random adequate: Not done Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: Yes Follow-up: Yes Validation of tools: Not clear	0 0 0 0 1 1 0 Total: 2	Considering methodological issues (study design and quality), with inadequate control for confounding (heterogeneous sample) evidence seems less strong for an important effect. Most information from the study seems at low or unclear risk of bias.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Dibble et al (2007) United States	To compare differences in CINV among three groups (acupressure, placebo acupressure, and usual care). It was designed as a prophylactic intervention.	Randomised controlled trial/ 160 breast cancer patients who were beginning their second or third cycle of chemotherapy randomised to one of three groups acupressure to PS point (active), acupressure to 513 point (placebo), or usual care only. All subjects completed a daily log for 21 days containing measures of N&V and recording methods (including anti-emetics and acupressure) used to control these symptoms.	No effect of acupressure on acute nausea and vomiting but found reduction of delayed nausea and vomiting by acupressure.	Using large sample-size. Well-designed randomised into three arms: acupressure to PS point (active), acupressure to 513 point (placebo), or usual care only). Follow-up for 21 days.	Random adequate: Done Concealment adequate: Adequate Sham control: Yes Asses'r blind stated: Not reported Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 1 1 0 1 1 1 Total: 6	Methodologically well-designed. Most information from the study seems at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Molassio -tis et al (2007) UK	To evaluate the effectiveness of using acupressure in P6 acu-point in managing CINV. It was designed as a prophylactic intervention.	Randomised controlled trial/ 36 breast cancer patients who were chemotherapy naive, starting their first cycle of chemotherapy. Intervention group wore acupressure wristbands bilaterally throughout 5 days.	Acupressure is an effective complementary option in the management of CINV.	Small sample size, No sham arm. 34% attrition. Control group served as a wait list group could have influenced subjective report about symptom. No statistical analysis about change over time No post hoc analysis about daily difference.	Random adequate: Done Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: Yes Follow-up: Yes Validation of tools: Yes	1 0 0 0 1 1 1 Total: 4	Limitations in study design (small sample size, not sham arm…). Most information from the study seems at low or unclear risk of bias.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Taspinar & Sirin (2010) Turkey	To assess the effect of acupressure applied to the P6 acupuncture point with a wristband on N&V in addition to the standard antiemetic agents used to prevent CINV. It was designed as a prophylactic intervention.	Prospective research (pre- and post-tests)/ 34 patients with gynaecologic cancer who were receiving single dose chemotherapy. In the first stage patients wore wristbands bilaterally over 5 days.	Acupressure applied to P6 with wristbands may be effective in reducing chemotherapy-related nausea and may decrease the antiemetic use after chemotherapy.	Small sample size. Finding not to be statistically significant. Reliability of used tools not determined. Expectations accompanying the use of the wristbands might lead to psychological effect and thereby reduced nausea.	Random adequate: Not done Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: No Follow-up: Yes Validation of tools: No	0 0 0 0 0 1 0 Total: 1	Limitations in study design and its implementation might affect the study and decreased the quality level of the body of evidence.

Table 3-1: Summary of studies evaluating the effectiveness of acupuncture/acupressure in managing CINV							
Genç et al (2012) Turkey	To assess the efficiency of the acupressure in prevention of CINV	Randomized controlled trial/ Breast–gynaecology cancer (74) and lung cancer (46) were divided into experimental (67) and control groups (53). Changes observed during 5 days after the chemotherapy.	There was no difference between the groups statistically. Acupressure wristband was not an effective approach in preventing CINV.	No sham arm. Risk of bias (no information regarding attrition rate). Collected data limited by patients' memory as they called patients to get informed about the results.	Random adequate: Done Concealment adequate: Used Sham control: No Asses'r blind stated: No Dropouts accounted: Not known Follow-up: Yes Validation of tools: Yes	1 1 0 0 0 1 1 Total: 4	Limitations in study design (no sham arm, inappropriate data collection and follow up).
Suh (2012) South Korea	To evaluate the effects of pericardium 6 (P6) acupressure and nurse-provided counselling on CINV	Randomized controlled trial/ 120 breast cancer patients assigned into four groups: control (placebo on SI3), counselling only, P6 acupressure only, and P6 acupressure plus nurse-provided counselling.	The levels of CINV were different between the control group and the group with P6 acupressure plus nurse-provided counselling.	Small sample size. No sham arm. Risk of bias (no information regarding attrition rate).	Random adequate: Done Concealment adequate: No Sham control: No Asses'r blind stated: No Dropouts accounted: Not known Follow-up: Yes Validation of tools: Yes	1 0 0 0 0 1 1 Total: 4	Risk of delivery bias. Not enough information regarding the study was available.

3.5.1. Acupuncture studies

Several trials have been carried out to investigate the effect of acupuncture on CINV. Although some randomised controlled, parallel, and crossover studies demonstrated the benefit of acupuncture in acute chemotherapy-induced vomiting, only one study (Streitberger et al., 2003) was done in conjunction with modern anti-emetics (such as the 5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron). Several trials on acupuncture did not demonstrate significant protective effects on the control of acute nausea and vomiting or delayed symptoms. Only a few studies suggested the antiemetic effects of acupuncture in post-chemotherapy cancer patients (Table 3-1) (Ma, 2009).

Dundee et al (1987), in a crossover study, applied electro-acupuncture on patients receiving an infusion containing cisplatin as part of a regimen for testicular cancer immediately before or soon after the start of the infusion. Patients had acupuncture to the P6 (Neiguan) point or a "dummy" point near the right elbow. Every patient had five or six acupuncture treatments over 3 days, only one of which was a dummy. Their results showed that there was significantly less nausea and/or vomiting when P6 acupuncture was done than when the dummy point was used ($p < 0.001$). However, small sample size (10 participants), lack of using sham arm and also lack of using reliable tools to measure nausea and vomiting might affect the results. In addition, Dundee et al (1988) conducted a randomised controlled trial to evaluate the effect of electro-acupuncture on post-chemotherapy vomiting. However, this study was unpowered and had numerous reporting insufficiencies.

In another multi-facet study, Dundee at al (1989) evaluated the efficacy of P6 electro-acupuncture as an antiemetic in cancer patients receiving chemotherapy. The study involved 130 patients who had a history of distressing nausea and/or vomiting in previous chemotherapy cycle. Participants had electro-acupuncture administered at P6 point for 5 minutes, followed immediately by chemotherapy. Participants were asked to grade their nausea and/or vomiting on a four point scale. Their results showed that 63% of patients having complete absence of nausea and/or vomiting for at least 8 hours and only 5% showing no benefit at all.

The study reveals serious shortcomings in designing the study, such as lack of sham arm, and using valid and reliable tools for measurement the outcomes.

Aglietti et al (1990) conducted a pilot study to verify whether the addition of acupuncture to a standard antiemetic treatment could improve treatment of post-chemotherapy nausea and vomiting. A total of 26 women who submitted to cisplatin chemotherapy received as antiemetic treatment a combination of metoclopramide, dexamethasone and diphenhydramine. Acupuncture was also carried out in intervention group. There was no difference between the control and intervention groups in complete protection from both nausea and vomiting and from vomiting alone. However, complete protection from nausea, the mean number of vomiting episodes, the mean maximal score of nausea and the duration of nausea and vomiting were reduced by the addition of acupuncture. This pilot study was unpowered and did not use of sham arm. Also, other limitations such as lack of randomisation, lack of using reliable tools to measure nausea and vomiting, and risk of selection bias might influence the results.

McMillan and Dundee (1991) conducted a randomised crossover study in 16 hospitalised patients comparing the degree of nausea and/or vomiting over a 5 day period when the chemotherapy was accompanied by ondansetron or by ondansetron and transcutaneous electrical stimulation of P6. No significant differences were found between the two groups. Lack of using sham arm, small sample size and lack of information regarding the measurement tools considered as shortcomings of the study that might affect the results.

Pearl et al (1999) carried out a randomised, placebo-controlled trial with a follow-up crossover trial to evaluate the effectiveness of a miniaturised portable transcutaneous electrical nerve stimulation (TENS) unit (ReliefBand) as an adjunct to standard antiemetic therapy for controlling nausea and vomiting induced by cisplatin-based chemotherapy in gynaecologic oncology patients. Forty-two patients were recruited. All patients received a standardised antiemetic protocol and then wore the ReliefBand continuously for 7 days. The results showed that the incidence and severity of nausea and vomiting was similar for each group; however, the severity of nausea was lower in the active cycles during days 2 to 4. Risk of bias in this study was unclear because there was not sufficient detail to

determine how investigators were prevented from foreseeing group allocations before randomisation.

In a randomised controlled study carried out by Streitberger et al (2003), the effect of manual acupuncture in conjunction with modern anti-emetics was evaluated. The analysis revealed no effect of acupuncture beyond the effect of intravenous ondansetron (Streitberger et al., 2003). Nevertheless, Ezzo et al. (2005) proposed two possible reasons for the results of this study. Firstly, acupuncture might not offer anything beyond what modern antiemetic regimens can, due to a shared pathway of action. Secondly, the statistical power of the study (80%) might not be large enough to show a meaningful effect.

It is suggested that the biggest problem with acupuncture studies has been the placebo effect (Ma, 2009). Only a few previous studies (Shen et al., 2000; Streitberger et al., 2003) have used sham control to avoid the placebo effect of acupuncture. Shen et al. (2000) applied minimal needling at two acupuncture points that are supposed to be unrelated to nausea control in the control group. The study showed positive results for electro-acupuncture; however, it did not use 5-HT3 receptor antagonists. Streitberger et al. (2003) used manual acupuncture for the intervention arm, while the control group received electro-stimulation with a blunted placebo needle to simulate an acupuncture procedure without penetrating the skin. The results revealed no additional effect in combination with intravenous ondansetron on the prevention of nausea and vomiting in high-dose chemotherapy.

3.5.2. Acupressure studies

3.5.2.1. Studies with positive acupressure effect

In an RCT conducted by Dibble et al. (2000), 17 female breast cancer patients were randomised into two groups: eight patients conducted finger acupressure over one cycle of moderately to highly emetogenic chemotherapy, and nine patients in the control group received the antiemetic therapy only. The results indicated statistically significant differences related to the nausea experience ($p < 0.01$) and the nausea intensity ($p < 0.04$) compared with the patients in the acupressure group and those in the control group. It is notable that a significant

daily difference was found only on Day 2 ($P < 0.05$). The acupressure group received about five minutes of acupressure instruction, which could be interpreted as additional attention given to patients, which could then possibly have confounded the study results (Lee et al., 2008). Moreover, although the process of allocation was described as random, no detail of the method of randomisation was given. In addition, patients were recruited at two different oncology outpatient clinics in urban areas; however, it is not apparent how these patients were selected from the population of women receiving adjuvant chemotherapy for breast cancer in these clinics (Klein & Griffiths, 2004).

Treish et al. (2003) conducted a randomised double-blind study in which 49 adult cancer patients were randomised to receive either the active Reliefband (n=26) or an inactive device (n=23). Nausea severity and vomiting episodes and anti-emetics taken were measured by a daily diary. The participants received a 5-HT3 receptor antagonists (ondansetron) and dexamethasone. The results indicated that the difference in the mean number of vomiting episodes was not statistically reduced in the acute CINV. However, the difference in the mean number of vomiting episodes in the delayed CINV was reduced for patients in the intervention group (0.42 versus 1; p=0.032). Similarly, the severity of nausea was reduced in the acute (0.71 versus 2.3 mean cm/day; p=0.028) and delayed CINV (1.8 versus 3.3 mean cm/day; p=0.020). Although the demographic characteristics of the patients in the two groups were similar, there was a disproportionate number of patients in the inactive device group receiving cyclophosphamide-based regimens (eight versus one). As the investigators indicated, one of the weaknesses of the study was the inclusion of a diverse group of patients receiving a wide range of chemotherapy and antiemetic regimens. This led to: (1) potential for imbalances in the two treatment groups, despite randomisation, and (2) variation in the response observed between both groups clearly reduced the power of the study in terms of find a significant difference between them (Treish et al., 2003).

Shin et al. (2004) conducted an acupressure study involving 40 Korean stomach cancer patients who were receiving the first cycle of highly emetogenic chemotherapy. This study assigned the first 20 patients to the control group and the next 20 to the intervention group. Participants received a 5-HT3 receptor antagonist (ondansetron) and metoclopramide, which are suboptimal for highly

emetogenic chemotherapy. The results showed that all three average scores for severity, duration, and frequency of nausea and vomiting were significantly different between the acupressure and control groups ($P < 0.01$); however, daily comparisons showed that the most significantly different effects were demonstrated on days two to five for severity, and days three to five for duration and frequency measures ($P < 0.05$). Lack of randomisation, suboptimal antiemetic use, and the lack of controls for predisposing factors might have affect and weakened the results of the study.

Gardani et al (2006) conducted an experimental study to evaluate the efficacy of acupressure in the treatment of chemotherapy-induced vomiting resistant to the standard antiemetic therapies. Forty consecutive advanced cancer patients with untreatable chemotherapy-induced vomiting were recruited. Acupressure was made by PC6 point stimulation for at least 6 hours/day at the onset of chemotherapy. The results showed that an evident improvement in the vomiting symptomatology was achieved in 28/40 (70%) patients, without significant differences in relation to neither tumour histotype, nor type of chemotherapeutic agent. Lack of randomisation, heterogeneous sample, and lack of sham arm might increase the risk of bias and affect the study.

Molassiotis et al. (2007) carried out an RCT using Sea-Bands continuously for five days. The study recruited 36 female breast cancer patients receiving moderately to highly emetogenic chemotherapy. Participants received 5-HT3 receptor antagonists and dexamethasone in the acute phase, and various anti-emetics in the delayed phase. The control group received the usual care with chemotherapy, served as a waitlist group, and was told that they would receive the acupressure instructions and be given the wristbands to use for their next cycle of chemotherapy. The results showed significantly lower scores for nausea experience, nausea, vomiting occurrence and distress in the acupressure bands group for five days after chemotherapy ($p < 0.05$). However, no post hoc analysis was conducted; therefore it is difficult to evaluate the significance of the daily differences and phase-specific effects of the acupressure bands. Furthermore, the sample size might affect the results, as fifty patients were required to achieve a power of 80% at an alpha of 0.05. Another limitation of this study is high attrition

rate (34%). More patients in the intervention group failing to return the questionnaires was also an issue.

Taspinar et al. (2010), in a prospective pre-test–post-test study, assessed the effect of acupressure using a wristband for five days on the P6 acupuncture point on the wrists of gynaecologic cancer patients. They found that the wristbands had a significant effect in decreasing chemotherapy-induced nausea. The mean scores reduced for both acute and delayed nausea (acute nausea t= 2.227; p= 0.033; delayed nausea F=78.070; p= 0.001). However, the results showed no significant decrease in vomiting episodes. The rate of antiemetic medication taken also decreased from 82.4% to 50% following the use of wristbands. However, this study suffers from some limitations. First the trial within the study was not randomised. Secondly, as in the pre-test stage the patients were asked to record nausea, vomiting and antiemetic medication taken; it is therefore possible that, at the post-test stage, the expectations accompanying the use of the wristbands could have had a psychological effect and thus reduced their nausea. Another possibility is that patients desiring to continue to the second, post-test, stage might have developed a positive attitude towards non-pharmacologic treatments, and a belief in their usefulness. Thirdly, the relatively small sample size might have affected the results (Taspinar & Sirin, 2010).

Suh (2012) carried out an RCT to evaluate the effects of P6 acupressure and nurse-provided counselling on CINV. One hundred and twenty breast cancer patients who were beginning their second cycle of adjuvant chemotherapy after definitive surgery for breast cancer and who had more than mild levels of nausea and vomiting with the first cycle of chemotherapy were assigned randomly into four groups: control (placebo on SI3), counselling only, P6 acupressure only, and P6 acupressure plus nurse-provided counselling. The levels of CINV were significantly different between the control group and the group with P6 acupressure plus nurse-provided counselling. However, not enough information regarding the study was available.

3.5.2.2. Studies with negative acupressure effect

Roscoe et al (2002) conducted an RCT, using a 3-level crossover design, to examine the effectiveness of an acustimulation wristband for the relief of

chemotherapy-induced nausea. Twenty-five women and 2 men who experienced moderate or more severe nausea following their first chemotherapy treatment were recruited. Active acustimulation of the Pericardium 6 (PC-6) point on the ventral surface of the wrist compared with sham acustimulation (a corresponding point on the posterior surface of the wrist). A control group received no acustimulation. The results showed that although no statistically significant differences in average severity of nausea were observed between the 3 interventions, a difference close to statistical significance in the severity of delayed nausea reported during active acustimulation compared to no acustimulation (P <.06). In addition, patients took less anti-emetics during the active-acustimulation cycle of this experiment compared with the no-acustimulation phase (P <.05). This study well designed in terms of homogeneity of the participants, using different arms, and receiving same antiemetic agents in all groups. However, the study does not determine the efficacy of acustimulation in the amount of anti-emesis.

Roscoe et al. (2003) conducted a single-cycle trial to examine the acupressure effect on chemotherapy-naive patients (n= 739). Patients were recruited from 17 sites of a community clinical oncology programme. Most participants were female (92%) with breast cancer (85%) or haematological malignancy (10%). Patients in the intervention arm (n=233) were instructed on how to use and apply Sea Bands to give acupressure to the P6 (wrist) point. Patients in the control group (n=232) received the usual anti-emetics (5-HT3 receptor antagonists) only. The results showed that the acupressure group experienced significantly less acute nausea than the control group (P < 0.05); however, there was no significant effect (p >0.05) on vomiting, delayed nausea or antiemetic use. In addition, a positive relationship was found between the patients' expectations of the effectiveness of acupressure, and acute and overall nausea control, which shows the role of expectation in symptom control through acupressure. This, in part, can be considered as a placebo effect (Lee et al., 2008).

Another study that failed to show the efficacy of acupressure is that by Noga et al. (2002). This trial recruited 120 patients with hematologic malignancies. The patients received highly emetogenic chemotherapy, and 5-HT3 receptor antagonists anti-emetics (including ondansetron) and dexamethasone. The effect of continuous, bilateral wearing of Bio-bands, at P6 versus the sham point for 24

hours after chemotherapy, was compared. Patients in the intervention group had a significantly higher frequency and duration of, and distress from, nausea, and a higher nausea subtotal and total INVR score. These patients took significantly more additional anti-emetics ($p < 0.05$) (Noga et al., 2002). The study did not explain why the acupressure group experienced more nausea and took more additional anti-emetics according to differences in age, gender, chemotherapy regimen, diagnosis, or anticipatory nausea and vomiting. It is also problematic to assess the influence of the cancer type in relation to the acupressure effect, as this study only included patients with hematologic malignancies (Lee et al., 2008).

Roscoe et al (2005) carried out a randomised three-arm trial (active acustimulation, sham acustimulation, and no acustimulation) to examine the efficacy of an acustimulation wrist band for the relief of chemotherapy-induced nausea. Ninety nine female breast cancer patients who experienced nausea at their first chemotherapy cycle were recruited. Five outcomes related to wrist band effectiveness (acute nausea, delayed nausea, vomiting, QoL, and total amount of antiemetic medication used) were examined. The results showed that there were no significant differences in any of these study measures among the three treatment conditions ($P > 0.1$ for all). The instruments used to collect the data had previously established reliability and validity (Rhodes INVR). However, limitations in reporting (particularly of the outcomes) limit the utility of the study.

Dibble et al. (2007) conducted a multicentre randomised controlled trial. Female breast cancer patients (n=160) who had at least moderate nausea in a previous chemotherapy cycle were randomly assigned to three groups (intervention group (usual care plus finger acupressure at P6), attention group (usual care plus acupressure to SI3, a point on the ulnar edge of the hand), and control group (usual care only). The results indicated that no difference was found in acute CINV among the different intervention groups. However, delayed vomiting was significantly reduced in the intervention group, compared to the attention group ($P < 0.01$) and the control group ($P < 0.01$).

Genç et al. (2012) conducted a single-blind randomised trial to assess the efficiency of acupressure in the prevention of CINV. Patients were divided into intervention (n=67) and control groups (n=53). The results indicated that no

statistical difference was found between the groups. The study determined that CINV is directly related to the treatment, and the use of acupressure wristbands was not an effective approach in preventing CINV (Genç et al., 2012).

3.5.3. Summary

Differences in acupuncture/acupressure modality, the emetogenecity of chemotherapy agents, antiemetic use, and sample characteristics make comparisons between existing research studies difficult. These methodological limitations preclude definitive conclusions. Additionally, less evidence is available concerning the mechanism of acupuncture/acupressure. Considering the methodological issues relating to the studies included in this review, and the lack of consistency in the results and outcomes of the trials, it can be concluded that the effectiveness of acupuncture/acupressure on CINV needs further research using the current antiemetic regimens, with bigger sample sizes, and an effective sham control arm. Furthermore, the mechanism of acupuncture/acupressure and their prophylactic effects on CINV needs to be explored further. In general, although some studies suggest that acupuncture/acupressure has a role in controlling CINV, its implication in current clinical practice remains unclear.

Based on the results of these studies, it might be assumed that the efficiency of acupressure is controversial and unclear.

3.6. Psycho-behavioural techniques

It is suggested that not only physiological mechanisms, but also psychological aspects are involved in CINV (Carvalho et al., 2007). A wide range of behavioural interventions have been used in managing the side effects of chemotherapy, either alone or in combination with standard pharmacological therapy (Fallowfield, 1992; Molassiotis et al., 2002b; Carvalho et al., 2007). In this section, interventions using relaxation techniques (such as progressive muscle relaxation training (PMRT), guided imagery, hypnosis and cognitive/virtual distraction, and music therapy) in controlling CINV are examined.

3.6.1. Relaxation techniques

Relaxation techniques such as progressive muscle relaxation training (PMRT), guided imagery, and hypnosis have been suggested to be helpful in managing

nausea and vomiting in cancer patients receiving chemotherapy (Bayuk, 1985). PMRT is the most investigated and widely used among the psychological interventions (Luebbert et al., 2001; Molassiotis et al., 2002b).

3.6.2. Progressive muscle relaxation training (PMRT)

The effects of using relaxation training prophylactically to control nausea and vomiting among cancer patients receiving chemotherapy has been investigated in three randomised control trials (Lyles et al., 1982; Holli, 1993; Molassiotis et al., 2002b) and one pre-post test study (Carvalho et al., 2007) (Table 3-2).

Table 3-2: Summary of relaxation interventions used to relieve chemotherapy- induced nausea and vomiting							
Author(s) / Country	Research aim/ theme	Research approach / Participants	Findings / outcomes	Appraisal of study	Quality assessment/ Grade		Strength of evidence
(Holli, 1993) Finland	To evaluate the effect of relaxation on post-chemotherapy vomiting/ Relaxation before and during the chemotherapy infusion. It was designed as a prophylactic intervention.	RCT/67 adult cancer patients randomised into intervention (n=43) and control (n=24) groups.	Relaxation was ineffective on chemotherapy-induced vomiting. Participants in intervention group vomited more frequently but the difference was not statistically significant. Also, chemotherapy to be more intolerable but there was no significant difference.	Heterogeneity of sample size in terms of diagnosis and treatment. Not enough information regarding the method and data analysis.	Random adequate: Unclear Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: Unclear Follow-up: Unclear Validation of tools: Unclear	? 0 0 0 ? ? ? Total: ?	Limitations and ambiguity of the study design and its implementation make it difficult to evaluate the study.

Table 3-2: Summary of relaxation interventions used to relieve chemotherapy- induced nausea and vomiting							
(Molassiotis et al., 2002b) Hong Kong	To assess the effectiveness of progressive muscle relaxation training in CINV. It was designed as a prophylactic intervention.	RCT/ 71 breast cancer patients were randomised either to receive anti-emetics plus PMRT (n=38) or serve as the control group (n=31) receiving anti-emetics only. Used PMRT 1 hours before chemotherapy and daily thereafter for another 5 days.	The use of PMRT considerably decreased the frequency and duration of both nausea and vomiting($p<0.05$), but not the intensity.	Not enough sample size. Lack of sham arm. Risk of selection bias.	Random adequate: Done Concealment adequate: Not used Sham control: No Asses'r blind stated: No Dropouts accounted: Done Follow-up: Done Validation of tools: Done	1 0 0 0 1 1 1 Total: 4	Some methodological issues such as small sample size and lack of sham arm might affect the study. However, Most information from the study is at low risk of bias. Plausible bias unlikely to seriously alter the results.

Table 3-2: Summary of relaxation interventions used to relieve chemotherapy- induced nausea and vomiting							
(Carvalho et al., 2007) Brazil	To determine the effect of a progressive muscle relaxation intervention on CINV/ using muscle relaxation technique. The intervention used in response to N&V.	Pre-test/post-test pilot study / 30 haematology patients.	Progressive muscle relaxation lead to statistically significant changes (reduce) in nausea and vomiting. Wilcoxon test: for nausea (Z= - 4.729) for vomiting (Z= -.4.739), (p=0.0).	Small sample size. Heterogeneous sample (difference in medical diagnosis), difference in antiemetic and chemotherapy type and dosage. Lack of control group and randomisation.	Random adequate: Not done Concealment adequate: Not done Sham control: No Asses'r blind stated: No Dropouts accounted: Unclear Follow-up: Done Validation of tools: Done	0 0 0 0 ? 1 1 Total:2	Using heterogonous sample might affect the quality of the study. It increased the risk of selection bias. Plausible bias raised some doubt about the results.
(Lyles et al., 1982) USA	To compare the effectiveness of progressive muscle-relaxation training and guided-relaxation imagery in CINV. The intervention used in response to N&V.	RCT/ 50 patients with various types of cancer randomised to one of three groups: PMRT, attention-control, or no-treatment.	Patients in the PMRT group exhibited significantly (p=0.05) less psychological distress and nausea (but not vomiting).	Small sample size, participant were not naïve to chemotherapy. Risk of selection bias as all patients participating in the study were recommended by the charge nurse.	Random adequate: Done Concealment adequate: Inadequate Sham control: Yes Asses'r blind stated: No Dropouts accounted: Done Follow-up: Done Validation of tools: Done/ unclear	1 0 1 0 1 1 1 Total:4	Limitations in the design (small sample size, inadequate concealment …) and implementation of the study suggesting high likelihood of bias.

In a randomized controlled study carried out by Hollis (1997), it was shown that relaxation was ineffective on chemotherapy-induced vomiting. Nevertheless, heterogeneity of the population in terms of diagnosis and treatment, lack of information regarding the method used, and insufficient information about the data analysis make it difficult to draw a definitive conclusion. In another study by Carvalho et al. (2007) the results indicated that progressive muscle relaxation leads to statistically significant changes in physiological and muscle conditions, and in nausea and vomiting levels. The small sample size (as it was a pilot study and not sufficiently powered, it recruited only 30 participants) and other shortcomings of the study (Table 3-2) preclude definitive conclusions. In a similar study conducted by Molassiotis et al. (2002), the differences between the two groups (intervention and control) in terms of the frequency (mean number of episodes of nausea), duration and intensity of nausea were analysed. This study was well designed and conducted. Both acute and delayed phases of nausea and vomiting were considered. Rescue anti-emetics were controlled and a trained person administered the treatment. Another researcher collected the questionnaires, and an objective tool to measure relaxation (measuring blood pressure) was used. The results showed a difference in the frequency and duration of nausea and/or vomiting between the groups. However, the results did not indicate a significant reduction in the intensity of nausea and vomiting after chemotherapy. Nevertheless, it was concluded that using PMRT with guided imagery is superior to standard therapy alone in controlling acute and delayed chemotherapy-related nausea and vomiting. It is notable that it is difficult to compare this study result with the current antiemetic standard treatment, as the scheduled antiemetic agents are not in keeping with the current guidelines. Furthermore, the small sample size (the sample size required was 92 chemotherapy-naive patients, 46 in each arm; however, only 71 subjects were recruited to the study) and lack of sham arm might affect the study.

Summary

Reviewing the literature has shown that only a few studies have been conducted to examine the effectiveness of relaxation interventions in controlling CINV. They were designed even either as a prophylactic intervention (Holli, 1993; Molassiotis et al., 2002b), or in response to nausea and vomiting (Lyles et al., 1982; Carvalho

et al., 2007). While progressive muscle relaxation training has been shown to have a superior adjunct antiemetic with pharmacological treatment in three previous studies (Lyles et al., 1982; Molassiotis et al., 2002a; Carvalho et al., 2007), it is difficult to draw an explicit conclusion. Considering the methodological limitations relating to these studies, the lack of strong evidence (see Table 2-6) and the unclear mechanism of action, more research in this area is needed.

3.6.3. Guided imagery/hypnosis

Only two randomised controlled trials (Feldman & Salzberg, 1990; Troesch et al., 1993) were found which assessed the prophylactic antiemetic effects of guided imagery on CINV. Another randomised control trial (Lyles et al., 1982) was conducted to compare the effectiveness of progressive muscle relaxation training and guided relaxation imagery in CINV. Also, only one randomised control trial (Syrjala et al., 1992) tested the efficacy of training in either hypnosis or cognitive behavioural coping skills in reducing treatment-related cancer pain and nausea and vomiting (Table 3-3).

Table 3-3: Summary of guided imagery / hypnosis interventions used prophylactically to relieve chemotherapy- induced nausea and vomiting							
Author(s) / Country	Research aim/ theme	Research approach / Participants	Findings / outcomes	Appraisal of study	Quality assessment/ Grade		Strength of evidence
(Lyles et al., 1982) United States	To compare the effectiveness of progressive muscle-relaxation training and guided-relaxation imagery in CINV. The intervention used in response to N&V.	RT/ 50 patients with various types of cancer randomised to one of three groups: PMRT, attention-control, or no-treatment.	Patients in the PMRT group exhibited significantly ($p < .05$) less psychological distress and nausea (but not vomiting).However, the dropout rate was significantly higher in the relaxation-training condition than in the other two conditions, $x^2(2) = 9.0$, $p < 0.05$.	Small sample size, participant were not naïve to chemotherapy. Heterogeneity of sample size in terms of gender, diagnosis and treatment. Nurses rated patients to be nauseated during the chemotherapy. Reliability of used tools not determined.	Random adequate: Done Concealment adequate: Inadequate Sham control: Yes Asses'r blind stated: Not done Dropouts accounted: Done Follow-up: Done Validation of tools: Done/ unclear	1 0 1 0 1 1 ? Total:4	Limitations in the design (small sample size, inadequate concealment…) and implementation of the study suggesting high likelihood of bias.
(Feldman and Salzberg, 1990)	Assessed the effects of guided imagery on adverse reactions to cancer therapy. It was designed as a prophylactic intervention.	RCT/ 60 cancer patients randomised into one of the four groups : guided imagery, hypnosis, hypnosis-imagery or standard care.	No significant differences were shown between the three different interventions or between the control group and hypnosis-imagery group, the guided imagery group or the hypnosis group alone.	No detail given about types of cancer. No blinding of the outcome assessor or method of randomisation was reported. No information regarding the used tool(s).	Random adequate: Done/ unclear Concealment adequate: Unclear Sham control: Yes Asses'r blind stated: Not done Dropouts accounted: Unclear Follow-up: Unclear Validation of tools: Unclear	? ? 1 0 ? ? ? Total:1	Limitations of given information about the study design and its implementation make it difficult to assess the strength of evidence of the study.

Table 3-3: Summary of guided imagery / hypnosis interventions used prophylactically to relieve chemotherapy- induced nausea and vomiting							
(Troesch et al., 1993)	To determine the additional effect of guided imagery in reducing CINV, retching and distress. It was designed as a prophylactic intervention.	RCT/ 28 cancer patients randomised to two groups. The intervention group used a chemotherapy-specific guided-imagery audiotape three times: 60 min before chemo session (in the clinic), the following morning before breakfast, and evening at bedtime.	No statistically significant difference in occurrence of N&V. Significant difference in emotional response: chemotherapy experience more positive in the GI group.	Small sample size, heterogeneous sample. No blinding to assessors.	Random adequate: Done Concealment adequate: Unclear Sham control: No Asses'r blind stated: Unclear Dropouts accounted: Done Follow-up: Done Validation of tools: Done	1 ? 0 ? 1 1 1 Total:1	Some methodological issues such as small sample size , heterogeneous sample and lack of sham arm might affect the study. The proportion of information from the study seems to be at high risk of bias and may sufficient to affect the interpretation of results.
(Syrjala et al., 1992) United States	To test the efficacy of psychological techniques for reducing cancer pain or post-chemotherapy N&V. The intervention used in response to N&V.	RCT/ 45 bone marrow transplant patients with haematological malignancies were randomly assigned to one of four groups prior to beginning transplantation conditioning: (1) hypnosis training (2) cognitive behavioural coping skills training (Korfage et al.) therapist contact control or (Poli-Bigelli et al.) treatment as usual.	The cognitive behavioural intervention, was not effective in reducing the symptoms measured	Small sample size (sufficiently not powered). Inappropriate tools for measuring N&V.	Random adequate: Done/unclear Concealment adequate: No Sham control: Yes Asses'r blind stated: Unclear Dropouts accounted: Unclear Follow-up: Yes Validation of tools: No	? 0 1 ? ? 1 0 Total:2	Limitations in study design might affect the study and decreased the quality level of the body of evidence. Plausible bias likely to alter the results.

In a randomised controlled study conducted by Lyles et al. (1982), patients in the experimental group displayed significantly less psychological distress and nausea (but not vomiting) compared with the attention-control and control groups. As participants in this study had already experienced adverse side effects, the authors concluded that progressive muscle relaxation training plus guided imagery was effective in reducing side effects. However, there was no evidence concerning the effectiveness of the progressive muscle relaxation training plus guided imagery in preventing the chemotherapy side effects (particularly anticipatory CINV) (Boudreaux, 1995). In another study carried out by Feldman and Salzberg (1990), the ability to detect differences between groups with respect to nausea and vomiting was limited due to the low prevalence rates of these symptoms. In addition, no blinding of the outcome assessor or method of randomisation was reported. The heterogeneity of the population (no detail given about types of cancer) and the fact that the patients recruited had chemotherapy experience (and thus a possible conditioned or learned response) prior to study are shortcomings that might affect the results. In a randomised controlled study conducted by Troesch et al. (1993), similar results were seen. Nevertheless, this study used a small sample size, and heterogeneity of cancer diagnosis among participants might have affected the outcome. Moreover, no blinding of the outcome assessor was reported. It is notable that although in guided imagery it is impossible to blind patients, blinding the outcome assessor is feasible (Roffe et al., 2005).

Reviewing the literature revealed that guided imagery did not have a significant effect on physical symptoms, such as nausea or vomiting; nevertheless, it has been suggested that guided imagery may be beneficial as a psycho-supportive adjuvant therapy for cancer patients (Feldman & Salzberg, 1990; Troesch et al., 1993; Roffe et al., 2005).

Most studies (Feldman & Salzberg, 1990; Troesch et al., 1993; Roffe et al., 2005) incorporated the use of audiotapes with guidance by a health practitioner. The use of audiotapes is often preferred over face-to-face sessions with a practitioner in order to reduce costs. However, adherence to the intervention and assessment of the outcomes might be affected. It was suggested that the effect size of guided imagery increased over the first five to seven weeks, but decreased at 18 weeks. Furthermore, although no adverse effects were reported in any of the trials, it was

not indicated whether any opportunities were specified for comments or follow-up discussions with a practitioner (Roffe et al., 2005).

In research conducted by Syrjala et al. (1992), only 45 participants completed the study and the results showed that levels of nausea and vomiting did not differ significantly between treatment groups. The authors justified factors which might limit the impact of either cognitive behavioural training or hypnosis on nausea and vomiting, as (1) the participants were receiving higher doses of emetogenic agents compared to the other cancer patients, (2) adequate training to learn relaxation techniques did not allow participants to be completely familiar with and master the techniques with milder symptoms before applying training to intense symptoms, as the most severe emetic challenge commenced directly with the first dose of chemotherapy, rather than having a gradual inception. Moreover, no information was provided about the method of randomisation and/or blinding of assessors. In addition, the measurement tools used [(The Sickness Impact Profile (SIP) and Brief Symptom Inventory (BSI)] to provide information on health status and psychological symptomatology pre-transplant are not suitable for measuring nausea and vomiting.

Askay et al (2009) argued that over the past 25 years, researchers have been investigating ways to make hypnosis more standardised and accessible; however, in spite of the encouraging scientific and clinical findings, hypnosis is not universally used in clinical practice. The authors signify that one reason for this is that the training and skill required for hypnosis entails considerable time and effort (Askay et al., 2009). In addition, cultural and religious factors may play a role in patient acceptance of hypnosis (Figueroa-Moseley et al., 2007).

Summary

Few studies have been conducted to examine the effectiveness of guided imagery or hypnosis in controlling CINV. It has been shown that guided imagery may be psycho-supportive and increase comfort; however, there is no significant evidence from trials to suggest that it has prophylactically antiemetic effects on CINV. In most studies, explicit descriptions of the intervention procedures and duration were lacking. Moreover, poor reporting of the studies' results make it difficult to draw firm conclusions.

3.6.4. Cognitive/virtual distraction

The effectiveness of cognitive distraction in reducing the adverse side effects of chemotherapy in adult cancer patients was assessed in only one RCT (Vasterling et al., 1993). Two crossover studies (Schneider et al., 2004; Schneider 2007) also explored the use of virtual reality as a distraction intervention to relieve symptom distress in adults receiving chemotherapy (Table 3-4).

Table 3-4: Summary of cognitive/ virtual distraction interventions used prophylactically to relieve chemotherapy- induced nausea and vomiting							
Author(s) / Country	**Research aim/ theme**	**Research approach / Participants**	**Findings / outcomes**	**Appraisal of study**	**Quality assessment/Grade**		**Strength of evidence**
(Vasterling et al., 1993)	To assess the effectiveness of cognitive distraction in reducing the adverse side effects of chemotherapy in adult cancer patients. It was designed as a prophylactic intervention.	RCT (2x3) factorial design/ 60 cancer patients were assigned to one of six groups, using a stratified random assignment procedure, formed by a 3(distraction, relaxation training, routine treatment control) x 2(high anxious, low anxious) factorial design.	Results indicate that distraction was an effective intervention for reducing the distress of chemotherapy (less nausea reported).	Small sample size, not considered all indictors to N&V experience.	Random adequate: Done Allocation concealment: Not used Blinding: Not used Baseline comparability: Done Dropouts accounted: Done Follow-up: Done Validation of tools: Not for N&V	1 0 0 1 1 1 0 Total:4	Considering methodological issues (study design and quality), might be affect the study and decrease the quality level of the body of evidence. Plausible bias raised some doubt about the results.

Table 3-4: Summary of cognitive/ virtual distraction interventions used prophylactically to relieve chemotherapy- induced nausea and vomiting							
(Schneider et al., 2004) United States	To explore the use of virtual reality as a distraction intervention to relieve symptom distress in women receiving chemotherapy for breast cancer. It was designed as a prophylactic intervention.	Crossover study/ 20 female breast cancer patients were assigned randomly to receive the virtual reality distraction intervention during one chemotherapy treatment and received no distraction intervention (control condition) during an alternate chemotherapy.	Decreases in symptom distress and fatigue occurred immediately following chemotherapy when participants used the virtual reality intervention.	Not enough information regarding the study given.	Random adequate: Not done/ not applicable Allocation concealment: Not used Blinding: Not used Baseline comparability: Done Dropouts accounted: Unclear Follow-up: Not done Validation of tools: Unclear	0 0 0 1 ? 0 ? Total:1	Limitations of given information about the study design and its implementation make it difficult to assess the strength of evidence of the study.
(Schneider 2007) United States	To explore VR as a distraction intervention to relieve symptom distress in adults receiving chemotherapy treatments. It was designed as a prophylactic intervention.	Crossover study/ 123 participants received the VR distraction intervention during one chemotherapy treatment and then received no intervention (control) during an alternate matched chemotherapy treatment.	No significant differences in symptom distress immediately or two days following chemotherapy.	Lack of sham arm, blinding.	Random adequate: Not done/ not applicable Allocation concealment: Not used Blinding: Not used Baseline comparability: Done Dropouts accounted: Unclear Follow-up: Not done Validation of tools: Done	0 0 0 1 ? 0 1 Total:2	Although the study suffered from a strong study design (RCT), it can be considered as a well-conducted study with suggesting low likelihood of bias.

In a study carried out by Vasterling et al. (1993), an attempt was made to use a homogeneous sample size; therefore, before randomisation, participants in each group were equated as closely as possible in terms of the site of cancer, the chemotherapy emetic potential and the antiemetic medication. However, other indicators, such as age or previous experience of nausea and vomiting, were not considered. The results of this study show that the effects of distraction and relaxation interventions were not significant for each measure at each session. Nevertheless, the authors support the use of cognitive distraction and relaxation training (as they were generally effective) in reducing chemotherapy side effects such as nausea and vomiting. Furthermore, the study indicated that distraction was as effective as behavioural relaxation. Therefore, using distraction would be a more appropriate intervention as it would be a more cost-effective than using professional therapists to provide relaxation training (Vasterling et al., 1993). Nevertheless, the authors suggest that more research is needed in this area.

Two crossover studies have been carried out by Schneider (2004, 2007); the first study had several shortcomings, such as small sample size, lack of sham arm and blinding, and questionable reliability of the measurement tools (which are not mentioned), which might have affected the results. In the second study, the author cited that the findings show that participants had an altered perception of time when using virtual reality, which validates the distracting capacity of the intervention. However, data analysis verified that there were no significant differences in symptom distress from chemotherapy (Schneider 2007). The author concluded that positive experiences of using virtual reality intervention did not lead to reducing symptom distress. It was stated that the findings support the idea that using virtual reality can influence patients to make chemotherapy treatments more tolerable. However, it was also suggested that health-care professionals should not suppose that use of virtual reality will improve chemotherapy-related symptoms (Schneider 2007).

Summary

In summary, it has been suggested that cognitive distraction may be effective with chemotherapy patients. Distraction might be the major active ingredient of behavioural interventions such as progressive muscle relaxation training. It was

shown that although the distraction and relaxation interventions were generally effective, their effects were not significant for each measure at each session. In particular, the effects were the strongest during the initial training sessions and weakest (or nonexistent) during the last training and/or follow-up session. This pattern of results suggests that the interventions may have had their major impact at the initial stages of treatment, when patients are least experienced in the nature and side effects of chemotherapy.

These interventions were more focused on reducing the psychological symptoms (distress) than the physiological symptoms, such as nausea and vomiting. Considering limitations relating to the consistency of the outcomes and results, it can be concluded that well-conducted trials with the aim of assessing the prophylactic effects of cognitive distraction/virtual reality interventions on CINV are needed.

3.6.5. Music therapy

The effects of using music to control nausea and vomiting among cancer patients receiving chemotherapy has been investigated in four experimental studies (two randomised control trials (Standley, 1992; Ezzone et al., 1998), one repeated measures design (an alternating fashion with the two conditions counterbalanced across participants) (Gimeno, 2010), and one pre-post test design (Karagozoglu et al., 2012) (Table 3-5).

Table 3-5: Summary of music interventions used to relieve chemotherapy- induced nausea and vomiting							
Author(s) / Country	Research aim/ theme	Research approach / Participants	Findings / outcomes	Appraisal of study	Quality assessment/Grade		Strength of evidence
(Standley, 1992)	To examine the effect of music on nausea and vomiting – related chemotherapy.	RCT/ before & after test. Using 4 groups (2 music groups & 2 control groups). 15 adults cancer patients (aged 38-73 yrs) undergoing 4 or more chemotherapy were randomly assigned to listen to music during Treatments 1-4 or during Treatments 2-5.	Both music groups reported less nausea than controls. The length of time before nausea onset was longer for the music groups. Benefits for nausea reduction were rated the lowest. No statistical information provided.	Small sample size. Not enough information regarding the study given.	Random adequate: Done Allocation concealment: Unclear Blinding: Not Applicable Baseline comparability: Done Dropouts accounted: Done Follow-up: Done Validation of tools: Unclear	1 ? 0 1 1 0 0 Total:3	Limitations of given information about the study design and its implementation make it difficult to assess the strength of evidence of the study.
(Ezzone et al., 1998)	To test whether use of music as a diversional intervention during high-dose chemotherapy administration would affect perception of nausea and episodes of vomiting.	RCT 33 patients undergoing bone marrow transplant randomised in the control group (n=17) and the music intervention group (n=16).	Differences were found between group scores on a visual analog scale for nausea and number of episodes of vomiting, demonstrating that the experimental group experienced less nausea and fewer instances of vomiting. No statistical information provided.	Small sample size. Lack of sham arm. Not enough information regarding the study given	Random adequate: Done Allocation concealment: Not used Blinding: Not used Baseline comparability: Done Dropouts accounted: Done Follow-up: Done Validation of tools: Unclear	1 0 0 1 1 1 ? Total:4	Limitations of given information about the study design and its implementation make it difficult to assess the strength of evidence of the study.

Table 3-5: Summary of music interventions used to relieve chemotherapy- induced nausea and vomiting							
(Gimeno, 2010) United States	To examine the effectiveness of music and imagery in managing acute and delayed post-chemotherapy nausea and vomiting.	20 (16 women and 4 men) participants allocated in 3 groups (guided imagery with music group [MI] , guided imagery[IO], and control and). Heart rate, nausea, and vomiting were measured before and after each of six intervention sessions.	Results indicated a statistically significant decrease on post-heart rate for MI as well as for IO interventions ($p < 0.01$). There were no statistically significant differences in heart rate, nausea, or vomiting between the two experimental interventions.	Small sample size. Risk of selection bias (16 women and 4 men). Not used control group. Heterogeneous sample (difference in medical diagnosis), difference in antiemetic and chemotherapy type and dosage.	Random adequate: Non Allocation concealment: Unclear Blinding: Not used Baseline comparability: Done Dropouts accounted: Unclear Follow-up: Done Validation of tools: Done	0 ? 0 1 ? 1 ? Total:2	The proportion of information from the study seems to be at high risk of bias and may sufficient to affect the interpretation of results.
(Karagozoglu et al., 2012) Turkey	To examine the effects of music therapy and visual imagery on CINV	Pre–post-test design consisting of 40 (9 female and 31 male) cancer patients.	Results indicated that music therapy and visual imagery reduced the severity and duration of CINV significantly ($p < 0.05$).	Small sample size. Risk of selection bias (16 women and 4 men). Lack of control group. Risk of delivery bias.	Random adequate: Non Allocation concealment: Non Blinding: Not used Baseline comparability: Done Dropouts accounted: Unclear Follow-up: Done Validation of tools: Done	0 0 0 1 ? 1 1 Total:3	Methodological issues (lack of a well-study design) might decrease the quality level of the evidence. Plausible bias raised some doubt about the results.

In a randomised controlled trial carried out by Standley (1992), patients listened to preferred music prior to and during chemotherapy for approximately 30 minutes. The results of this study show that the music groups reported less nausea than did the no-music groups. Patients who listened to music during chemotherapy experienced less nausea than those who did not, and that the length of time before nausea began was longer. However, this study is limited by a very small sample size, and was not done in conjunction with modern anti-emetics (such as the 5-HT3 receptor antagonists [ondansetron, granisetron, dolasetron, and palonosetron]). Moreover, the methodological limitations make it difficult to assess the strength of evidence in the study. In another randomised trial conducted by Ezzone et al. (1998), patients were randomly assigned to a control group (usual antiemetic protocol) or the intervention group (usual antiemetic group plus music during the 48 hours of high-dose cyclophosphamide administered as part of the preparative regimen). The study results showed that significant differences were found between group scores on a visual analogue scale for nausea and number of episodes of vomiting, indicating that the intervention group experienced less nausea and fewer occurrences of vomiting. However, the heterogeneity of the population in terms of diagnosis and treatment, given the small sample size, lack of sham arm and insufficient information regarding the method used, make it difficult to draw a firm conclusion.

A recent study by Gimeno (2010) aimed to examine the effectiveness of music in managing acute and delayed CINV. Participants in this study were drawn from a cancer population receiving chemotherapy, with different diagnoses and treatments. Two conditions were administered in an alternating fashion in this study; 10 participants began with the guided imagery with music condition, and 10 participants began with the guided imagery only condition. The first condition used music and verbal suggestion, and the second condition used verbal suggestion only (without music). Each participant received a weekly intervention session for a six-week period. Each session commenced during chemotherapy infusion and continued for the next five weeks, whether or not chemotherapy was administered weekly. The results of this study showed a decrease in the frequency and occurrences of nausea and vomiting across weeks. However, the investigator indicated that it is unknown whether this reduction was the effect of interventions,

and/or the therapeutic relationship that may have developed between the investigator and each participant, and/or the administration of antiemetic medications. Another limitation of this study was the method used for collecting data. It might have been more suitable to take data only during the week after the chemotherapy administration, rather than every week. In addition, the small sample size and lack of control condition/group are further shortcomings.

In line with previous findings, the most recent study conducted by Karagozoglu (2012) indicated that music therapy and visual imagery affect the levels of CINV and reduce the severity of perceived nausea and vomiting. However, this study also used a small sample size, and also lacked a control group; in addition, a risk of delivery bias might have affected the internal validity of the study.

Summary

The literature review has shown that only a few studies have been conducted to examine the effectiveness of music interventions in controlling CINV. Although these preliminary findings indicate that music can be used as an effective adjunct to a pharmacologic antiemetic regimen for lessening nausea and vomiting post-chemotherapy, and may improve the QoL in this clinical population, considering the methodological limitations relating to these studies revealed that additional research is needed to attain a clearer and more complete understanding of the specific relationships between music experiences and managing CINV.

3.7. Summary of the literature review

Several hypotheses have been proposed that attempt to explain how and why non-pharmacological interventions may be effective for cancer patients. These explanations range from simple placebo effects, to theories involving the conditioning or psychological process.

The literature review revealed that various degrees of effectiveness regarding the use of non-pharmacological intervention in preventing and controlling CINV (as prophylactically antiemetic interventions) have been achieved in previous studies. However, it is difficult to draw conclusions about the effectiveness of most of these interventions. For example, in 2005, Ezzo published a meta-analysis concluding that acupuncture combined with standard anti-emetics significantly reduced acute

CINV (relative risk: RR=0.82 (95%); confidence interval: CI=0.69, 0.99, p=0.04). However, remarkable differences were found in the modality, sample size and characteristics of participants regarding the previous nausea and vomiting experience and a wide variation in the acupuncture “dose” used in the trials (Bao, 2009; Ezzo et al., 2009). Moreover, there are several studies that find no effect from acupuncture/acupressure on CINV. For example, in 2007 and 2012 both Dibble and Genç found no effect of acupressure on acute CINV.

Various methodological flaws need to be rectified before conclusions can be drawn. For example, an attention-control group should be included and larger sample sizes should be employed to enable detection of significant differences with sufficient power. Moreover, boundaries between the various types of mind-body practices are blurred, and combinations of techniques are commonly employed according to the practitioner and the user. However, for a clear evaluation, individual therapies (ideally individual techniques) also need to be assessed in isolation (Roffe et al., 2005).

Methodological issues relating to the included trials, such as small samples, inadequate allocation concealment, and ambiguity about control for confounding and missing data, affect the strength of evidence. The inconsistency of the results and outcomes make it difficult to draw a firm conclusion. Therefore, it can be concluded that it is inappropriate to integrate such techniques in the patients’ direct care without the availability of scientific, unbiased evidence. More research, with well-designed trials, is needed in this area.

Moreover, most current non-pharmacological interventions require extensive provider training in order for the interventions to be effective as CINV management modalities. Most of them also require considerably more time and effort to administer, compared to the current standard therapies. Therefore, although there are promising results, it is necessary to examine more effective, less time-consuming and more cost-effective methods in this area.

A more recent such non pharmacological innovation is Nevasic audio programme. This may have potential to reduce chemotherapy related nausea and vomiting and may help for better management of these symptoms. Nevasic as a non-pharmacological intervention will be explored below.

3.8. What is Nevasic?

The manufacturer of the Nevasic programme suggests that Nevasic is an audio programme which uses specially constructed audio signals to generate an antiemetic reaction. It is suggested by the manufacturer that Nevasic may stabilise the balance receptors in the inner ear in order to provide relief from nausea. It is proposed that Nevasic may act by delivering engineered stabilising audio pulses and frequencies, which are present in music. In addition, the frequencies and pulses from the programme may desensitise and stabilise the vestibular system, while bordering on the recognisable audio spectrum. However, to date, no scientific justification has been provided for the use of this mechanism (http://www.nevasic.com/whats-nevasic.html).

3.8.1. Previous studies using Nevasic

From a review of the relevant databases, no study was found in relation to Nevasic (or Travelwell, which is an alternative name for Nevasic). However, from the Nevasic website, two studies regarding the effectiveness of using the Nevasic to increase tolerance to nauseogenic motion and morning sickness in pregnant woman were found (Table 3.6).

Table 3-6: Previous studies of Nevasic							
Author(s)	**Research aim/ theme**	**Research approach / Participant**	**Findings / outcomes**	**Appraisal of study**	**Quality assessment/ Grade**		**Strength of evidence**
(Sang et al., 2003)	To compare the effectiveness of controlling breathing and Nevasic on increasing tolerance to motion-induced nausea.	Crossover /24 healthy volunteers, 10 males and 14 females.	The music audiotape (Nevasic) provided significant protection against motion sickness.	Not enough information regarding study design given. Did not use validated tools to measure N&V. Reliability of used tools not determined.	Random adequate: Not used Concealment adequate: Not used Sham control: Yes Asses'r blind stated: No Dropouts accounted: Yes Follow-up: ? Validation of tools: Not used (not specific for measuring N&V)	0 0 1 0 1 ? 0 Total:2	Methodological issues (lack of a well-study design) might decrease the quality level of the evidence. Plausible bias raised some doubt about the results.
Winchester and Eastleigh NHS Trust	To evaluate the effectiveness of Nevasic in controlling the morning sickness in pregnant woman	No information given	Results showed 9 out of 10 pregnant women experienced a reduction or elimination of their symptoms of nausea and vomiting in morning sickness	No information given therefore it is impossible to evaluate the study.	Random adequate: Unclear Concealment adequate: Unclear Sham control: Unclear Asses'r blind stated: Unclear Dropouts accounted: Unclear Follow-up: Unclear Validation of tools: Unclear	? ? ? ? ? ? ? Total:?	No information given therefore it is impossible to evaluate the study.

In a study conducted by Sang at al. (2003), the effectiveness of using Nevasic (called Travelwell at that time) in increasing tolerance to nauseogenic motion was evaluated. A total of 24 healthy participants were recruited. Each participant was tested under three experimental conditions: controlling breathing, listening to music, or without intervention as a control. The order of testing was balanced across subjects, according to a replicated factorial design, and performed at approximately the same time of day, with an interval of at least one week in between each test. Motion sickness was provoked by whole body rotation coupled with head movements. The experience is similar to the disturbing sensations produced by nodding or rolling the head whilst rotating on a playground merry-go-round, but is much more intense.

The results showed that controlling breathing and listening to the music audiotape (Nevasic) provided significant protection against motion sickness. The authors indicated that their findings concerning Nevasic were the first to provide evidence from a controlled trial regarding Nevasic's efficacy as a motion sickness countermeasure. In addition, they stated that the mechanism of its action is unknown, and may involve distraction or a placebo effect, which may also be the case for other types of music. However, the authors performed exploratory tests with other techniques (e.g. a mental arithmetic task involving subtraction of serial sevens) which did not appear to be as effective as Nevasic, indicating that mental distraction cannot be the absolute explanation for the effectiveness of this method. Furthermore, there is some evidence that distraction or placebo effects do not, by themselves, appear to be very effective against motion sickness (Sang et al., 2003).

Sang et al.'s (2003) study suffers from several shortcomings and limitations. One is the lack of reliable tools used, particularly for measuring nausea and vomiting. Another is that the behavioural countermeasures were initiated once mild nausea was experienced. The study did not determine whether prior initiation of controlled breathing, or using the Nevasic audiotape (i.e. at the start of motion, prior to any symptoms), would have improved, or even degraded, the degree of protection afforded. Moreover, it was not reported whether the participants experienced any adverse effects, and no opportunities were specified for comments or follow-up discussions with a practitioner.

In another study, which was commissioned by the Winchester and Eastleigh NHS Trust in conjunction with mothers attending the Andover NHS Birth Centre, the effectiveness of Nevasic was evaluated in controlling morning sickness in pregnant woman. The results showed that 9 out of the 10 pregnant women studied experienced a reduction or elimination in nausea and vomiting from morning sickness by using Nevasic (branded as MorningWell) (http://www.nevasic.com/whats-nevasic.html).

No information was provided regarding the methodological issues (designing, conducting, and analysis) used in this study. Therefore, it is impossible to evaluate the study.

3.9. Conclusion

Overall, this review of the literature formed a strong empirical base that a) despite advances in antiemetic management, nausea and vomiting are still important problems in clinical practice; b) various non-pharmacological interventions (such as mind–body techniques), in addition to conventional anti-emetics, have been examined over the years and might be helpful in controlling post-chemotherapy nausea and vomiting, however, more research is needed; c) Most current non-pharmacological interventions require the extensive provider training in order for the interventions to be effective as chemotherapy related nausea and vomiting management modalities. In addition, most of them require far more time and effort to administer than the current standard therapies; and d) there is sufficient evidence to support the development of an intervention that can potentially reduce CINV and facilitate better management of these symptoms.

Using a novel programme, Nevasic, could potentially solve some mentioned problems and eliminate the need for the physical presence of a clinician at most interventions. With less dependence on the skill of a trained therapist, such simple technology may increase the capacity to reach a greater number of patients who could benefit from it. Nevasic, as a low-tech and cheap self-managed intervention with no (or minimum) side effects, is worth to evaluate the hypothesis behind it and examine its effectiveness on CINV. With the move toward telemedicine and providing more services to patients in rural areas and underserved regions, this is an exciting concept to explore.

The development of an intervention to prevent CINV would be enhanced with the use of a well-designed trial, and outcomes measures that have well-established reliability and validity (Ryan et al., 2011). Based on the findings of the literature review, the next chapter will present details of the methods, particularly the choice of methodology, sample recruitment, randomisation, and assessment and selection of tools.

Chapter Four: Research methods

This chapter is divided into two sections. The first explores potential different study designs to evaluate the effectiveness of interventions. The relationship between the research question(s) and design and components of this clinical study are explored and discussed. The methods of the feasibility study are presented, along with the rationale for any decisions that have been made. In the second section, working methods and details of the design of this trial, including the processes of sampling, data collection, and procedure, are described. In addition, a detailed examination of the validated measurement tools appropriate for use in the study is conducted.

4.1. Research design

4.1.1. Study question

What is the effect of using the Nevasic audio programme versus music intervention and standard antiemetic therapy (no intervention) on the rates of CINV in breast cancer patients?

4.1.1.2. Aim

To assess the feasibility of running a randomised controlled trial using the Nevasic audio programme to control CINV in female breast cancer patients.

4.1.1.3. Objectives

a) To assess the feasibility of recruitment procedures in an RCT using the Nevasic audio programme.

b) To evaluate the acceptability of the intervention and attention study arms to participating patients, and to understand the reasons for study attrition in both arms.

c) To estimate the burden (negative impact) on patients in the intervention and attention arms from participating in the study.

d) To assess the effect of Nevasic on CINV in female breast cancer patients.

e) To evaluate the suitability of using the chosen outcome measures.

4.1.2. The relationship between the research question(s) and design

The relationship between the question this research sets out to answer and the research design used to answer the question is fundamental to the whole research process. It is known that if an inappropriate design has been applied to answer a research question, the quality of the research project will be fundamentally undermined (Draper, 2004). To answer different research questions, different research designs and methods are needed (Closs & Cheater, 1999). Therefore, the most appropriate study design is dependent upon the nature of the question being asked. The chosen research design should be capable of answering the research question(s) (Bragge, 2010; Nichol et al., 2010). An appropriate and well-executed research design ensures that this is done in the most rigorous way possible (Closs & Cheater, 1999; Draper, 2004).

Therefore, the selected method should be the one that will be the most effective with respect to collecting the data needed to answer the research question, or to test the hypothesis. For this study, the research question involved examining the effect of using the Nevasic audio programme versus music and standard antiemetic therapy on the rates of CINV in breast cancer patients. A quantitative design was considered appropriate to examine the cause-effect relationship of an intervention. Therefore, quantitative research methods seemed to be the most appropriate for examining the effectiveness of the audio programme.

4.1.3. Level of evidence and choice of design

Study designs are often ranked from most to least robust in a “hierarchy of evidence” (Deeks et al., 2003). For clinical issues such as the effectiveness of therapy, this hierarchy ranks a systematic review of RCTs highest, followed by RCT (the highest ranked primary study), pseudo-RCT, non-randomised controlled study, and case series designs (Coleman et al., 2008). It should be noted that hierarchies of evidence differ according to the purpose of the research. For example, if the clinical issue is related to “prognosis”, a prospective cohort study – rather than an RCT – may be the highest ranked primary study design. The ranking or hierarchy of different study designs depends on the question being asked (Ryan et al., 2007).

As mentioned above, the method selected should be the one that will be the most effective to collect the data needed to answer the research question or to test the hypothesis. The question will also determine the most appropriate study design. In this study, the research question is related to the effectiveness of an intervention (therapy); therefore, an RCT could be the most appropriate design for such a study. In addition, considering the absence of any previous study examining the effect of Nevasic in managing post-chemotherapy nausea and vomiting, it is apparent that the strongest evidence that could be obtained from a systematic review (of clinical trials) was not applicable in this case.

Furthermore, the study question focused on comparisons, and how an intervention compared with an alternative intervention and control arms. It is documented that the most suitable type of study to investigate this kind of question is an RCT (Ryan et al., 2007). It has also been suggested that music (audio programme) therapy is generally not associated with negative side effects, and can be easily implemented with high treatment compliance (Brandes et al., 2010; Olofsson & Fossum, 2009a). Therefore, balancing the risk of harm with the potential benefit, and minimising the risk, which are the major ethical issues in conducting an RCT, should be given due consideration. Consequently, this question might best be answered with a randomised trial.

The choice of study design is also influenced by a variety of factors other than ranking in a hierarchy of evidence. These include the specific research question posed, and practical issues such as resources (staff, infrastructure, and time), feasibility and ethical considerations (Bragge, 2010). Although an RCT design has known superiority and high credibility in detecting cause-effect relations, it still has serious defects which diminish its value. These defects, usually known as study limitations, arise from unavoidable and/or unremarked absence of one or more important features or concepts of a well-designed RCT.

In this study, choosing an RCT design might be the most reliable form of scientific evidence in the hierarchy of evidence that reduce spurious causality and bias. However, this choice faced limitations such as time and resources. Recruiting patients and conducting an RCT usually takes a long time. It is known that time is an important aspect in any implementation study, and such a design might be

unsuitable for researchers with limited time, such as student researchers (Rubin & Babbie, 2009). In addition, lack of support staff with limited financial resources represents additional barriers to running such a clinical trial. Nevertheless, various strategies are applied to minimise the effect of these factors. These strategies are reviewed in the following section.

It is stated that RCTs are the most rigorous way to evaluate the effectiveness of interventions (Gatchel, 2001). However, most RCTs focus on outcomes, not on the processes involved in implementing an intervention (Oakley et al., 2006). In addition, it is suggested that qualitative and quantitative techniques should be combined to evaluate complex interventions in clinical research. For example, patients were interviewed following completion of the study to obtain their explicit perspectives on the interventions. This information added richness and depth to the quantitative data obtained from the trial (Iversen & Petersson, 2006). However, it might be argued that a combination of quantitative and qualitative data may not represent a true integration of quantitative and qualitative research, because one will tend to be subordinated to the other (Bryma, 2006). In the evaluation of an intervention, integrating quantitative and qualitative research may improve the rigour of the research, and provide guidance to others about what researchers intend to do or have done. In fact, multi-strategy research can be helpful to researchers in clarifying the nature of their intentions or accomplishments (Iversen & Petersson, 2006). Moreover, participants' perspectives on the intervention can help to identify how the intervention is implemented, distinguish between components of the intervention, investigate contextual factors that affect the intervention, monitor dose to assess the reach of the intervention, and study the ways in which effects vary in subgroups (Rychetnik et al., 2002). Qualitative approaches can improve understanding of the process of interaction, and may help to identify the ways in which patients benefit. In this study, one of the objectives was to assess the burden (negative impact) on patients from completing the study, and also to understand the reasons for study attrition and issues related to fidelity. Therefore, it was necessary to use complementary qualitative approaches to provide insight into the participants' beliefs, satisfaction and experience. Qualitative methodologies are ideal to investigate areas such as this, and to provide insight into the range of beliefs and experience (Bannister et al.,

1995). Focus groups are usually used to explore participants' experiences and ideas (Kitzinger, 1995); therefore, a qualitative, semi-structured focus group content analysis was considered appropriate.

Considering the absence of any previous study examining the effect of Nevasic in managing post-chemotherapy nausea and vomiting, it seemed prudent to investigate the feasibility of testing the intervention by conducting a pilot study. As this is the true nature of a working pilot (Beebe, 2007), it was apparent that the most appropriate evidence could be obtained by conducting a pilot RCT in an appropriate clinical setting. Additionally, one of the objectives of this study was to evaluate the acceptability of each of the study arm interventions to participating patients, and it is known that acceptability of interventions (which has implications for retention) can also be determined from pilot studies (Beebe, 2007). This underlines the importance of conducting a pilot study, which would also be a pre-requisite for successfully completing an RCT in the future.

4.1.4. Pilot study

There are a variety of methods by which to conduct pilot studies; these range from informally trying out procedures on a handful of participants, to efficacy studies, or to small-scale clinical trials of interventions (Hertzog, 2008). Most RCTs are costly and time-consuming (Lancaster et al., 2004). It is known that the feasibility of research methods and the cost of research procedures can be examined by conducting pilot studies (Beebe, 2007).

In a pilot study it is imperative to have clear aims and objectives to ensure for the pilot study's methodological rigour. Generally, the aims suggested for a pilot study can be assessed by considering the issues shown in Table 4-1.

Table 4-1: Main aims of running a pilot study	
Aim of pilot study	**Applicable to this study**
Feasibility	Yes
Integrity of study protocol	Yes
Recruitment and consent	Yes
Sample size calculation	Yes
Adequacy of instrumentation	Yes
Answering methodological questions	Yes
Randomisation procedure	Yes
Acceptability of intervention	Yes
Planning a larger study	Yes
Problems and testing of data collection strategies and proposed methods	Yes
Obtaining sufficient preliminary data to justify a grant award	Yes

Adapted from Beebe, 2007

The aim of this study was to assess the feasibility of running a randomised, controlled trial using the Nevasic audio programme to control CINV. It has also been documented that the main purpose of a pilot study is to discover how feasible it is to test the intervention (Becker et al., 2008). Feasibility, in general, covers a wide range of possible issues for identifying and resolving problems relating to implementing an intervention (Hertzog, 2008). Factors which can affect feasibility include methodological concerns, which require an estimation of population values, and are important for planning any future study; recruitment issues; sufficiency of resources; and procedural problems (Beebe, 2007). Time to complete questionnaires, rates of patient adherence, and attrition rates are some other examples of methodological concerns (Becker et al., 2008; Hertzog, 2008). Therefore, a pilot study is not just a small exploratory study aimed at the generation or refining of hypotheses (Becker et al., 2008). Although one of the outcomes of this study was to examine the effectiveness of Nevasic for the control of CINV, as mentioned above, the main outcome was to assess the feasibility of running a trial for the use of Nevasic. Hence, the study design, aim and objectives were set according to this main objective.

Conducting this pilot study could help to identify any design flaws, and develop strategies for data collection and analysis plans. Acceptability of the intervention, feasibility of recruitment procedures, and adequacy of instrumentation could also be determined from this pilot study.

When designing a randomised, controlled trial, several decisions concerning control strategies should be made. For example, researchers must decide whether to use a sham (false) treatment and, if a sham treatment is chosen, decide which one is appropriate for the study. It is challenging to design a sham protocol that is both ineffective (carries little or no therapeutic effect) and plausible (Noll et al., 2004).

4.1.5. Placebo control and selection of control groups

A comparison of the intervention with a placebo control is usually executed to determine the “true” effects of the intervention or new treatment, over and above any placebo effects (Dowrick & Bhandari, 2012). Understanding the strengths and weaknesses of the control group(s) used in an RCT is crucial, because comparisons of outcomes between the investigational and control groups form the basis of interpretations regarding the efficacy of the investigational treatment(s) (Au et al., 2007).

There are several positive attributes to carrying out a sham (attention) controlled trial. For example, from a methodological perspective, if the goal is to mimic the active treatment as closely as possible, then using an attention (placebo) arm is logical (Wilcox, 2008). However, selecting a comparator depends on complex factors, such as the research question being asked, the most plausible competing rival hypotheses, and considerations related to ethics, methodology and feasibility (Caspi et al., 2004).

The goal of using an attention arm is to control for the potentially therapeutic effects of the placebo (Noll et al., 2004), as it has been stated that placebos may improve outcomes in up to 30-40% of patients with a wide range of clinical conditions (Wilcox, 2008). Therefore, when a therapeutic intervention is being investigated, it may be even more important to include at least one control group that mimics the intervention (Wilcox, 2008). For this study, therefore, to control for the placebo effect and to mimic the intervention as closely as possible, an attention arm was used. As Nevasic therapy is presented in the form of music, the use of music for the attention arm was considered appropriate. In the next section, issues are explored regarding the selection of music for the research.

It has been suggested that in any trial comparing a treatment with a placebo control, it may be necessary to include a third arm of “standard medical treatment” in order to be able to account for the natural course of the disease or symptoms which are often put forward as possible reasons for the placebo effect. The “true” placebo effect can be interpreted by subtracting any benefit of the placebo from the usual treatment (i.e. non-treatment or observation) and comparing that to any benefit of the active treatment (Dowrick & Bhandari, 2012). Therefore, a randomised, controlled clinical trial with a three-parallel arm (intervention: using the Nevasic (active sounds) plus usual care (standard antiemetic therapy); attention: listening to music plus usual care (standard antiemetic therapy); and control: receiving usual care (standard antiemetic therapy) was employed for this study to avoid a methodologically flawed study design.

4.1.6. Selection of music

Music therapy, as an intervention, is attractive because it is regarded as readily available, non-invasive, low cost, and easy to distribute (Olofsson & Fossum, 2009b). Music therapy is presented, and may be conceived, in various ways (Aldridge, 1993a); therefore, there are several issues that should be considered when using music as an intervention. Some concerns relevant to this study are discussed here.

In music therapy one challenging issue is who selects the music (researcher (therapist) or participant (listener). This has been explored by a number of authors in music therapy (Clark et al., 2006; Pelletier, 2004; Krout, 2007; Engwall & Duppils, 2009; Wheeler & Baker, 2010).

In a systematic review of music as an intervention for postoperative pain (Engwall & Duppils, 2009), one of the research questions concerned music and music selection. The results showed that in most studies, the research team either selected the music (7 studies) or asked the participants to choose from a selection of various types of music which had been suggested by investigators (5 studies). In just one study (Taylor et al., 1998) the participants brought their own music, and in one other study (Tse et al., 2005) the participants had the choice of either bringing their own music, or choosing from a selection derived by the investigator (Engwall & Duppils, 2009).

Engwall and Gill (2009) argued that although it has been acknowledged that consideration of the individual's musical preference is imperative and can contribute to the therapeutic effect, only in two studies were the participants allowed to bring their own music. It is notable that in spite of this, the majority still reported significant findings regarding the effect of music on participants. Furthermore, in the study where patients brought their own music, there were no significant differences in outcomes between the music and control groups (Engwall & Duppils, 2009).

In a randomised, controlled trial carried out by Clark et al. (2006), patients who listened to self-selected music reported lower anxiety and treatment-related distress (Clark et al., 2006). In a meta-analytic review of research articles in music therapy, the author pointed out that using pre-selected music had a greater effect than music selected by the listener (Pelletier, 2004). It has also been documented that in passive music therapy, whereby the patient, or a group of patients, listen to a therapist who plays live, or to recorded music, the music is often chosen by the research team to suit particular patients (Aldridge, 1994). However, there is no "gold standard" approach, and each investigator has developed an individual way of applying their particular therapy, which is adapted to meet the needs of each patient (Aldridge, 1993b). Therefore, for this study, it was considered appropriate for the participants to choose from a selection made by the investigator.

4.1.6.1. Other factors influence music selection

It is well known that the individual's response to music is influenced by factors such as earlier experiences of music, gender, age, culture, mood, and attitude (Olofsson & Fossum, 2009b). Therefore, considering these factors are crucial when selecting music for use in music therapy (Wheeler & Baker, 2010). For this study, among the factors mentioned, type of music and cultural issues (as the study setting was Iran) required specific consideration.

4.1.6.1.1. Type of music

Krout (2007) argued that consideration of music preference is an important factor when choosing what music to listen to as part of a relaxation experience or regimen, because music which is perceived to be soothing or relaxing to one

person may not be so for another. Nevertheless, there are several other factors that may be helpful to bear in mind when selecting music. The elements that are often found in music composed for relaxation and classical, include a slow and stable tempo (pace or speed), low volume level and soft dynamics, consistent texture (combination of sounds and instruments), absence of percussive and accented rhythms, gentle timbre (sound or tone colour), legato (connected) melodies, and simple harmonic or chord progressions (Silverman, 2010).

4.1.6.1.2. Culture and music therapy

While there is a broad range of literature covering the application of music therapy as a therapeutic medium, most studies that use music are conducted in a Western context. Furthermore, there is an almost complete absence of cross-cultural studies, which may bring other insights into music therapy (Aldridge, 1994).

Wheeler and Baker (2010) suggest that music therapists, or researchers who use music, need to be aware not only of the music itself, but also the meaning of music in other cultures. It is acknowledged that music therapists (or researchers) must be familiar with cultural issues, including values, beliefs and cultural teachings (Aldridge et al., 2003). Moreover, it has been documented that one of the cultural and ethical implications involved in music selection is the protection of clients' rights, since clients from different cultures may be vulnerable, or have been oppressed, and therefore require particular sensitivity (Wheeler & Baker, 2010). The individual's music preferences and accuracy in terms of the choice of music are essential considerations that contribute to the stated therapeutic effect (Engwall & Duppils, 2009). As the setting of this study was Iran, it was necessary to consider the Iranian culture and how it is interwoven with peoples' lives, customs, and Persian poems, with respect to current cultural restrictions and whether music therapy could be of true medical value (Abdollahnejad, 2004), since using music as a treatment modality might be looked upon with scepticism by the culture in question. Moreover, most studies conducted recently in Iran regarding music therapy interventions (Moradipanah et al., 2009; Taghinejad et al., 2010) chose to use relaxing music, which seems to be more culturally accepted in Iran. Therefore, with the above information in mind and considering the patients' situation (their feeling after chemotherapy), a selection of music was provided for

the participants to choose from. The suggested music was relaxing and calming, and was either accompanied by the sound of ocean waves, consisted of soft classical music, used slow/soft melodies, or was peaceful pan flute music without lyrics or words. The music lasted 20–30 mins in duration (as suggested by Krout, 2007).

The next section explains the working methods and the design choices made for the pilot RCT.

4.2. Working methods

4.2.1. Research hypotheses

The pilot study was primarily concerned with feasibility issues; the secondary objectives of the study were to examine the following research hypotheses:

H1: Female breast cancer patients using the Nevasic programme report less nausea and vomiting compared with the attention and control groups.

H2: Female breast cancer patients using the Nevasic programme experience higher HR-QoL compared with the attention and control groups.

4.2.2. Participants

A determination of the most appropriate population from which to draw the sample for this study was made with reference to the literature discussed in section 2.6.2, regarding risk factors relating to CINV. The intention was to select from the population most likely to experience the symptoms of interest. Therefore, female breast cancer patients were considered as the target population for the study because, firstly, females experience nausea and vomiting more often than males (Levin et al., 2009); secondly, breast cancer is the most common cancer among women, with a high percentage of unsolved post-chemotherapy nausea and vomiting (Levin et al., 2009); and thirdly, the most common chemotherapy regimens for the treatment of adjuvant breast cancer (anthracyclines) are considered to be moderately high emetogenics.

Younger patients (<40 years) are more likely to experience nausea and vomiting after chemotherapy (Wiser & Berger, 2005; Levin et al., 2009); therefore, the variable of age was stratified to ensure that there would be adequate representation of patients aged <40 vs. >40 years in the three study groups.

4.2.2.1. Inclusion criteria

To be included in the study, the patients had to be:

1) Diagnosed with breast cancer (i.e. had medically confirmed breast cancer (a histological breast tumour with no metastasis)).

2) Aware of diagnosis.

3) Chemotherapy naive.

4) Female.

5) Aged over 18 years, and legally independent with respect to signing the consent form.

6) Scheduled to receive moderately high emetogenic chemotherapy of equivalent regimens. Moderately high emetoginic chemotherapies in the study were Anthracyclines (Daunorubicin, Doxorubicin, and Epirubicin): AC [Doxorubicin Hydrochloride (Adriamycin) (60mg/m2) and Cyclophosphamide (600mg/m2) intravenous (IV)], CAF [Cyclophosphamide: 600mg/m2, Doxorubicin: 60mg/m2, and 5-Fluouracil: 600mg/m2) IV] and CMF [(Cyclophosphamide: 600mg/m2, Methotrexate: 40mg/m2, and 5-Fluouracil: 600mg/m2) IV]. All of the patients included in the study were scheduled to receive standard anti-emetics. The regimen that was generally used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy at the sites at the time of recruitment was bolus intravenous doses of 8mg Ondansetron (Zofran TM) or any equivalent 5-HT3 RA (such as Granisetron 3mg) plus Dexamethasone 8mg. Anti-emetics were given prophylactically 30–60 mins before the start of chemotherapy for acute CINV control, followed by oral doses for the first two days; these were then continued with 10-20mg Metoclopramide three times a day, as necessary, for the following days for delayed nausea and vomiting.

7) Able to read and write in Persian (Iranian language): participants were able to read and write in Persian (and have at least a primary school education) in order to complete the questionnaires and provide informed consent.

4.2.2.2. Exclusion criteria

Patients, who had any other disease, were undertaking any concomitant treatment which might affect the severity of their nausea and vomiting, had any condition resulting in them not being able to listen to Nevasic or relaxation music, or were participating in another trial which could have influenced this study, were excluded. Specifically, patients were excluded if they:

1) Were unable to understand or cooperate with study procedures.

2) Had medical conditions which could affect nausea and vomiting perception and severity. Many medical conditions or treatments have been found to influence patients' nausea and vomiting sensitivity, while conditions such as metastases, gastrointestinal problems (ulcer, obstruction, gastritis, oesophageal reflux disease, hiatus hernia, pharyngeal irritation, and chronic heartburn ulcer), and concurrent treatment (i.e. radiotherapy) can lead to a worsening of the nausea and vomiting experience. Vestibular causes (middle ear infection/VIII tumours, brain tumour, and central nervous system) could cause ongoing nausea and vomiting (Wiser & Berger, 2005; Keeley, 2008).

In contrast, participating in antiemetic drug studies or using another therapy (i.e. hypnotherapy) may improve the symptom experience. Therefore, patients with any of the above conditions were excluded from the study (Miller & Kearney, 2004; Jakobsen & Herrstedt, 2009).

3) Were receiving other cancer treatments (e.g. radiotherapy) at the same time as receiving chemotherapy.

4) Were participating in another research study which may have interacted with this study, or affect nausea and vomiting perception.

5) Had hearing difficulties or were unable to listen to Nevasic or relaxation music.

4.2.3. Sample size

The main purpose of conducting a pilot study is to examine the practicality of an approach, including: the feasibility of recruitment, randomisation, rates of recruitment, attrition and non-compliance, assessment procedures, and implementation of the novel intervention (Leon et al., 2011). A pilot study is not statistically powered. Inferential statistical tests are usually used in a hypothesis testing study. Therefore, power analyses are used to determine the sample size that is needed to provide adequate statistical power to detect a clinically meaningful difference with the specified inferential statistical test. Power analyses are presented in an application for a hypothesis testing study, but not a pilot study. In fact, a pilot sample size is usually based on pragmatic issues and the necessity

of examining feasibility (Leon et al., 2011). For this pilot study, therefore, no formal sample size calculation was conducted.

Lancaster et al (2004) suggested that 30 participants per group is an adequate sample size for a pilot RCT. Hertzog (2008) suggested that 30 per group may be required for a good estimation of the recruitment and attrition rate. For this study, 30 participants seemed feasible in terms of time and resources, and a 20% attrition rate by the study end point was derived from previous studies conducted in the site (Tatari et al., 2009 ; Jangjoo et al., 2010). It was planned to randomise 114 participants equally to one of three groups, with 38 per group.

4.2.4. Sampling and setting

The trial used a convenience recruitment method, as neither the centres nor the participants were randomly selected. However, the participants were randomly assigned to either 1) the intervention, 2) the attention, or 3) the control group using randomised lists (generated by a sample size calculation programme called nQuery Advisor), constructed by a statistician who was independent of this study.

It was proposed that the study was conducted in the out-patient chemotherapy department of Omid cancer research hospital in Mashhad, Iran, which is one of Iran's leading cancer centres and serves a population of 7 million across Khorasan province. This research centre was affiliated to Mashhad University Medical Sciences (MUMS) (http://www.mums.ac.ir/omid/en/history). During 2008, 1,074 people were diagnosed by this centre as new cancer cases. The number of new female breast cancer cases was 208 in the same year. Based on two previous research studies conducted by Tatari et al. (2009) and Jangjoo et al. (2010) with female breast cancer patients at this site, it was expected that approximately 20% of the patients would not meet the inclusion criteria and/or would not be interested in participating in the pilot study. It was expected that approximately 114 participants would be recruited in the allotted 9-month recruitment period. However, within the first month of the trial, it became apparent that the recruitment rate was lower than expected. Thus, the protocol was changed to include two additional centres as the study setting. The second centre was a hospital with an oncology department and out-patient chemotherapy unit. This hospital was also

affiliated with MUMS. The third centre was a radiation and oncology centre that was run by a charity.

4.2.5. Trial arms

This was a placebo-controlled, pilot randomised trial with three parallel arms (intervention, attention, and control).

4.2.5.1. Intervention: Nevasic programme

It was proposed that using Nevasic is safe, as it is documented that music (audio programme) therapy is generally not associated with negative side effects (Brandes.V & al., 2010). It is advised that the Nevasic music should be listened to when suffering or enduring the symptoms of nausea and/or vomiting, and not if there are no symptoms. General guidance and instructions provided by the manufacturer regarding use of the programme are:

1) Start Nevasic at the first signs of symptoms of nausea or vomiting.

2) Listen to Nevasic all the way through, or until you are comfortable, repeat if your symptoms return.

3) When your symptoms stop – stop using Nevasic.

4) Nevasic must always be listened to via headphones.

5) To maintain complete freedom, it is suggested that a portable player is used.

6) Do not attempt to skip any part of Nevasic in an effort to speed up the process of relief.

7) It is not necessary to lie down while using Nevasic.

8) Do not use through ambient speakers - ALWAYS use headphones.

9) Do not play in car stereos (http://www.nevasic.com/nausea.html).

Although it is possible to use speakers, cars stereos, etc., it is recommended that Nevasic be listened to through headphones. It has been proposed that the active components of the programme can be easily overwhelmed by the other components by listening to the track using specific equipment; for example

speakers allow too much dilution of the working components before they reach the ear; consequently, it is claimed that great amounts of efficacy will be lost (http://www.nevasic.com/nevasic.html).

It is stated that music therapy predominantly refers to listening to music using a headset. This may be convenient in terms of both avoiding causing disturbances to others, and reducing disturbance to the listener (Chlan, 2000). Listening with headphones also seals off external noise, which may enhance the listener's attention.

Participants received their standard anti-emetics prophylactically 30–60 mins before the start of their chemotherapy infusion. They were asked to take their anti-emetics post-chemotherapy as prescribed.

4.2.5.2. Attention: music

The procedures for the attention group were the same or similar to those used for the intervention group, except for the "active" component of the intervention, as Nevasic's frequencies and pulses concealed by an over-layer of music. Participants in the attention group listened to selected music which had previously been downloaded onto their CD player. Participants could choose one kind of the music and listen to it as soon as they felt nausea after chemotherapy administration. The music was discontinued either when the nausea stopped, or after 27 minutes had elapsed. The patients were instructed to listen to the music according to guidance provided on an instruction sheet. They were asked to listen to the music whenever they felt nausea for five days following chemotherapy. The participants received their standard anti-emetics prophylactically 30–60 mins before the start of their chemotherapy infusion. They were asked to take their anti-emetics post-chemotherapy as prescribed by their physicians.

4.2.5.3. Control

Participants in the control group received only their standard anti-emetics prophylactically 30–60 mins before the start of their chemotherapy infusion. They were asked to take their anti-emetics post-chemotherapy as prescribed.

4.2.6. Study outcome measures

As this was a feasibility study, the data collected was used to assess the practicality of patient recruitment and the suitability of the randomisation procedure and protocol violations. The suitability of the data collection instruments was also considered. In this section, potentially relevant data collection instruments are reviewed and the most appropriate tools for use in this study identified.

4.2.6.1. Measurement instruments for nausea and vomiting

Patient reporting is considered a gold standard for symptom assessment and the best technique to measure the subjective and unobservable experience of nausea compared with other behavioural measures, such as observer rating and physiological approaches (Brearley et al., 2008). However, such tools must be able to accurately and reliably measure the symptoms.

A variety of tools have been developed to measure the experience of nausea, vomiting and retching among patients in different settings (Table 4-3). These scales have been used either to illustrate patients' experience, or to measure the efficacy of a new antiemetic medication or non-pharmacological intervention (Brearley et al., 2008). Each instrument for measuring nausea, vomiting and retching has its own characteristics, benefits and weaknesses (Wood et al., 2010).

The chosen scale should comprehensively assess the dependent variables. Moreover, the scale's clarity, validity, reliability and the time frame for recalling events should be considered. In addition, the tools to measure nausea and vomiting should be able to describe the specific components, such as domains (nausea, vomiting, retching), phases (anticipatory, acute, delayed), and aspects (duration, frequency, severity, distress) (Wood et al., 2010). For this study, the choice of measurement tools was made by referring to criteria suggested by (Fitzpatrick et al., 1998) (Table 4-2), and recommendations from Brearley et al. (2008) and Wood et al. (2010) (Table 4-3, 4-4).

Table 4-2 : Criteria for choosing the measurement tools(Fitzpatrick et al., 1998)	
Criteria	**Explanation**
Appropriateness	How well does the instrument match the specific purpose and questions of the study?
Reliability	The instrument should be reproducible and internally consistent. This is measured by Cronbach's alpha (α), which can range from 0.0 to 1.0. measurement instruments with α values less than 0.70 should not be employ, ratings in the 0.70 s show moderate reliability, those in the 0.80 s indicate good reliability and α values of >0.90 indicate redundancy.
Validity	Does an instrument measures what it aims to measure?
Responsiveness	Whether an instrument is able to detect change.
Precision	The number and accuracy of distinctions made by an instrument.
Interpretability	How meaningful are the scores from an instrument.
Acceptability	How acceptable an instrument is for respondents to complete.
Feasibility	With the extent of effort, burden and disruption to staff and clinical care arising from use of an instrument.

The most popular self-reporting questionnaires in terms of their reliability, validity and usefulness as clinical assessment tools, and comparisons of these, are displayed in Table 4-3.

Table 4-3 : Some of the self-assessment nausea and vomiting measurement tools (Fitzpatrick et al., 1998; Brearley et al., 2008)							
Criteria	**INVR***	**MAT***	**NV5***	**FLIE***	**MANE***	**MANE-FU***	**CINE QoL***
Appropriate-ness	It covers all domains, phases, and aspects of CINV.	Nausea and vomiting specific measure	It covers all phases of CINV	More about QoL than measurement of N&V	N&V(NOT retching) measure	N&V(NOT retching) measure	N&V measure.
Reliability	Spearman correlation coefficient (for total INVR) r=0.87. Individual items 0.71 to 0.95.	Cronbach α=0.77	Cronbach's α=0.85	Internal consistency Cronbach's α=>0.9	Mean test–retest reliability at 4th cycle r=0.76 to 0.96	Does not appear to have been tested for reliability	Cronbach α from 0.59 to 0.85. Test–retest coefficient from 0.44 to 0.84.
Validity	High rate of agreement between INRV and INV-2.	Spearman's correlation (MAT and INVR) ranged from 0.44 to 0.99.	Validated for use with the EORTC QLQ-C30 tool.	Pearson correlation between FLIE scores (after treatment) and patient reported nausea and vomiting, r=−0.65 and −0.68, respectively. Correlation of nausea related subscale with FLIC nausea related factor=0.83.	Construct validity r=0.26 to 0.33	Does not appear to have been tested for validity	Positive correlation between the two EORTC nausea and emesis items, the Osoba module, and the retching module.
Responsive-ness	Measures all three dimensions, plus the duration of nausea and amount of vomiting using five response options.	Assesses the domains of N&V through the acute and delayed phases of CINV, treating each as distinct phenomena.	Measures N&V in all three phases and domains N&V, plus quantify the occurrence, frequently, intensity and duration.	It is designed to evaluate symptoms related to the first 24 h post-chemotherapy (acute phase), and the subsequent 48-h period (initial delayed phase).	Measures anticipatory and acute N&V. (frequency, severity and duration).	Measures anticipatory and acute N&V (frequency, severity , duration and occurrence).	Measures all three dimensions plus frequency, occurrence and severity of N&V.

Table 4-3 : Some of the self-assessment nausea and vomiting measurement tools (Fitzpatrick et al., 1998; Brearley et al., 2008)							
Precision	It can conceivably cover anticipatory, acute and delayed phases.	Each phase is assessed by four items that measure the occurrence of CINV, duration of Nausea(10-point scale) and frequency of vomiting (number of episodes)	It assess impact on functioning (appetite, sleep, physical, social, enjoyment) and antiemetic use	It focuses on the impact of CINV on daily functioning, particularly quality of life after chemotherapy	Frequency, severity limited to 24-h post-treatment	Frequency, severity limited to 24-h post-treatment	Lack of clarity over the exact nature of items.
Interpretabili-ty	Using 5 response options. use a straightforward scoring system to produce sub scores (for the domains) and global scores	Straightforward to assess.	Needs interpretation	Use a straightforward scoring system to produce sub scores (for the domains) and global scores	Needs interpretation	Needs interpretation	Needs interpretation
Acceptabilit-y	Easy to complete. 8 items	Easy to complete. Take about 4 min to complete. 8 items	5 items in 4 Likert scale: N&V	18 items	Total number of items unclear (14/16/17)	16 items	Long instrument, with duplication of items
Feasibility	Self-administered every 12 hours	Self-administered.	Self-administered. Requires information to be added by the clinical team before administration.	Self-administered	Self-administered	Self-administered	Self-administered at baseline, after this administered by phone. Require training time

* Abbreviations: INVR=Rhodes Index of Nausea, Vomiting and Retching; MAT= Multinational Association of Supportive Care in Cancer Anti-emesis Tool; NV5= Osoba nausea and vomiting quality-of-life module; FLIE= The Functional Living Index-Emesis; MANE= Morrow Assessment of Nausea and Emesis; CINE QoL= Chemotherapy-Induced Nausea and Vomiting –Quality Of Life

4.2.6.1.1. Rhodes Index of Nausea, Vomiting and Retching

The Rhodes Index of Nausea, Vomiting and Retching (INVR) was designed to measure the severity of nausea and vomiting, and includes subjective and objective measurements. It is an eight-item instrument that uses a five-point Likert scale and consists of three subscales: nausea (range, 0–12), vomiting (range, 0–12), and retching (range, 0–8), giving a total range of 0–32. It measures the frequency, distress and duration of nausea, and the amount of vomiting (Rhodes & McDaniel, 1999). It focuses on all three domains (nausea, vomiting and retching), and the occurrence, amount and duration of these (Rhodes et al., 2000). In INVR, the vomiting assessment addresses volume as measured in cups. The instrument is designed to be administered every 12 hours (morning and evening), and can conceivably cover anticipatory, acute and delayed phases (Brearley et al., 2008). The INVR was developed from the INV-1 and INV-2 (Chou et al., 2005), both of which showed good levels of reliability (Belluomini et al., 1994; Zhou et al., 1999), (Cronbach's α=0.89–0.97 and 0.98, respectively) and good concurrent validity, with a correlation coefficient of 0.87 (Rhodes & McDaniel, 2001; Chou et al., 2005). The INV-2 has been used in numerous countries and a variety of disciplines, including oncology, obstetric and post-anaesthesia, and in medical and surgical patients (Fu et al., 2002; Chou et al., 2005). Prior studies have proven that the INVR, a new format of the INV-2, is reliable, more consistent, and more user-friendly than the INV-2 (Rhodes & McDaniel, 1999). It has been used in several clinical trials (Farley et al., 1997; Martin et al., 2000; Dibble et al., 2003), and has also been translated into Chinese and Korean languages (Glaus et al., 2004; Kobayashi et al., 1999).

4.2.6.1.2. The MASCC Anti-emesis Tool

Developed by the Multinational Association of Supportive Care in Cancer, the MASCC Anti-emesis Tool (MAT) assesses the domains of nausea and vomiting (but not retching) during both the acute and delayed phases of CINV. However, it is not able to assess nausea and vomiting in the anticipatory phase. Nausea and vomiting are measured in acute and delayed phases by four items which measure the occurrence of CINV, duration of nausea (10-point numerical analogue scale),

and frequency of vomiting (number of episodes) (Molassiotis et al., 2007a; Brearley et al., 2008). It cannot measure the volume of vomiting.

The MAT is a short, self-administered scale (eight items), which can be used in clinical practice. It can be used as a communication tool to facilitate discussions between clinicians and patients about their nausea and vomiting experience after chemotherapy, thereby providing opportunities to plan appropriate interventions or modify antiemetic regimens before the next chemotherapy cycle. In a prospective study by Molassiotis et al. (2007), it was found that the MAT is a feasible instrument, which aids patients' symptom management, and increases their satisfaction with treatment. However, before using the MAT in clinical trials, its responsiveness and sensitivity to changes in nausea and vomiting over time must be demonstrated (Molassiotis et al., 2007a). Furthermore, there is no evidence of its use in research or practice (Brearley et al., 2008). It is also unable to measure the intensity of nausea and vomiting (Table 4-4). In addition, it does not use a scoring system, and there is no assessment of the impact on function (Wood et al., 2010).

4.2.6.1.3. Osoba nausea and vomiting quality-of-life module (NV5)

The NV5 is a retrospective, 5-item (4-point Likert scale) instrument, based on the design of the EORTC QLQ-C30 scale. It contains five questions related to the impact of nausea and vomiting on appetite, sleep, physical activities, social life and enjoyment of life. The NV5 possesses sufficient reliability and validity to be used in conjunction with the QLQ-C30 (the Osoba module has not been validated for use on its own) (Miller & Kearney, 2004). NV5 represents a modular approach to assessing anticipatory, acute and delayed nausea and vomiting, and to quantifying the occurrence, frequency, intensity and duration of CINV, and its impact on functioning (Miller & Kearney, 2004; Brearley et al., 2008). However, it is a long instrument (potentially 69 items with the additional tools), and needs information input from the clinician prior to administration (Brearley et al., 2008).

4.2.6.1.4. The Functional Living Index – Emesis 5-day recall

The FLIE instrument was replicated after the FLIC. It is designed to assess symptoms related to the first 24 hours following chemotherapy (acute phase), and

the subsequent 48-hour period (initial delayed phase). It contains 18 items, with 9 items in each of the domains of nausea and vomiting measured on a seven-point visual analogue scale which are completed on day 1, before chemotherapy, and again at the end of day 3 (as opposed to day 5, as in the FLIE 5-day recall) (Lo & Hayman, 1999). However, minimal attention has been given to quantifying the aspects of occurrence and amount of nausea and vomiting.

Although the FLIE is a validated nausea- and vomiting-specific tool, it focuses on the impact of CINV on some aspects of daily functioning, such as: ability to enjoy meals/liquids, ability to prepare meals/do household tasks, ability to perform daily functions, ability to perform usual recreation/leisure activities, and willingness to spend time with family and friends, rather than as a record of the incidence or severity of CINV (Brearley et al., 2008; Martin et al., 2003).

4.2.6.1.5. MANE/MANE-FU

The MANE scale is a retrospective tool, which asks separate questions in the areas of anticipatory and post-treatment nausea and vomiting. There is an inconsistency in the literature about the number of items in the scale (which varies from 14 to 17). The scale assesses two phases of CINV (anticipatory and acute), and its focus falls within the first 24 hours following treatment. While the MANE is a fairly self-explanatory scale in terms of its completion, the scoring system is not described and is not self-evident. Moreover, no attention is given to functional impact (Brearley et al., 2008).

4.2.6.1.6. CINE-QoL

The CINE-QoL was intended to combine broad QoL measures with symptom-specific measures to generate a single, standardised measure. It uses the three existing scales (European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the Osoba Nausea and Emesis Module, and the MANE). It is a long instrument which consists of (more than) 57 items (EORTC: 28 × 4-point Likert scale, 2 × 7-point numerical analogue scale; Osoba: 5 item x 2: 4-point Likert scale: nausea/vomiting, retching and MANE: nausea, vomiting and retching plus items about satisfaction with antiemetic treatment and treatment in general). The lack of clarity about the content and administration of this tool, along with the

obvious duplication of items, makes it rather confusing as to how the CINE-QoL was intended to be used in practice (Brearley et al., 2008). Table 4-4 summarises the measurement tools for nausea, vomiting, and retching.

Table 4-4: Summary of measures for nausea, vomiting, and retching (Brearley et al., 2008; Wood et al., 2010)

Tools	Nausea				Vomiting				Retching				Phase			No, of questions	Period	Scale
	Duration/	Frequency/	Severity/	Distress	Duration/	Frequency/	Severity/	Distress	Duration/	Frequency/	Severity/	Distress	Anticipatory/	Acute/	delayed			
* INVR	X	X	-	X	-	X	X	-	X	-	X	X	X	X	X	8 Questions	Previous 12h	5-Point Likert
MAT	X	-	X	-	X	X	-	-	-	-	-	-	-	X	X	4 Questions	Once per chemotherapy cycle	Yes/no, NRS for nausea severity
NV5	- .	X	-	-	-	-	X	-	-	-	-	X	X	X	X	4 Questions (2 questions if yes, Then Likert)	Past week	Yes/no, plus 5-point Likert
FLIE	X	-	-	-	X	-	-	-	-	-	-	-	-	X	X	18 Questions	Past 5 days	7-Point Likert (100-mm VAS)
MANE	X	-	X	-	X	-	(X)	X	-	-	-	-	X	X	-	5 Questions with multiple components	During and until 24h after treatment	Yes/no, no. of h, Likert scales
MANE-FU	X	-	X	-	X	-	-	X	-	-	-	-	X	X	-		Timing	Time when worse
CINE QoL	X	X	X	-	X	X	X	-	X	X	-	-	X	X	X	57 items (description of the items in the scale exceeds 57)	During and until 7 days after chemotherapy	38 Likert scale, 2×7 numerical pt analogue scale

* Abbreviations: INVR=Rhodes Index of Nausea, Vomiting and Retching; MAT= Multinational Association of Supportive Care in Cancer (Roila et al.) Anti-emesis Tool; NV5= Osoba nausea and vomiting quality-of-life module; FLIE= The Functional Living Index-Emesis; MANE= Morrow Assessment of Nausea and Emesis; CINE QoL= Chemotherapy-Induced Nausea and Vomiting –Quality Of Life

4.2.6.2. Choosing the nausea and vomiting instrument

When asked about their chemotherapy experience, patients may not report having had an emetic episode if no matter was expelled. This can potentially reduce assessment information. By separating out the retching experience, a more complete understanding of the patient's experience may develop (Wood et al., 2010).

Several tools (MAT, FLIE, MANE, and MANE-FU) do not include all three nausea, vomiting and retching symptoms. Moreover, three characteristics of nausea are typically measured by only two tools (INVR and CINE-QoL). Of the tools that address nausea, many have been designed to focus on the patient's more broad functional status or QoL issues (NV5, CINE-QoL, FLIE). It is imperative to minimise the potential for an additional burden being placed on patients by the use of lengthy assessment tools such as NV5, with potentially 69 items with the additional tools, and which also needs information input from the clinician before administration or CINE, which contains 57 items.

Considering all of the above-mentioned factors (Table 4-3, 4-4) (such as differentiating between nausea, vomiting and retching, assessing each component of nausea and vomiting separately, reliability, easiness to complete, and requiring little or no training or time to explain usage to patients), the INVR seems to be the most appropriate tool to use for this study. It has also been suggested that the INVR is an accurate and effective research-based instrument, and is the better choice of instrument to be translated (Fu et al., 2002). Moreover, as the participants were followed for a short period to measure nausea and vomiting experience on different occasions, it was necessary to use an instrument that maximises the information gathered, whilst minimising burden (negative impacts) to the patient. The INVR (<10 items) is considered to be easy to administer, with a completion time of between 5 and 10 minutes (Appendix 4).

As the setting for the research was cancer centres in Mashhad, Iran, and the INVR had not been translated to Persian prior to this study, an initial requirement was to translate the tool. The process of translation and the psychometric tests used are explained in the following chapter.

4.2.6.3. Choosing a Health-Related Quality of Life (HR-QoL) instrument

QoL is a multidimensional concept, which is considered a crucial aspect of clinical and social care. The main aim of using a QoL assessment in clinical trials is to provide an additional outcome measure for comparisons and evaluations of different interventions or treatments (Holzner et al., 2006). QoL outcomes are ideal for determining the efficacy and impact of a treatment or intervention in cancer care (Ferrans, 2010). The importance of including a HR-QoL measure in clinical trials relates to the scale's capacity to guide a treatment decision by comparing the HR-QoL state before and after the examined intervention (Enzo & Fausto, 2003). The impact of CINV on patients' QoL is often substantial (Ballatori et al., 2007), and therefore any statistical improvement detected in the HR-QoL follow-up scale compared to the baseline scale could provide additional information about the effectiveness of a treatment.

HR-QoL questionnaires vary in their content and coverage. Generally, QoL instruments are recognised as generic or disease-specific. Generic tools are intended to measure QoL generally – typically across all the domains of life. In contrast, disease-specific instruments are used to focus on a specific type of cancer or treatment. Beyond the issue of disease specificity, HR-QoL questionnaires may focus on particular treatments such as hormone therapy or chemotherapy (treatment-specific), or symptoms such as pain or nausea (symptom-specific) (Ferrans, 2010; Luckett et al., 2010). Most available cancer HR-QoL scales are designed to evaluate the balance between side effects and HR-QoL during conventional treatment (active cancer phase); some are created for palliative care populations, when curative treatment is impossible; and others are designed for cancer survivors (Holmes & Dickerson, 2003).

To select the best and most appropriate instrument for any study, the aim(s) of the study, the target population, and the anticipated treatments, symptoms, and adverse effects should be considered as the most important factors in order to determine the most appropriate tool(s). Other vital points of consideration are the tool's sensitivity, which refers to its ability to distinguish between different clinical groups (e.g. those undergoing vs. not undergoing treatment), and responsiveness, which is its ability to register clinically important changes in HR-QoL over time.

Furthermore, other factors (some of which have been mentioned above), such as reliability, validity, guidance for interpretation of scores, ease of use and scoring, cost for permission for use and cultural appropriateness, should be also considered (Ferrans, 2010; Luckett et al., 2010).

There are several well accepted and psychometrically tested questionnaires currently in use; however, it has become increasingly unlikely that one instrument can be regarded as a "gold standard". Three of the most popular instruments used with cancer patients are: the European Organisation Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC QLQ-C30), the Functional Assessment of Cancer Therapy (FACT/FACIT) and the SF-36 Health Survey (Browall et al., 2008; Ferrans, 2010). Table 4-5 shows a comparison of these instruments against Fitzpatrick's (1998) criteria.

Table 4-5: Comparison of three commonly used HR-QoL instruments

Criteria	EORTC QLQ-C30	FACT/FACIT	SF-36
Appropriateness	Cancer specific measure	Cancer patients measure (cancer-specific).	Generic measure of QoL
Reliability	Alpha coefficient between 0.72 and 0.79.	The Cronbach's alpha of the total scale is 0.89 and the subscales range from 0.82 to 0.69.7(Winstead-Fry & Schultz, 1997).	The Cronbach's alpha coefficient range from 0.77 to 0.93 (Apolone & Mosconi, 1998).
Validity	There is evidence for satisfactory internal consistency and clinical validity(Nicklasson.M & B, 2007).	Pearson correlation with the FLIC was between 0.79- 0.84 (Cella et al 1993; Winsted-Fry& Schultz 1997).	SF-36 scales have been shown to perform with about 80–90% empirical validity in studies involving physical and mental health "criteria". r = 0.40 or greater (WareJr & Gandek, 1998).
Responsiveness	Statistically significant changes in functional and symptom levels were observed for those patients whose performance status had either improved or deteriorated (Aaronson et al., 1993).	Able to show statistically significant changes in the total score and subscales (Cella et al 1993; Winsted-Fry& Schultz 1997). FACIT is more sensitive and responsive than the FACT-G (Luckett et al., 2010).	Designed to measure generic health status (Sanson-Fisher. R.W & Perkins.J.J, 1998).
Precision	Measure QoL among cancer patients with general cancer or specific disease by using the scale and the specific-disease module. Measure : Physical functioning (5 items); role functioning (2 items); emotional functioning (4 items) Social functioning (2 items) Cognitive functioning (2 items) Pain, fatigue, and nausea and vomiting (2 items each) Dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact (1 item each) A global health status/quality-of-life scale (2 items)	Measure four domains of quality of life: Physical well-being (7 items), Social/family well-being (7 items), Emotional well-being (6 items), Functionalwell-being (7 items, including global QoL question).	Measure 9 domains of QoL: Physical functioning (10 items) Role limitations due to physical problems (4 items), Bodily pain (2 items), General health (5 items) ,Vitality (4 items) Social functioning (2 items), Role limitations due to emotional problems (3 items), Mental health (5 items), Perception of change in health over the past year (1 item) (Luckett et al., 2010).
Interpretability	The directions given by the scale developers	The directions given by the scale developers.	The directions given by the scale developers
Acceptability	Easy to complete (most patients are able to complete the questionnaire without assistance).	Easy to complete. Have 27 items with a 5 point Likert response format.	Easy to complete
Feasibility	Self-administered. Take about 11-12 min to complete. Contains 30 items.	Self-administered	Self-administered. Take 5-10 min to complete.

4.2.6.3.1. The European Organisation Research and Treatment of Cancer-Quality of Life Questionnaire

The EORTC QLQ-C30 is designed to measure the physical, psychological, and social functioning of patients with cancer. It is considered one of the most practical, valid and reliable methods to measure QoL among cancer patients with general cancer or specific diseases by using a scale and specific-disease module (Bottomley et al., 2005). EORTC QLQ-C30 version 3 is the most commonly used measure in oncology (Fayers & Bottomley, 2002; Rodary et al., 2004). It is a short core measure for general use with cancer patients, and can be supplemented by additional modules (Fayers & Bottomley, 2002). The EORTC QLQ-C30 scale (Appendix 1- 2) contains 30 items. The first 28 use a 4-point Likert-type self-reported scale, which is coded as “No at all”, “A little”, “Quite a bit”, and “Very much”, while the remaining 2 questions are 7-point numerical scales (Fayers & Bottomley, 2002).

4.2.6.3.2. Functional assessment of cancer therapy

The Functional Assessment of Cancer Therapy – General (FACTG) questionnaire has been adopted as a modular approach based on a core questionnaire and cancer-site-specific modules. This instrument is the most frequently used measure in the USA (Rodary et al., 2004). Functional Assessment of Chronic Illness Therapy (FACIT) was adopted in 1997 to portray the expansion FACT series of questionnaires into other chronic illnesses and conditions. Therefore, FACIT is a broader, more encompassing term that comprises the FACT questionnaires under its umbrella. FACT-G has been developed and modified several times. However, it is believed that these modifications have not compromised the demonstrated reliability and validity of the questionnaires, and all investigators are recommended to use the new version (Rodary et al., 2004; Fairclough & Celia, 1996). FACT-G (Version 4) is a 27-item set of general questions that are divided into four primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being (Rodary et al., 2004).

In a study conducted by Rodary et al. (2004), 737 cancer patients completed both EORTC QLQ-C30 and FACT-G. The results showed that although the same percentage of patients (19%) preferred the QLQ-C30 and the FACIT, the FACIT

had the greater number of missing data items (9% versus 5%, P<0.001) and scored the highest rates for items considered inadequately worded (29% versus 19%, non-significant) or intrusive (24% versus 3%, P<0.001). As a result, the authors concluded that the QLQ-C30 is the most acceptable questionnaire to use.

4.2.6.3.3. SF-36 health survey

The SF-36 is a generic measure of QoL, which assesses health-related dysfunctions in daily living areas and measures change over time. The SF-36 includes one multi-item scale assessing eight components: limitations in physical activities; limitations in social functioning; limitations in role activities because of physical health; general mental health; limitations due to emotional problems; vitality; and general health perceptions (Yost et al., 2005).

Scores for these eight scales can be combined into two summary scales: the physical component summary scale, and the mental component summary scale. The SF-36 was designed to assess general health status; however, it has often been interpreted as a measure of health-related QoL (Yost et al., 2005).

4.2.6.4. Comparison of measurement tools for quality of life

Ferrans (2010) states that there are several differences in these three instruments (EORTC QLQ-C30, FACT, SF-36 Health Survey) regarding what they actually measure, which mean that they will all provide different information. Therefore, the items (questions) in the instruments themselves should be examined in order to identify which one provides the best and most appropriate information for the situation and use. For example, FACT-G mainly measures symptoms (3:1 ratio of symptom to functioning items), EORTC QLQ-C30 is similar, but more balanced (3:2 ratio of symptom to functioning items). SF-36 mostly measures functioning items (1:2 ratio of symptom to functioning items). In addition, there are no questions about general health perception in FACT-G, only one in EORTC-QLQ C30, and two in the SF-36. There is one item regarding overall QoL in both FACT-G and EORTC-QLQ C30, while no item or question aims to assess QoL in SF-36 (Ferrans, 2010).

The study was conducted in Iran, and the most common instrument to measure HR-QoL among cancer patients in Iran is EORTC-QLQ C30 (Iranian version); the

validity and reliability of this instrument has been confirmed (Safaee & Dehkordi, 2007). Considering all the above-mentioned factors regarding choosing an instrument for measuring QoL, EORTC QLQ-C30 appears to provide the best fit for the present study.

In addition, breast cancer module (BR23) which is a supplementary questionnaire module employed in conjunction with the QLQ-C30. It can provide more detailed information relevant to evaluating the QoL in specific patient populations (breast cancer). The module comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective (Appendix 2). The validity and reliability of this supplementary questionnaire has also been confirmed (Aaronson et al, 1993; Safaee & Dehkordi, 2007).

4.2.7. Study questionnaires

It is known that the quality and quantity of data collected from each participant might be influenced by the questionnaire design (Streiner & Norman, 2004) . A good questionnaire design for a clinical trial will minimise bias and maximise precision in estimates of the effectiveness of an intervention. Several guidelines exist for questionnaire development, which may help investigators to design a questionnaire for a clinical trial. These guidelines insist that the form and content of the information collected should be in full accordance with the protocol, and should focus on the data necessary to implement the planned analysis required to confirm protocol compliance or identify important protocol deviation. The designed questionnaire, in compliance with study outcomes, should measure parameters of interest (Edwards, 2010).

For this study, some attempts have been made to develop appropriate self-administered questionnaires based on published literature and existing guidelines. These questionnaires were divided, based on the time when they were to be completed, into two parts. Part one, the baseline data, consisted of questions related to socio-demographic variables which might influence participants' experience of nausea and vomiting after chemotherapy. These variables included age, educational level, marital status, experience with nausea in the past, such as during pregnancy, motion sickness or nausea when eating certain foods, and

experience with other complementary therapies used to manage nausea in the past. This part was administered at baseline (before starting the chemotherapy), prior to randomisation. The participants were also requested to fill out the QoL-C30 (plus BR23) questionnaires at baseline, and on day 6 following chemotherapy (the primary time-point was day 6 post chemotherapy). Medical information such as cancer diagnosis, stage of disease, chemotherapy protocol used and dosage was obtained from the patients' medical records.

Part two, the treatment progression, served as a daily diary of the patients' nausea and vomiting experience over the study period (Table 4-6). A short (structured) questionnaire was designed to collect data about how often participants used Nevasic in the intervention group, or listened to music in the attention group. Patient satisfaction with using Nevasic (intervention group) or listening to music (attention group) and perceived effectiveness were determined by completing two 6-point Likert scales. On day 6, participants in all groups were asked to answer questions about their experience of using Nevasic, listening to music or being in the control group. A free text response to a questionnaire was available to ensure participants had an opportunity to report unanticipated issues, and provide more feedback on their thoughts and feelings (Appendix 3 - Study questionnaires).

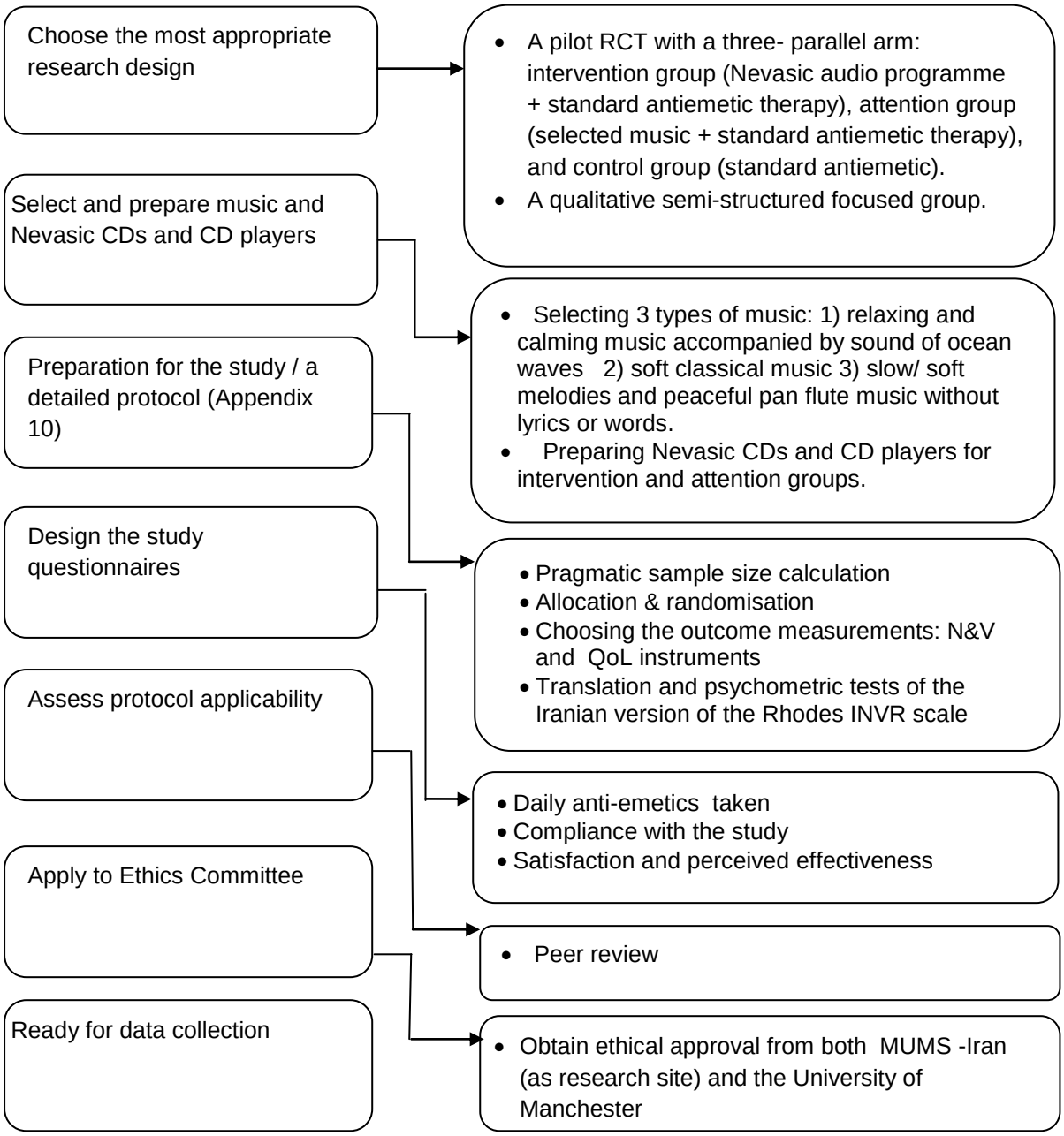
Table 4-6: Study Instruments and timing of administration

Time	Instrument
D-1 or D1 (prior to chemotherapy administration)	QoLC30 (Plus BR23) questionnaires Socio-demographic data questionnaire
D1 (evening of chemotherapy administration)	Daily diary of sickness's questionnaire
D2 – D5 (daily in the evening)	Daily diary of sickness's questionnaire
D6 (in evening)	Daily diary of sickness's questionnaire.
D6 (evening or later)	QoL C30 (Plus BR23) questionnaires. Questionnaire about experience of study.

4.2.8. Study preparation

The preparation step is a crucial part of any trial. It is always not straightforward, and may take a long time to complete before the trial can be conducted. In this pilot RCT, several steps were completed before implementation. The steps are shown in Figure 4-1, and explained in this chapter.

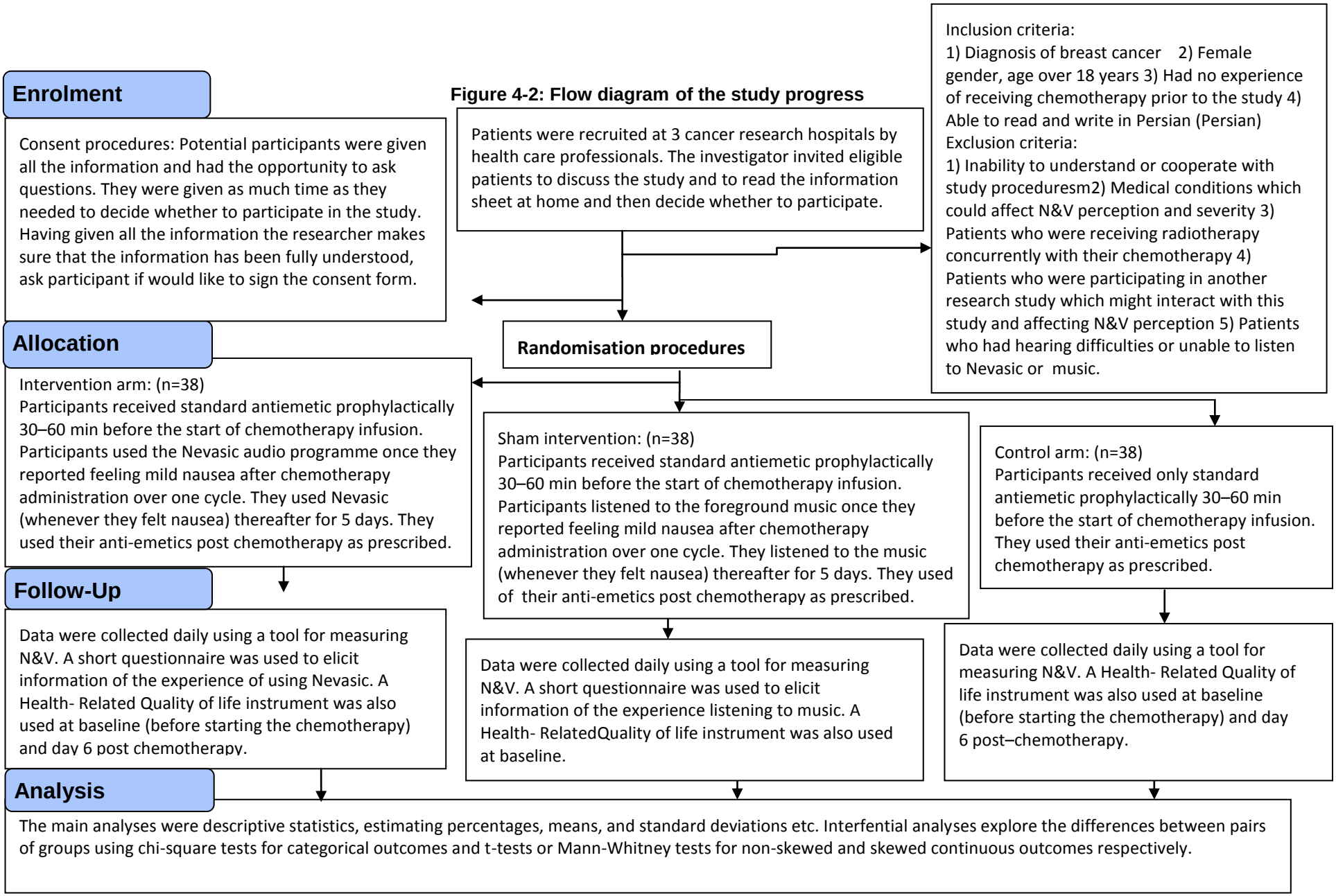
Figure 4-1: Research preparation steps flowchart



4.2.9. Overview of the study structure

The pilot RCT incorporated a three-parallel arm: intervention group (Nevasic audio programme plus standard antiemetic therapy), attention group (selected music plus standard antiemetic therapy), and control group (standard antiemetic therapy). The study was conducted at three cancer research hospitals in Mashhad, Iran. Figure 4-2 illustrates the structure of the study.

Figure 4-2: Flow diagram of the study progress



4.2.10. Procedures

The researcher attended the chemotherapy unit at all three cancer research hospitals (in Mashhad, Iran) for a few days prior to recruitment, in order to introduce the study to the health-care professionals (oncologists and nurses) and provided them with a study pack which contained an information sheet, invitation letter, and consent form (Appendix 7-8). The oncologists were requested to identify suitable patients and invite them to participate. The oncologists briefly explained the study to eligible patients, and then introduced them to the researcher. The invitation letter and information sheet were given to potential patients by the researcher at that time. Patients were given detailed information about the study and the research process by the researcher; the same explanations were given to all patients to reduce bias. They then had the opportunity to ask questions.

On the day of the patients' chemotherapy, or one day before, having been given all the information, which was confirmed by the researcher as being fully understood, the potential participants were asked to sign a consent form. The participants were then randomised to one of the three groups using a computer-generated list. After randomisation, the participants in the intervention and attention groups were given a CD player, patient instruction sheet (Appendix 9), and study questionnaires.

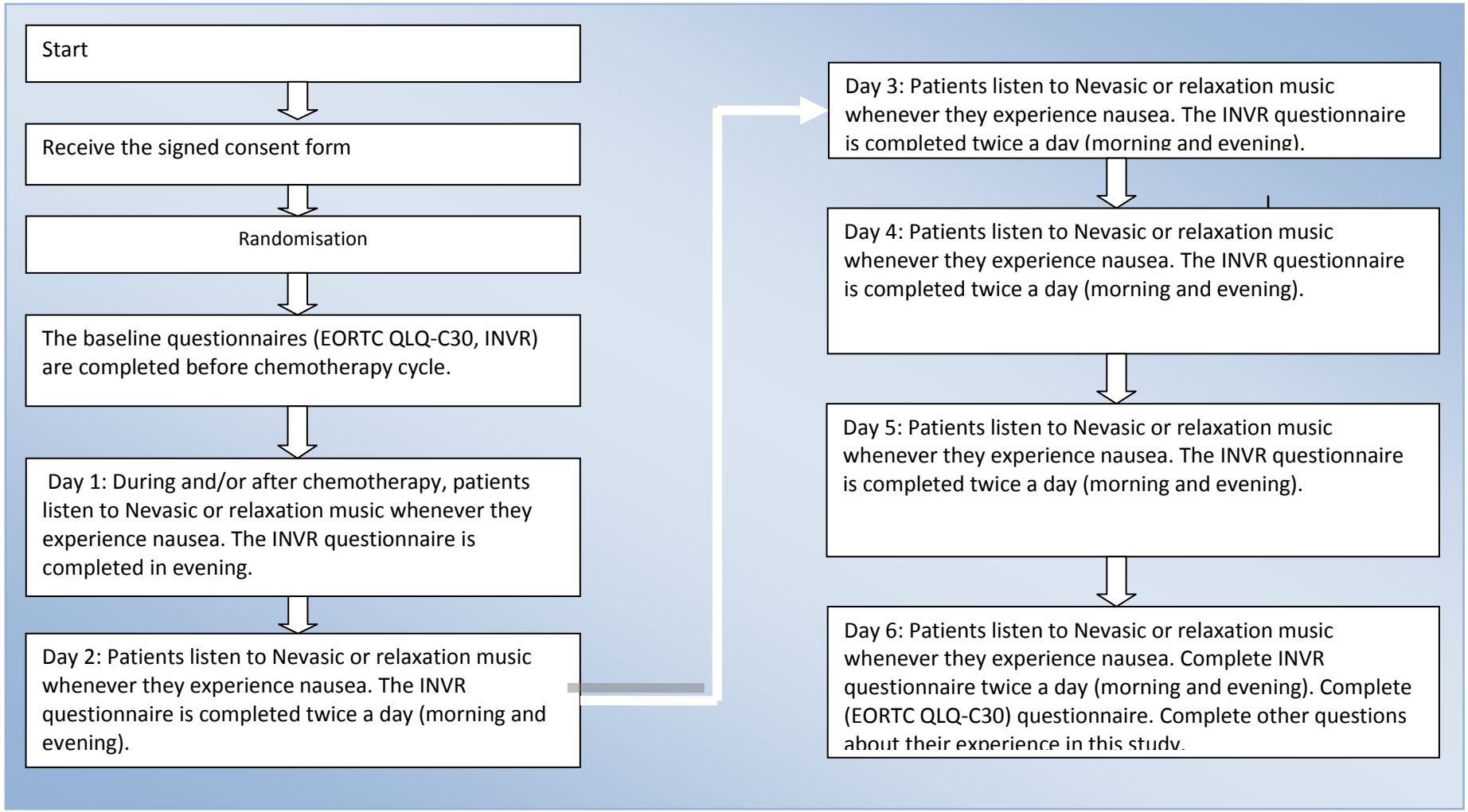
The participants were instructed by the researcher as how to complete the measures and follow-up questionnaires. The participants were asked to return the measures (except for the EORTC QLQ-C30 and BR23 questionnaires, which were completed prior to starting the chemotherapy) and questionnaires via pre-stamped envelope. A two-week time limit was allowed to elapse before a reminder letter was send to prompt their reply, as participants may have forgotten to post it. Permission to send a reminder letter was sought during the initial meeting or contact.

On the day of their chemotherapy, the participants (in every group) were asked to hand over the completed EORTC QLQ-C30 and BR23 questionnaires to the researcher or chemo nurse (prior to starting the chemotherapy). The participants received their antiemetic prophylactically at least 30 minutes before chemotherapy

administration. The participants in the intervention group received Nevasic through their CD player and headphones once they reported feelings of nausea. The manufacturer of Nevasic states that it works to control nausea or vomiting only when the relevant symptoms of these are present. Therefore, the participants were asked to use Nevasic as soon as they felt nausea after chemotherapy administration. The use of Nevasic was discontinued either when the nausea stopped, or after the 27 minutes of the Nevasic programme time had elapsed. The participants in the intervention arm used Nevasic for 6 days whenever they felt nausea. The patients were instructed to use Nevasic according to the general guidance and instruction regarding using the programme provided by the manufacturer and mentioned in the information sheet.

The study process, from signing the consent form until returning the questionnaires, is summarised in Figure 4-3.

Figure 4-3: Implementation flow chart



Socio-demographic and treatment characteristics were obtained from the patients' records and the patients themselves. Details of any medication used (standard and rescue anti-emetics) during the study period were also obtained from the pharmacy records. The total daily intake of the prescribed antiemetic medicines, the regular intake and the pro re nata (PRN – as necessary doses) were measured by a related question in the study questionnaire. This question aimed to compare the anti-emetics used across all three arms of the trial. It may be impossible to determine whether all participants genuinely followed the instructions or completed the study questionnaires correctly. Therefore, there is a risk with respect to judging whether the effect is genuinely related to the intervention (Nevasic or music), or is only a (delayed) response to the anti-emetics. However, the data were compared and analysed across the groups (not individuals); therefore, potential differences among the groups could be assessed.

4.2.11. Focus groups

To assess the burden on patients to complete this study and also to understand the reasons for study attrition, some participants (who completed the study and/or accepted to participate however did not adhere to the study) were invited to semi-structured focus groups. The selection based on the criteria that they had something to state on the mentioned topics and were comfortable talking to the interviewers and each other and prepared to engage in the discussion. Limited the number of specific questions (6 to 8 questions regarding issues with questionnaires, listening to music or Nevasic, practical ability to use them and adherence to the study and ended with any suggestions or questions) were designed and asked participants to freely talk about them. The sessions were run by the researcher and an oncologist from cancer research centre affiliated to MUMS.

Participants did not know each other; therefore it prevented set behaviours relating to pre-existing relationships and encouraging more honest and spontaneous expression of views and a wider range of responses (Rabiee, 2004). However, the researcher attempted to create an environment in which the participants feel relaxed and encouraged to engage and exchange feelings, views and ideas about the matters that came up for discussion. In addition, the researcher and the

oncologist observed non-verbal interactions. Exchanges of views and the general content of discussion were documented. Observational notes were written immediately after each focus-group interview.

Each group interview lasted approximately one and half hour and was tape-recorded with participants' consent. Four sessions were hold in the main site (Omid cancer research centre) and one session was hold in Reza radiation and oncology centre. All the participants were informed about their time commitment.

Data were analysed using thematic content analysis. After each session recorded data were transcribed, read repeatedly and extra and irrelevant information was removed. Taken notes were compared and key points were discussed. Then data were categorised and tabulated and an agreed list of themes was formulated in order to address the initial goal of the study. A constant process of comparison and contrast of themes was employed to write a description of the patients' perceptions. Frequencies of themes were used to assist in determining their importance in the interpretations of the participant's answers to the interview questions. In order to minimise the potential bias in analysing and interpreting data, the analysis was systematic, sequential, and continuous.

4.2.12. Barriers and strategies to improve recruitment

It is well known that recruiting participants to clinical trials can be extremely difficult, and this makes it challenging to detect a treatment effect. Consequently, low participation rates may delay the potential introduction of new treatments (Fayter et al., 2007; Treweek et al., 2010). Difficulties in recruitment can lead to delays, increased cost, protocol changes, an underpowered study (which limits the statistical power of the trial in terms of detecting a treatment effect), and even premature closure (McNair et al., 2008; Treweek et al., 2010). McNair et al. (2008) cited that (in England) approximately 4% of patients with a new diagnosis of cancer were recruited into clinical trials in 2001. In addition, Fayter et al. (2007) indicated that adult participation stood at 10.9% of incident cancer cases in the UK.

Researchers use various interventions to improve recruitment. Although there have been numerous systematic literature reviews detailing a variety of underlying

difficulties in carrying out RCTs, there remain few strategies to improve recruitment to trials, and the ones that do exist are of limited quality (Salis et al., 2008).

In order to examine the potential efficiency of the methods employed, seven systematic review studies (Hunninghake et al., 1987; Ross et al., 1999; Abraham et al., 2006; Fayter et al., 2007; Rendell et al., 2007; Treweek et al., 2011; Treweek & Loudon, 2011), which aimed to undertake a systematic review of the relevant literature, and also three studies (Wragg et al., 2000; McNair et al., 2008; Salis et al., 2008) relating to the barriers, modifiers and strategies to improve recruitment of participants to RCTs, were explored. These studies investigated factors influencing patient participation in trials (from the patient perspective and/or health-care professional perspective), assessed the evidence, and quantified the effects of strategies to improve the recruitment of participants to RCTs. The findings were summarised according to two broad categories: recruitment barriers (Figure 4-4), and interventions and strategies to improve recruitment to RCTs (Figure 4-5).

These review studies evaluated the effect of strategies to improve recruitment to RCTs. However, as mentioned by almost all the authors listed above, the interventions used in these studies varied significantly and made it difficult to pool data. Additionally, most studies failed to provide clear evidence of any benefits. Several studies were small, and carried a great risk of bias. Hypothetical trials included in these reviews made it unclear how applicable their results were to real trials. However, a few interventions to increase recruitment do appear to be effective, and may be worth using as strategies to improve recruitment in RCTs.

Figure 4-4: Identified barriers to participations in randomised controlled trials

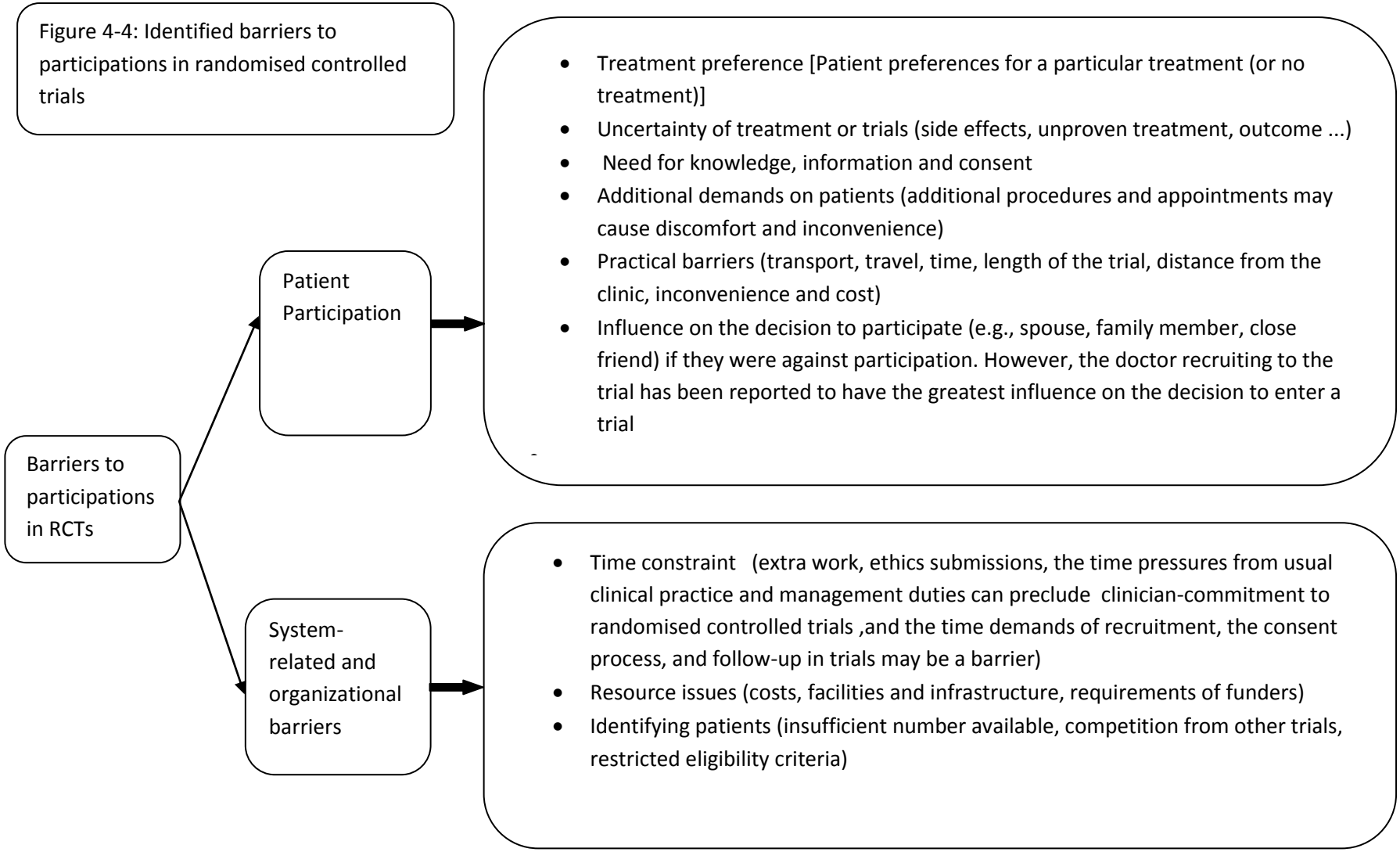


Figure 4- 4: Identified barriers to participations in randomised controlled trials **(continued)**

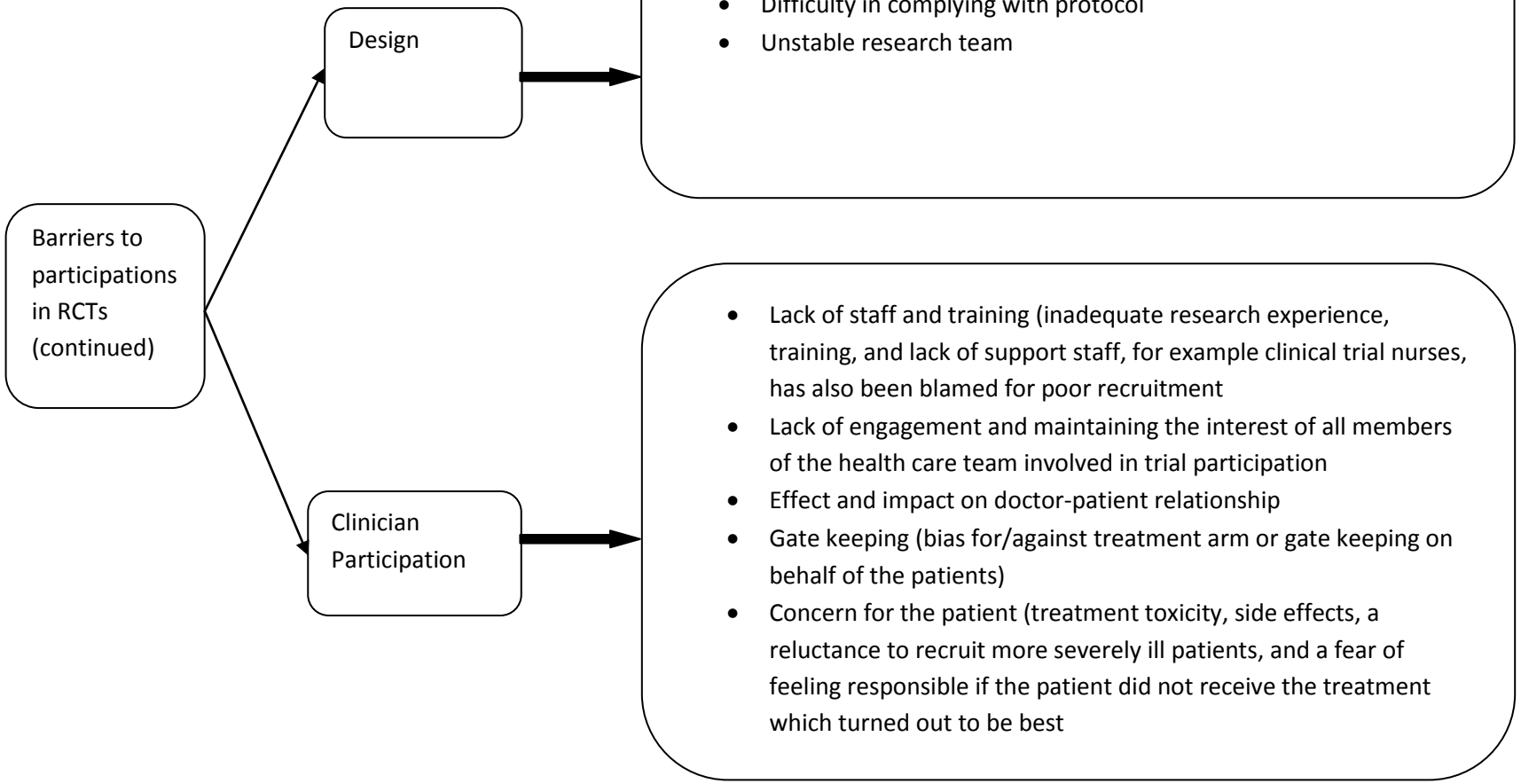
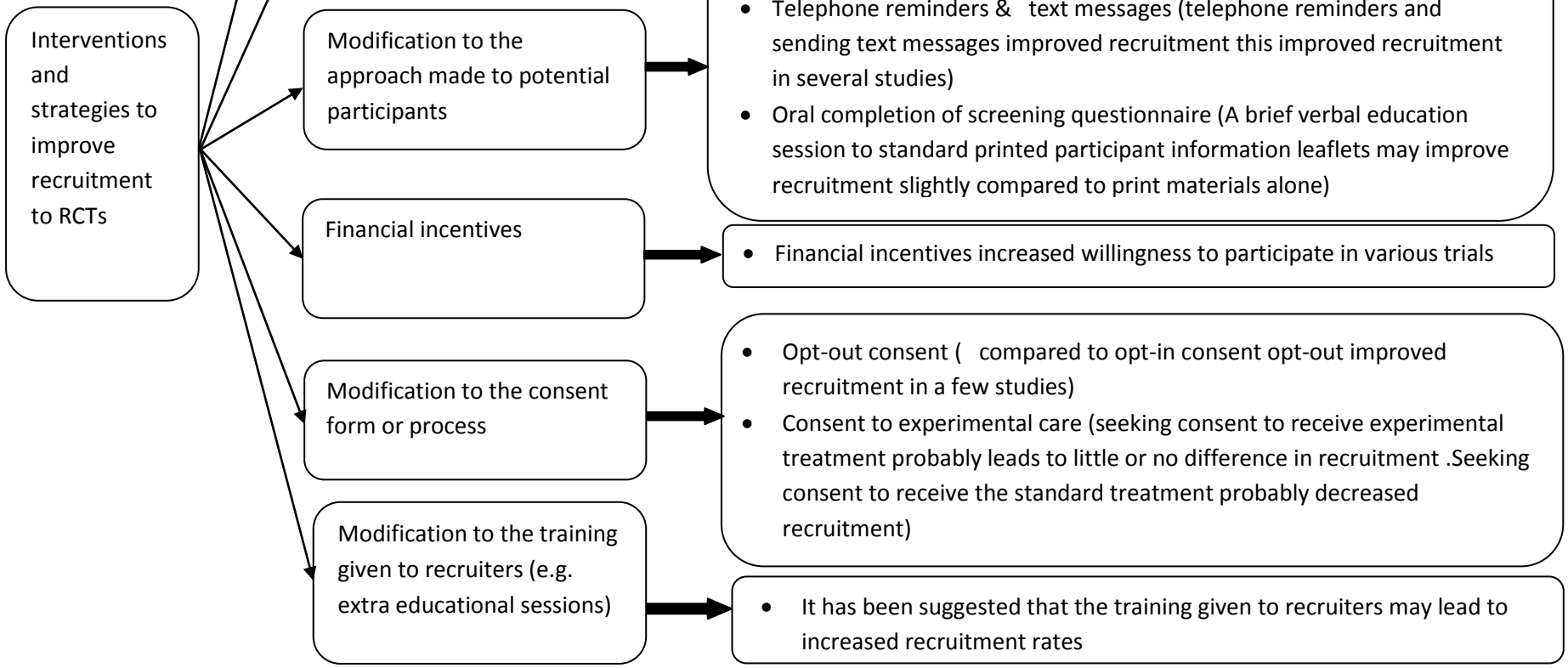


Figure 4-5: Interventions and strategies which may improve recruitment to randomised controlled trials



4.2.12.1. Implications for this study

As recruitment of patients for the current study faced unanticipated difficulties, some of the above-mentioned strategies were applied to improve the recruitment rate and the quality of the data collected. The barriers and strategies used to improve recruitment are summarised in Table 4-7.

Table 4-7: Barriers and strategy in current trial

Barrier	Strategy
Some health care professionals are not interested in referring eligible patients to researcher	Financial incentives for chemo-nurses: offer US$10 per patient they refer as a token of appreciation and motivation to refer patients to researcher. Make a well-planned communication with physicians to overcome their concerns (no toxicity or side effect when using Nevasic) and clarify the importance of the trial. Face-to-face contact to engage and maintain the interest of all members of the health care professionals involved in trial. The demands on clinicians keep to a minimum.
Additional demands and burden on patients to complete long questionnaires	Modify the questionnaire and ask to fill out the Rhode INVR questionnaire daily (just evening time). The demands on patients kept to a minimum.
Having 3 centres on board and not able to attend to all centres at the same time. Lack of support staff	Present in the most productive clinic (main centre) in the mornings and one of the other two centres in afternoons. Asking chemo-nurses to contact researcher when he is not present in the clinic and a potential participant is interested to take part the trial.
Some participants did not complete and answer all questions for the duration of an individual's participation in the study (6 days).	Personal telephone calls from the researcher (as a reminder) and encourage patients to answer all questions completely. Modify the questionnaire, merged and reduced the number of questions.
Quality of the data collected and the level of follow-up data is not good	Persist in follow-up efforts by contacting participant during the participation period at least twice to make sure all queries are met. Asking district nurses to follow-up patients who live in distant areas (where the researcher cannot access them).
Family members as a barrier	Researcher explain to them that this programme may have potential to reduce chemotherapy related nausea, Given as much time as they need to decide whether to participate in the study.
Administrative functions (monitoring the recruitment activity)	Chemo-nurses serve as liaisons between the local clinics and the researcher. Considering alternative strategies if recruitment is lagging.
Potential recruitment problems are not anticipated	Provisions exist for consultation to make decisions regarding the appropriate corrective actions (joint researcher from MUMS & supervisors in the University of Manchester).

4.2.13. Study discontinuation and drop-out

It was proposed that a participant would be withdrawn from the study if no response was received at the end of the research period due to relocation or a loss of contact for any reason. Those who did not return the follow--up questionnaires, and patients who refused to continue participation after consenting, were considered to be drop-out cases.

4.2.14. Data analysis

4.2.14.1. Data analysis methods

Intention to treat (ITT) was used as a strategy for analysis of the results to avoid various potentially misleading artefacts such as non-random attrition of participants from the study. ITT is widely accepted for the analysis of RCTs. In addition, it is known that the estimated effectiveness of intervention may be biased if an intention to treat analysis is not done (Hollis & Campbell, 1999).

The data were analysed using different methods according to the types of variables and the number of participants in the study groups. Descriptive statistics were used to summarise the sample characteristics and demographics.

Frequency tables were constructed, and chi-square statistics were computed to assess any significant differences between the participants in the three groups in relation to age, occupation, marital status, number of people living with the participant, education level, history of motion sickness, history of labyrinthitis, nausea with pregnancy, psychological problems such as emotional distress and anxiety, previous exposure to chemotherapy, concomitant cancer treatment (such as radiology), fatigue, and susceptibility to nausea by eating certain foods, current use of prophylactic and scheduled antiemetic medications and recruitment centre. In some instances, the chi-square test was not valid due to low cell counts, and it was therefore replaced by Fisher's Exact test.

The term "score" was used in order to estimate the outcome parameters, and was defined as the sum of the answer scores. Percentages were based on the available responses. Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to test the Normality of the variables distribution for the three groups before chemotherapy administration (day 0), through to day 6 post chemotherapy. The

differences in nausea and vomiting experience were examined for all participants in the three groups. Due to non-Normal distributions of the scores, the non-parametric Kruskal-Wallis test was used to determine the differences in nausea, vomiting, and retching experience change scores between the three groups for acute and delayed CINV.

By looking at the profiles over time for individuals, it was established that the mean values at each time-point were fair summary of the sample. Moreover the baseline (Day 0) values for the two groups of patients (those who completed all assessments, and those who dropped out before Day 6) was examined. Based on a clinically relevant difference in nausea score of 10% (= 12 x 0.1 = 1.2), it was observed that differences occurred at baseline between these two groups, which meant that attrition had not occurred at random. It is known that standard analysis techniques (e.g. repeated measures ANOVA) require complete data from patients; consequently when drop-outs are not random, this can lead to bias in the analysis. Therefore, a mixed model approach was chosen which utilises all the data, estimates values based on the correlation structure between time-points, and is less susceptible to bias due to non-random attrition. Moreover, the score data was positively skewed. An assumption of linear models is that the model residuals are approximately normally distributed (Gaussian), which can occur with ill-fitting models or non-normal data. However, attempts to transform this endpoint (e.g. log, sqrt, etc.) did not improve its properties. After model fitting, the residuals were roughly normally distributed, and the main results were confirmed with simple non-parametric tests (i.e. Kruskal-Wallis test between each group at the time-points, and Friedman's test between the time-points).

In order to assess the effect of Nevasic (intervention group) and music (attention group) on patients' follow-up HR-QoL scores, and to control for baseline score differences between the control and the other two groups, the nonparametric Wilcoxon signed rank test was performed. This test was required because the HR-QoL change scores did not have a normal distribution.

The patients' satisfaction with and perceptions of the effectiveness of the music or Nevasic were examined using a frequency table and chi-square tests.

4.2.14.2. Coding method

According to the instructions for administering and scoring the Rhodes INVR, items 1, 3, 6, and 7 were reversed. Then, a numeric value was assigned to each response; this ranged from 0 (the least amount of distress) to 4 (the most distress). The total symptom experience from nausea and vomiting was calculated by totalling the patients' responses to each of these 8 items on the INVR. Therefore, the potential range of scores ranged from a low of 0 to a maximum score of 32. The INVR also enables the measurement of nausea, vomiting and retching occurrence, and the distress arising from these symptoms by calculating sub-items from the questionnaire (Table 4-8).

Table 4-8: Scoring the INVR for data analysis

Subscales for Symptom	Items on Scale	Potential Range of Scores
Experience		
Nausea experience	4, 5, 7	0-12
Vomiting experience	1, 3, 6	0-12
Retching experience	2, 8	0-8
Total Experience Score	All Items	0-32
Occurrence		
Nausea occurrence	4, 7	0-8
Vomiting occurrence	1, 6	0-8
Retching occurrence	8	0-4
Total Occurrence Score	All Items	0-20
Distress		
Nausea distress	5	0-4
Vomiting distress	3	0-4
Retching distress	2	0-4
Total Distress Score	All Items	0-12

To examine the effect of the intervention on acute and delayed symptoms separately, the daily INVR scores for nausea and vomiting experience were calculated from 24 hours following chemotherapy administration, to the end of the study.

According to the EORTC QLQ-C30 scoring manual, QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status/QoL scale, and six single items (Table 4-9). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale (Fayers et al., 2001).

Table 4-9: The EORTC QLQ-C30 scale and related items in the scale**

Scales	Number of items	Item range*	Item numbers
Global health status / QoL:			
Global health status/QoL (QL)	2	6	29,30
Functional scales:			
Physical functioning (PF)	5	3	1,2,3,4,5
Role functioning (RF)	2	3	6,7
Emotional functioning (EF)	4	3	21,22,23,24
Cognitive functioning (CF)	2	3	20,25
Social functioning (SF)	2	3	26,27
Symptom scales / items:			
Fatigue (FA)	3	3	10, 12, 18
Nausea and vomiting (NV)	2	3	14, 15
Pain (PA)	2	3	9, 19
Dyspnoea (DY)	1	3	8
Insomnia (SL)	1	3	11
Appetite loss (AP)	1	3	13
Constipation (CO)	1	3	16
Diarrhoea (DI)	1	3	17
Financial difficulties (FI)	1	3	28

***** Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
**Adapted from Fayers et al. 2001

For all scales, the *Raw Score* (*RS)*, is the mean of the component items:

RS= (I_1+ I_2+ I_3+ ..+ I_n) **/** n

Functional scales: $Score = \left\{ 1 - \frac{(RS-1)}{Range} \times 100 \right\}$

For symptom scales / items and global health status / QoL**:**

$Score = \{(RS - 1) / range\} \times 100$

The breast cancer module (QLQ- BR23) comprised 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective (Table 4-10). The scoring approach for QLQ-BR23 is identical in principle to that of the function and symptom scales/single items of the QLQ-C30 (Fayers et al., 2001).

Table 4-10: The EORTC QLQ-BR23 scale and related items in the scale

Scales	Number of items	Item range*	Item numbers
Functional scales			
Body image (BRBI)	4	3	9 ,10,11,12
Sexual functioning (BRSEF)	2	3	14,15
Sexual enjoyment (BRSEE)	1	3	16
Future perspective (BRFU)	1	3	13
Symptom scales / items			
Systemic therapy side effects (BRST) Breast	7	3	1,2,3,4,6,7,8
symptoms (BRBS)	4	3	20,21,22,23
Arm symptoms (Guirimand, #429)	3	3	17,18,19
Upset by hair loss (BRHL)	1	3	5

***** "Item range" is the difference between the possible maximum and the minimum response to individual items.

** Adapted from Fayers et al. 2001

4.2.15. Ethics in the context of clinical research

Ethical review processes have progressed since the World Health Organisation issued the Declaration of Helsinki in 1964, which led to the creation of a framework for the principles of biomedical research. The major issues enshrined in the principals pertain to the essential elements of informed consent, setting standards for preventing risks, protecting confidentiality and specifying conditions for terminating experiments (Lacombe, 1997; Green & Pace, 2006). It outlines the moral and scientific principles that are important in conducting research (Marion, 1989; MRC, 2002).

Ethics, which is a moral philosophy, considers several questions which are related to research conduct and address issues such as clinical practice and human experimentation (Marion, 1989; DOH, 2005). Although each area of health-care research has its own ethical issues, ethical considerations are critical for several different aspects, from research design to the protection of individual patients' confidentiality and rights (MRC, 1998).

The three main ethical issues to take into consideration when researching human subjects are: balancing the risk of harm with potential benefit, ensuring consent, and protecting confidentiality (RCN 2004).

The first major ethical consideration in this study relates to methods. Ethical standards require that researchers do not put participants in a situation where they might be at risk of harm, or any physical or mental discomfort as a result of their participation. (Chung and Kotsis, 2011) argue that every research, no matter how small, entails some risk. Therefore, it is essential to assess the risks and benefits to subjects or others before conducting the research. Research risks must be minimised through sound research design.

It was determined that, for this study, the risk of harm to participants was minimal, as the manufacturer of Nevasic confirms that it contains no chemicals, has no side effects and is safe to use. Moreover, as mentioned above, it has been documented that music (audio programme) therapy is generally not associated with negative side effects, and can be easily implemented with high treatment compliance (Brandes et al., 2010). However, the participants were informed about

the fact that Nevasic is designed to be used at low volume settings, and that they should be able to talk and communicate easily and safely at all times while using Nevasic. They were informed that it is the content of Nevasic, and not the volume, that is important, and that loud or excessive volume does not improve the performance of the product, and can damage the ears. Therefore, the participants were strongly advised against using the Nevasic at high volume. It was assumed that the risk of harm for the attention group patients was also minimal; however, it is also possible that listening to certain kinds of music may be uncomfortable for some individuals. Participants were required to report any occurrence of adverse effects to the researcher.

Autonomy and self-determination (which allows participants to withdraw from the study at any point), avoiding harm, and upholding justice are the ethical principles that are involved in obtaining informed consent (Marion, 1989). Informed consent contains *information* (disclosure and comprehension) and *consent* (voluntary consent and competence to consent). Informed consent consists of informing the participants, as completely as possible, of the details, risks, and benefits of the research procedure (Marion, 1989). The researcher should also ensure that the participants' autonomy is respected. Appropriate mechanisms for consent should be in place, including providing adequate information to facilitate choice and freedom to decide, without influence from the researcher. Therefore, all participants must be sufficiently informed of the aims, expected benefits and potential risks of the study. The participants must also be informed about the right to withdraw their participation at any time, without reprisal (Green & Pace, 2006).

Ensuring the participants' anonymity and confidentiality are also ethical issues regarding the use of patients as research subjects (Marion, 1989; DOH, 2005). Confidentiality refers to not disclosing the names or any personal information about the participants during the study, and entails that the information be used for the study only, and not for any other purpose. The results must also be reported as group data, without reference to individual participants. Any information collected about the study participants was kept confidential, and all personal information was coded and anonymous; the questionnaires were stored in a locked filing cabinet. Individual identity numbers were used to identify the participants. Consent forms with the names of the participants were kept in a

locked filing cabinet, separate from the questionnaires. The data collected from the questionnaires was entered onto a computer, and consent to hold the information in this way was obtained from all participants. Access to the data in the computer was limited to the authorised individuals, as the system was password protected (encrypted). The questionnaires will be discarded after the recommended length of time (between 5-10 years) (Sieber, 1998).

4.2.15.1. Obtaining ethical approval

All human research should follow appropriate ethical principles and be approved by an appropriately constituted ethics committee (Green & Pace, 2006). As the study was carried out in three cancer hospitals, two of which were affiliated with Mashhad University of Medical Sciences in Mashhad, Iran, obtaining approval to use the clinical setting and to study the patients in that setting was necessary; therefore, obtaining permission from the ethics committee in Mashhad University of Medical Sciences, which is responsible for approving research, was required. The ethics committee at the University of Manchester was also contacted to obtain their permission (Appendix 5-6). The process of obtaining the approval took about 5 months (mid November 2010–April 2011).

As the setting of this research was cancer centres in Mashhad, Iran and the selected instrument for measuring nausea and vomiting, the Rhodes INVR, had not previously been translated to Persian, it was necessary to translate it for use in this study. The process of translation and psychometric testing is described in next chapter.

Chapter Five: Preparatory study for the translation and validation of the Iranian version of the Rhodes INVR scale

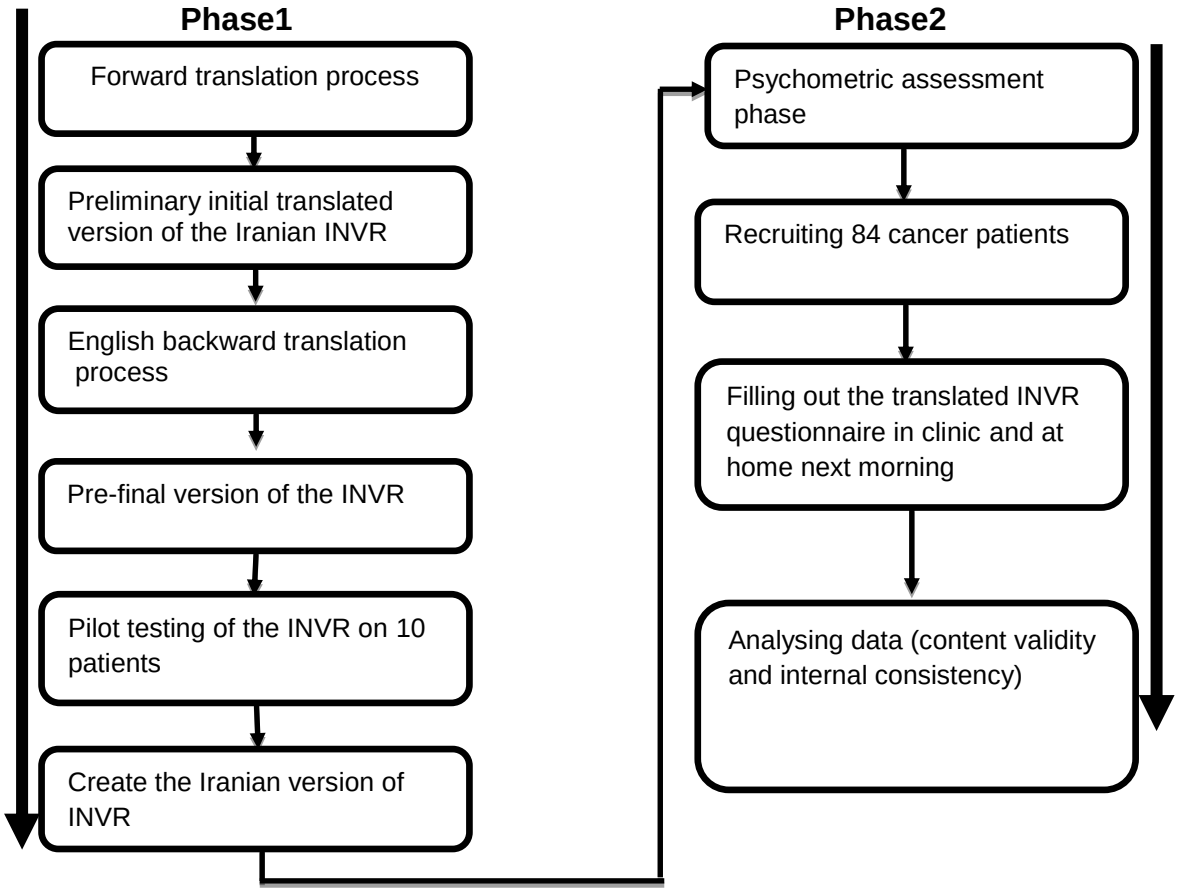
5.1. Translation and validation of the Iranian version of the Rhodes INVR scale

There is no assessment measure for nausea and vomiting currently available to nurses and other healthcare providers in Iran, and accurate, concise, and effective research-based instruments are therefore needed. In this section, the translation and cultural adaptation of the Rhodes INVR and the results of an initial psychometric testing process with Iranian cancer patients receiving chemotherapy is explained. Permission to use and translate the Rhodes INVR to Persian was obtained (Appendix 14).

5.2. Methods

The whole cultural adaptation process is outlined in two phases, each of which entails its own methods and results. Phase 1 represents the iterative forward–backward translation/linguistic process, and phase 2 describes the results of the initial psychometric testing of the INVR in Iranian cancer patients (Figure 5-1).

Figure 5-1: Flow chart of the process of translation and validation of the Iranian version of the INVR



This was a translation and multiphase instrumentation study to determine internal consistency, test–retest reliability, and face and content validity in the translated version of the INVR.

5.2.1. Participants

A total of 94 patients took part in the study (10 patients in phase one and 84 patients in phase two). Each participant was receiving chemotherapy as a part of their treatment for cancer. The patients were recruited from a cancer research centre if they met the following inclusion criteria: aged 18 years old or over, having a confirmed diagnosis of cancer, having received adjuvant chemotherapy that might make them nauseous, able to read and write Persian, and willing to participate.

Permission and approval for this study was sought from Mashhad University of Medical Sciences. Data were collected from a cancer research centre (Omid Educational Hospital of Mashhad University of Medical Sciences) in Mashhad, Iran.

5.3. Phase one: Translation procedure and pilot testing of the INVR

5.3.1. Forward translation

Guidelines for the translation, adaptation and validation of instruments or scales for use in cross-cultural health-care research were followed (Sousa & Rojjanasrirat, 2011) during the translation. The original (English) version of the instrument was translated to Persian by two bilingual health professionals. Translators 1 and 2 were bilingual (Persian and English), and were native Persian speakers. Translator 1 was a consultant oncologist, and had lived and studied in London (UK) for 4 years (London University graduate), while the other was an academic translator, majoring in foreign language education (English as a second language). The first translator was knowledgeable about health-care terminology. The second translator was familiar with colloquial phrases, health-care slang and jargon, idiomatic expressions, and common emotional terms used in Persian. The second translator did not have any special knowledge about medical terminology and/or the construct of the instrument. This approach led to generating two translated versions that contained words that covered both the medical and

Persian spoken language, with its cultural nuances. The two independent translators and the translation coordinator (the researcher) compared the translated versions and selected the most appropriate wording; the result became the preliminary initial translated version of the Iranian INVR.

5.3.2. Backward translation

The preliminary initial translated version of the Iranian INVR was translated back into the English by two other independent translators (translators 3 and 4). Both translators were completely blind to the original version of the instrument. Translator 3 was a consultant oncologist and translator 4 was an academic translator majoring in foreign language education (English as a second language). The equivalence of the original and back-translated versions was evaluated by a committee including one experienced chemo nurse, all four translators and a coordinator. The English back-translations were compared against the original English version by the committee to ensure that the meanings of the original questions were preserved. The committee checked the scales for any discrepancies. Slight discrepancies were solved by consensus with the committee members. The result was a pre-final version of the INVR.

5.3.3. Pilot testing of the INVR

As suggested by Koller et al. (2007), 10 follow-up cancer patients were asked to complete the pre-final version of the questionnaire. All patients voluntarily agreed to participate in the pilot testing of the pre-final version of the INVR, following a detailed explanation by the translation coordinator. Informed consent was obtained from all participants. After completing the questionnaire, the participants were asked, in a short, semi-structured interview, whether the translated questionnaire items were difficult to answer, confusing, or difficult to understand. The patients were also asked whether they would have worded the questions in a different way (Koller et al., 2007; Sousa & Rojjanasrirat, 2011). Most of the patients were male (7 out of 10) and elderly (ranging from 53 to 67 years). Persian was the only language used by the participants. Their educational levels ranged from junior high school to university degree. The time since their chemotherapy ranged from 3 weeks to 1 year. The results of the pilot testing revealed that the questionnaire

could be completed in 3–5 mins, and most patients confirmed that the questionnaire was easy to read and understand.

5.3.4. Content and face validity

According to Streiner and Norman (1995), 3 to 10 experts are appropriate for a panel to estimate the content validity of an instrument. Therefore, to further determine the conceptual and content equivalence of the items of the pre-final version of the INVR, an expert panel included one nurse and one general practitioner who were working in supportive cancer care, including control and management of nausea and vomiting in patients receiving chemotherapy; in addition, one language expert was chosen by the translation coordinator. None of the panel of experts was involved in prior steps of scale development. The expert panel was asked to systematically examine the content of the Iranian-language versions of the INVR, review the items and determine whether the items covered a representative sample of the behaviour domain to be measured (Polit & Hungler, 1997). They independently rated the Iranian versions of the INVR in terms of the instrument's applicability to cancer patients in Iran, including its content and cultural relevance, and language equivalence to the original instrument. The expert panel was asked to indicate whether each item on a scale was congruent with (or relevant to) the construct; the percentage of items deemed to be relevant for each expert was then computed, and an average taken for the percentages across all of the experts. They were also asked to evaluate each item of the instrument for content equivalence (content-related validity (relevance)) using the following scale: 1= not relevant, 2=somewhat relevant, 3= quite relevant, 4= highly relevant (Sousa & Rojjanasrirat, 2011). Based on the comments from the expert panel and the participants in the study, the instrument was modified. The final Iranian version of the INVR was created (Appendix 11), and phase 2 of the study (initial psychometric testing) began.

5.4. Phase two: psychometric assessment of the instrument

5.4.1. Sample size

Test/re-test reliability was estimated using an intra-class correlation coefficient (ICC). The sample size required an ICC estimate of 0.75, with at least a 95% margin of error of ±0.1; this was calculated as 75 using Sample Size Tables for

Clinical Studies Software (Machin et al., 2009). The internal consistency or reliability of the scale was estimated using Cronbach's alpha. The sample size required an alpha value of equal to 0.75 for an 8-item scale with a 95% confidence interval with a margin-of-error of ±0.1; the value was estimated to be 61, using a formula from Bonett (2002). Conservatively allowing for a 10% drop-out between testing and re-testing, the required sample size was set to 84, which would allow a good estimation of both an ICC and Cronbach's alpha. A total of 84 cancer patients were recruited. A convenience sampling method (consecutive sampling technique) was used to recruit consecutive eligible patients. This technique was used because it includes all available subjects, making it a better representation of the entire population. The characteristics of the participants and the setting were the same as in phase one.

5.4.2. Procedure

A self-reporting method was used to collect the data. Health-care professionals identified eligible patients and referred them to the researcher. The researcher then informed patients of the aim of the study and the time needed for self-administration of the instrument, and explained how to complete the questionnaire. The participants were informed that all the information gathered from the study would be kept confidential. Their names and other identifying information were not included in the questionnaires, and a code number was assigned to ensure confidentiality. Potential participants were asked to sign a consent form. After obtaining informed consent, the participants were given the demographic questionnaire and the INVR scale to fill out. When the participants had completed these at the clinic, a second INVR questionnaire was given to them (with a pre-paid envelope) to take home and fill out in the next morning. All participants were asked to provide suggestions about the wording of the instruments, in order to determine face validity. These steps were continued until 84 participants were obtained. A one-week time limit was given before contacting the patient, as a reminder, to send back their questionnaire, as participants might have forgotten to post it.

5.4.3. Statistical analysis

An instrument's reliability can be examined using tests of internal consistency, replication with different samples, and test–retest using the same sample (Hendrickson et al., 1993). The most common approach in the assessment of reliability is to measure the same type of participants on two occasions, separated by hours or days (Lexell & Downham, 2005). It has been also indicated that ICC is generally the preferred retest correlation coefficient (Lexell & Downham, 2005). In addition, Walters (2009, pp. 92-94) and Streiner and Norman (2008, p. 177) suggested that an ICC for a two-way random effects analysis of variance, where all participants are measured at each of two time-points and both sources of variation are considered to be random, should be used. An ICC is preferred to a simple correlation, such as Pearson's or Spearman's, because it measures agreement rather than correlation, and can be used with small sample sizes (Lexell & Downham, 2005). Therefore, the internal consistency and test–retest reliability coefficients were examined for the INVR scale. Cronbach's alpha was computed to measure the inter-item correlation (reliability) of the Iranian version of the INVR.

However, using ICCs alone to analyse reliability would not be sufficient. Thus, the next step in the reliability analysis was to calculate changes in the mean from the measurements obtained from the two test occasions (Lexell & Downham, 2005). Paired t-tests (or their non-parametric equivalent) were conducted to determine the difference in responses (Hendrickson et al., 1993).

It is stated that test, re-test reliability may be measured by the ICC when the data are continuous and normally distributed (Bruton et al., 2000; Baumgarter, 1989). In addition, correlations are not an ideal statistical method to measure test, re-test reliability. In the case of ordinal data (which is the case here) the weighted kappa should be used (Table 5-1)(Baumgarter, 1989).

4.4.5. Results

The 84 participants in this study ranged in age from 18 to 74 years. The participants' socio-demographic characteristics are described in Table 5-1. As

shown, the majority of participants were female, educated only up to primary school level, and married.

Table 5-1 Demographic data of patient participants (n= 84)

Gender	N (%)
Male	35 (41.7%)
Female	49 (58.3%)
Age (year)	
<20	5 (6%)
20-29	9 (10.7%)
30-39	16 (19%)
40-49	17 (20.2%)
50-59	17 (20.2%)
60-69	12 (14.3%)
>70	8 (9.5%)
Education	
Primary school	51 (60.7%)
Secondary school	14 (16.7%)
High school diploma	16 (19%)
University degree	3 (3.6%)
Employment	
Manual work	12 (14.3%)
Housekeeper	44 (52.4%)
Farmer	8 (9.5%)
Clerical/admin	7 (8.3%)
Unemployment	8 (9.5%)
Other	5(6%)
Marriage	
Single	8 (9.5%)
Married	67(79.8%)
Separated (divorced)	3 (3.6%)
Widow	6 (7.1%)
Diagnosis	
Lymphoma	15 (17.9%)
Sarcoma	5 (6.0%)
Head and neck cancers	4 (4.8%)
Gastrointestinal cancers	23 (27.4%)
Breast cancer	19 (22.6%)
Genito-urinary cancers	4 (4.8%)
Other	14 (16.6%)

In total, 71 participants returned the questionnaire, making an actual attrition rate of 15%. As the differences between the score of the first and second administration were not normally distributed, the non-parametric two-sample Wilcoxon signed rank test was used to analyse the difference in responses. The results of the participants' mean responses and the weighted kappa between individual scales items are shown in Table 5-2. The scores in the first administration were generally lower than they were the second time around.

Table 5-2: Two sample Wilcoxon test and correlation between initial and second administration for each Item

Item	Test T1 Mean(SD)	Test T2 Mean(SD)	T1-T2 Mean(SD)	Wilcoxon P-value	Weighted Kappa
Question 1	1.24 (0.72)	1.25 (0.65)	0.03 (0.61)	0.94	0.68
Question 2	1.29 (0.63)	1.37 (0.81)	0.04 (0.55)	0.46	0.68
Question 3	1.24 (0.67)	1.38 (0.87)	0.04 (0.84)	0.25	0.63
Question 4	1.38 (0.90)	1.55 (1.01)	0.11 (0.90)	0.28	0.65
Question 5	1.36 (0.83)	1.54 (0.97)	0.14 (0.61)	0.46	0.74
Question 6	1.23 (0.61)	1.21 (0.53)	0.06 (0.41)	0.23	0.73
Question 7	1.31 (0.73)	1.42 (0.92)	0.56 (0.56)	0.42	0.74
Question 8	1.31 (0.76)	1.35 (0.81)	0.01 (0.62)	0.85	0.79
Total Score	10.34 (4.82)	11.07 (5.62)	0.99 (5.10)	0.32	

As shown above, the weighted kappa, as a measure of test–retest reliability, was between 0.63-0.79, indicating “substantial agreement” and stability between the initial and subsequent administrations for each Item (Viera & Garrett, 2005). Analysis of the individual questions using the weighted kappa performed in SAS v9.3.

To calculate the ICC (total score) based on two time-points, a two-way mixed ANOVA with single measures in SPSS was used. The participants are the random factor, and we consider the time points fixed factors. The ICC for the total score was calculated (ICC=0.79) assuming people effects are random and time effects are fixed. Overall Cronbach’s alpha was 0.88; alpha was 0.92 for the initial and 0.94 for the second administration of the questionnaire.

Both the internal consistency and the stability coefficients of the INVR scale were high and satisfactory.

5.4.6. Discussion

The lack of a specific tool to measure nausea, vomiting and retching in cancer patients in Iran led us to develop (translate, culturally adapt and pilot test) and validate the self-reported INVR scale. Therefore, the purpose was to produce and

test the validity and reliability of the INVR in Iranian cancer patients to use for the study. Previous studies showed good reliability and validity of the INVR among different patients in different countries (Fu et al., 2002; Glaus et al., 2004; Chou et al., 2005; Kobayashi et al., 1999).

The integrative translation method presented a systematic, methodical and valid method for translating an instrument from the source language to the target language (Fu et al., 2002). Forward and backward translations and professional review of the target language version provided a valid method for establishing equivalence of the target language version. A few changes were made during the translation and validation process of the Iranian version of the INVR. As Fu et al. (2002) indicated, several assumptions might explain this phenomenon. First, nausea, vomiting, and retching are universal symptoms; few differences were disclosed in comparing the conceptual equivalence between the English and Persian languages. This universal conceptual equivalence led to less mix-up and uncertainty during the translation process. Secondly, short and simple English sentences are more easily translated into another language (Fu et al., 2002; Brislin et al., 1973). The sentences in INVR contain fewer than 20 words, and one introductory statement for each question, plus insertion of 1 of the 5 possible patient responses. The simple sentence structure in the INVR resulted in less confusion in the translation process.

These results demonstrate that the Iranian version of the INVR probably can be used as a reliable and valid tool for the assessment of nausea, vomiting and retching in Iranian cancer patients. The outcomes of the study may improve patients' self-care and quality of life by helping them to better control nausea and vomiting in clinical settings.

The study was carried out only on patients with cancer in one of the provinces in Iran. The geographic limitation of the sample restricts the generalisability of the study. The study would have been improved by re-evaluating the validity and reliability of the scale on different and larger patient populations for widespread use of the scale in other clinical settings in Iran.

5.5. Conclusion

So far in this thesis, the non-pharmacological literature and trials investigating interventions for the prevention and control of CINV have been discussed and Nevasic, as a novel programme, has been considered as an intervention worthy of further study. The methodological choices for this study began with the purpose of the research and considering the philosophical and practical perspectives. These are discussed in detail, along with the methods undertaken. A pilot RCT, with a complementary qualitative element (focus group) was adopted. The following chapter presents the results of the study.

Chapter Six: Results

6.1. Introduction

The results are presented in four sections. The first explores the acceptability of the study, describing issues such as adherence and reasons for attrition and participant burden. The second presents descriptive data relating to the feasibility of running a full trial. The third explores Nevasic's effect on nausea and vomiting over time using linear mixed-effects models. The fourth presents data about the effect of nausea and vomiting on HR-QoL.

Study feasibility

6.2. Adherence, usability, and acceptability of the study

Five focus groups with a total of 15 participants were formed, including: four participants from the intervention group (three of them did not complete the study), five from the attention group (two of them did not complete the study), and six from the control group (four of them completed the study). Table 6-1 outlines details of the participants in the five focus groups.

Table 6-1: Details of the focus group sessions

Focus group	Participant number	Socio-demographics			Group in the main study	Adherent to the study
		Age	Employment	Education		
1	Participant 1	49	Teacher	University degree	Nevasic	No
	Participant 2	41	Self-employed	High school diploma	Control	Yes
	Participant 3	31	House worker	High school diploma	Control	Yes
2	Participant 4	52	House worker	University degree	Nevasic	No
	Participant 5	33	House worker	High school diploma	Music	No
	Participant 6	44	Teacher	University degree	Music	Yes
3	Participant 7	43	House worker	High school diploma	Nevasic	No
	Participant 8	38	House worker	High school diploma	Control	No
4	Participant 9	46	House worker	High school diploma	Nevasic	Yes
	Participant 10	43	House worker	High school diploma	Music	No
	Participant 11	51	House worker	Primary School	Music	Yes
	Participant 12	35	Teacher	University degree	Control	Yes
5	Participant 13	48	House worker	University degree	Music	Yes
	Participant 14	39	House worker	High school diploma	Control	Yes
	Participant 15	53	Clerk	University degree	Control	No

The participants were generally responsive when answering questions related to their experience of participating in this research and listening to Nevasic or music.

The analyses of focus group results involved a transcript of the discussion and a summary of the conclusions that was drawn. Once the focus group discussions were transcribed frequencies of themes were used for emerging themes and to assist in determining their importance. Three main aspects emerged from the analysis of the focus group data; these are shown in Table 6-2.

Table 6-2: Emergent aspects from post-treatment focus groups

Issues
1) Questionnaires (Too many questions) After chemotherapy, felt unwell and did not want to do such a task. Needed help to answer some questions; however staff did not help them properly. Did not believe that these questions were important in their treatment procedure. There were some sensitive questions, & which most people did not like to answer.
2) Listening to music or Nevasic: After chemotherapy, did not like to listen to anything. Did not feeling comfortable with CD player to listen to Nevasic or music, as it was not practical. Did not believe that it worked (music or Nevasic).
3) Adherence to the trial: Staff were not properly trained for this study. Wanted for someone to contact them to answer their questions. Follow-up of patients was valuable, and encouraged patients adhere to their treatment & to the study.

6.2.1. Issues with questionnaires

Many participants believed that there were too many questions in the diary questionnaire which was used in the study. Most participants stated that a shorter questionnaire should be used in future. Some participants mentioned that after chemotherapy they felt unwell and did not want to complete the questionnaire task. For example, one participant who had the CAF (Doxorubicin + Cyclophosphamide + 5-Fluorouracil) chemotherapy regimen mentioned:

"After just two hours of receiving chemotherapy, I felt unwell, weak and tired and did not want to do anything. Even after resting, I could not do any activities. So in the evening I could not answer many questions and after filling out the first table I dropped out of the study." (participant 4)

Another participant continued:

"I agree with her. You know that chemotherapy makes patients tired and we need to take more rest. I could not concentrate on anything during the first 24 hours. For me it was not easy to concentrate on all questions and answer all of them. I suggest you ask fewer questions if it is possible." (participant 6)

Almost all of the participants mentioned that there were some sensitive questions in the QoL questionnaires which asked about their personal life (sexual activity). They believed that people would like their privacy to be respected and preferred not to be asked these kinds of questions if it was not crucial to their treatment. As a result, most people avoided answering question numbers 44-46 in the EORTC QoL-BR 23 questionnaire (see Appendix 2):

"Question[s] about sexual activities are sensitive in almost all cultures, as far as I know. So, you should not expect all people answer these questions. Although I answered the questions, I did not feel comfortable with [them]." (participant 12)

Some participants stated that they did not believe that these questions were important to their treatment procedure. As a consequence, they did not pay a great deal of attention to filling out the subsequent questionnaires, although they had initially agreed to do so:

"It was my first cycle of chemotherapy and I thought the study was related to my treatment. After that I realised that these questions were about my nausea and vomiting. To be honest I do not believe these questions are important in my treatment, so I completed the questionnaire for the first three days only." (participant 3)

A few participants said that they needed help to answer some questions. Although some of the chemo nurses who facilitated the study were trained and had been asked to answer patients' queries, the participants felt that the staff did not provide adequate help:

"When I was in the chemotherapy unit, I asked one of the staff to explain how to complete the questionnaires. She said that I have to wait for another chemo nurse to come. She said that she did not have any information about the project. I was there for about 3-4 hours; however they could not find someone to help me." (participant 11)

6.2.2. Issues related to listening to music or Nevasic

Some interviewees who were in the music or Nevasic groups stated that after chemotherapy, they do not want to listen to anything:

"*I know that listening to music or therapeutic sounds may help patients to relax; however I prefer silence." (participant 1)*

Moreover, almost all of the participants agreed that choosing and listening to music is a very personal thing. While some people find one particular type of music very helpful and supportive during treatment, others may find it unhelpful:

"[It] can be very helpful when you are feeling anxious or overwhelmed [to listen to] peace [ful] or calming music. But preferences are different." (participant 5)

Some participants said that they did not feel comfortable using a CD player to listen to Nevasic or music, or that it was not practical. Two participants complained about the quality of their CD players:

“I would suggest you to find a better way [of] listening to the music as handling the CD player was an extra burden, particularly after the first days of chemotherapy.” (participant 7)

“You know, I think the quality of the instrument was not good enough. If the CD player was lightly shaken it sometimes stopped working and I got continual pauses.” (participant 13)

Some participants said they did not believe that listening could help to reduce their nausea or vomiting:

“I agree with [participant 5] that music may reduce patients’ anxiety, but I could not believe that by listening to something my nausea or vomiting would be treated. I even checked the Nevasic website and still do not believe it. Nevertheless, it would be wrong to be too pessimistic.” (participant 4)

6.2.3. Issues with adherence to the trial

All participants believed that following up with patients is a valuable piece of work, and encourages patients not only adhere to the study, but also to their treatment. In addition, they said that they would like to have someone to contact if they had any questions:

“When diagnosed with cancer and then having to have surgery, I really lost my confidence, and energy. After chemotherapy, I was uncertain [about whether] to continue my scheduled treatment. I had decided to quit treatment because I had a very unpleasant feeling about this. But when [the researcher] called me and listened to me and talked about my concerns, I felt better and decided to continue. If you ask me, I do believe contacting patients during and even after treatment will help them so much to adhere to their treatment and adhere to your study.” (participants 9)

“*When you contacted me and emphasised how [important] my participation and my answers to the questions [were] for the research team, I decided to actively adhere to the study and complete the questionnaires carefully.” (participant 15)*

Some participants said that staff were not properly trained for this study. They suggested using more nurses, and also improving their training so as to ensure they were able to meet all patients' needs regarding their participation:

"*You know nurses in the chemotherapy unit are so busy, particularly in [the] mornings, and just a few of them were aware of this research […] even some nurses who were aware and involved in this research could not help us properly regarding some of our questions." (participant 8)*

The focus groups that were conducted presented an opportunity to understand participations' viewpoints regarding the burden on patients to complete this study, listening to Nevasic or music, and the reasons for study attrition. Although these groups were not representative of all breast cancer patients, the opinions obtained provide a foundation for understanding the use of Nevasic in this population. These findings indicate that patients do not have a strong willingness to use Nevasic or music to manage CINV.

6.3. Descriptive statistics

6.3.1. Patient enrolment, allocations and demographics

During the recruitment period, 392 breast cancer patients were scheduled to receive moderately to high emetogenic chemotherapy regimens for the treatment of cancer within the three centres (Figure 6.1). Of the eligible patients, 18 (4.6%) patients refused to participate/did not provide consent. Chi-square tests indicated that there were no differences between the participants and the non-participants regarding the categorical demographic data (age, marital status, occupation, education) (Table 6-4).

The researcher recruited patients on a daily basis from the three centres until February 2012, when 99 patients gave consent to participate in the study, 46 (46.5%) from the main setting, 21 (21.2%) from the second and 32 (32.3%) from the third (Table 6-3).

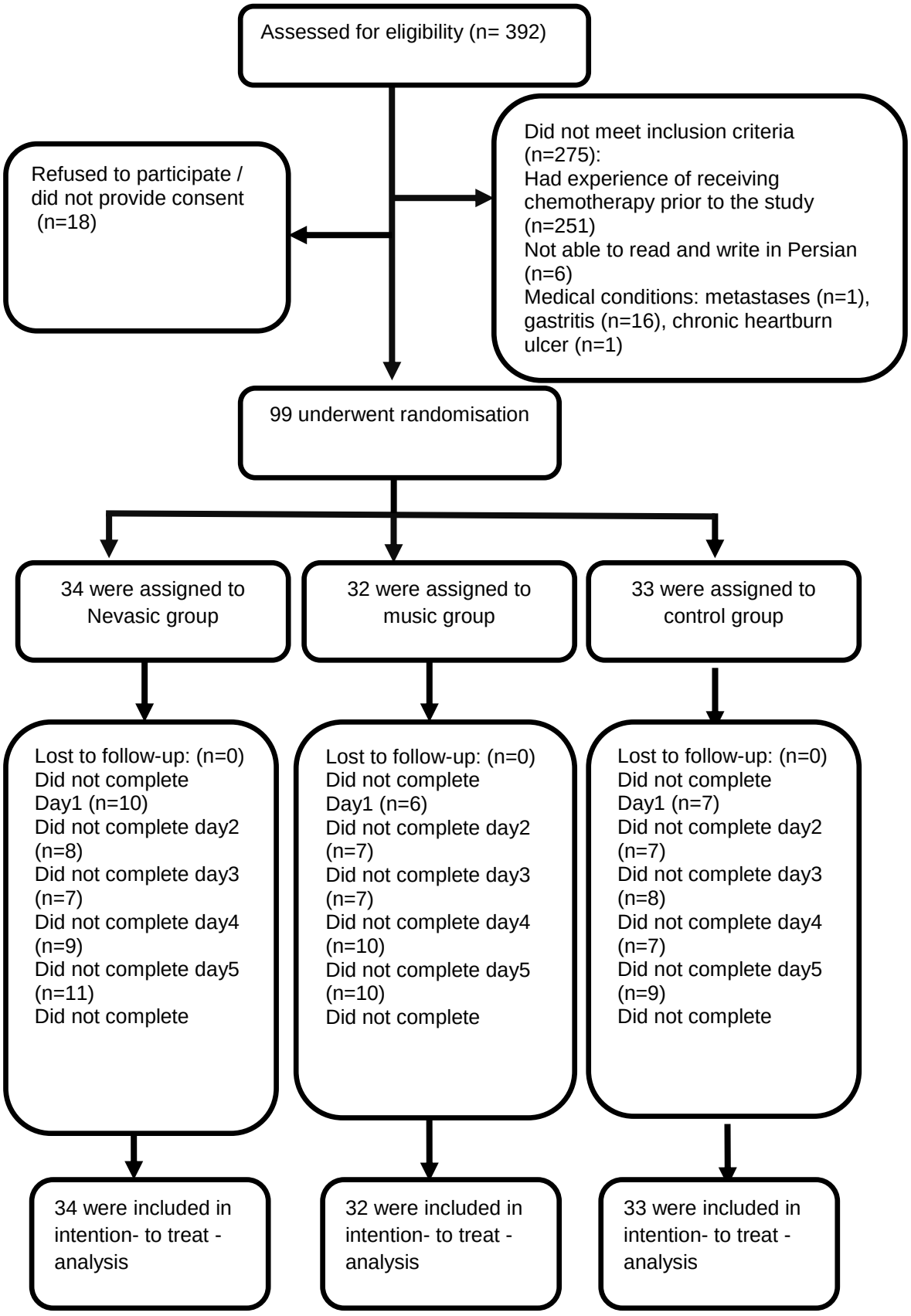
Table 6-3: Patients' recruitment per centre

Centre	Study group			
	Nevasic N=34(%)	Music N=32(%)	Control N=33(%)	Total N=99(%)
Centre 1	16 (47.1%)	14(43.7%)	16 (48.5%)	46 (46.5%)
Centre 2	7 (20.6%)	6 (18.7%)	8 (24.2%)	21 (21.2%)
Centre 3	11 (32.3%)	12 (37.5%)	9 (27.3%)	32 (32.3%)

Chi- square tests indicated there were similar proportions from these 3 centres in the groups (X^2 (2) = 0.64, p=0.72).

The 99 patients were randomised (according to randomisation lists, and regardless of the centre they attended) to three groups: Nevasic (n= 34), music (32), and control (33). However, 10 patients did not continue their participation (5 in the Nevasic group, 2 in the music group, and 3 in the control groups), after obtaining socio-demographic and treatment characteristics and randomisation. Figure 6-1 shows detailed information on the enrolment and follow-up stages.

Figure 6-1: The progress through the trial



Participants in the Nevasic group were asked to listen to Nevasic during the study period, while in the music group the participants chose one of the three selected pieces of music shown in Table 6-4.

Table 6-4: Music selected by participants in the music group

Number (%)	Kind of music
18 (56.2%)	Relaxing and calming music accompanied by sound of ocean waves
8 (25%)	Soft classical music
6 (18.7%)	Slow/ soft melodies and peaceful pan flute music without lyrics

As shown in Table 6-5, most patients (73.7%) received the same prophylactic anti-emetics (Ondansetron + Dexamethason or Granisetron+ Dexamethason) whilst 26 (26.3%) patients received an additional antiemetic to the previous regimen. Due to non-normally distributed data, the Kruskal-Wallis test was used was used to compare between treatment groups for continuous variables. No significant differences were found between the participants in the three groups (Table 6-5).

Table 6-5: Patients' demographics and characteristics								
Variable	Category	Nevasic (n=34) No(%) [Range]	Music (n=32) No(%) [Range]	Control (n=33) No(%) [Range]	Total (n=99) No(%) [Range]	Stat	df	p.
Age		Mean=51.26 (SD= 11.82) [31-82]	Mean=46.06 (SD= 11.23) [27-70]	Mean=51.48 (SD=10.21) [29-70]		5.52†	2	0.63
Job	House worker Teacher Clerk Self-employment Retired	28 (82.3%) 2(5.9%) 0(0%) 2(5.9%) 2(5.9%)	23(71.9%) 6(18.7%) 0(0%) 1(3.1) 2(6.2%)	25(75.7%) 2(6%) 2(6%) 1(1%) 3(9%)	76(76.8%) 10(10.1%) 2(2%) 4(4%) 7(7.1%)	0.76	2	0.68
Education	Primary school High school Diploma University degree	11(32.3%) 8(23.5%) 11(32.3%) 4(11.8%)	16(50%) 4(12.5%) 6(18.7%) 6(18.7%)	16(48.5%) 7(21.2%) 5(15.1%) 5(15.1%)	43(43.4%) 19(19.2%) 22(22.2%) 15(15.2%)	1.29	2	0.52
Marital Status	Single Married Separated Widowed	1(2.9%) 24(70.6%) 1(2.9%) 8(23.5%)	1(3.1%) 28 (87.5%) 0(0%) 3(9.4%)	1(3 %) 27 (81.8%) 1(3%) 4(12.1)	3(3%) 79(79.8%) 2(2%) 12(12.2%)	2.89	2	0.23
Stage of disease	Stage I Stage II Stage III	5(14.7%) 21(61.8%) 8(23.5%)	2(6.2%) 21(65.6%) 9(28.1%)	3(9%) 23(69.7%) 7(21.2%)	10(10.1%) 65(65.7%) 24(24.2%)	0.85	2	0.65
Chemotherapy regimen	AC CAF	9(26.5%) 25(73.5%)	17(53.1%) 15(46.9%)	10(30.3%) 23(69.7%)	36(36.4%) 63(63.6%)	0.85	2	0.65
Antiemetic regimen	Grn(or Ond)+Dex Grn(or Ond) +Dex+Apr	27(79.4%) 7(20.6%)	24(75%) 8(25%)	22(66.7%) 11(33.3%)	73(73.7%) 26(26.3%)	1.43	2	0.49

AC= doxorubicin/adriamycin, cyclophosphamide, CAF= doxorubicin/adriamycin, cyclophosphamide, 5-FU (Fluorouracil), Ond=Ondansetron, Dex=Dexamethason, Grn= Granisetron, Apr= Aprepitant, †=Kruskal-Wallis test.

Some patients had one or more of the risk factors outlined in the patients' demographics questionnaire in relation to their history of nausea. As shown in Table 5-6, participants in the Nevasic group had a greater risk of experiencing nausea and vomiting as they had more risk factors. In the Nevasic group, 15 (44.1%) patients had more than one risk factor compared to 7 (21.8%) patients in control group and 7 (21.2%) patients in music group.

It is apparent from the data (Table 6-6) that in the Nevasic group 64.7% had a history of nausea, compared to 46.9% in the music group and only 39.4% in the control group. Due to the fact that the data were non-normally distributed, Fisher's exact test, which compare groups against a categorical variable (such as number of risk factors), was used to identify any statistical significant differences. There was no statistically significant difference between the groups (H (2) = 2.8, P = 0.25).

Table 6-6: History of nausea and vomiting among participants				
History related to nausea *	Nevasic (n=34) No(%)	Music (n=32) No(%)	Control (n=33) No(%)	Total (n=99) No(%)
Motion sickness	2 (5.9%)	3 (9.4%)	2 (6.1%)	7 (7.1%)
Nausea with past pregnancy	2 (5.9%)	3(9.4%)	3 (9.1%)	8 (8.1%)
History of labyrinthitis	0 (0%)	1 (3.1%)	0 (0%)	1 (1.0%)
History of psychological problems	2 (5.9%)	0 (0%)	1 (3.0%)	3 (3.0%)
Fatigue	1 (2.9%)	1 (3.1%)	0 (0%)	2 (2.0%)
Motion sickness and Nausea with past pregnancy	6 (17.6%)	2(6.2%)	2 (6.1%)	10 (10.1%)
Motion sickness and Nausea with past pregnancy and psychological problems	5 (14.7%)	3 (9.4%)	5 (14.7%)	13 (13.1%)
History of labyrinthitis and Nausea with past pregnancy	1 (2.9%)	0 (0%)	0 (0%)	1 (1.0%)
Nausea with past pregnancy and Fatigue	1 (2.9%)	0 (0%)	0 (0%)	1 (1.0%)
Nausea with past pregnancy and History of psychological problems	2 (5.9%)	2 (6.2%)	0 (0%)	4 (4.0%)
Total	22 (64.7%)	15 (46.9%)	13 (39.4%)	50 (50.5%)

* Some patients reported more than one item

6.3.2. Listening to Nevasic or music

To assess the frequency, duration and effectiveness of listening to Nevasic or music, the self-reported questionnaire was used. Table 6.7 shows the descriptive statistics for listening to Nevasic or Music.

Table 6-7: Descriptive statistics for listening to Nevasic or music (Day 1 and Day 2-6)Day 1: Listening to Nevasic or Music			
Day 1 : Listening to Nevasic or music		**Nevasic group (%)**	**Music group (%)**
	Total Number	29 (100%)	26 (100%)
Number of times	0 time	10 (34.5%)	14 (53.8%)
	One time	11 (37.9%)	7 (26.9%)
	Two times	2 (6.9%)	4 (15.4%)
	Three times	4 (13.8%)	0 (0.0%)
	Four times	1 (3.4%)	1 (3.8%)
Duration	< 10 min	1 (3.4%)	1 (3.8%)
	10-15 min	4 (13.8%)	3 (11.5%)
	16-20 min	1 (3.4%)	1 (3.8%)
	>20 min	12 (41.4%)	7 (26.9%)
Effectiveness	1 Not at all	2 (6.9%)	3 (11.5%)
	2	3 (10.3%)	4 (15.4%)
	3	4 (13.8%)	2 (7.6%)
	4	6 (20.7%)	1 (3.8%)
	5 Completely	4 (13.8%)	1 (3.8%)
Day 2- 6 : Listening to Nevasic or music	Total Number	28 (100%)	22(100%)
Number of times	0 time	15 (53.6%)	10 (45.4%)
	One time	5 (17.8%)	2 (9.0%)
	Two times	2 (7.1%)	2 (9.0%)
	Three times	2(7.1%)	2 (9.0%)
	Four times	1 (3.5%)	2 (9.0%)
	> four times	1 (3.5%)	0 (0%)
Duration	< 10 min	1 (3.5%)	1 (4.5%)
	10-15 min	2 (7.1%)	2 (9.0%)
	16-20 min	3 (10.7%)	1 (4.5%)
	>20 min	5 (17.8%)	4 (15.4%)
Effectiveness	1 Not at all	1 (3.5%)	3 (11.5%)
	2	4 (14.3%)	3 (11.5%)
	3	2 (7.1%)	2 (9.0%)
	4	3 (10.7%)	1(4.5%)
	5 Completely	3 (10.7%)	1 (4.5%)

On the day of chemotherapy administration (Day 1), 29 patients (85.3%) in the Nevasic group answered the questions related to listening to Nevasic. Of these, 19 (65.1%) said they listened to Nevasic at least once. In the music group, 26 (81.2%) patients answered the questions related to listing to music. Of these, 12 (46.1%) said they listened to the music at least once. Additionally, 12 patients (41.4%) in the Nevasic group and 7 patients (26.9%) in the music group listened to Nevasic or music for more than 20 minutes. It is notable that Nevasic is recommended to be listened to for at least 27 minutes if participants felt their nausea was not getting better. A total of 10 patients (34.9%) responded (on a Likert-type scale accompanied by a visual analogue scale with 5 ordered response levels) that Nevasic was satisfactory or completely effective in reducing their nausea and/or vomiting. Only 2 patients (7.6%), in the music group responded that music was satisfactory or completely effective in reducing their nausea and/or vomiting on the day of chemotherapy administration.

As the data illustrate, 11 (39.3%) patients listened to Nevasic at least once during days 2–6. In the music group, 8 (36.4%) patients listened to music at least once during this period. In addition, 6 (21.4%) of the patients responded that Nevasic was satisfactory or completely effective in reducing their nausea and/or vomiting, while in the music group only 2 (9.0%) patients mentioned that music was effective in reducing their nausea and/or vomiting.

Spearman's rank correlation coefficient was used to determine the relationship between the frequency, duration, and effectiveness of listening to music or Nevasic and the levels of nausea, vomiting and retching (NVR) for Day 1 (acute phase) and Day 2-6 (delayed phase). No statistically significant correlations between the above items were found (Table 6-8), although it should be noted that there were very few observations in the delayed phase.

Table 6-8: Spearman's correlation between listening to music or Nevasic and the level of NVR							
Groups	Items	Level of NVR in Day 1			Level of NVR in Day 2-6		
		N	r_s	p	N	r_s	p
Music group	Number of times listening to music	12	-0.17	0.59	3	0.00	1.00
	Duration listening to music	12	-0.44	0.16	3	0.00	1.00
	Effectiveness of listening to Music	11	0.15	0.67	3	-0.50	0.67
Nevasic group	Number of times listening to Nevasic	16	0.33	0.21	1	-	-
	Duration listening to Nevasic	16	-0.26	0.33	1	-	-
	Effectiveness of listening to Nevasic	17	0.18	0.49	1	-	-

6.3.3. Taking rescue antiemetic

The self-reported questionnaire was used to assess the prescribed anti-emetics which were taken among the three groups. Table 6-9 shows the descriptive statistics for the used anti-emetics.

It is apparent from the data that in the first 24 hours post-chemotherapy 41.2% of patients in the Nevasic group took their prescribed anti-emetics, while 69.7% of patients in the control group and 59.4% in music group used the rescue anti-emetics ($p = 0.03$). The results also show that during the study period, of the patients in the Nevasic group only 50.0% took their prescribed anti-emetics, while 75.8% of patients in the control group and 59.4% in the music group used the rescue anti-emetics (six days after chemotherapy) ($p = 0.03$). The Pearson's chi-square test was used and statistically significant differences were found between the groups for Days 1–5 (Table 6-9).

Table 6-9: Taking prescribed anti-emetics during the participation period						
Taking prescribed anti-emetics	Nevasic group N (%)	Music group N (%)	Control group (N (%)	Pearson's Chi-squared test		
				X^2	df	p
Day 1	14 (50.0%)	19 (70.4%)	23 (82.1%)	6.74	2	0.03
Day 2	14 (48.3%)	15 (57.7%)	22 (84.6%)	8.22	2	0.01
Day 3	10 (35.7%)	13 (50.0%)	19 (70.4%)	6.66	2	0.03
Day 4	9 (31.2%)	6 (25.0%)	18 (69.2%)	11.85	2	0.01
Day 5	6 (26.1%)	6 (25.0%)	14 (56.0%)	6.57	2	0.03
Day 6	4 (17.4%)	4 (17.4%)	6 (25.0%)	0.57	2	0.75
Day 1-6	17 (50.0%)	19 (59.4%)	25 (75.8%)	6.84	2	0.03

6.3.4. Nausea, vomiting and retching (NVR) experience

This section summarises the participants' experience of NVR before the day of chemotherapy administration, and within 24 hours after chemotherapy (acute nausea) and over days 2–6 post chemotherapy (delayed nausea). It is mainly descriptive data which highlighted the severity of the CINV among breast cancer patients undergoing moderately high emetogenic chemotherapy (MEC) for the first cycle.

6.3.4.1. Anticipatory NVR experience (prior to chemotherapy administration)

Before chemotherapy was administered, 19 patients (3 in the Nevasic group, 9 in the music group, and 7 in the control group) experienced NVR. Three patients (1 in the Nevasic group, 1 in the music group, and 1 in the control group) experienced vomiting. In total, 9 patients (1 in the Nevasic group, 7 in the music group, and 1 in the control group) experienced retching.

It is apparent from the data that NVR were experienced more in the music group than in the other two groups. In order to examine whether there was any difference in the number of patients experiencing anticipatory NVR across the groups, the Kruskal-Wallis test was used. The results show significant differences between the groups in terms of retching ($p = 0.01$) (Table 6-10). It should be noted that the "range" is from min–max.

Table 6-10: Descriptive statistics for anticipatory NVR (before chemotherapy - Day 0)									
Group	Nevasic (N=34)		Music (N=32)		Control (N=33)		Kruskal-Wallis test		
Experience (score)	N (%)	mean(SD) median/range	N	mean (SD) median/range	N	mean (SD) median/range	X^2	df	p
Nausea (0-12)	3 (8.7%)	0.45 (1.64) 0/0-8	9 (27.9%)	1.60 (3.29) 0/0-12	7 (21.0%)	0.63 (1.45) 0/0-6	3.58	2	0.17
Vomiting (0-12)	1 (2.9%)	0.70 (0.37) 0/0-2	1 (3.1%)	0.20 (1.09) 0/0-6	1 (3.0%)	0.03 (0.18) 0/0-1	0.00	2	0.10
Retching (0-8)	1 (2.9%)	0.21 (1.11) 0/0-6	7(21.7%)	0.70 (1.70) 0/0-8	1 (3.0%)	0.67 (0.36) 0/0-2	8.38	2	0.01
Total (0-32)	0 (0.0%)	0.0 (0.00) 0/0-00	0 (0.0%)	0.0 (0.00) 0/0-00	0 (0.0%)	0.0 (0.00) 0/0-00	-	-	-

6.3.4.2. Acute NVR experience

The Rhodes INVR was used to assess acute NVR experience (within 24 hours after chemotherapy). In total 26 (76.5%) patients the Nevasic group answered the question about their nausea within the 24 hours after chemotherapy and 19 (73.1%) patients of them experienced nausea ,12 (48.0%) patients experienced vomiting, and 14(56.0%) had retching. In the music group 18 (69.2%) patients out of 26 experienced nausea, 7 (26.9%) patients experienced vomiting, and 14 (53.8%) had retching. In the control group 15 (57.7%) out of 26 patients, who answered the question, experienced nausea, 6 (23.1%) patients experienced vomiting, and 9 (34.6%) patients had retching.

In order to examine whether there was any difference in the number of patients experiencing acute nausea, vomiting and/or retching across the groups, the Kruskal-Wallis test was used, and no statistically significant differences were found (Table 6-11).

Table: 6-11: Descriptive statistics for INVR scores for acute period (first 24 hours after chemotherapy) among the patients in the three groups

Group		Nevasic (N=34)		Music (N=32)		Control (N=33)		Kruskal-Wallis test		
Experience	(score)	N (%)	mean(SD) median/range	N (%)	mean(SD) median/range	N(%)	mean(SD) median/ range	X^2	df	p
Nausea	(0-12)	26(76.5%)	3.85 (3.57) 3/0-11	26(81.2%)	4.31 (4.31) 3/0-12	26 (78.8%)	3.00 (3.33) 2/0-12	1.33	2	0.51
Vomiting	(0-12)	25(73.5%)	2.16 (2.92) 0/0-9	26(81.2%)	1.38 (2.70) 0/0-9	26 (78.8%)	1.46 (3.29) 0/0-11	3.07	2	0.21
Retching	(0-8)	25 (73.5%)	2.04 (2.26) 1/0-6	26(81.2%)	1.65 (2.23) 1/0-7	26 (78.8%)	1.38 (2.14) 0/0-7	1.93	2	0.38
Total	(0-32)	24(70.6%)	8.21 (8.26) 7/0-24	26 (81.2%)	7.35 (8.48) 3/0-27	26(78.8%)	5.85 (8.10) 2/0-30	1.54	2	0.46

6.3.4.3. Delayed NVR experience

To assess delayed NVR experience, the Rhodes INVR was used. Within 24 to 120 hours following chemotherapy administration, 56 (86.1%) patients experienced nausea: 19 of these were in the Nevasic group, 19 were in the music group, and 18 were in the control group. In addition, 44 (67.7%) patients experienced vomiting: and 48 (72.7%) patients experienced retching: 15 in the Nevasic group, 15 in the music group and 18 in the control group. In total, 52 (86.7%) patients experienced NVR: 18 in the Nevasic group, 17 in the music group and 17 in the control group.

The mean score for INVR within the delayed phase for all three groups was 34.17 (SD= 29.24), and ranged from 0–118 in a possible range from 0–160 (Table 6-12). Table 6-12 shows the experimental data on the daily delayed NVR experience of the three groups. The range of the INVR score for NVR was computed and reported separately. Table 6-12 also lists the means and standard deviations of the INVR scores for each group.

Table 6-12: Descriptive statistics for INVR scores for delayed period (D2 to D6) among the patients in the three groups										
Group		**Nevasic (N=34)**		**Music (N=33)**		**Control (N=32)**		**Kruskal-Wallis test**		
								X^2	**df**	**p**
Experience(score) Day		N(%)	mean/SD median/ range	N(%)	mean(SD) median/ range	N(%)	mean(SD) median/ range			
D2	Nausea (0-12)	26(76.5%)	4.85 (3.84) 5/ 0-12	26(78.8%)	4.80 (4.26) 4/ 0-12	26(78.8%)	3.81(4.37) 1/ 0-12	0.97	2	0.61
	Vomiting (0-12)	25(73.5%)	1.74 (2.86) 0 / 0-12	26(78.8%)	1.36(2.36) 0/ 0-9	26(78.8%)	1.67 (3.28) 0/ 0-12	0.47	2	0.79
	Retching (0-8)	25 (73.5%)	2.58 (2.50) 0/ 0-8	26(78.8%)	2.24 (2.85) 1 / 0-8	26(78.8%)	2.00(2.84) 0/ 0-8	1.70	2	0.43
	Total (0-32)	24(70.6%)	9.23 (8.27) 8 / 0-32	26(78.8%)	8.40 (8.66) 6/ 0-29	26(78.8%)	7.61 (9.90) 1/0-31	1.78	2	0.41
D3	Nausea (0-12)	27(79.4%)	4.70 (3.27) 5 / 0-12	25(75.7%)	5.56 (4.32) 5/ 0-12	27(81.8%)	3.89 (4.16) 3/0-11	1.96	2	0.37
	Vomiting (0-12)	27(79.4%)	2.04 (2.62) 1 / 0-9	26(78.8%)	1. 04 (2.20) 0/ 0-10	26(78.8%)	1.58 (2.71) 0/ 0-10	2.48	2	0.29
	Retching (0-8)	27(79.4%)	2.04(1.81) 2 / 0-5	26(78.8%)	2.00 (2.66) 1/0-8	26(78.8%)	2.19(2.55) 1/ 0-7	0.41	2	0.81
	Total (0-32)	27(79.4%)	8.78(6.46) 10/ 0-23	25(75.7%)	8.64 (7.87) 7/ 0-26	25(75.7%)	8.08 (8.93) 5/ 0-27	3.79	2	0.15
D4	Nausea (0-12)	26(76.5%)	3.23(3.25) 3 / 0-12	23(69.7%)	4.60(3.60) 4/ 0-12	26(78.8%)	3.96 (3.89) 3/ 0-11	2.25	2	0.32
	Vomiting (0-12)	25(73.5%)	1.56(2.26) 0/ 0-6	23(69.7%)	0.87 (1.66) 0/ 0-6	26(78.8%)	1.42 (2.19) 0/ 0-8	1.37	2	0.50
	Retching (0-8)	26(75.5%)	1.58(1.70) 1 / 0-5	22(66.7%)	1.77(2.62) 0/ 0-8	26(78.8%)	2.00(2.40) 1/0-7	0.36	2	0.84
	Total (0-32)	25(73.5%)	6.56(6.20)	22(66.7%)	7.45(7.25)	26(78.8%)	7.38 (7.86)	3.72	2	0.16

Table 6-12: Descriptive statistics for INVR scores for delayed period (D2 to D6) among the patients in the three groups									
		6/ 0-17		6 / 0-24		4/0-23			
D5	Nausea (0-12)	24(70.6%)	2.46(2.98) 2/ 0-11	23(69.7%)	3.48 (3.65) 3/0-12	24(72.7%)	2.71 (2.90) 2/0-12	1.85	2 0.40
	Vomiting (0-12)	23(67.6%)	1.04(1.69) 0/ 0-6	22(66.7%)	0.54 (1.40) 0/ 0-4	25(75.7%)	1.04 (1.72) 0/0-7	3.94	2 0.14
	Retching (0-8)	23 (67.6%)	1.17(1.75) 0/ 0-6	23(69.7%)	1.13 (2.24) 0/ 0-8	25(75.7%)	1.12 (1.74) 0/0-7	0.22	2 0.90
	Total (0-32)	23(67.6%)	4.78(6.02) 2.00/ 0-21	22(66.7%)	5.36 (6.72) 4.00/ 0-24	24 (72.7%)	4.79 (5.76) 4.00/ 0-26	3.13	2 0.21
D6	Nausea (0-12)	22(64.7%)	2.09(3.16) 0/ 0-11	22(66.7%)	2.86 (3.63) 1/0-12	25(75.7%)	1.64 (2.67) 0/ 0-10	0.67	2 0.71
	Vomiting (0-12)	21 (61.8%)	0.81(1.40) 0/ 0-5	22(66.7%)	0.59(1.14) 0/ 0-4	25(75.7%)	0.68 (1.31) 0/ 0-5	0.51	2 0.77
	Retching (0-8)	22 (64.7%)	1.32 (2.03) 0/ 0-7	22(66.7%)	1.27 (2.27) 0/ 0-8	25(75.7%)	0.84 (1.25) 0/0-4	0.32	2 0.85
	Total (0-32)	21(61.8%)	4.38 (6.46) 0/ 0-23	22(66.7%)	4.73 (6.70) 1/0-24	25(75.7%)	3.16 (4.84) 0/ 0-17	2.73	2 0.25
D2-6	Nausea (0-60)	22(64.7%)	17.64 (13.87) 16/ 0-58	20(60.6%)	21.45 (17.27) 17/ 0-60	23(69.7%)	15.48 (14.22) 11 / 0-40	1.04	2 0.59
	Vomiting (0-60)	21(61.8%)	7.58 (8.65) 4 /0-28	20(60.6%)	3.85 (6.00) 1 / 0-19	24(72.7%)	6.42 (7.33) 3/ 0-22	2.14	2 0.34
	Retching (0-40)	22(64.7%)	8.45 (7.68) 6 / 0-25	20(60.6%)	8.95 (11.25) 5 / 0-39	24(72.7%)	8.29 (8.70) 5 / 0- 28	0.23	2 0.90
	Total (0-160)	21(61.8%)	34.57 (27.33) 26 / 0-80	18(54.5%)	36.50 (33.46) 29 /0- 118	21 (63.6%)	31.76 (28.49) 22/ 0-87)	3.56	2 0.17

6.4. Inferential statistics: efficacy of Nevasic in managing CINV/efficacy-quality of life

The efficacy of the interventions on NVR and total NVR experience was examined. A linear mixed-effects model (MIXED) was conducted to explore the impact of the interventions on NVR scores at different times (time 0 (before chemotherapy) to time 6 (day 6 post chemotherapy). This statistical test examined the impact of the interventions (group, a between-subject variable) on patients' daily NVR experience (times, a within-subject variable) and included a group-by-time interaction term as well. Antiemetic use was additionally included as a covariate, as otherwise this would have been confounded with the treatment effect. It is worth restating that, prior to interpreting the results, the score for nausea can range from 0–12; for vomiting 0–12, for retching 0–8, and for all three symptoms 0–32.

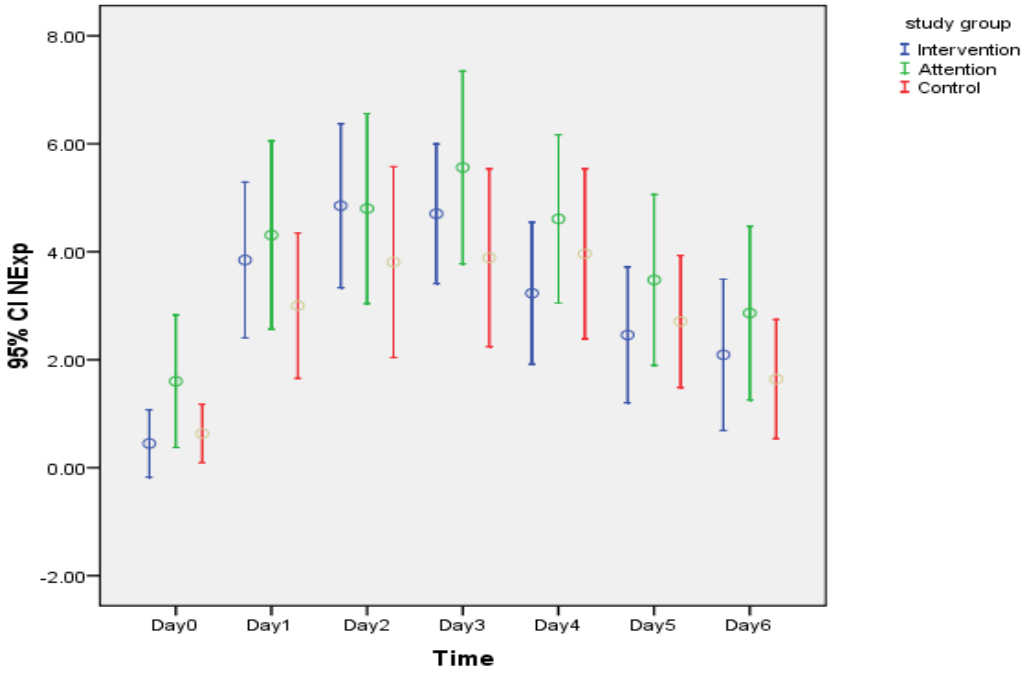
An advantage of mixed models over linear models is that they do not require complete data, and so can base estimates on all the available data. Preliminary analysis suggested that the attrition over time was not random, which might have biased a simple linear model approach.

6.4.1. Effects on nausea

The choice of covariance structure was chosen to minimise the Akaike information criterion (AIC), which is a measure of the relative goodness of fit of a statistical model (Technical report, 2005), and includes a penalty for model complexity. The model was also checked to make sure it had produced realistic estimates of parameters and variances. The AIC criteria led to the choice of an auto-regressive heterogeneous (AR1: Het) structure over time. This structure assumes that there is a correlation between the values of an individual at neighbouring time-points, which is realistic for this type of data. The within-time-point random effect covariance structure was always left as default variance components, which assumes that the within-time-point random effect is constant.

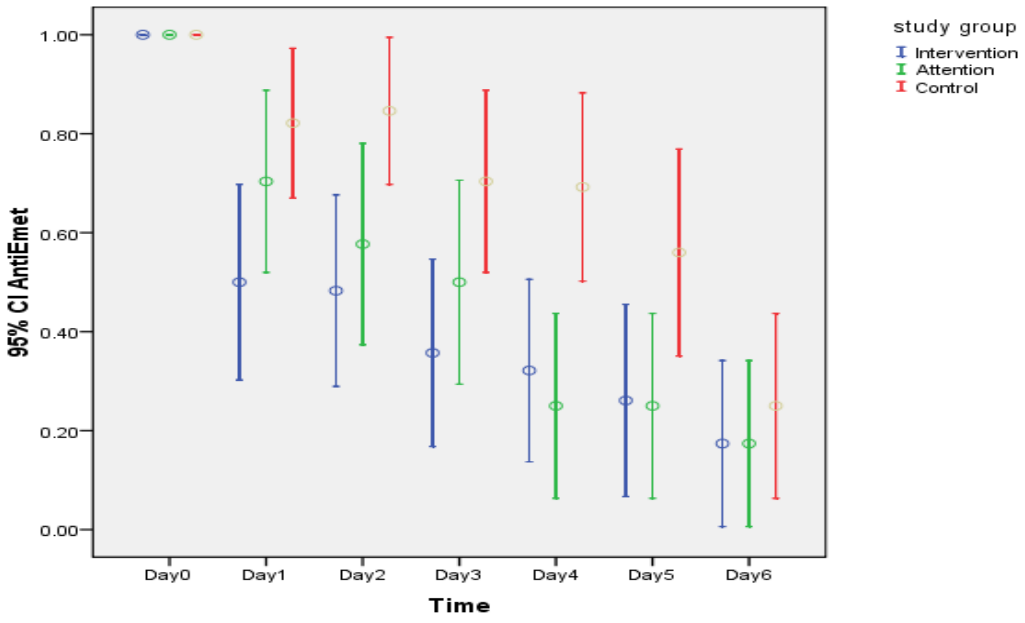
The results indicated that there was no significant difference between groups, either overall (df = 94.32, p = 0.26), between intervention and control (df = 0.39, p = 0.55), between attention and control (df = 1.08, p = 0.11), or between intervention and attention (df = 0.68, p = 0.30) (Figure 6-2).

Figure 6-2: Nausea experience during participation period among the three groups



There were significant differences between time-points (p<0.001), which was caused by the Day 0 nausea score values being significantly lower compared to in the following days. The time by group interaction term was not significant. However, the covariate of antiemetic use was significant (p=0.036) (Figure 6-3).

Figure 6-3: Taking prescribed anti-emetics during participation period among the three

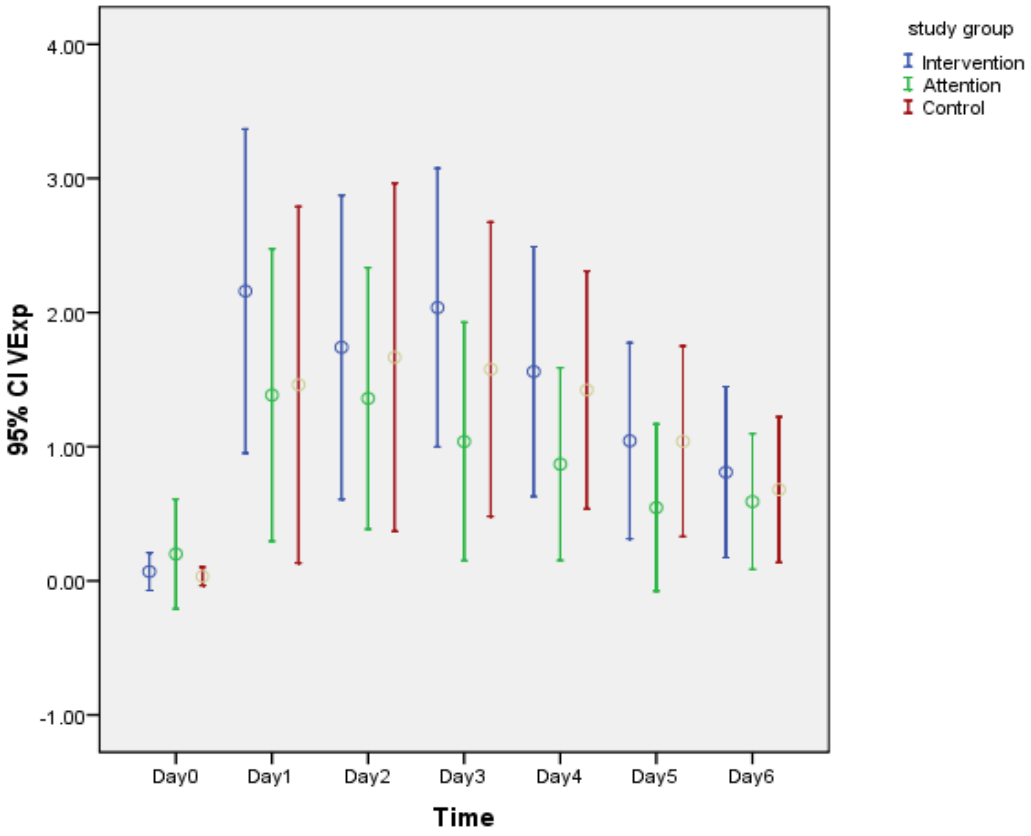


After model fitting, the residuals were found to be approximately normally distributed, and the main results were confirmed with simple non-parametric tests (Kruskal-Wallis test between each group separately at the time-points, and also by Friedman's test between the time-points for each of the three groups).

6.4.2. Effects on vomiting

The same tests used for nausea were used also for vomiting experience. This time, a diagonal covariance structure was deemed to be appropriate (this has different variances at the time-points, and zero correlation between time-points). The results from the linear mixed model indicated that there was no significant difference between groups, between intervention and control (df = 0.84, $p < 0.001$), between attention and control (df = 0.28, $p < 0.001$), or between intervention and attention (df = 0.56, $p < 0.001$) (Figure 6-4).

Figure 6-4: Vomiting experience during participation period among the three groups

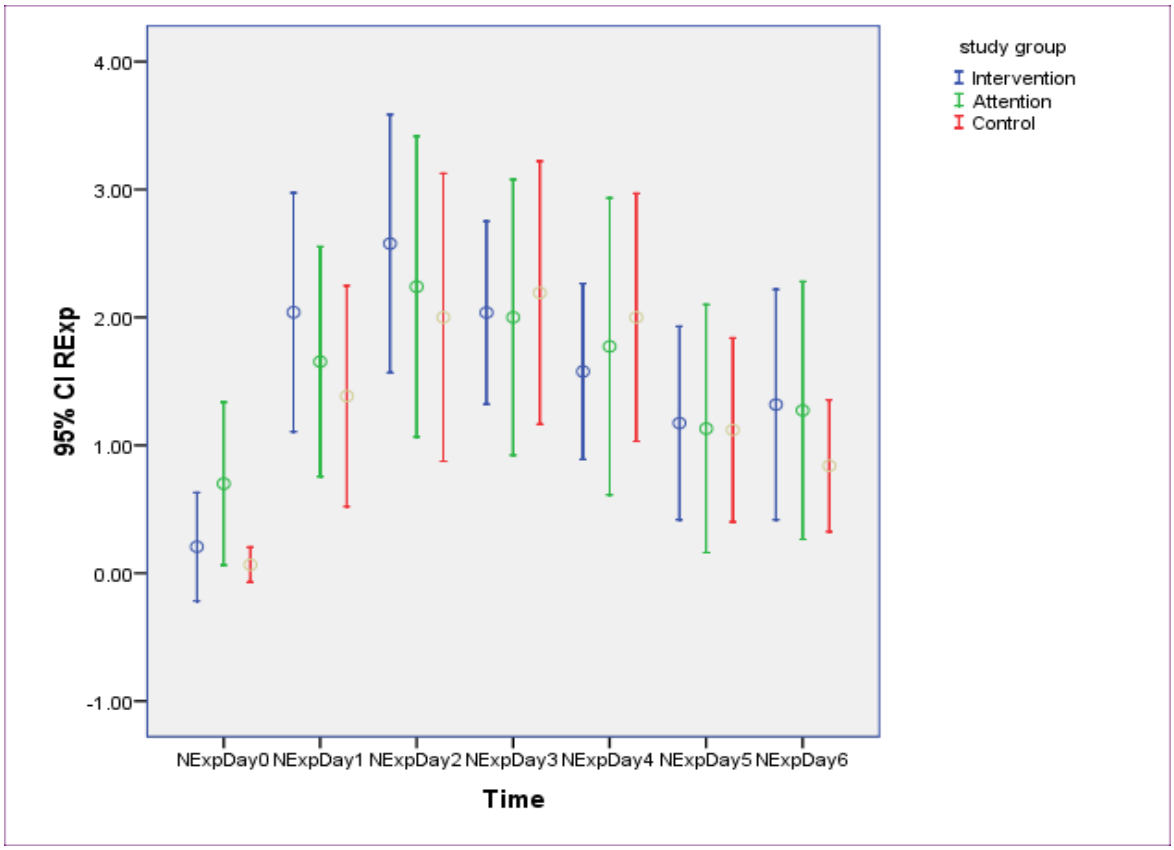


The Kruskal-Wallis test also indicated that there was no significant difference in vomiting scores across the three groups (chi-square= 2.14, df= 2, p=0.34) (Table 6-12).

6.4.3. Effects on retching

For retching experience, this time an auto-regressive (1) (AR1) diagonal covariance structure was appropriate. The linear mixed model indicated that there was no statistically significant difference in the retching scores between the three groups, either overall (p = 0.88), between intervention and control (df = 0.22, p = 0.62), between attention and control (df = 0.07, p = 0.86) or between intervention and attention (df = 0.14, p = 74) (Figure 6-5).

Figure 6-5: Retching experience during participation period among the three groups

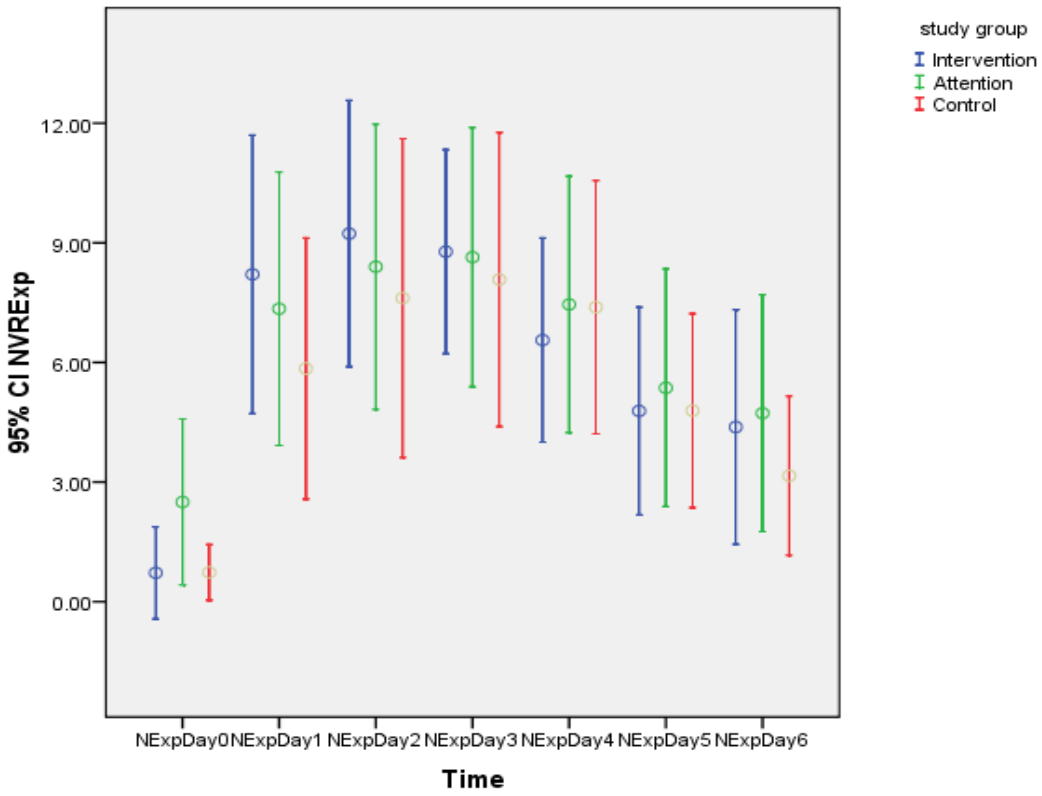


The Kruskal-Wallis test was also used and indicated that there was no significant difference in retching scores across the three groups (chi-square= 0.23, df= 2, p=0.90) (Table 6-12).

6.4.4. Effects on total NVR experience

The effect on total NVR experience was also assessed, and this time another time-series covariance structure was used: the ARMA1 (auto-regressive moving average). In simple terms, this means that the current value depends on the past values, but most depend on the most recent past value. The linear mixed model indicated that there was no statistically significant difference in the total NVR experience scores between the three groups, either overall (df = 54.06, p = 0.75), between intervention and control (diff = 1.09, p = 0.50), between attention and control (df = 1.00, p = 0.53), or between intervention and attention (df = 0.09, p = 0.96) (Figure 6-6).

Figure 6-6: Nausea, vomiting, and retching experience during participation period among the three groups



6.5. Effects on patients' HR-QoL

The patients' HR-QoL was measured twice in this pilot clinical trial; before the interventions (baseline data) and 6 days after chemotherapy administration. In order to assess the effect of the two interventions on patients' follow-up HR-QoL scores (i.e. EORTC QoL-C30 and EORTC QoL-BR 23), and to control for the baseline score differences among the three groups, it is suggested that if the scores are normally distributed between the groups, an analysis of covariance (ANOVA) should be used (Vickers 2005). As one of the assumptions of ANOVA is a normal distribution of the dependent variable in the population, preliminary checks were carried out to ensure that this test was reliable and there was no violation of the assumptions of the EORTC QoL-C30 functional scales scores (physical, role, emotional, cognitive and social); symptom scales scores (nausea and vomiting, fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial problems); and global health status/HR-QoL scores among the three groups. Normality was also assessed for the EORTC QoL-BR23 functional scales scores (body image, sexual functioning, sexual enjoyment and future perspective); and symptom scale scores (for systematic therapy, breast symptoms, arm symptoms, and hair loss). Table 6-13 presents the HR-QoL baseline mean scores, and Table 6-14 presents the follow-up scores. It should be noted that a high score for functional scale represents a high/healthy level of functioning. A high score for the global health status/QoL represents a high QoL. In contrast, a high score for the symptom scale represents a higher level of symptoms/problems (Aaronson et al., 1993).

Table 6-13: Mean and standard deviation for EORTC HR-QoL scale *baseline* scores			
EORTC scale	Nevasic group Mean/SD	Music group Mean/SD	Control group Mean/SD
EORTC-QLQ			
Global health status / QoL (GL) #	66.66/20.86	61.39/22.37	68.01/21.53
Physical functioning #	85.21/16.48	82.22/15.79	85.21/19.80
Role functioning#	82.32/19.52	77.96/26.67	84.89/21.32
Emotional functioning#	71.97/27.39	66.93/23.81	78.64/23.28
Cognitive functioning#	88.89/18.48	85.00/19.25	94.27/11.68
Social functioning#	81.31/24.21	79.57/27.12	81.18/25.00
Total functional scales#	81.39/16.97	77.32/17.87	83.87/15.91
Fatigue¶	21.21/19.71	27.41/28.25	18.75/20.04
Nausea and vomiting¶	2.52/8.46	15.60/28.20	1.04/4.99
Pain¶	23.74/22.45	28.49/26.24	16.67/20.74
Dyspnoea¶	3.03/9.73	10.75/18.03	2.08/8.20
Insomnia¶	17.17/26.51	26.89/31.53	17.71/29.31
Appetite loss¶	17.17/29.01	22.58/30.29	20.83/30.23
Constipation¶	6.06/13.05	30.00/36.46	7.29/16.36
Diarrhoea¶	3.03/9.73	2.15/8.32	0.00/0.00
Financial difficulties¶	42.67/34.05	51.85/38.49	21.80/26.57
Total symptom scales / items¶	16.00/11.01	24.92/20.88	11.64/9.18

Table 6-13: Mean and standard deviation for EORTC HR-QoL scale *baseline* scores			
EORTC-BR23			
Body image#	67.68/30.95	61.90/30.89	81.45/24.22
Sexual functioning#	88.89/16.94	90.91/15.19	86.42/18.51
Sexual enjoyment#	78.79/22.47	88.89/16.26	84.85/19.86
Future perspective#	59.60/37.97	48.27/37.36	73.96/26.41
Systemic therapy side effects ¶	14.28/16.59	26.09/22.97	14.60/14.14
Breast symptoms¶	15.40/19.00	18.61/18.66	16.14/21.16
Arm symptoms¶	19.86/18.37	29.63/30.09	22.96/24.05
Upset by hair loss¶	30.55/43.71	61.11/37.15	8.33/15.43

*The normality test was assessed for each group separately, N= Normally distributed, X= Not normally distributed, # =High score indicates better function/QoL, ¶= High score indicates more worse from symptom and lower QoL.

Table 6-14: Mean and standard deviation for EORTC HR-QoL scale ***follow-up*** scores			
EORTC scale	Nevasic group Mean/SD	Music group Mean/SD	Control group Mean/SD
EORTC-QLQ			
Global health status / QoL (GL) #	49.04/20.04	50.00/25.00	59.94/18.71
Physical functioning #	74.36/20.37	69.49/18.00	79.74/16.27
Role functioning#	62.82/26.80	59.61/25.02	79.01/18.83
Emotional functioning#	61.22/23.44	50.93/23.61	64.20/30.29
Cognitive functioning#	74.67/27.27	72.84/23.64	85.18/20.32
Social functioning#	67.95/21.04	62.34/28.34	78.39/29.53
Total functional scales#	68.53/17.62	63.50/15.61	76.58/15.20
Fatigue¶	44.44/20.61	53.00/24.00	38.68/24.72
Nausea and vomiting¶	28.85/26.90	30.86/23.43	27.16/28.17
Pain¶	32.05/22.57	41.97/22.82	29.63/28.62
Dyspnoea¶	11.54/20.96	19.75/23.13	8.64/21.86
Insomnia¶	37.18/30.30	44.44/39.22	38.27/37.78
Appetite loss¶	46.15/34.09	45.68/35.98	43.21/34.36
Constipation¶	33.33/31.27	49.38/36.24	14.81/23.27
Diarrhoea¶	0.26/27.92	12.34/26.39	4.94/12.07
Financial difficulties¶	42.67/34.05	51.85/38.49	21.79/26.57
Total symptom scales / items¶	32.82/14.90	40.04/16.54	27.91/15.15

Table 6-14: Mean and standard deviation for EORTC HR-QoL scale ***follow-up*** scores			
EORTC-BR23			
Body image#	58.68/34.71	53.39/30.77	72.76/27.84
Sexual functioning#	88.67/17.16	86.11/16.05	87.88/17.20
Sexual enjoyment#	44.00/34.32	38.89/32.10	42.42/34.40
Future perspective#	42.67/31.21	24.70/31.48	70.51/27.21
Systemic therapy side effects ¶	33.91/20.31	42.86/20.46	70.51/27.21
Breast symptoms¶	16.33/20.48	24.07/20.06	18.00/18.89
Arm symptoms¶	27.78/23.15	39.51/24.33	30.22/22.11
Upset by hair loss¶	29.41/30.92	52.38/40.24	37.88/40.23

*The normality test was assessed for each group separately, N= Normally distributed, X= Not normally distributed, # =High score indicates better function/QoL, ¶= High score indicates more worse from symptom and lower QoL.

As shown in the last column in Tables 6-13 and 6-14, none of the baseline scores (25 scores) were normally distributed, and only 3 follow-up scores (global health status, fatigue, and systemic therapy side effects) out of 25 were normally distributed among the three groups.

The data for the HR-QoL scales are not normally distributed. However, it was expected that the changes in HR-QoL scores from baseline to post-intervention may be normally distributed. Descriptive statistics were determined for the change scores in HR-QoL (follow-up minus baseline) to find out how the change scores behave. The mean change scores, standard deviation (SD) and median are listed in Table 6-15. It should be noted that a minus score (lowest mean score) for functional scales and the global health status represent a high/healthy level of functioning or health status, and indicate improvement (the lower the mean score, the better the QoL patients achieved). However, for the symptom scales, minus scores indicate no improvement. In fact, the lower the mean score, the worse the QoL patients achieved (no improvement).

It is apparent that the HR-QoL changes scores do not have a normal distribution, and therefore the Krukal-Wallis test was used on the change score. This non-parametric test indicates that there are no statistically significant differences in HR-QoL change scores across the three groups (Table 6-15). The results show that there was a borderline significant result for global health status ($p = 0.06$). In addition, the changes were larger in the Nevasic group than in the control group for some functional scales (role functioning, cognitive functioning and social functioning), although these were not significant.

Table 6-15: Means and standard deviations for EORTC scales changes scores, normality test and Kruskal-Wallis test									
EORTC Scales	HR-QoL changes scores			Normality test			Kruskal-Wallis test		
EORTC-QLQ	Nevasic group Mean/SD/ Median	Music group Mean/SD/ Median	Control group Mean/SD/ Median	Nevasic	Music	Control	**X^2**	**df**	**p.**
Global health status / QoL (GL) #	-17.00/13.500.00	-11.86/17.98/-8.33	-8.67/20.48/-12.50	N	X	X	5.6	2	0.06
Physical functioning #	-11.20/10.67/-13.33	-12.00/13.74/-6.67	-7.94/13.99/3.33	N	X	N	1.52	2	0.46
Role functioning#	-20.51/22.76/-16.67	-1795/31.94/-33.33	-7.41/21.35/0.00	X	N	N	4.84	2	0.09
Emotional functioning#	-13.78/22.48/0.00	-16.67/25.94/-16.67	-14.20/24.98/-4.17	X	N	N	0.48	2	0.78
Cognitive functioning#	-17.33/22.81/-16.67	-7.69/18.99/-16.67	-9.26/19.24	N	N	-	2.82	2	0.24
Social functioning#	-17.95/24.00/0.00	-14.81/23.27/-16.67	-3.85/28.40/0.00	X	N	N	4.89	2	0.09
Fatigue¶	23.08/20.10/22.22	23.11/26.82/22.22	20.58/2014/0.00	N	N	N	1.57	2	0.45
Nausea and vomiting¶	25.64/30.63/16.67	16.66/23.11/0.00	26.54/27.45/25.00	N	N	X	0.33	2	0.85
Pain¶	7.69/20.13/0.00	12.96/24.16/16.67	13.58/28.51/0.00	X	N	X	0.49	2	0.78
Dyspnoea¶	8.98/20.13/0.00	8.64/23.74/0.00	7.41/16.88/0.00	X	N	X	0.15	2	0.93
Insomnia¶	21.79/33.92/0.00	14.81/31.12/0.00	24.69/32.81/0.00	X	X	N	1.19	2	0.55

Table 6-15: Means and standard deviations for EORTC scales changes scores, normality test and Kruskal-Wallis test									
Appetite loss¶	26.92/38.89/0.00	23.46/34.36/33.33	24.69/30.09/16.67	N	N	N	0.27	2	0.87
Constipation¶	25.64/28.76/33.33	14.10/39.07/0.00	7.41/29.72/0.00	N	N	X	4.43	2	0.11
Diarrhoea¶	7.69/28.76/0.00	9.88/25.84/0.00	4.94/12.07/0.00	-	N	X	0.81	2	0.67
Financial difficulties¶	0.00/0.00/-	0.00/0.00/-	0.00/0.00/-						
EORTC-BR23									
Body image#	--9.72/24.65/-50.00	-9.72/32.94/0.00	-7.67/28.660.00	N	N	N	0.48	2	0.79
Sexual functioning#	4.76/23.05/33.33	0.00/11.43/-	5.00/14.41/8.33	-	N	N	1.16	2	0.56
Sexual enjoyment#	-33.33/50.39/0.00	-48.48/27.34/-33.33	-45.83/20.64/-50.00	N	N	N	0.94	2	0.62
Future perspective#	-16.00/36.16/-	-26.67/46.15/0.00	-1.28/35.88/0.00	-	N	X	3.90	2	0.14
Systemic therapy side effects ¶	18.65/18.14/19.04	18.81/20.52/23.81	17.90/13.13/11.90	N	N	N	0.12	2	0.94
Breast symptoms¶	1.00/10.57/0.00	5.45/13.52/0.00	1.33/24.73/-12.50	N	X	X	1.71	2	0.42
Arm symptoms¶	8.12/20.50/0.00	7.69/18.26/0.00	8.80/21.97/0.00	X	X	N	0.14	2	0.93
Upset by hair loss¶	23.81/31.71/0.00	3.70/26.06/0.00	22.22/40.37/16.67	X	N	N	1.55	2	0.46

N= Normally distributed, X= Not normally distributed, # =minus scores indicate improvement; the lowest mean score the better QoL patients achieve, ¶= minus scores indicate no improvement; the lowest mean score the worse patients achievement (no improvement).

6.6. Conclusion

This study has benefitted from the combination of qualitative and quantitative research methodology. The quantitative research (RCT) has enabled the examination of the outcome data, such as the level of nausea and vomiting and taken anti-emetics. In addition, qualitative research (focus groups) has put that data in a context which has allowed the researcher to explore participants' perceptions on the intervention and the acceptability of using Nevasic. Taken together, the two approaches showed evidence that the proposed full-scale RCT to assess the effectiveness of Nevasic on CINV was feasible and identified areas within the study that would need to be considered for future studies. The next chapter will discuss the findings from the two approaches in detail.

Chapter Seven: Discussion

7.1. Introduction

This chapter begins with a brief review of the thesis. The discussion then focuses on issues related to the primary outcome of this study, including the feasibility issues, treatment fidelity and process evaluation. The participants' perceptions of the intervention and the acceptability of using Nevasic for preventing and controlling CINV are explored. In addition, the suitability of using the chosen outcome measures is evaluated. This is followed by an examination of the study strengths and limitations, and recommendations for practice and further research.

7.2. Review of the thesis

Chapter one highlights the problem of CINV in cancer patients and draws attention to the popular use of different non-pharmacological interventions in cancer symptom management. The incidence and factors associated with, and the impact of CINV on patients' QoL, are explored. It is also highlighted that pharmacological therapy is only partially effective in preventing or treating CINV in many cases; therefore, the need for additional methods to reduce the symptoms has been highlighted.

The literature related to non-pharmacological CAM (mind–body) interventions (acupuncture/acupressure, progressive muscle relaxation, guided imagery, hypnosis, virtual reality, and music therapy) in controlling nausea and vomiting in cancer patients receiving chemotherapy is reviewed in Chapter two. This reveals that it is difficult to draw conclusions about the effectiveness of most of these interventions. Therefore, the need for additional relief has led to research interest not only in developing new antiemetic medications, but also new non-pharmacological adjuncts to medications.

The methods of the feasibility study are presented in Chapter three, along with the rationale for any decisions made. The processes of sampling, data collection, and procedure, and a detailed examination of the validated measurement tools appropriated for use in the study are described. In Chapter four, the process of translation of the Rhodes INVR into Persian and the psychometric tests used are also explained.

In a pilot RCT, 99 breast cancer patients were randomised to usual care (standard anti-emetics) plus one of (1) intervention group (using Nevasic), (2) attention group (listening to music), and (3) control group, receiving no additional intervention. Patients were recruited from three cancer centres in Mashhad, Iran. Data were collected daily using the INVR and a structure-diary questionnaire. The EORTC QLQ-C30 (and BR23) were used at baseline and day 6 post chemotherapy.

The results of the study are presented in Chapter five. The findings show that there was no statistically significant difference among the groups in terms of level of post chemotherapy nausea and vomiting, either overall, between the intervention and the control group, between the attention and the control group, or between the intervention and the attention group. However, statistically significant differences were found between the groups in terms of anti-emetics taken for day 1–5 ($p = 0.03$). During the study period, 50.0% of patients in the Nevasic group took their prescribed anti-emetics, while 75.8% of patients in the control group used the rescue anti-emetics. In addition, the results show borderline non-significant ($p=0.06$) better global health status (HR-QoL) in the Nevasic group.

Participants' views regarding the burden (negative impacts) of completing this study, the acceptability of using Nevasic or music, and the reasons for study attrition, were obtained by conducting focus groups. The findings indicate that there was no robust willingness in patients to use Nevasic or music to manage CINV.

The main purpose of this study was to assess the feasibility of conducting an RCT to evaluate the effectiveness of Nevasic in controlling CINV in breast cancer patients. Therefore, the main study outcomes in terms of the feasibility issues, treatment fidelity and process evaluation will now be discussed.

7.3. Feasibility issues

Feasibility studies can help to reveal whether the intervention is acceptable in terms of delivery method and those who are receiving it, where and by what method; what outcome measures are most appropriate; and whether changes occur in the intended domains (Bennett & Closs, 2011). Therefore, patient

recruitment, randomisation, suitability of selecting control arms, appropriateness of outcome measures, and treatment fidelity which are all crucial aspects of feasibility studies, will be discussed below.

7.3.1. Feasibility of patient recruitment

The National Cancer Research Network (NCRN) noted that adult participation in clinical trials was 10.9% of incident cancer cases in the UK in 2004 (NCRI, 2004), and even lower rates of recruitment have also been reported (Fayter et al., 2007; McNair et al., 2008; Swain-Cabriales et al., 2013). There is no precise and confirmed information on the proportion of patients who are enrolled in such trials in developing countries like Iran. However, a number of factors are known to influence recruitment, such as socio-demographics (age, sex, ethnicity, and socioeconomic status), biomedical variables (illness status), the target population size and location (multicentre and multi-institutional studies), patient- health care professional relationship, and cultural issues (Castel et al., 2006; Mancini et al., 2007; Mills et al., 2006). Participation rates are reported in few cancer studies, particularly in studies conducted in Iran. In this study, the recruitment rate was 84.6% and only 15.4% refused to participate. In a study conducted in northern Iran the average participation rate was 71% (Islami et al., 2009), while higher average rate of participation (79.5%) has also been reported in another study (Kamangar et al., 2005). This shows that generally patients' refusal rates appear lower in Iran compared with studies conducted in developed countries, although the refusal rates vary from 28% (Jenkins & Fallowfield, 2000) to greater than 50% (Ellis et al., 2002; Simon et al., 2004; Castel et al., 2006). The higher rate of participation in Iran might be partly related to patient-health care professional relationship and/or cultural factors (public attitudes toward participation in cancer clinical trials). It was observed in this study that most breast cancer patients preferred to delegate the responsibility of participating to their physicians, as they do when it comes to the choice of treatment (Moradian et al., 2012) . Moreover, it is revealed (from the focus groups) that the other important factors facilitating recruitment in this study were patients' attitude regarding participation in the trial, and positive communication with patients. It has been documented that patients who are naturally altruistic may be more likely to consent to research (Bevan et al., 1993; Jenkins and Fallowfield, 2000). In this study, 84 participants (85%) mentioned that

the main reason for participating was a belief that their participation would benefit future patients with the same condition. This is consistent with Morrill & Avis's (1996) study which aimed to identify the factors that female breast cancer patients consider important in deciding whether to enrol in a breast cancer clinical trial. They showed that the most important factors in favour of participation were helping others with breast cancer (Morrill & Avis, 1996). In our study, patients were very positive about their participation. Patients signified a wish to recognise any possibility that could contribute to helping prevent chemotherapy side effects such as nausea and vomiting. Therefore, inconvenience related to the trial was considered relatively minor.

It should be noted that the researcher adequately assessed and responded to patients' queries regarding the trial, and they had an opportunity to ask questions and to elicit information that was important to them. The initial face to face recruitment (in most cases) and follow-up telephone calls facilitated the development and maintained a good relationship with the participants. During the phone calls participants verbalised their appreciation for being contacted by the researcher, as they saw it as an opportunity to check out their concerns about their illness and treatments they received despite the fact that this was not the purpose of the call. As some participants in focus groups mentioned, a warm, caring, positive attitude, as well as a personal approach, were crucial in recruiting patients for this trial. One explanation for this may relate to the unmet needs and lack of support throughout the illness trajectory among Iranian cancer patients, as highlighted in previous studies (Moradian et al., 2012). Several studies have also found that positive communication about participation in a clinical trial is a key factor in recruiting patients (DiMatteo et al., 1986; Comis et al., 2003; Pittens et al., 2012).

Other demographic factors may also be important: people who are less educated and from lower socioeconomic backgrounds have been reported to be more likely to take part in clinical trials (Prescott et al., 1999; Ellis 2000). In this study, 76% of participants were homemakers, and 43% had only a primary school level of education.

The uncertainty of participating in a trial might create additional worries. Previous studies have revealed that patients are concerned about uncertain side effects, uncertain outcomes and the possibility of unnecessary tests (Fayter et al., 2007). In this study, of those declining to participate, 14 patients (77.8%) stated that an unfamiliarity with the research and a feeling that participating in clinical trials would add to their anxiety were the most important factors in their decision not to take part. An issue that arose in a more limited way in the literature was that of timing of the approach to participate in a trial. It was proposed that patients were being asked to participate in trials often at a time when they are feeling vulnerable, possibly soon after diagnosis (Fayter et al., 2007). It is revealed that patients felt that participating in clinical trials would add to their anxiety particularly if approached shortly after diagnosis (Fayter et al., 2007; Mancini et al., 2007; Sala et al., 2011). This might be the main reason for refusing to participate, as in this study patients were diagnosed with breast cancer and started treatment shortly before the study. In addition, participants were naïve to chemotherapy which itself can increase anxiety (Hipkins et al., 2004). Furthermore, 11 patients (61.1%) of those declining to participate mentioned that one of their reasons for refusing to participate was the influence of others (e.g. spouse, family member, close friend) who were against participation.

Overall, the patients' perceptions about their participation were very encouraging. Effective communication (verbal and non-verbal communication of warmth, caring and positive regard) and a personal approach (sensitivity to the participants' concerns) were considered crucial in how patients perceived information, as well as recruitment. Although the acceptance rate for participation in the study was good, the issue of the length of time taken to reach the recruitment target was the matter and an adaptation was made to address it. The recruitment of participants was slower than initially predicted. It was necessary to extend the planned one cancer centre to three centres. This was partly due to the slower development of the chemotherapy service than was initially predicted and a month of low activity due to Ramadan (a month of fasting).

It is notable that the patient population included only patients treated at 3 cancer centres in Mashhad, Iran in 2011, and therefore had the population distribution at that specific place and time. It is likely that different patient populations evaluated

at a different point in time or elsewhere would possess different characteristics and may need more time to reach the recruitment target.

7.3.2. Feasibility of randomisation

Lancaster el al. (2004) stated that pilot studies would allow for examining randomisation. Although a strict sampling procedure was adopted to homogenise the sample as far as possible, considering the possible extraneous variables, the study shows differentiation in the patients' history in relation to nausea and vomiting. As the results show, 44% of participants in the Nevasic group had more than one risk factor compared with the other two groups (music and control), in which about 21% of the patients had more than one risk factor. Highly susceptible patients in the Nevasic group could negatively affect the result, as these patients are more likely to experience severe nausea and vomiting. This means that participants in the Nevasic group were among the higher-risk patients, compared with the other two groups, in relation to experiencing nausea and vomiting. Randomisation procedure used in the present study was utilised and is a viable option for future studies. However, failing to adequately control patients' history in relation to nausea and vomiting affected the homogeneity of the sample. Therefore, it cannot be ensured that any essential differences between groups in the outcome event was attributed to the intervention, and not to some other factors (Stolberg et al., 2004). This is shown in other studies, for example, in a study conducted by Celio et al. (2012), the effect of established risk factors such as age, gender, and alcohol consumption in preventing CINV due to moderately emetogenic chemotherapy was assessed. The results show that the rate of overall complete response to antiemetic treatment (Palonosetron plus 1-day Dexamethasone) was lower among high-risk patients (for instance in the subgroup of younger patients undergoing AC-based chemotherapy), compared with the response rate among low-risk patients (Celio et al., 2012).

When designing the study, stratification of patients by age was considered to control this factor; however, due to the low incidence of breast cancer in women under 40 years old in the general population, only 18 patients (18.2%) who were under 40 years old were recruited to the study. Although findings from previous studies (Harirchi et al., 2000; Harirchi et al., 2004) suggest that breast cancer

affects Iranian women who are at least one decade younger than women in developed countries, with the mean age ranging from 47.1 to 48.8 years, stratified randomisation by age group was not feasible for the study period (11 months).

7.4. Selection of control arms and blinding

Use and choice of control groups (control and/or attention), which is a prerequisite in RCT designs, is always a critical decision in designing a clinical trial. That choice might even affect the inferences that can be drawn from the trial (European Medicines Agency., 2001). Selecting control arm(s) is not straightforward in most clinical trials. Nevertheless, it can be more difficult to design the control arm(s) in non-pharmacological trials when the mechanism of action of the intervention arm is poorly understood, as the main purpose of using the control arm(s) is to distinguish the effect of the intervention (the specific effect) from the effect of other factors (the context effect) that might explain the outcome.

Placebo effects and the expectation of a positive effect might be considered to be greater in non-pharmacological studies, as in non-pharmacological interventions, the separation of specific effects from context effects is more complicated (Bennett & Closs, 2011). In ideal circumstances, a clinical trial will show that while context effects may be associated with some improvement in outcomes (the placebo effect); the intervention is associated with considerably more improvement (the specific effect).

Two types of control group were used in this study: (1) no intervention (standard therapy), (2) placebo. According to Nevasics' manufacturer, Nevasic delivers audio pulses and frequencies (as a test treatment) in a blend of music. Therefore, the music (as a seemingly identical treatment) was selected as the most appropriate placebo for this study, with the aim of matching, as closely as possible, the experience of the comparison group with that of the Nevasic group. However, music therapy has been used in a number of previous studies for the relief of symptoms such as CINV (Beck, 1991; Frank, 1985; Kwekkeboom, 2003; Smith et al., 2001; Updike, 1990; Zimmerman et al., 1989). It has been documented that music therapy is an effective form of supporting cancer care for patients during the treatment process (Stanczyk, 2011). Considering the definition of a placebo as an inactive substance or procedure, using music was not an

entirely appropriate choice, as music could be considered as an intervention of its own, and therefore differences between the attention and intervention groups might have been less pronounced for this reason. Using an inactivated form of the Nevasic (by deleting the engineered stabilising audio pulses and frequencies, as proposed by the manufacturer) could be more appropriate for the attention group. In addition, in pharmacological interventions with placebo control design, double-blind techniques are almost always applied. In fact by allowing blinding and randomisation and including a group that receives an inert treatment, controls for all potential influences on the outcome, except for the study treatment. In this, however, requirements for these two aspects (randomisation and blinding) were not completely met.

One other limitation in clinical trials of non-pharmacological interventions is blinding. Effectively blinding the intervention and control arm(s) in non-pharmacological interventions is problematic because of the nature of most non-pharmacological interventions. A good example is using acupuncture in clinical trials. Streitberger et al. (2003) used a non-skin-penetrating placebo needle, which simulates penetration of the skin. Placing the placebo needle in the same manner and at the same location as the acupuncture needle might ensure effective blinding of the patients. However, blinding of the acupuncturists was not possible using this placebo method (Streitberger et al., 2003). This aspect applies to a range of other non-pharmacological interventions as well, such as educational interventions, transcutaneous electrical nerve stimulation (TENS), and assessment procedures (Sindhu, 1996; Oldenmenger et al., 2007; Bennett et al., 2009). In other words, although single blinding (the patient is not aware of the allocation) may be possible, double blinding (neither the patient nor the researcher are aware of the allocation) is almost impossible to achieve in non-pharmacological interventions. This limitation may affect the validity of the design and interpretation of the findings (Bennett & Closs, 2011).

No blinding was used for this study and participants were aware of which arm they were in, although there was the possibility to apply single blinding. As suggested above, if an inactivated form of the Nevasic had been used, the attention and intervention groups would have been much more similar, making it easier to distinguish the effect of the Nevasic. Also by applying, at least, single blinding; it

may have helped to increase the validity of the design and interpretation of the findings. Blinding is an important safeguard against bias and participants may respond differently if they are aware of their treatment assignment, in addition, lack of blinding may also influence adherence to the study and risk of dropping out of the trial (Wood et al., 2008). Therefore participants blinding would be considered for future trial.

7.5. Mechanism of action and effective use of Nevasic

Pharmacological interventions typically use an accurate and well-defined approach that is derived from a detailed knowledge of a particular pathophysiological mechanism and drug pharmacology. In contrast, non-pharmacological interventions differ in terms of the mechanism of action, which is not completely understood (if at all) for many of these interventions. In fact, in non-pharmacological interventions the mechanisms of action are often vague, multiple, and poorly defined. Moreover, in (almost all) pharmacological interventions it is known what dose of drug is safe and, in particular, the dose and method of application is acknowledged to ensure that the drug affects the pathophysiological mechanism that is being targeted. However, in non-pharmacological interventions the “effective dose” is hardly determined, and is usually delivered as single or episodic applications. Consequently, the result is that the effects of non-pharmacological interventions are usually intermittent, and any benefits might be harder to identify.

In this study, as mentioned before, the manufacturer of Nevasic suggests that it “stabilises the balance receptors in the inner ear in order to provide relief from nausea”. It has been proposed that the frequencies and pulses from the programme, which border the recognisable audio spectrum, may desensitise and stabilise the vestibular system. However, no scientific justification has been provided for Nevasic’s mechanism. In fact, the mechanism of action has not been fully defined. The manufacturer also suggests that users could possibly pre-empt about of nausea and/or vomiting at the first signs of symptoms. However, no specific instruction for using Nevasic in terms of frequency and duration (in terms of effective dose) is recommended. It has been suggested that users discover their own "best practise" for using Nevasic, as the results can vary for each person.

Therefore, it was expected that finding reliable evidence for the effects of this non-pharmacological intervention would be complicated. Our aim to determine the effectiveness of Nevasic as a non-pharmacological intervention to relieve post chemotherapy nausea and vomiting was not completely met as the mechanism of Nevasic is not yet clear and failed to identify any direct effect on CINV. This makes interpretation of the results challenging.

Generally, additional information is required to understand the roles of non-pharmacological interventions in cancer supportive care as limited information available on the relative efficacy (and even safety) of most of these approaches. It can be concluded that it is necessary to develop knowledge of the mechanisms underlying non-pharmacological interventions which can point out physiologically relevant processes leading to better identifying benefits of these interventions.

7.6. Treatment fidelity

Although treatment fidelity has been addressed over the two past decades, Moncher and Prinz's (1991) article was the first to formally introduce a definition and guidelines for the enhancement of treatment fidelity. Previously, treatment fidelity was usually considered as treatment integrity, which meant that the treatment condition had been implemented as intended. Moncher and Prinz (1991) developed upon this earlier definition to include the concept of treatment differentiation, or whether the treatment conditions differ from one another in the manner intended. In other words, treatment fidelity consists of two general components: treatment integrity (the degree to which a treatment is implemented as intended) and treatment differentiation (the degree to which two or more study arms differ along critical dimensions)(Borrelli, 2011).

Treatment fidelity has a direct impact on the internal and external validity of a study. If the intervention being tested does not adhere to the study protocol then the study will have poor internal validity. This means that the results may be uncertain regarding the utility of the intervention, and it will be impossible to know whether the results of the study are actually a function of the proposed intervention, or have arisen due to extraneous factors (Moncher & Prinz, 1991; Borrelli, 2011).

The issue of treatment fidelity has been considered in both pharmacological and non-pharmacological contexts (Moncher & Prinz, 1991). In pharmacological trials, determining whether all patients received the right dose of drug for the specified duration is important in order to ensure that the drug has had a chance to work. This refers to the degree to which an intervention maintains its original form, and the extent to which the trial protocol was administered as intended (Cohen et al., 2008). However, Bennett and Closs (2011) argued that treatment fidelity may be more crucial in non-pharmacological clinical trials because of the complex nature of the interventions and the potential for bias in the design.

Some aspects of general components of treatment fidelity related to treatment delivery and receipt are discussed in the following section.

7.6.1. Participants' adherence to the interventions

Ellis et al. (2012) identified a number of issues in the development and delivery of a non-pharmacological intervention in symptom management in patients with lung cancer. Their study showed that participation adherence for symptom management is influenced by several factors, such as: perceptions of relevance, convenience, and beliefs about the intervention (Ellis et al., 2012). Their findings also suggested that patients usually do not have a strong preference for using potential techniques and methods that they supposed to be of little relevance to them, particularly in cases where symptom control is not a priority. In our study the patients received chemotherapy as part of their treatment plan for breast cancer; therefore, using Nevasic or music to prevent and/or control post chemotherapy nausea and vomiting was not considered completely relevant to them, as their main concern was about cancer-treatment.

Beliefs of patients also can influence the extent to which they will engage in techniques, methods, and interventions. In one study, adherence beliefs among breast cancer patients taking tamoxifen were investigated. It was reported that non-adherers were more likely to state that taking tamoxifen did not have any effect, while adherers were more likely to report that tamoxifen would prevent the development of breast cancer (Grunberg et al., 2004). In our study, the results show that during Day 2–6, 15 participants (53.6%) never listened to Nevasic and 17.8% of participants listen to Nevasic only once per day. Additionally, the results

clearly illustrate that Nevasic was not used as suggested, since it was used for longer than 20 minutes per session by only five participants (26.3%). One explanation for this might be patients' beliefs regarding the effect of Nevasic or their experience of its effectiveness on day 1. Abdollahnejad (2004) mentioned that using music (or a blend of music) as a treatment modality may be looked at from a pessimistic perspective. It means that patients might not believe that Nevasic or music can help them. The results from the focus groups also revealed that about half of the participants reported a belief that there was nothing to be gained from using Nevasic or listening to music.

Patients are more likely to adhere to methods, techniques, and interventions that are simple and fit easily into their daily routines (Gritz et al., 1989). In one study that described adherence to exercise in women treated for breast cancer, it was highlighted that in order to adhere to a non-pharmacological intervention the intervention must be acceptable to the patients (Daley et al., 2007). In this study, most of the participants (66.7%) mentioned not feeling comfortable with the CD player provided for the Nevasic or music. Therefore, listening to Nevasic using a CD player might not be entirely appropriate, since it might be considered difficult to use or a poor fit with the patients' daily lives. Therefore, listening to Nevasic using other available devices, such as an iPhone or iPod which may demonstrate higher acceptability and portability to patients, might be more convenient for this population (cancer patients) and increase adherence.

Grunfeld (2005) argued that the role of health-care professionals in informing patients of the purpose of their treatment and for the development of symptom management interventions, as well as its relevance to the patients, plays a key role in patients' adherence. In this study, however, the trial was not considered important or relevant by some health-care professionals (particularly some oncologists). This might have affected the patients' preferences and/or perceptions of using Nevasic or listening to music. This dilemma (staff disinterest) has been documented in previous studies (Fayter et al., 2007; Kaanoi et al., 2002).

Nevertheless, the results strongly suggest that Nevasic was often under-dosed in terms of frequency and duration. Inadequate use of Nevasic might lead to an underestimation of its effects, and prevent reliable conclusions from being drawn

regarding its effects on nausea and vomiting for this group. This situation can be interpreted as one in which there is a lack of evidence of effect, rather than reliable evidence of lack of effect. In fact, inadequate adherence to the intervention may explain the underestimation of the intervention effects, and account for the inconclusive findings.

7.7. Treatment fidelity and process evaluation in randomised controlled trials

It has been documented that RCTs are the most rigorous way in which to evaluate the effectiveness of both pharmacological and non-pharmacological interventions (Gatchel, 2001; Bajard et al., 2009). However, most RCTs focus on outcomes, not on the processes involved in implementing an intervention (Oakley et al., 2006). Process evaluations within trials also investigate the implementation, receipt, and setting of an intervention, and help in the interpretation of the outcome results. Participants' perspectives on the intervention may be examined to find out how the intervention is implemented, distinguish between components of the intervention, investigate contextual factors that may affect the intervention, monitor dose to assess the reach of the intervention, and study the ways in which the effects vary across subgroups. The evaluation of evidence should be able to distinguish between the fidelity of the evaluation process in detecting the success or failure of an intervention, and the success or failure of the intervention itself. Furthermore, if an intervention shows insufficient evidence of success, the process evaluation may help to differentiate between interventions that are inherently faulty (failure of intervention concept or theory) and those that are poorly delivered (implementation failure). Study design alone is an inadequate marker of evidence quality in interventions evaluation (Rychetnik et al., 2002). Process evaluation is particularly essential in multisite trials, where the "same" intervention may be implemented and received in different ways (Oakley et al., 2006).

In our study, several aspects of fidelity (i.e. potential sources of bias that may lead to an underestimation of the intervention effect) were examined, and several areas of concern identified. These included the perspectives of both the health-care professionals and the patients, lack of special instruction for using the Nevasic (frequency and duration as effective dose), lack of blinding, poor reporting of the pattern and duration for using Nevasic, and the use rescue medications. These

issues might lead to inadequate adherence to the intervention. As mentioned above, almost half of the participants never listened to the Nevasic, and most patients listened to it only once per day. This suggests that Nevasic was under-dosed in terms of intensity or frequency and duration. The process evaluation disclosed that several issues related to the context of the intervention confounded the anticipated outcomes. In fact, although inferential statistics analysis show no significant difference between the groups, other data derived from the descriptive statistics analysis, qualitative interviews and focus groups (which explored the patients' views on different aspects of the intervention) show that many other factors might have influenced the results regarding the efficacy of Nevasic in managing CINV.

This is not extraordinary in non-pharmacological trials. For example, in a trial of pain algorithm introduced into nursing practice, no change in pain scores might have been considered a failure (Seers et al., 2004). However, as Bennett and Closs (2011) argued, considering other data derived from the process evaluation demonstrated that many other factors influenced the results, such as: inconsistencies in the motivation and attitudes of staff, a lack of confidence in using research-based evidence, variable organisational support, a resistant ward culture, and a reliance on junior staff who were not always able to facilitate practice change. Obviously, if these data had not been collected their influence would have been missed.

7.8. Outcome measures

Choosing which outcomes to measure in a study requires the researcher to decide on what will be important to measure in order to determine whether the interventions being tested have a useful effect (Anon., 2010). A first step for the researcher is to decide what the trial should look for, so as to identify whether the intervention has any effect (Tierney, 2001). It has been documented that any assessment or measurement of effectiveness must assess the intended effects. For example, in chronic pain management "pain intensity" and "pain relief" are two important clinical outcomes (Dworkin et al., 2008). The literature review showed that in almost all non-pharmacological interventions with the aim of controlling and managing CINV, the (primary) outcome was to measure the experience of nausea

and vomiting (amount or extent, duration and/or intensity) (Klein & Griffiths, 2004). However, it has been argued that the measurement of additional outcomes in non-pharmacological trials is imperative, and may help to provide clarification; this is especially relevant when the mechanism of action of the intervention is less clearly defined. Such outcomes might include medication adherence, and participants' satisfaction or experience (Bennett et al., 2009). In this study, nausea and vomiting experience was considered the main outcome, and the efficacy of the intervention was examined by measuring these. No significant differences between the groups were found in terms of nausea and vomiting experience; however, there were significant differences in terms of the rescue antiemetic medications taken among the three groups, which might affect the results. Therefore, selecting other outcomes, such as measuring the frequency of taking rescue anti-emetics, use of PRN anti-emetics and/ or health care costs might be more appropriate and the key outcome to measure for future trial.

7.9. Suitability of assessment instruments

It has been emphasised that in clinical trials, when examining the effectiveness of any intervention, it is crucial to use valid methods for accurate assessment of the outcome of interest, and its success is dependent upon the reliability and validity of endpoint measures (Morrow, 1992). For this study, three questionnaires were used: EORTC QLQ-C30 (plus EORTC QoL-BR23), Rhodes INVR, and a designed diary questionnaire.

7.9.1. The European Organisation Research and Treatment of Cancer – Quality of Life Questionnaire

The assessment of HR-QoL as part of RCTs is common in the cancer field. Furthermore, outcomes in antiemetic trials are often measured not only using diaries but also HL-QoL instruments (Pater et al., 1996; Osoba, 1999). The EORTC QLQ-C30 and EORTC QLQ-BR23 were considered suitable, highly reliable and valid. They have been used in a wide range of clinical cancer trials, by a large number of research groups worldwide.

As described in Chapter 3, appropriate tools for the study were selected following the eight essential criteria of Fitzpatrick et al. (1988): appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility.

Reliability was assessed in terms of having internal consistency coefficients (Cronbach's α) in the range 0.7 to 0.9 (Munro, 2001). It is shown that the Iranian version of EORTC QLQC30 (version3.0) is a reliable and valid QoL measure for cancer patients. Safaee et al (2007) show that the internal consistencies of the scales, as assessed by Cronbach's α coefficients, were above the acceptable level of 0.7. In addition, its validity level is satisfactory, and the structure of the questionnaire is confirmed. However, in this study, a few questions were not answered; specifically those concerning sexual issues. A similar problem was reported by the authors of the scale (Aaronson et al., 1993). A possible explanation for this is that such issues are considered very personal, and should therefore not be explicit, even for research purposes. In the interviews, some of the patients mentioned that they did not feel comfortable answering such questions, and considered these areas to be very sensitive. This is inconsistent with previous studies indicating that the instrument was well accepted by Iranian breast cancer patients (Montazeri et al., 1999; Safaee & Dehkordi, 2007); although in our study patients found the questions easy to understand. This was not unexpected because such a problem (feeling of violation of privacy) was stated even in some European studies (Rodary et al., 2004) where the questionnaire was originally developed. Despite the fact that the sample in this study stemmed from a culturally diverse population, the EORTC QLQC30 can be used as a reliable and valid measure of QoL in cancer patients in Iran.

7.9.2. The Rhodes Index of Nausea, Vomiting and Retching

In this study, and for the measurement of nausea and vomiting, as discussed in Chapter 3, the Rhodes INVR was selected. As the INVR had not been translated into Persian prior to this study, it was necessary to do so. The process of translation and psychometric testing is also explained and discussed in Chapter 3.

The patients reported that the Rhodes INVR scale (Iranian version) was easy to understand and use; it takes 2–3 minutes to complete. However, some patients found that the repetition (every 12 hours) of the same scale over six days placed additional demands on them. This problem prevents the accurate completion of such time- and energy-consuming scales (Molassiotis et al., 2007a). The INVR was designed to be completed every 12 hours (Rhodes & McDaniel, 1999);

however, to keep the demands on patients to a minimum, patients were asked to fill out the questionnaires once daily (in the evening). This problem was also reported in some previous studies and several studies used the INVR over 24hrs (Molassiotis et al., 2007a) and hence the validity of this approach exists and makes sense to do so in order to enhance completion.

Generally, as mentioned in Chapter 3, this is the first time that an instrument for measuring nausea, vomiting, and retching to health professionals in Iran have introduced and can be used in clinical trials or other studies of outcome research. In spite of the fact that a number of instruments measuring nausea and vomiting and their impact on quality of life do exist (Morrow, 1984; Rhodes & McDaniel, 1999; Martin et al., 2003), it is not surprising that to our knowledge this is the first study of its type in Iran. However, to improve the psychometric properties of this translated instrument further studies will be needed, and it is expected that the present study could contribute to the use of standard nausea and vomiting measures in Iran and other developing countries, since it is possible to translate and validate such instruments even within a culturally diverse population (Montazeri et al., 1999).

7.9.3. Diary questionnaire

In addition to the above outcome measures, a diary questionnaire (in compliance with the study outcomes) was designed. This questionnaire measured parameters of interest such as antiemetic intake. As mentioned in Chapter 3, the questionnaire served as a daily diary for patients' nausea and vomiting experience over the study period. While using diary questionnaires have the advantage of being patient-reported, there are difficulties inherent in their use (Bolger et al., 2003). Since these questionnaires are unsupervised, it is more likely that errors occur (Lauritsena et al., 2004; Fisher et al., 2012). Problems associated with this kind of questionnaire are that patients may misunderstand questions, miss questions, select more than one response option where one is intended, and may be completed just before attending a study visit at the clinic (Lauritsena et al., 2004). This has implications on memory retrieval of symptom occurrence and intensity, i.e., fluctuations during the day/week might be missed, time of onset might not be recorded correctly, and the last impressions of either adequate or inadequate

symptom resolution might be overestimated (Lauritsena et al., 2004). Some diary studies (Burtona et al., 2007; Fisher et al., 2012) suggesting to use electronic diaries to minimise these shortcoming. In electronic diaries, users enter data via a touch screen and a stylus. By selecting options from on-screen lists or by completing Likert-type or visual analog scales (VAS) user-friendliness is achieved. All entries are date stamped and time stamped, and data are kept in the device for later retrieval (Burtona et al., 2007). However, several difficulties in using electronic diaries have been identified. For instance, participants need to be confident, willing, and able to use them, as using of the device is more complicated and not understood by all patients (Fisher et al., 2012).

Using an electronic diary was not considered for this study, although it might have some advantages. Firstly, to our knowledge, there was not available device and related software to use, particularly in Persian. Secondly, it might increase study setup time and cost (Fisher et al., 2012) which were against the nature of this study (as PhD programme).

7.10. The impact of attrition on the trial

One of the main aims in designing an RCT is to minimise bias in the estimation of the intervention effect. Randomisation eliminates the problem of selection bias, which is the selection of seemingly more desirable interventions by either the researchers or the participants. Consequently, the investigational and comparison cells tend to be balanced on baseline demographic and clinical characteristics. To prevent selection bias, all randomised participants should be included in the analysis at the primary outcome point. Whilst attempting to minimise bias, it is also necessary for the RCT design to control type I error by adapting for multiplicity. Simultaneously, the sample size should provide adequate statistical power (Leon et al., 2006; Hewitt et al., 2010). Furthermore, attrition, as the study duration progresses, and which can be considered to be another form of self-selection, can destruct randomisation. This has the potential to introduce attrition bias, cause imbalances to arise among the previously randomised groups, and, therefore, threaten the internal validity of the RCT (Leon et al., 2006). Attrition has the potential to harm random assignment, resulting in groups for which the expected value of the baseline differences is not zero (Valentine & McHugh, 2007). In fact,

attrition interferes with the above-mentioned aims of an RCT, and can lead to biased estimates of the intervention effect (Leon et al., 2006).

Although attrition is common among clinical trials, the point at which it becomes a serious threat to trial validity is unclear. Leon et al. (2006) argued that although attrition reduces the amount of data available for analyses, with a corresponding reduction in statistical power, only non-random attrition will result in bias. Furthermore, Valentine and McHugh (2007) argued that it is more likely that 5% non-random attrition on an important prognostic variable will introduce bias than 20% random attrition, since non-random attrition may cause differences in baseline characteristics for one or more covariates to move away from zero. In this study, the baseline (day 0) value for two groups of patients was examined: those who completed all assessments, and those who dropped out before day 6. It was observed that there were differences at the baseline between these two groups, which meant that the attrition had not been random.

As discussed above, this could lead to bias in the analysis, and might increase the appearance of type I errors (Shek & Ma, 2011). They stated that in longitudinal studies, in which problems of participant attrition and other forms of missing measurements relating to individuals are encountered, using linear mixed models to analyse data might help to decrease type I errors. They stated that this method provides researchers with a more flexible and powerful approach when handling unbalanced data (e.g. unequal sample size, inconsistent time interval, and missing data). Therefore, to analyse the data and minimise the risk of bias in the study, a mixed model approach was chosen. This model utilises all the available data, estimates values based on the correlation structure between time-points, and is less susceptible to bias due to non-random attrition (Vickers, 2005). Moreover, Leon et al. (2006) argued that researchers should not assume that equal attrition between trial arms is not a cause for concern, as the reasons for attrition might be quite different within each group. For instance, in a placebo drug trial, attrition from participants in the placebo group may arise due to a lack of efficacy, while those in the active group may withdraw because of side effects. Nevertheless, the results from our study show that the reasons for non-completion and attrition among all the three groups were similar (as mentioned in Chapter 6). However, it is worth noting that although contacting participants during the study period (6 days after

chemotherapy) was considered unethical at first (respect individual privacy), almost all participants were satisfied about being contacted. Follow up was considered valuable by the patients, and lead to a reduction in the attrition rate. Therefore, effective health-care professional (or researcher)-patient communication, and the provision of appropriate information and support during the participation period, were useful strategies to improve recruitment and minimise attrition rate. Moreover, this would be considered the ethical norm in clinical trials (Wilson et al., 2005).

7.11. Study outcomes

In the following section, the findings of the current study will be discussed and placed in the context of the literature.

7.11.1. Nausea, vomiting and retching incidence

This study supports prior studies suggesting that more symptoms are experienced in the delayed phase of CINV than in the acute phase. In addition, acute nausea was reported to be more intensive than vomiting (Grunberg et al., 2004; Lee et al., 2008; Grote et al., 2006).

The incidence of acute nausea and vomiting in our study was higher than previous findings in cancer patients receiving moderately emetogenic chemotherapy (MEC) (Grunberg et al., 2004; Bloechl-Daum et al., 2006; Molassiotis et al., 2008). In an observational study of adult cancer patients, 35% of patients experienced acute nausea (Grunberg et al., 2004); in our study, 68% of patients reported acute nausea. Grunberg et al. (2004) also reported that 13% of patients experienced acute vomiting, compared with our results which show that 32% of patients experienced acute vomiting. In our study, delayed nausea was reported in 71%, which was higher compared with Grunberg's study (52%). Also, delayed vomiting was 56%, compared to 28% of MEC patients in Grunberg's study. Our findings show a much higher rate of delayed vomiting (56%) experienced by patients in all three groups.

This is inconsistent with other studies (Lee et al., 2008; Grote et al., 2006). One explanation might related to the lack of a specific policy for the prevention of CINV in Iran. Moreover, physicians may be noticeably underestimating the incidence of

CINV after MEC, as there is no research in this area in Iran. This explanation can be supported by the fact that health-care professionals have underestimated the incidence of CINV after both high emetogenic chemotherapy (HEC) and MEC in different settings of practice (Grunberg et al., 2004; Pérez-Altozano et al., 2009). The impact of CINV may therefore warrant more attention than perhaps it has received. These results show a continuing need for progress in control of CINV and emphasise the need for continuing research on this area. There is undoubtedly room for improvement regarding control and/or treatment of CINV in cancer settings in Iran.

7.11.2. The effectiveness of Nevasic in controlling CINV

Although the main aim of this pilot study was to examine the feasibility of running an RCT, assessing the antiemetic effect of Nevasic was one of the outcomes. Anti-emetics and the amount of anti-emetics taken have a very important place in the treatment of cancer patients undergoing chemotherapy (Raynov, 2001). The prevalence of adherence to outpatient antiemetic regimens that are prescribed for delayed CINV prevention in breast cancer patients is limited in the literature. Chen et al (2011) evaluate the prevalence of adherence to anti-emetics among breast cancer patients. They found that 57.9% of the Asian breast cancer patients were adherent to their antiemetic regimens (Chan et al., 2011). In this study, antiemetic medications were prescribed as PRN (“as necessary”) and were not scheduled; instead, administration was left to the patients. The results show that about 50.0% patients in the Nevasic group took their anti-emetics, while 75.8 % of patients in the control group and 59.4% in the music group used the rescue anti-emetics during the study period (6 days after chemotherapy). One explanation for taken fewer anti-emetics in the Nevasic group might be the perceived effectiveness of Nevasic, as the results show more than 28% of the participants in Nevasic group stated that using Nevasic was (at least moderately) effective, compared with 13% in the music group. It might be proposed that the need for patients in the Nevasic group to take antiemetic medication was less pronounced than it was for the two other groups, and that they might have deliberately stopped taking their anti-emetics. In fact, they might not have needed to take any anti-emetics, as they may have not felt CINV. Using Nevasic as a complementary therapy might increase the individual’s feeling of control, and reduce the amount of antiemetic medications

needed. Therefore, it may contribute not only to improving patient well-being, but also to a reduction in terms of the patient's economic burden. Previous studies have revealed that up to 15% of patients undergoing chemotherapy suffer from the side effects of the anti-emetics that they use to control their nausea and vomiting (Raynov, 2001). The possible and common side effects include: headaches, fatigue, insomnia, indigestion and constipation which all can negatively impact on patients' QoL (Macmillan Cancer Support, 2012). It has also been documented that the cost of antiemetic therapy for CINV is substantial within health-care systems around the world (Hamada et al., 2012).

7.11.3. Effect of Nevasic on health-related quality of life

Assessments of HR-QoL may benefit as an important variable and a valid and useful endpoint in addition to other clinical outcomes (Crosbya et al., 2003). It is recommended that QoL endpoints be used when treatments are expected to be equivalent in efficacy but a QoL benefit is offered by one, or when a new treatment shows a small benefit that is offset by QoL deterioration (Gotay & Moore, 1992).

The aim of using a QoL assessment in this study was to provide an additional outcome measure for comparisons and evaluations of Nevasic in order to determine its efficacy and impact on participants. The mean changes from baseline to Day 6 generally indicated no significant differences (or clinically meaningful changes) across the EORTC QLQ-C30 function and symptom subscales. However, a borderline significant difference ($p= 0.06$) in global health status was observed. The mean change in scores for the Nevasic group was -17 vs. -11.86 and -8.67 for music and control groups, respectively. In fact, the results indicate that the negative impact of CINV on patients in the Nevasic group was less than in the other two groups. Although this difference is not statistically significant, it might be clinically meaningful. This can make the interpretation complicated: it is known that statistical significance is not equivalent to clinical significance (Osoba et al., 1998). In addition, from the patients' perspective, a meaningful change in HR-QoL may result in a decrease in symptoms or improvement in function. On the contrary, a meaningful change for health-care professionals may be one that indicates a change in the therapeutic treatment or in the prognosis of the disease. These perspectives may not always be in

agreement (Crosbya et al., 2003). The issue of statistical versus clinical significance is discussed below.

7.12. Statistical significance vs. clinical importance

One debateable issue in many studies is the importance of the differences between statistical significance and clinical importance (Haase et al., 1989). Statistical significance does not tell us directly *how big* the difference was while clinical importance is one of clinical judgment such as considering the magnitude of benefit of each treatment, the respective profiles of side effects of the different treatments, their relative costs, the comfort of administration of a new therapy, and the patient's preferences (University of Ottawa, 2012). It is known that by increasing the sample size, we can find any effect size to be statistically significant; however, a statistically significant change is not necessarily clinically importance (Cella et al., 2002). Hogan (2007) cautioned that many of the reported results from RCTs may be statistically significant, but researchers should go a step further to prove that these benefits are clinically importance. One of the suggestions to avoid this exaggeration of results is to report the effect size.

The “statistical significance" answers the question, how real is the observed intervention or treatment effect. In general, the "clinical importance” answers the question of how effective the intervention or treatment is. In terms of testing clinical treatments, practical significance ideally leads to quantified information about the importance of a finding, using metrics such as effect size. Effect size can provide imperative information about the results of a study, and is recommended to be reported in addition to statistical significance (Peterson, 2008; Vacha-Hasse et al., 2000). This approach (effect size) to assessing clinical significance is often inferred when discussing the distribution-based approach, which is based on statistical distributions such as effect size measures, and other measures using means and SDs obtained from previous research studies (Sloan et al., 2003).

The literature review revealed that although for many pharmacological interventions for the prevention of CINV a minimum significant difference of 10% is considered to be a clinically meaningful difference (Saito et al., 2009), this varies in non-pharmacological interventions. For example, in an RCT examining the effect of ginger on CINV, the minimum significant difference was considered to be

30% (Sontakke .S et al., 2003), while in another non-pharmacological intervention evaluating the effect of acupuncture on post-chemotherapy fatigue, 15% improvement was considered a minimally important difference (MID) (Vickers et al., 2004). A 20% absolute risk reduction has been defined as a clinically relevant effect for the prophylaxis of postoperative nausea and vomiting using non-pharmacologic techniques (Lee & Done, 1999).

Approaches to determining clinical importance vary and have not been standardised. In the absence of established standards, the clinical researchers pick what seems like a reasonable value (Man-Son-Hing et al., 2002). Naylor and Llewellyn-Thomas (1994) identified approaches which the subjective opinions of clinician experts are the basis of clinical practice, sometimes using consensus development (Pauker & Kassirer, 1980; Naylor & Llewellyn-Thomas, 1994). While others suggested that the perspective of patients is also important in the determination of clinical importance (Man-Son-Hing et al., 1996). In general, different disciplines use divergent approaches to determining the clinical importance of their interventions. There is also no agreement on the appropriate method(s) of determining the clinical importance of therapies. Depending on many factors, including the seriousness of the condition, the outcome being measured, the potential of the intervention to cause adverse effects, and the availability of alternative treatments, these approaches may be too strict or vice versa (Man-Son-Hing et al., 2002). For this study, using a low-tech and cheap self-managed intervention with no (or minimum) side effects, the clinically meaningful effect size was considered to be 10% (0.1x12=1.2). This is considered key for interpreting the results. Our findings therefore reveal that Nevasic does not have an effect in this regard. The observed effect size for nausea was: intervention–control = 0.4, intervention–attention = -0.7, and attention–control = 1.1 – all of which were not statistically significant.

Although, this study did not detect any statistically significant differences in post chemotherapy nausea and vomiting among the three treatment groups, the results show statistically significant differences in the used anti-emetics among the groups which is also imperative in terms of clinical importance. In addition, the primary research aim was to examine the feasibility of running an RCT to assess the effects of Nevasic on CINV and the findings concerning this aim were positive.

Therefore, considering the issues that raised from this pilot study, Nevasic might be worth further investigation. In fact, it might be required to investigate the effect of Nevasic on the use of PRN antiemetic medication during both acute and delayed phases of CINV as the key outcome to measure, rather than only looking at the level of nausea and vomiting or its effect on HR-QoL.

7.13. Sample size calculation and power analysis for future study

The INVR scores for acute and delayed period among the patients in the three groups (Table 6-11& 6-12) may be used as the basis for sample size calculations for a future study.

The calculation was based on a test (i.e. difference between pairs of groups) using a Mann Whitney U test. This sample size calculation was prepared by Dr. Mark Pilling, Research Statistician, School of Nursing Midwifery and Social Work, University of Manchester. This was done by calculating the sample size required for a t-test (assuming common standard deviation), and then scaling the sample size up by a factor of 1/0.995 for the non-parametric Mann Whitney U test (Prajapati et al., 2010).

The sample size required to detect a clinically meaningful effect size of 1.2 (10%) between two groups for acute nausea, given a common standard deviation of 3.8 and using 5% significance level with a statistical power of 80%, would be 163 participants per group. Assuming a conservative attrition rate of 30% at 6 days, the overall sample size required would then be 232 participants per group, or 696 in total for three groups. This sample size would also be sufficient to test for differences in acute vomiting, delayed nausea and delayed vomiting.

4.14. Study strengths and limitations

7.14.1. Study strengths

This is the first study regarding the use of Nevasic for the management of nausea and vomiting in cancer patients receiving MEC. This study was strengthened through the adoption of different research methods. The flexibility of such a design allowed the researcher to use different data collection methods and sources. In fact, this study used both quantitative and qualitative data sources, collection

methods and analyses, which resulted in a more comprehensive understanding of how to conduct a new non-pharmacological intervention in practice. In addition, both approaches were complementary in terms of providing a better understanding of the outcomes. The study not only focused on feasibility issues and outcomes, but also on fidelity and process evaluation with respect to the trial, which helps in the interpretation of the outcome results. This contributes to building a broader understanding of the issues studied.

Recruitment is one of the main difficulties in conducting an RCT, and is frequent among RCTs (Fayter et al., 2007; McNair et al., 2008). In our study, recruitment started from the main centre, and because of slow patient accumulation, the second and third centres were added at three-week intervals to increase the recruitment rate. The use of multi-site studies apparently led to higher rates of recruitment; however, conducting studies at more than one site may not always be feasible due to financial or staff limitations (Gul & Ali, 2010). The high participation rate facilitated the recruitment of a large majority of eligible participants during the study period.

7.14.2. Study limitations

The obvious limitation of this study is that prior research studies on the topic, and a defined mechanism of action, are lacking. In fact, the lack of an accurate and well-defined mechanism of action derived from detailed knowledge of a particular pathophysiological mechanism make it difficult to find a scientific justification for its proposed effectiveness. Therefore, it was difficult to justify the aims of the study and encourage oncologists to refer their patients to the researcher. This led to a lack of success in terms of engaging all health professionals involved. Barriers to, and motivational factors for, the participation of health-care professionals in clinical trials, have been reviewed extensively (Wragg et al., 2000; McNair et al., 2008; Salis et al., 2008); however many of the issues identified are not applicable to this feasibility study, as they focus on the use of health-care professionals to recruit patients into either large, multi-site, commercially funded studies, or barriers to health-care professionals conducting their own research. A sufficiently interesting research question has been suggested as a factor motivating health-care professionals to become involved in trials (Ross et al., 1999). In addition, lack of

support staff, lack of time and time pressures from usual nursing care and duties have been identified as a barrier to involving chemo nurses. Staff training (providing information and basic skills regarding conducting the study and how to meet participants' queries) was a challenge for the researcher. After initial training sessions were conducted in the clinical centres, staff turnover complicated the situation and threatened implementation fidelity. It also leads to a need to provide retraining.

Another issue is sampling bias (in terms of recruitment and allocation to the treatment arms). This study relied on a convenience sample; therefore, the recruited patients might not be representative of the overall population of patients with breast cancer, although their characteristics were compared. Nevertheless, the participants were randomly assigned to the study groups. It should be noted that in a pilot study, a convenience sample makes it possible to obtain basic data and trends about the study, without the complications of using a probability sample (Emmanuel, 2012). This study used restricted inclusion criteria to recruit patients. The rationale for this was to obtain a homogenised sample as far as possible. However, it was hampered by its limited generalisability. Moreover, in the current sample, some inconsistencies were noted between the patients' history in relation to nausea, and vomiting.

Another limitation of this study was stratification. Due to the low incidence of breast cancer patients who are under 40 years old in the general population, stratified randomisation by age group was not feasible for this study.

Using self-reported data can also be considered a study limitation. Relying on pre-existing self-reported instruments is limited by the fact that it can rarely be independently verified. In fact, self-reported data might contain several potential sources of bias, as patients tend to complete them retrospectively (meaning that they can be affected by failures of memory), and/or might exaggerate when responding to the questions asking them about their experience (making them sound more significant than actually were) (Gritz et al., 1989; Oldenmenger et al., 2007). The Rhodes INVR is designed to be administered every 12 hours (morning and evening); however, in this study, to minimise the burden on participants, they were asked to complete it once daily (in the evening); however, in this study, to

minimise the burden on participants, they were asked to complete it once daily (in the evening). This might have influenced its reliability, although in previous studies (Molassiotis et al., 2007a) patients completed the INVR every evening, and the reliability of the instrument was proven. Another limitation was the language used regarding the subjective data sources (interview and focus group), as all the interviews were conducted in Persian, which then needed to be translated to English. Although the researcher was keen to correctly translate the text into English, reflecting the exact meaning was still not guaranteed, which may have threatened the internal validity of the study.

This pilot trial was not powered to prevent the risk of type I or type II errors. However, its main aim was to determine feasibility, compliance, and acceptability, rather than identify significant differences between the groups. Therefore**,** it would not be appropriate to place excessive significance on the results, and the study should thus be treated as preliminary and interpreted with caution (Lancaster et al., 2004).

No blinding was used for this study, and participants were aware of which arm they were in. This limitation may have affected the validity of the design and the interpretation of the findings. Another challenge was the development of a true control condition that would not produce beneficial effects. Using music was not an entirely appropriate choice for this study. If an inactivated form of the Nevasic had been used, not only would the attention and intervention groups have been much more similar, making it potentially easier to distinguish the effect of Nevasic, but blinding would also have been possible, and the validity of the design and interpretation of the findings would therefore have been improved.

Poor adherence to the interventions confounds their effectiveness. Inadequate use of Nevasic and its suboptimal dosage, combined with inappropriate adherence to the prescribed anti-emetics, might have undermined the treatment effects. This might be considered a source of potential bias, in that it may have influenced the estimation of the intervention's effect (Bennett et al., 2011)**.**

It is advised that feedback should be provided to patients following a clinical trial, including some form of appreciation (e.g. in the form of a thank-you letter) and information about the trial outcome. Otherwise, patients may be left feeling cut off

and abandoned (Wilson et al., 2005; Pittens et al., 2012). A follow-up letter was not feasible in the current study because of the complex nature of the report (PhD thesis) and the lengthy distance between the researcher (in the UK) and the participants (in Iran) during the writing phase.

7.15. Future studies

This study aimed to test the feasibility of implementing and conducting a randomised controlled trial using the Nevasic programme. In addition, another aim was to evaluate the potential antiemetic effect of the intervention on female breast cancer patients. Several questions arise from this study which could be addressed in future non-pharmacological research regarding the prevention of CINV. Based on the findings, recommendations are shown in Table 6-1

Table 7-1: Recommendations for future trials	
Issue	**Explanation and recommendation**
Mechanism of non-pharmacological interventions	More evidence is required to understand the roles of non-pharmacological interventions in cancer supportive care as limited information available on the efficacy (and even safety) of most of these approaches. More research is needed in this area to develop knowledge of the mechanism(s) underlying each non-pharmacological intervention which can point out physiologically relevant processes leading to better identifying benefits of these interventions.
Recruitment rate	Although in this study patients' perceptions about their participation were very encouraging and the acceptance rate for participation was good, recruitment rate was lower than expected. The issue of the length of time taken to reach the recruitment target is always a problem in clinical research. It is likely that different patient populations evaluated at a different point in time or elsewhere would possess different characteristics and may need more time to reach the recruitment target. Use appropriate interventions and strategies to improve recruitment. Designing a multi-centre study can increase the level of recruitment. Broader inclusion criteria (e.g. including metastatic patients) would improve recruitment. Although these patients may have other reasons for their nausea and vomiting, the treatment might improve their more frequent complaints. In such trials, stratification of the disease prognosis is recommended before the randomisation process. When large scale non-pharmacological interventions are planned, it would be appropriate to take into account patients' likely perceptions. In fact, process evaluations within trials can investigate the implementation and even participants' perspectives of the intervention.

Table 7-1: Recommendations for future trials	
Relationship with health care professionals	Make a well-planned communication with physicians to overcome their concerns regarding the toxicity or side effects of the intervention, and clarify the importance of the trial. Explaining the scientific rational of the trial: a well-defined mechanism of action and method of application may lead to successfully engaging health professionals. Clinicians from the site should be consulted early during the trial design process in order to work through and voice any potential problems. Have a face-to-face contact to engage and maintain the interest of all members of the health care professionals involved in trial participation. Keep to a minimum the demands on clinicians. Financial incentives may increase the willingness of support staff to participate in trials.
Outcomes measures	The results of this study show that patients in the Nevasic group took fewer anti-emetics than two other groups. Taken fewer anti-emetics in the Nevasic group might be the perceived effectiveness of Nevasic. More research is required to investigate the effect of Nevasic on the use of PRN antiemetic medication during both acute and delayed phases of CINV as the key outcome to measure. Health care costs, participants' satisfaction or their experience may also be appropriate outcomes to measure in future studies.
The Rhodes INVR (Iranian version)	This study was an initial psychometric test of the Iranian version of the INVR. Further studies are needed to improve the psychometric properties of this translated instrument and re-evaluate the validity and reliability of the scale on different and larger patient populations for widespread use of the scale in other clinical settings in Iran.
Incidence of CINV in Iran	The impact of CINV in Iran needs more attention than it has received. The findings highlight the need for a better understanding of the incidence of CINV in Iran. There is a continuing need for progress in control of CINV and emphasise the need for continuing research on this area. There is undoubtedly room for improvement regarding control and/or treatment of CINV in cancer settings in Iran.

7.16. Summary and conclusion

A number of interventions have been examined for the prevention of post-chemotherapy nausea and vomiting. Such interventions have varied in terms of their cost and complexity. Developments in cancer treatment have taken a great step in terms of new chemo medications with fewer side-effects, a new generation of antiemetic medications, and novel approaches to controlling and managing chemotherapy side effects. However, a consistent benefit of any particular approach has yet to be demonstrated.

Non-pharmacological interventions, in addition to conventional anti-emetics, have been examined over the years, including acupuncture, relaxation training, coping preparation, imagery, and distraction techniques, with positive results found in several studies. Numerous hypotheses attempting to explain how and why non-pharmacological interventions are effective for cancer patients have also been proposed. These explanations range from simple placebo effects, to theories involving conditioning or psychological processes.

The literature review revealed that various degrees of success have been achieved in previous studies. However, it is difficult to draw conclusions about the effectiveness of most of these interventions. Several methodological flaws need to be rectified before conclusions can be drawn.

Moreover, most current non-pharmacological interventions require extensive provider training in order for them to be effective as chemotherapy-related nausea and vomiting management modalities. In addition, most of them require far more time and effort to administer than the current standard therapies (Schneider & Hood, 2007). Therefore, although promising results have been found, there is a need to examine more effective, less time-consuming and more cost-effective methods in this area. It is proposed that using a novel programme such as Nevasic could potentially solve some of the above-mentioned problems and eliminate the need for the physical presence of a clinician at most interventions.

This thesis has combined an appraisal of the literature with empirical research, and has used lessons learned from previous studies to examine the theory behind Nevasic in terms of preventing nausea and vomiting. Therefore, this pilot trial was

conducted to test the feasibility of implementing and conducting a randomised controlled trial using the Nevasic programme. In addition, the study aimed to evaluate the acceptability and potential effect of the Nevasic on breast cancer patients undergoing chemotherapy.

This research demonstrates that difficulties exist in conducting a non-pharmacological intervention using such an audio programme. Several difficulties and limitations exist, which make it difficult to draw a decisive conclusion about the effectiveness of Nevasic in controlling CINV. This study did not detect any evidence for the effectiveness of Nevasic on post-chemotherapy nausea and vomiting. About half of the participants believed that there was nothing to be gained from using Nevasic or listening to music to prevent or control their nausea and vomiting. In addition, issues of its acceptability, such as inconvenience in using the CD players, and a lack of definitive instruction for using it in terms of duration and frequency, can be clearly highlighted as weaknesses of the programme when used for cancer patients. However, the results show statistically significant differences in the anti-emetics used among the groups. These findings are also clinically significance, and suggest a need for further investigation.

The findings from the trial highlight the need for several modifications to the design and mode of delivery of the interventions. This was the first trial to evaluate the effectiveness of Nevasic in controlling CINV in cancer populations; further research is required to detect its implication from other aspects such as use of PRN antiemetic medication and/or health care costs.

7.17. Reflection on the PhD programme as an international student

The experiences I have had while carrying out my PhD study was one of the most character-building experiences in my life, although I had a really hard time. Generally, it was an amazing journey, an intellectual enrichment and a personal development opportunity like no other. Probably the worst could be a lot of uncertainty about all sorts of things related to the research and how to deal with such uncertainty rationally and then avoid unhelpful worrying.

From a professional view, I have learnt that research process and conducting a clinical research is a complex task. I have learnt that running a trial needs different

requirements. Critical thinking regarding the background and literature review and gathering satisfactory information, designing the study, selecting the appropriate measurement tools, choosing the setting and location of research, obtaining ethical approval and selecting the methods of data analysis fit for the study aims, all were challenge tasks and I never expected their complexity. In real-world, recruiting patients and data collection were much harder and existing barriers were much greater than I assumed.

I supposed that translating and preliminary psychometric tests of the INVR instrument would be uncomplicated. I did not realise that there were a number of issues that needed to be considered and how hard it is to follow the related standard procedures. The translation process of Rhodes INVR was a great challenge for me. Essentially, the challenge was to fit all these important parts together to form the thesis.

A traditional view of a PhD was as a kind of professional degree certifying one's ability to carry out independent research (Lawson, 2002). However, conducting original research in the PhD programme is only a part of a broader training. A wider set of skills, abilities and competencies than just specialised knowledge in a given topic are required to progress through the PhD programme (Melin & Janson, 2006). It is no longer enough to be a good researcher; to some extent, researchers also need to be team leaders and managers (Melin & Janson, 2006); therefore there is a need to develop other skills such as effective communication and presentation skills, and knowledge about leadership as well as knowledge about administrative procedures (Groccia, 2012). Skills learned and develop through my PhD programme include (but are not limited to):

- Improved ability to connect and communicate with international colleagues in networks
- Insight into research and how to employ appropriate research methodologies
- Time & project management
- Good clinical practice training
- Critical thinking to create new ways of understanding and judgement
- Learned to critique the broader implications of applying knowledge to particular contexts

- Knowledge of statistical testing, particularly the use of mixed models
- Developed effective writing and publishing skills
- Developed interpersonal skills

Although, the PhD programme should have at its core the development of research and empirical skills, as an international student, I believe other broader and essential skills (beyond academic/research training) should be recognised and more support provided. Providing an opportunity for international research students to develop skills such as teaching (in English), public speaking and presentation skills, administration and service seems encouraging for international students and give them the opportunity to improve not only their English but also their confidence.

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Appendices

Appendix 1: EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 2: EORTC QLQ - BR23

ENGLISH

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 3: Study questionnaires

Part one questionnaires (Baseline data)

Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme (Version II, 5th November 2011)

To be completed by researcher

Study Number: ……

Date of Birth: ……

Hospital Number: …….

Date of (first) chemotherapy cycle: ……..

Date of study end: (Sixth day after chemotherapy administration) ……....

Cancer diagnosis: ……..

Stage of disease: ……

Chemotherapy protocol used and dosage :
……
……
……
……
……
……

Antiemetic medications prescribed and dosage:

.....
.....
.....
.....
.....
.....

Part One

Please fill this part (question one to question six) two days or less before the chemotherapy day or in the morning of your chemotherapy cycle.

Q.1. What is your age/ date of birth: ……

Q.2. What is your occupation? ……..

Q.3. Select the highest educational level you have attended: (please tick one box)

[ ] Primary school [ ] Secondary school [ ] High school diploma

[ ] University degree [ ] Postgraduate education

Q.4. Marital status: (please tick one box)

[ ] Single [ ] Married [ ] Divorced [ ] Separated [ ] Widowed

Q.5. *Including you,* how many people live in your house? .....

Q.6. Do you have: (please tick the box)

[ ] history of motion sickness

[ ] nausea with pregnancy

[ ] history of labyrinthitis (inflammation of the inner ear that is characterized by dizziness accompanied by hearing loss, feelings of motion sickness and/or a sensation of ringing in the ears)

[ ] psychological problems such as emotional distress and anxiety

[ ] previous exposure to chemotherapy/ concomitant cancer treatment (such as radiology) .

[ ] fatigue

[ ] susceptibility to nausea by eating certain foods

[ ] non

Thank you for completing part one of the questionnaire

Please return this part of the questionnaires (part one) to the researcher on your (first) chemotherapy cycle day or post it in the attached pre-stamped envelop to the following address:

Saeed Moradian

Cancer Research Centre -Omid Hospital

B. Part Two. Questionnaire (Daily diary of sickness)

[Nevasic group]

Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme (Version II - 5th November 2011).

Questionnaire: Version II - 5th November 2011

To be completed by researcher

Study Number: …….

Date of Birth: ……

Hospital Number: …….

Date of (first) chemotherapy cycle: ……..

Date of study end: (Sixth day after chemotherapy administration) …….....

Part two- [Nevasic group- Version 2]

Please fill this part in the scheduled days (from chemotherapy day to day 6 after chemotherapy administration). Please follow the headed instruction in each questionnaire page.

Please fill question 1 in the morning of chemotherapy day before your (first) chemotherapy cycle.

Date: ……..

Q.1. How do you feel now regarding the nausea, vomiting and retching?

Please mark the box in each row that most clearly corresponds to your experience. (Please mark *one* mark on each line)

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Please fill in the scheduled days (from chemotherapy day to day 6 after chemotherapy administration). Follow the headed instruction in each questionnaire page.

Day 1 (chemotherapy day)

Please fill questions 1-5 in the evening of your chemotherapy day.

Date: ……..

Q.1. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.2. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.3. Did you listen to the Nevasic today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.4. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.5. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 2

Q.6. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.7. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.8. Did you listen to the Nevasic today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.9. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.10. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 3

Q.11. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.12. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.13. Did you listen to the Nevasic today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.14. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.15. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 4

Q.16. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.17. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.18. Did you listen to the Nevasic today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.19. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.20. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……
……..

Day 5

Q.21. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.22. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.23. Did you listen to the Nevasic today?

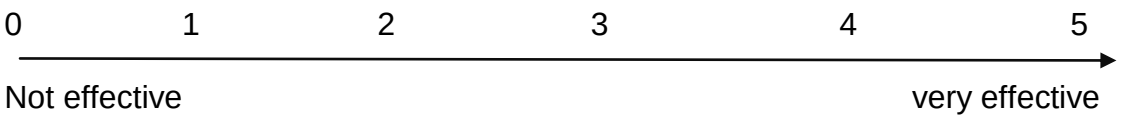
Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.24. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number



Q.25. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 6

Q.26. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]
If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.27. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.28. Did you listen to the Nevasic today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.29. How effective did you find listening to the Nevasic in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.30. Did you experience any side effect (adverse effect) from listening to the Nevasic today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Q.31. What is your experience of listening to the Nevasic?

……
……
……
……

Q.32. Do you have any other comments to make about this research?

……
……
…….....
.....
……...

Q.33. How long did the study's questionnaires take time to complete every day (in average)?

……
…….....
.....
.....

Thank you for completing the study
Please return the questionnaire with the previously completed questionnaires (if not previously handed to the researcher) in the pre-stamped envelope to the mentioned address.

Saeed Moradian

Cancer Research Centre -Omid Hospital

Alandash Square, Koohsangi Avenue,

Mashhad

Part two- [Music group- Version 2]

Please fill this part in the scheduled days (from chemotherapy day to day 6 after chemotherapy administration). Please follow the headed instruction in each questionnaire page.

Please fill question 1 in the morning of chemotherapy day before your (first) chemotherapy cycle.

Date: ……..

Q.1. How do you feel regarding the nausea, vomiting and retching?

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Day 1(chemotherapy day)

Please fill questions 2 - 6 in the evening of your chemotherapy day.

Date: ……..

Q.2. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.3. Did you listen to the music today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.4. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.5. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.6. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 2

Q.7. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.8. Did you take any anti-emetics medication given to you by your doctor today? Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.9. Did you listen to the music today?

Yes [ ] No [ ]

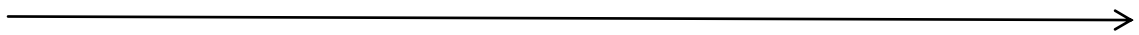
If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.10. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5



Not effective very effective

Q.11. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 3

Q.12. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.13. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.14. Did you listen to the musictoday?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.15. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.16. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 4

Q.17. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.18. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.19. Did you listen to the music today?

Yes [ ] No [ ]

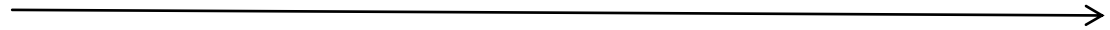
If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.20. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5



Not effective very effective

Q.21. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 5

Q.22. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.23. Did you take any anti-emetics medication given to you by your doctor today? Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.24. Did you listen to the music today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.25. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5

Not effective very effective

Q.26. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Day 6

Q.27. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.28. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets	Time
Ondansetron (Kytril™ ,Zofran ™					
Dexamethason					
Methocolopramide					
Cyclizine					
Other( )					

Q.29. Did you listen to the music today?

Yes [ ] No [ ]

If yes, please fill the table:

No	Time of start	Time to finish	Duration
1			
2			
3			
4			
5			
6			

Q.30. How effective did you find listening to the music in terms of reducing your nausea and/or vomiting today? (From 0 to 5)

Please circle one number

0 1 2 3 4 5 →

Not effective very effective

Q.31. Did you experience any side effect (adverse effect) from listening to the music today?

[ ] Yes [ ] No

If yes, what was it?

……
……
……
……

Q.32. What is your experience of listening to the music?

……
……
……
……

Q.33. Do you have any other comments to make about this research?

……
……
……
……

Q.34. How long did the study's questionnaires take time to complete every day (in average)?

……
……

Thank you for completing the study
Please return the questionnaire with the previously completed questionnaires (if not previously handed to the researcher) in the pre-stamped envelope to the mentioned address.

Part two [Control group- Version 2]

Please fill this part in the scheduled days (from chemotherapy day to day 6 after chemotherapy administration). Please follow the headed instruction in each questionnaire page.

Please fill question 1 in the morning of chemotherapy day before your (first) chemotherapy cycle.

Date: ……..

Q.1. How do you feel regarding the nausea, vomiting and retching?

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Day 1(chemotherapy day)

Please fill questions 2 and 3 in the evening of your chemotherapy day.
Date: ……..

Q.2. Did you take any anti-emetics medication given to you by your doctor today?

Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.3. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Day 2

Q.4. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.5. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Day 3

Q.6. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.7. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Day 4

Q.8. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.9. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Day 5

Q.10. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.11. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Day 6

Q.12. How do you feel regarding the nausea, vomiting and retching? Fill the table in ***evening.***

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make ***one*** mark on each ***line (horizontal line).***

a.	In the last 24 hours, I vomited…..time.	7 or more	5-6	3-4	1-2	I did not vomit
b.	In the last 24 hours, from retching or dry heaves I have felt……..distress.	no	mild	moderate	great	severe
c.	In the last 24 hours, from vomiting, I have felt……..distress.	severe	great	moderate	mild	no
d.	In the last 24 hours, I have felt nauseated or sick in my stomach……. .	not at all	1 hours or less	2-3 hours	4-6 hours	more than 6 hours
e.	In the last 24 hours, from nausea/ sickness in my stomach, I have felt……..distress.	no	mild	moderate	great	severe
f.	In the last 24 hours, each time I vomited, I produced a ……..amount.	Very large(3 cups or more)	Large (2-3 cups)	Moderate (1/2 – 2 cups)	Small (up to ½ cup)	I did not vomit
g.	In the last 24 hours, I have felt nauseated or sick in my stomach……times.	7 or more	5-6	3-4	1-2	no
h.	In the last 24 hours, I have had periods of retching or dry heaves without bringing anything up …… times.	no	1-2	3-4	5-6	7 or more

Q.13. Did you take any anti-emetics medication given to you by your doctor today?
Yes [ ] No [ ]

If yes, what and how much did you take today?

Antiemetic drug	Please tick the box	Dose	Frequency	Number of tablets
Ondansetron (Zofran)				
Granisetron (Kytril)				
Aprepitant (EMEND)				
Dexamethason				
Methocolopramide				
Cyclizine				
Other( )				

Q.14. What is your experience of being in the control group?

……
……
……
……
.....

Q.15. Do you have any other comments to make about this research?
……
……
……
.....
.....
……
...

Q.16. How long did the study's questionnaires take time to complete every day (in average)?
……
……
.....
.....
.....

Thank you for completing the study
Please return the questionnaire with the previously completed questionnaires (if not previously handed to the researcher) in the pre-stamped envelope to the mentioned address.

Appendix 4: The Rhodes INVR & Instruction for administration and scoring

Index of Nausea, Vomiting, and Retching (INVR)

Directions: Please mark the box in each row that most clearly corresponds to your experience. Please make *one* mark on each *line.* **I.D. Number: ____ Date: __ Time: _____**

1.	In the last 12 hours, I threw up _____ times.	7 or more	5-6	3-4	1-2	I did not throw up
2.	In the last 12 hours, from retching or dry heaves I have felt _____ distress.	no	mild	moderate	great	severe
3.	In the last 12 hours, from vomiting or throwing up, I have felt _____distress.	severe	great	moderate	mild	no
4.	In the last 12 hours, I have felt nauseated or sick at my stomach _____.	not at all	1 hour or less	2-3 hours	4-6 hours	more than 6
5.	In the last 12 hours, from nausea /sickness at my stomach, I have felt _____ distress.	no	mild	moderate	great	severe
6.	In the last 12 hours, each time I threw up I produced a _____ amount.	very large (3 cups or more)	large (2-3 cups)	moderate (½ - 2 cups)	small (up to ½ cup)	I did not throw up
7.	In the last 12 hours, I have felt nauseated or sick at my stomach _____ times.	7 or more	5-6	3-4	1-2	no
8.	In the last 12 hours, I have had periods of retching or dry heaves without bringing anything up _____ times.	no	1-2	3-4	5-6	7 or more

INSTRUCTIONS FOR ADMINISTERING AND SCORING
THE INDEX OF NAUSEA, VOMITING, AND RETCHING (INVR)

Verna Adwell Rhodes, EdS, FAAN
Roxanne W. McDaniel, PhD, RN

The Index of Nausea, Vomiting and Retching (INVR) is an 8-item, 5 point Likert-type self-report pencil and paper instrument that measures the patient's perceived (a) duration of nausea, (b) frequency of nausea, (c) distress from nausea, (d) frequency of vomiting, (e) amount of vomiting, (f) distress from vomiting, (g) frequency of dry heaves, and (h) distress from dry heaves. Total scores for nausea, total scores for vomiting, total scores for dry heaves, and subscale scores for each can be derived from the INVR. The INVR has a concise format and has tested reliability and validity.

Subjects should be instructed to mark through or draw around the sentence in each row that most clearly corresponds to their experience or describes how they feel. The instrument is designed to be administered every 12 hours. The subject should be asked to choose the best hour for his/her schedule. Beginning with the chosen hour, the subject should complete one INV Scale every 12 hours at the same clock hour for the desired length of time.

The INVR is designed to be folded in thirds to display instructions on the back of the form. The form can be conveniently placed in a pocket or purse.

In order to score the INVR reverse items 1, 3, 6, and 7. Then assign a numeric value to each response from 0, the least amount of distress, to 4, the most distress. Total symptom experience from nausea and vomiting is calculated by summing the patient's responses to each of the 8 items on the INVR. The potential range of scores is from a low of 0 to a maximum score of 32.

Subscales for Symptom Experience	Items on Scale	Potential Range of Scores
Nausea experience	4, 5, 7	0-12
Vomiting experience	1, 3, 6	0-12
Retching experience	2, 8	0-8
Total Experience Score	All Items	0-32
Subscales for Symptom Occurrence	**Items on Scale**	**Potential Range of Scores**
Nausea occurrence	4, 7	0-8
Vomiting occurrence	1, 6	0-8
Retching occurrence	8	0-4
Total Occurrence Score	All Items	0-20
Subscales for Symptom Distress	**Items on Scale**	**Potential Range of Scores**
Nausea distress	5	0-4
Vomiting distress	3	0-4
Retching distress	2	0-4
Total Distress Score	All Items	0-12

Appendix 5: Ethical approval

Ref: 490350
Date: 14 MAR 2011

Mashhad University of Medical Sciences

معاونت پژوهشی
Vice Chancellor for Research

To whom it may concern,

This is to certify that the research project entitled "**Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme**" proposed by Dr. Mohammad Reza Ghavam Nasiri and Saeed Moradian has been approved by Research Council of Mashhad University of Medical Sciences (MUMS) on March 2, 2011 and by MUMS Ethical Committee on March 12, 2011.

Yours sincerely,

Jalil Tavakol Afshari, PhD
Vice-Chancellor for Research

MASHHAD-IRAN
Tel:+98 511 8411538
P.O.Box:91735-951
Fax:+98 511 8430249
www.mums.ac.ir/research
E-mail:vcresearch@mums.ac.ir

Dear Mr Moradian

Committee on the Ethics of Research on Human Beings

Moradian, Walsh, Malassiotis: *Management of chemotherapy-induced nausea: a pilot randomised controlled trial using Nevasic audio programming (ref 10410)*

I write to confirm that the amendments to the information sheet and consent form satisfy the concerns of the Committee and that the above project therefore has ethical approval.

The general conditions remain as stated in my letter of 30th March 2011.

Finally, I would be grateful if you could complete and return the attached form at the end of the project or by March 2012, whichever is earlier. When completing this form, please reference your project as: Moradian, Walsh, Malassiotis: Management of chemotherapy-induced nausea: a pilot randomised controlled trial using Nevasic audio programming (ref 10410).

We hope the research goes well.

Yours sincerely

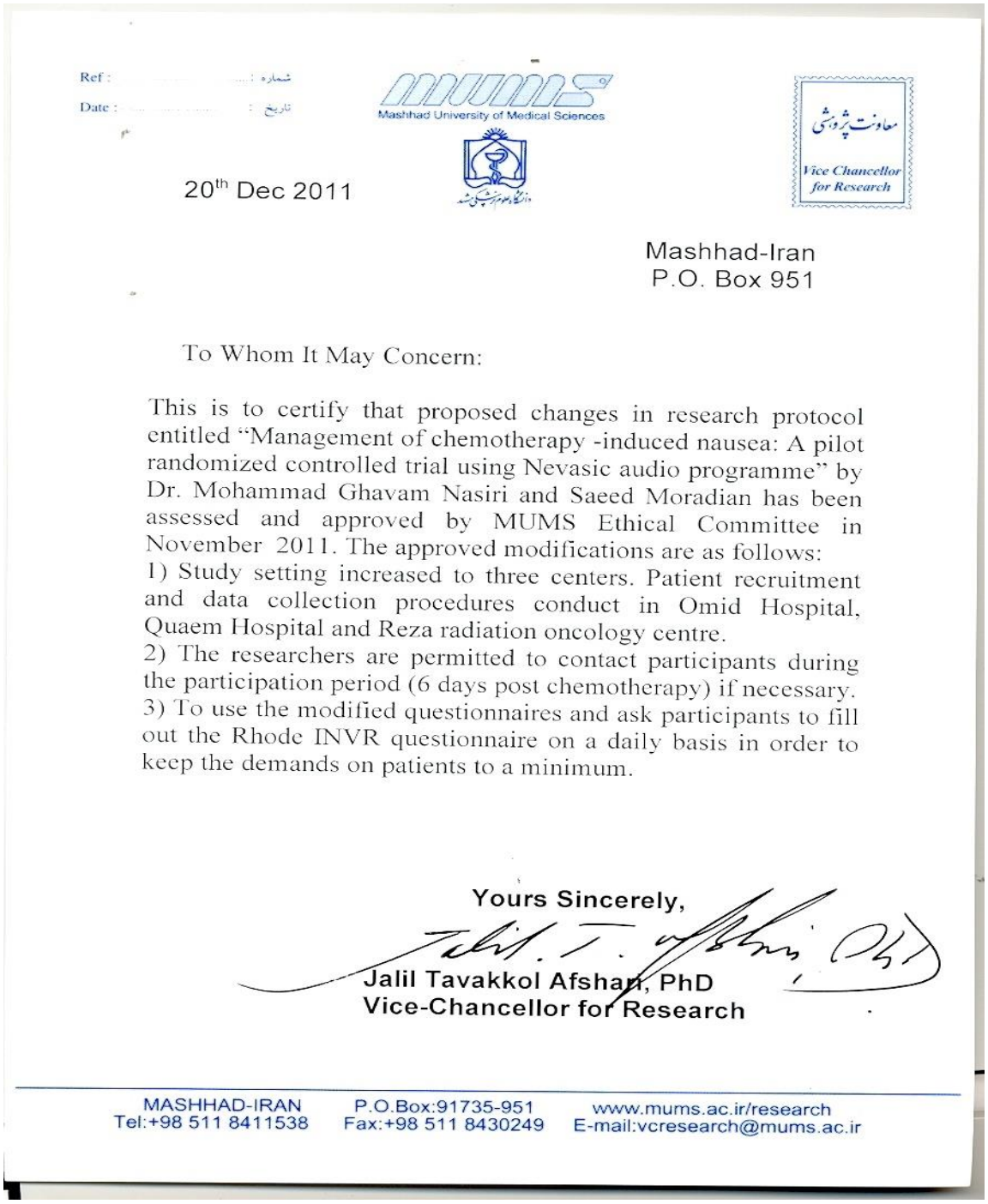
Katy Boyle
Secretary to the Committee

Katy Boyle

Project Officer to the Associate Dean for Research
Faculty Research Office
Faculty of Medical and Human Sciences
University of Manchester
Room 3.53, Simon Building
Brunswick Street
Manchester
M13 9PL

☎ +44(Poli-Bigelli et al.)161 275 1360
E: katy.boyle@manchester.ac.uk

Appendix 6: Ethical approval for amendment



Ref : شماره :
Date : تاریخ :

Mashhad University of Medical Sciences

معاونت پژوهشی
Vice Chancellor for Research

20th Dec 2011

Mashhad-Iran
P.O. Box 951

To Whom It May Concern:

This is to certify that proposed changes in research protocol entitled "Management of chemotherapy -induced nausea: A pilot randomized controlled trial using Nevasic audio programme" by Dr. Mohammad Ghavam Nasiri and Saeed Moradian has been assessed and approved by MUMS Ethical Committee in November 2011. The approved modifications are as follows:
1) Study setting increased to three centers. Patient recruitment and data collection procedures conduct in Omid Hospital, Quaem Hospital and Reza radiation oncology centre.
2) The researchers are permitted to contact participants during the participation period (6 days post chemotherapy) if necessary.
3) To use the modified questionnaires and ask participants to fill out the Rhode INVR questionnaire on a daily basis in order to keep the demands on patients to a minimum.

Yours Sincerely,

Jalil Tavakkol Afshar, PhD
Vice-Chancellor for Research

MASHHAD-IRAN
Tel:+98 511 8411538
P.O.Box:91735-951
Fax:+98 511 8430249
www.mums.ac.ir/research
E-mail:vcresearch@mums.ac.ir

Faculty of Medical and
Human Sciences
The University of Manchester
Oxford Road
Manchester M13 9PT

+44(Poli-Bigelli et al.)161 306 0100
www.manchester.ac.uk

Secretary to Research Ethics Committee 1

Email: katy.boyle@manchester.ac.uk
Phone : 0161 375 1360

Mr Saeed Moradian
c/o Dr Catherine Walshe
School of Nursing, Midwifery & Social Work
University Place, 5.334
saeed.moradian@postgrad.manchester.ac.uk

ref: ethics/10410

12 January 2012

Dear Mr Moradian

Committee on the Ethics of Research on Human Beings

Moradian, Walsh, Malassiotis: *Management of chemotherapy-induced nausea: a pilot randomised controlled trial using Nevasic audio programming (ref10410)*

I write to confirm that the amendments that you have made to your study since the initial favourable ethical opinion was given on 5th April 2011 have been accepted by the Research Ethics Committee. The amended documents approved are:

- Study Protocol (version 2)
- Control Questionnaires (version 2)
- Second Group Questionnaires (version 2)
- Nevasic Questionnaires (version 2)

The general conditions remain as stated in my letter of 30th March 2011.

Yours sincerely

Katy Boyle
Secretary to University Research Ethics Committee 1

Appendix 7: Consent form

Version: 11/2010

Centre Number:
Study Number:
Patient Identification Number for this study:

Consent form

Title of project: Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme.

Name of Researcher: Saeed Moradian

Please tick to confirm

1) I confirm that I have read and understand the information sheet dated September 2010 version 1.0 for the above study have had the opportunity to ask questions. ☐

2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3) I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from The University of Manchester or from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4) I agree to my GP or other health care professionals being informed of my participation in the study. ☐

5) I agree to take part in the above research study. ☐

| --- | --- | --- |
| Name of Patient | Date | Signature |

| --- | --- | --- |
| Researcher | Date | Signature |

When complete, 1 copy for patient: 1 copy for researcher site file: 1 to be kept in medical notes

Appendix 8: Patient information sheet

PATIENT INFORMATION SHEET
(Version I, 16 Dec. 10)

Study title: Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme.

You are invited to participate in a research study. However, before you decide to accept this invitation to take part it is important that you fully understand the purpose of the research and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. You are also most welcome to ask the researcher, Saeed Moradian, about anything that is unclear or which you feel requires further explanation. Please take time to make up your mind and think about whether or not you would like to take part in this study.

What is the purpose of the study?

The purpose of this study is to assess whether there is any effect of using the specific sound (or music) on the management of nausea induced by chemotherapy. The study involves following up patients undergoing chemotherapy for cancer treatment over 6 days.

Why have I been chosen?

You have been chosen to participate because you are receiving chemotherapy for your breast cancer. Your participation will provide useful information, which could help to confirm the effectiveness of using the harmony sound programmes as a method of controlling nausea.

Do I have to take part?

No. it is up to you to decide whether or not to take part. If you do decide to take part, after being given information, you will be asked to sign a consent form. You have the right to withdraw from the study at any point. Your participation or not in the study will not interfere with the standard of care you receive.

What will happen to me if I take part?

If you agree to participate and after you have signed the consent form, you will be randomly allocated to one of the three research groups (harmony sound group1, harmony sound group 2, and standard treatment group). If you are allocated to the harmony sound group 2, you will be given an MP3 with downloaded harmony sound. If you are allocated to the harmony sound group1, you will be given an MP3 player with a harmony sound programme (called Nevasic) downloaded onto it. The decision about allocation to the groups will be decided randomly (by chance). At this point, some information will be obtained from your file about you such as any prescribed anti-emetics (antisickness medication), and the type of chemotherapy you will receive. This information will be used later in the study to help the researcher compare the results obtained between the groups.

Whatever group you have been assigned to, you will be handed a pack of questionnaires, the first of which you will need to complete on the chemotherapy day (in the morning) and another on each of the five days after that. There is another questionnaire which you are asked to complete in the day before (or on the morning of your chemotherapy) and then daily until the sixth day of you have had your chemotherapy. You will also receive an instruction sheet detailing when and how to fill in each questionnaire.

A pre-paid envelope will be enclosed for returning the questionnaires. A reminder letter will also be sent to those who do not return the questionnaires at the of the study period.

What do I have to do if I take part?

Your participation will involve the agreement to complete a series of short questionnaires (about your experience of nausea and your quality of life) and listen to the harmony sound programme whenever you feel nausea for the study period which is 6 days.

.**Will the research influence the treatment I receive?**

You will not be required to make any lifestyle or dietary changes while you are taking part in this study. The research does not alter the treatment you receive. The treatment will be in addition to your scheduled treatment.

What are the possible risks or side effects?

Listening to the harmony sound programme is considered safe.

Are there any possible benefits?

Participants in the harmony sound programme groups may be benefit from better control of their nausea and vomiting after receiving chemotherapy.

What if something goes wrong?

If you experience unbearable symptoms (nausea and/or vomiting) when listening to the harmony sound programme you need to stop listening to them and report the symptoms to the researcher.

Will my participation in the study be kept confidential?

Yes, all collected information about you will be kept confidential. Appropriate access controls will be in place to ensure that access to confidential research information is restricted to those who need access.

Who is organising and co-ordinating the study?

This study is self-sponsored and is a part of a PhD degree currently being undertaken in the School of Nursing at the University of Manchester.

What do I need to do now?

If you are interested in taking part in this study, then please see the researcher to sign the consent form. The researcher will be available in the outpatient department on the day you come to the clinic for blood tests or on the day of your chemotherapy treatment where he will try to answer any further questions you still may have. You will then be randomised to one of three study groups and you will receive the appropriate pack.

Whom to contact for further information?

For further information, please contact of the researcher:

Saeed Moradian
Mobile: 09353400448
Email: saeed.moradian@postgrad.manchester.ac.uk

Fill in the slip below and give it to your chemotherapy nurse or receptionist.

I am interested in taking part in this study (management of chemotherapy-induced nausea)

Hospital Number: …….

DOB: ……..

Signature: ……..

Thank you for considering taking part in this study and taking the time to read this information sheet. Please feel free to discuss this information with your family, or friends, if you wish.

Appendix 9: Patient instruction sheet

Patient instruction sheet
Version I, 4 Jan. 11
Nevasic group

Welcome to the Nevasic programme group. Please read this information before using the Nevasic programme.

When do I use the Nevasic programme?

The Nevasic programme can be used at any time, in almost any place and because there is no need to lie down while using the programme you can use it while doing what you want to do. In general it is advised that the Nevasic programme be listened to when you are feeling nauseous.

How to use the Nevasic programme
Please follow these simple instructions:

1) Start listening to the Nevasic programme as soon as you start to feel nauseous .
2) Listen to the Nevasic programme all the way through, or until you are comfortable, repeat if your nausea returns.
3) When you stop feeling nauseous- stop using the Nevasic programme.

Note: the Nevasic programme is designed to be used at low volume settings. You should be able to talk and communicate easily and safely at all times while using the Nevasic programme. It is the content of the harmony sound programme and not the volume that is important and loud or excessive volume does not improve the performance of the product, can damage your ears and is strongly advised against.

Guidance notes:

1)The Nevasic programme must always be listened to via headphones.
2) Do not attempt to skip any part of the Nevasic programme in an effort to speed up the process.
3) It is not necessary to lie down while using the Nevasic programme.
4) Do not use through ambient speakers - **ALWAYS use headphones**.
5) Do not play in car stereos.

Patient instruction sheet
Version I, 4 Jan. 11
Music group

Welcome to the music group. Please read this information before using the music.

When do I use music?

The music can be used at any time, in almost any place and because there is no need to lie down while using music you can use it while doing what you want to do. In general it is advised that the music be listened to when you are feeling nauseous.

How to use music
Please follow these simple instructions:

1) Start listening to the music as soon as you start to feel nauseous .
2) Listen to the music all the way through, or until you are comfortable, repeat if your nausea returns.
3) When you stop feeling nauseous- stop using the music.

Guidance notes:

1) The music must always be listened to via headphones.
2) Do not attempt to skip any part of the music in an effort to speed up the process.
3) It is not necessary to lie down while using the music.
4) Do not use through ambient speakers - **ALWAYS use headphones**.
5) Do not play in car stereos.

Appendix 10: Study protocol

Protocol Number: Version II, 5 November. 2011

Project title: Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme

Project summary

Study purpose: The primary objective of this study is to assess the feasibility of conducting a randomised controlled trial using the Nevasic audio programme to reduce chemotherapy related nausea. The secondary objective is to examine the proof of principle of Nevasic audio programme in the management of chemotherapy related nausea.

Study design: This is a pilot randomised controlled trial with three parallel arms (intervention, attention, control).

Study population: Study subjects will be female, 18 years or older, with diagnosed breast cancer, no metastases, and chemotherapy naïve who have been prescribed a course of moderately high emetogenic chemotherapy.

Study setting: Data will be collected from a cancer research centre. Patient recruitment and data collection procedures conduct in Omid hospital (affiliated to Mashhad University of Medical Sciences) in Mashhad, Iran. Data collection will begin after obtaining ethical approval from both the University of Manchester and Mashhad University of Medical Sciences (MUMS).

Duration of subject participation: Subjects in each trial arm will receive usual care (standard antiemetic therapy) plus one of (1) intervention group, using the Nevasic (active sounds) (2) attention group, listening to music or (3) control group, receiving no additional intervention. The duration of an individual's participation in the study is 6 days.

Study population and sample: Estimating 20% attrition by the study end point, 114 participants will be randomised to one of three arms (38 in each arm of the trial).

Project description

Introduction

Despite advances in the pharmaceutical management of chemotherapy related nausea, there are still no completely effective anti-emetic drugs. Approximately 50% of patients receiving moderately high emetogenic chemotherapy still experience nausea, highlighting the need for further developments in the field. Non-pharmacological interventions are suggested as possible adjuncts to standard anti-emetic therapy. A recently developed non-pharmacological intervention to alleviate nausea is Nevasic, but this has not yet been tested for its potential to affect chemotherapy induced nausea. This pilot trial will be run to test the feasibility of implementing and conducting a randomised controlled trial using the Nevasic programme.

Objective(s)

Aim: *T*o assess the feasibility of running a randomised controlled trial using the Nevasic audio programme to reduce chemotherapy-related nausea.

Objectives:

a) To assess the feasibility of recruitment procedures.

b) To estimate time taken to complete the study's questionnaires and its associated data collection activities.

c) To evaluate the acceptability of each of the study arm interventions to participating patients.

d) To estimate an attrition rate, and to understand the reasons for study attrition.
e) To evaluate the potential anti-emetic effect of the intervention on participants.
f) To determine the duration of effect of Nevasic to plan the follow-up period required in a main study.

Research design

The design of the study is a pilot randomised controlled trial with a three parallel arms (See Appendix 1). Each arm will consist of usual care (standard anti-emetics) plus one of (1) intervention group, using the Nevasic audio programme (for 6 days whenever they feel nausea) (2) attention group, listening to music (for 6 days whenever they feel nausea) and (3) control group, receiving no additional intervention. The duration of the patients' involvement will be over one cycle of chemotherapy only. The primary endpoint in time is day 6 post chemotherapy to cover both acute and delayed chemotherapy induced nausea and vomiting.
Several techniques and strategies (random assignment, homogeneity [gender, antiemetic and chemotherapy regimens]) will be used to maximise control over the study.

Research participants

Adult female breast cancer patients who have been prescribed a course of moderately high emetogenic chemotherapy will be recruited for this study.

Inclusion criteria

1) Diagnosis of breast cancer: patients, who have a medically confirmed breast cancer (who have a histologically confirmed breast tumour with no metastases), and who are informed of their diagnosis.
2) Have no experience of receiving chemotherapy prior to the study.
3) Female gender
4) Age over 18 years: patients who are competent to give consent and sign the consent form.
5) Patients who are scheduled to receive moderately high emetogenic chemotherapy of equivalent regimens are considered eligible to participate in the study.

Chemotherapeutic agents considered to have moderately high emetogenecity for the purpose of this study are anthracyclines (daunorubicin, doxorubicin, and epirubicin). Combination regimens are: AC [doxorubicin hydrochloride (Adriamycin) (60 mg/m 2) and cyclophosphamide (600 mg/ m2)], CAF [cyclophosphamide (500 mg/ m2), doxorubicin hydrochloride (Adriamycin) (50 mg/m 2) fluorourcil(500 mg/ m2) and CMF [cyclophosphamide(600 mg/ m2), methotrexate(40 mg/m2), and fluorouracil(600 mg/ m2)].
Patients will receive standard anti-emetics as bolus intravenous doses of 8 mg (0.15 mg/kg) or oral 16 mg (8 mg twice daily) Ondansetron (or any equivalent 5-HT3 RA) plus/minus Dexamethasone 4-8 mg (twice daily) for the first two-three days. Anti-emetics are given prophylactically 30–60 min before the start of chemotherapy for acute CINV control, followed by oral doses for the first two days, then to continue with 10-20 mg Metoclopramide three times a day, as necessary, for the following days for delayed nausea and vomiting.
6) Able to read and write in Farsi: participants should be able to read and write Farsi (at least primary school education) in order to fill out the questionnaires

Exclusion criteria

1) Inability to understand or cooperate with study procedures.

2) Medical conditions which could affect nausea and vomiting perception and severity: vestibular causes (middle ear infection, brain tumour, central nervous system and/or other cancer metastasis and gastrointestinal problems such as obstruction of digestive tract or a history of intestinal obstruction, ulcer, gastritis, hiatus hernia and pharyngeal irritation could lead to ongoing nausea and vomiting.
3) Patients who are receiving radiotherapy concurrently with their chemotherapy. Patients who are receiving hormone therapy are allowed to participate.
4) Patients participating in another research study which may affect nausea and vomiting perception.
5) Patients who have hearing difficulties or unable to listen to the Nevasic or music.

Sample size

Suggested sample sizes for each arm of a pilot randomised controlled trial vary from 12 – 30 (Lancaster et al., 2004; Julious, 2005; Hertzog, 2008).
Considering factors such as good estimation of recruitment rate, attrition rate, estimate standard deviations adequately which are required for the study and estimating 20% attrition by the study end point, it was decided to randomise 114 participants equally to one of three groups, 38 per group.

Procedure

Pre -study preparation

The researcher will attend the Cancer Research Centre after obtaining approval from both the University of Manchester and Mashhad University of Medical Sciences and before starting the recruitment to introduce the study to health care professionals (oncologists and nurses) and provide them with patient study packs which contain an information sheet, invitation letter, and consent form. Oncologists and chemo-nurses will be requested to identify suitable patients and invite them to participate.

Recruitment procedure

In the outpatients' clinic, oncologists (who are on duty) will briefly explain the study to eligible patients (who will receive the first chemotherapy cycle in next two weeks). The invitation letter and information sheet will be given to potential patients by the oncologists at this time and then, with their permission, introduce the patient to the researcher. The researcher will introduce the study to the patient and explain the research process, using the same explanations among patients to reduce biases. Patients will have the opportunity to ask questions. They will be given as much time as they need to decide whether to participate in the study. Patients can fill out a reply slip indicating their interest in the study and return it to the receptionist or their nurse if they cannot meet the researcher. They can contact the researcher by telephone if they have any queries.
When patients come to the clinic for blood tests before starting the cycle of chemotherapy (which is normally one or two days before their chemotherapy), the potential participants will be asked to sign a consent form if they would like to participate to the study. After signing the consent form, participants will be randomised to one of the three groups (intervention group using the Nevasic [active sounds], attention group listening to the music and control group). Randomisation will be generated by a sample size calculation programme (nQuery Advisor).
Baseline data collection (socio demographic, treatment characteristics, and the QoLC30 (BR23) will be completed before informing the participants of their randomised allocation, as responses may be affected by knowledge of group.

Participants in the intervention and attention groups will be given a CD player and headphone [as listening with headphones seals off external noise and may be convenient, both by avoiding causing disturbances to others and reducing disturbance to the listener (Chlan, 2000)].

Information about completing the measures will be discussed and participants will be instructed how to complete the follow up questionnaires. Participants will be asked to return the questionnaires and the measures by pre-stamped envelope. The researcher will contact participants during the participation period (6 days post chemotherapy) in the case of necessity. A two-week time limit will be considered before sending the reminder letter, to send back their reply, as participants may forget to post their reply. Permission to send a reminder letter will be sought during the initial meeting or contact.

On the day of chemotherapy, participants receive their antiemetic prophylactically at least 30 minutes before chemotherapy administration. Participants in the intervention group will receive the Nevasic through their CD player and headphone once they report feelings of mild nausea. As the manufacturer of the Nevasic declare that it works just to control the nausea or vomiting when the symptoms are present; therefore, the participants will be asked to use Nevasic as soon as they feel mild nausea during or after chemotherapy administration. Using the Nevaisc will be discontinued either when the nausea stops or after the 27 minutes of the Nevasic programme time elapses. The participants in the intervention arm will use the Nevasic (whenever they feel nausea) thereafter for 5 days. They will use of their anti-emetics post chemotherapy as prescribed (see appendix 2). The patients will be instructed to use the Nevasic (according to the general guidance and instruction regarding using the programme provided by the manufacturer and mentioned in the provided instruction sheet).

Participants in the attention group will listen to listening to the music which has been previously downloaded onto their CD player. Participants will listen to it as soon as they feel nausea after chemotherapy administration. Listening to the listening to music will be discontinued either when the nausea stops or after the 27 minutes time elapses. The patients will be instructed to listen to the music according to the guidance in the instruction sheet. They will be asked to listen to the music whenever they feel nausea) thereafter for 5 days. They will use their anti-emetics post chemotherapy as prescribed (see appendix 2).

Participants in the control group will receive only their standard anti-emetics.

Data collection

Measuring nausea: using the translated Rhodes Index of Nausea, Vomiting and Retching (INVR), participants will be instructed to complete the INVR questionnaire daily(in the morning & evening) from the chemotherapy day to day 6 (the primary endpoint in time – day 6).

Measuring quality of life: participants will be asked to complete the EORTC QLQC30 (and BR23) questionnaire at baseline (before starting the chemotherapy) and day 6 post chemotherapy to detect any changes in health related quality of life.

Measuring daily using of the Nevasic or listening to the music: a short questionnaire (a structure diary questionnaire) will be designed to collect data about how often participants use Nevasic in intervention arm or listening to the music in attention group. Patient satisfaction with using Nevasic (intervention group) or listening to the music (attention group) and perceived effectiveness will

be determined by completing two 5-point Likert scales. Participants in all groups will be asked to fill out the short questionnaire, about their experience of using Nevasic, listening to the music or being in the control group, on day 6. Free text responses to a questionnaire will be available to ensure participants have an opportunity to report unanticipated issues, and more feedback on their thoughts and feelings.

Socio-demographic and treatment characteristics: data will be obtained from the patients' records and the patients themselves after obtaining consent form and prior to informing the participants of their randomised allocation. These will include age, educational level, marital status, experience with nausea in the past such as during pregnancy, motion sickness or nausea when eating certain foods, use of experience with other complementary therapies to manage nausea in the past, cancer diagnosis, stage of disease, and chemotherapy protocol used and dosage.

Intake anti-emetics: the total daily intake of the prescribed antiemetic medicines, the regular intake and the PRN (as necessary doses) will be measured by the designed question in the study questionnaire and will be completed daily. Medication use (standard and rescue anti-emetics) during study participation will also be obtained from the pharmacy and nursing records.

Participants who will not use the Nevasic, those who do not return the follow-up questionnaires and patients who refuse to continue participation after consenting will be considered as dropout cases. However, they will be asked to explain (if they would like) the reason(s) for not adherence the study.

Adverse events

Listening to the music or using the Nevasic is assumed to be safe; however, if any participant experiences intolerable symptoms (nausea and/or vomiting) or feels uncomfortable using the Nevasic or listening to the music, she needs to stop using the Nevasic or listening to the music.

Participants will be withdrawn from the study if they experience intolerable symptoms (nausea and/or vomiting) or feel uncomfortable with using the Nevasic or listening to the music. Participants will be asked to report any adverse events to the investigator. They can contact him by phone, email or meet him at the clinic.

Data analysis

The main analyses will be descriptive statistics, estimating percentages, means, standard deviations and other appropriate summary statistics for outcome measures in each group, estimating 95% confidence intervals for differences in percentages or means between pairs of the three groups, and estimating related effect sizes. Inferential analyses will explore the differences between pairs of groups using chi-square tests for categorical outcomes and t-tests or Mann-Whitney tests for non-skewed and skewed continuous outcomes respectively. Where possible, 95% confidence intervals of differences between groups will be reported. Because the pilot study is not powered to detect statistically significant differences, the inferential results will be interpreted cautiously. Data will be analysed using SPSS.

Data from free text responses about patients' experience will be coded and a list of themes will be formulated. A constant process of comparison and contrast of themes will be employed to write a description of the patients' perceptions. Frequencies of themes will be used to assist in determining their importance in interpretations of the patients' answers to the question.

Ethical considerations

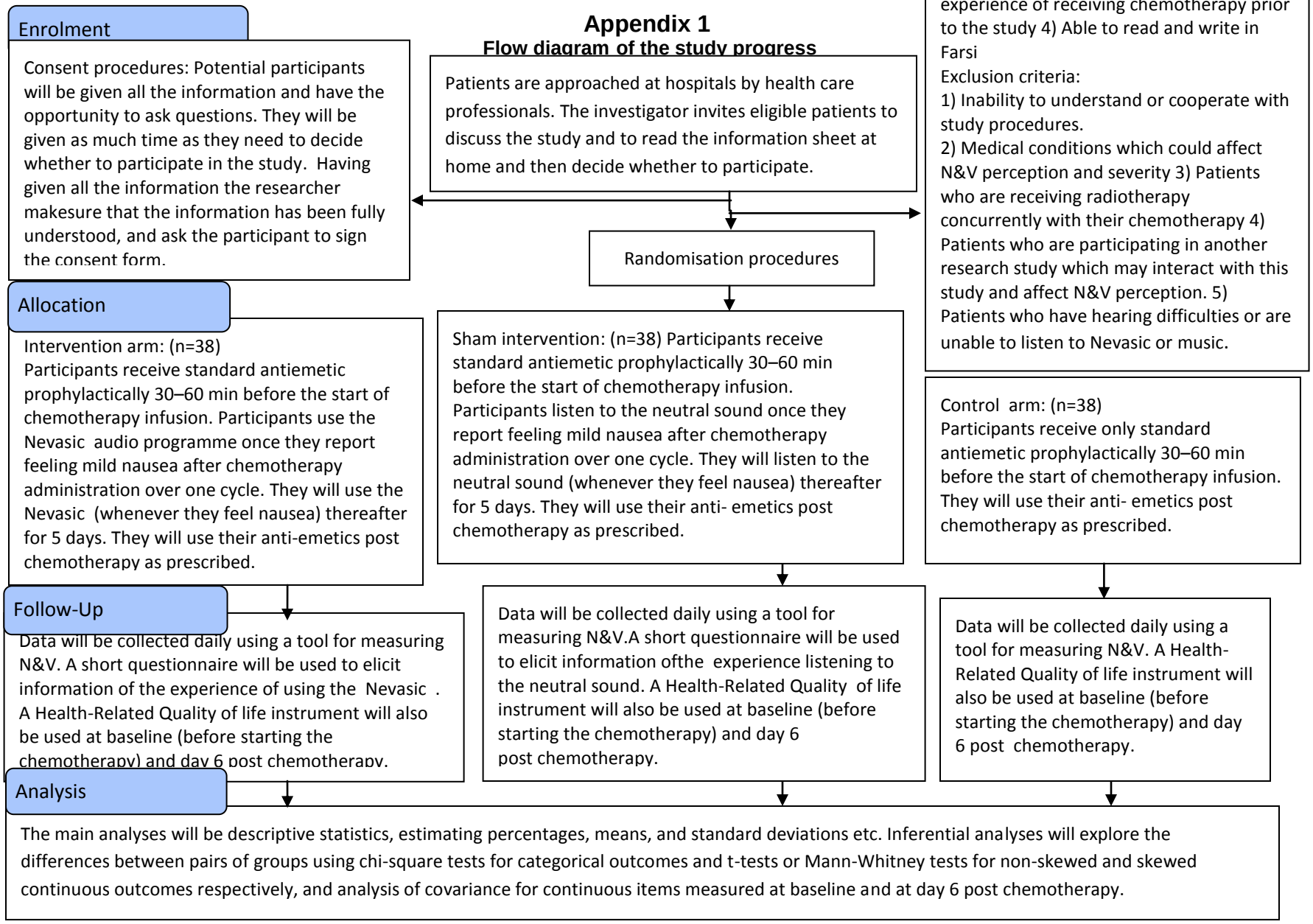
The three main ethical issues (balancing the risk of harm with potential benefit, ensuring consent, and protecting confidentiality) are considered in this study.

It is supposed that the risk of harm to participants is minimal, as the manufacturer of Nevasic signifies that it has no chemicals, no side effects and is safe to use. However, participants will be informed about the fact that Nevasic is designed to be used at low volume settings and participants should be able to talk and communicate easily and safely at all times while using Nevasic. They will be informed that it is the content of Nevasic and not the volume that is important and loud or excessive volume does not improve the performance of the product, and can damage the ears. Therefore, participants are strongly advised against using the Nevasic in high volume. It has been assumed that the risk of harm for attention group is also minimal; however, listening to music may be felt anxiety or discomfort for some participants in this group. Participants will be assured that they have the right to withdraw from the study at any point.

Confidentiality, which refers to not disclosing the names and any information of participants, will be maintained during the study and any given information will be used for the study only and not for any other purpose. The results will be reported as grouped data without reference to individual participants. Collected information about the study participants will be kept confidential and all personal information will be coded and anonymous, questionnaires will be stored in a locked filing cabinet. Individual identity number will be used to identify study participants. Consent forms with names of the participants will be kept in a locked filing cabinet separate from the questionnaires. Collected data from the questionnaire will be entered onto computer. Consent to hold this information will be obtained by participants. Accessing to the data in the computer is limited to the authorised individuals as the system is password protected (encryption). The questionnaires will be discarded after 5 years.

Appendix 1

Flow diagram of the study progress



Appendix 2: Study timetable

Study arms	Intervention	Use of prophylactic anti-emetics prior to/during chemotherapy administration	Use of prescribed anti-emetics in response to post-chemotherapy nausea	Data collection time points and tools			
				*D-1 or D1 (prior to chemotherapy administration)	D1 (evening of chemotherapy administration)	D2 – D5 (daily in the evening)	D6
Intervention arm - Nevasic	Advised to listen to the Nevasic through headphones whenever they feel mild nausea during or after chemotherapy administration. Each listening episode can cease either when the nausea stops, or the programme ends (27 minutes). Intervention continues for 5 days post-chemotherapy.	Yes	Yes	QOLC30(BR23) Socio-demographic data Chemotherapy protocols.	INVR Daily diary of sickness's questionnaire.	INVR Daily diary of sickness's questionnaire	INVR QOL C30(BR23) Daily diary of sickness's questionnaire. Questionnaire about experience of study.
Attention arm – listen to the neutral sound	Advised to listen to the neutral sound through headphones whenever they feel mild nausea during or after chemotherapy administration. Each listening episode can cease either when the nausea stops, or the programme ends (27 minutes). Intervention continues for 5 days post-chemotherapy.	Yes	Yes	QOLC30(BR23) Socio-demographic data Chemotherapy protocols.	INVR Daily diary of sickness's questionnaire	INVR Daily diary of sickness's questionnaire	INVR QOL C30(BR23) Daily diary of sickness's questionnaire Questionnaire about experience of study.
Control arm	No intervention	Yes	Yes	QOLC30(BR23) Socio-demographic data Chemotherapy protocols.	INVR Daily diary of sickness's questionnaire	INVR Daily diary of sickness's questionnaire.	INVR QOL C30(BR23) Daily diary of sickness's questionnaire Questionnaire about experience of study.

*** Chemotherapy day**

Appendix 11: Rhodes INVR (Persian version)

شاخص حالت تهوع – استفراغ و عق زدن **شماره شناسایی:**

تاریخ:

ساعت:

دستورالعمل: لطفاً مناسبترین گزینه که بیشترین شباهت به حالت شما را دارد انتخاب کنید. لطفاً در هر سطر فقط یک گزینه را علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 دفعه یا بیشتر	5 تا 6 دفعه	3-4 دفعه	1-2 دفعه	اصلا بالا نیاوردم
2	در 12 ساعت گذشته بعلت عق زدن (بدون بالا آوردن چیزی) من ..... احساس ناراحتي کرده ام.	اصلا	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته از استفراغ یا با لا آوردن من احساس..... ناراحتی کرده ام..	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع یا دل آشوبی داشته ام.	به هیچ وجه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع یا دل آشوبی من ..... احساس ناراحتی کرده ام.	اصلا	خفیف	متوسط	زیاد	خیلی شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاورد
7	در 12 ساعت گذشته من.....احساس حالت تهوع (بدون بالا آوردن چیزی) داشته ام.	7 دفعه یا بیشتر	5 تا 6 دفعه	3-4 دفعه	1-2 دفعه	هیچگونه
8	در 12 ساعت گذشته من..... حالت عق زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	اصلا	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

این شاخص را برای اولین بار در ساعات 8-7 یا 9 بعد از ظهر روز .....کامل نمائید.

مناسبترین ساعت را برای خود برنامه ریزی نمائید. تکمیل نمودن (این فرم) را با ساعت انتخابی خود شروع نموده و هر 12 ساعت در زمان معین برای شش مرتبه تکمیل نمائید. بطور مثال: 7 بعد از ظهر – 7 صبح

Appendix 12: Study questionnaire (Persian)

پرسشنامه قسمت دوم:(مخصوص گروه اول)

عنوان طرح: درمان تهوع ناشی از شیمی درمانی با کاربرد برنامه صوتی بنام Nevasic در بیماران مبتلا به سرطان سینه
این قسمت توسط محقق تکمیل می گردد :

Study Number: ……
Date of Birth: ……

Hospital Number: ……

Date of (first) chemotherapy cycle: ……

لطفاً ابتدا دستورالعمل مربوط به هر قسمت را مطالعه نموده و سپس نسبت به تکمیل پرسشنامه برای هر روز(از روز شیمی درمانی تا شش روز بعد) اقدام فرمایید.

لطفا سئوال 1 را در صبح روز شیمی درمانی قبل ازشروع شیمی درمانی تکمیل فرمایید.
تاریخ:.....
سئوال 1: آیا امروز صبح حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.
دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

روز اول(روز دریافت شیمی درمانی)

تاریخ:.....

سئوال2: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.

دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال3: آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفا علامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 4: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 5: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید.

1 **2** **3** **4** **5**

هیچگونه تاثیری نداشته است کاملا موثر بوده است

سئوال6: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟

بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید

.....

.....

.....

.....

روز دوم

سئوال7: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.
دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال8: : آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟
بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفا علامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 9: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]
اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 10: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید

1 2 3 4 5

هیچگونه تاثیری نداشته است **کاملا موثر بوده است**

سئوال11: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟
بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید
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روز سوم

سئوال12: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.

دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر .

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال13: آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟
بلی [ ] خیر[ ]
اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفا علامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 14: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]
اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 15: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید.

1 2 3 4 5

هیچگونه تاثیری نداشته است **کاملا موثر بوده است**

سئوال16: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟

بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید

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روز چهارم

سئوال17: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.
دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (2-3 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال18: آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟
بلی [ ] خیر[ ]
اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفاعلامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 19: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 20: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید.

1 2 3 4 5

هیچگونه تاثیری نداشته است ← **کاملا موثر بوده است**

سئوال21: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟

بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید

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روز پنجم

سئوال22: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.

دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (3-2 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال23: آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفا علامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 24: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 25: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید.

1 2 3 4 5

هیچگونه تاثیری نداشته است **کاملا موثر بوده است**

سئوال26: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟

بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید

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روز ششم

سئوال27: آیا امروز **بعد از ظهر (غروب)** حالت تهوع و استفراغ داشته اید؟ لطفا جدول زیر را تکمیل فرمایید.

دستورالعمل: لطفاً مناسبترین گزینه را که بیشترین شباهت را به تجربه شخصی شما دارد را در هر **ردیف** علامت بزنید.

1	در 12 ساعت گذشته من ..... بالا آوردم.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	بالا نیاوردم
2	در 12 ساعت گذشته بعلت اوغ زدن یا بالا آوردن من احساس.....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
3	در 12 ساعت گذشته بعلت استفراغ و یا با لا آوردن من احساس.....پریشانی و اضطراب کرده ام.	بسیار شدید	زیاد	متوسط	خفیف	هیچگونه
4	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	هیچگونه	1 ساعت یا کمتر	2-3 ساعت	4-6 ساعت	بیشتر از 6 ساعت
5	در 12 ساعت گذشته بعلت احساس حالت تهوع و یا سنگینی معده (دل آشوبی) من احساس .....پریشانی و اضطراب کرده ام.	هیچگونه	خفیف	متوسط	زیاد	بسیار شدید
6	در 12 ساعت گذشته من هر دفعه به میزان ..... بالا آورده ام.	خیلی زیاد (3 لیوان یا بیشتر)	زیاد (3-2 لیوان)	متوسط (نصف تا 2 لیوان)	کم (حدوداً نصف لیوان)	من اصلا بالا نیاوردم
7	در 12 ساعت گذشته من.....احساس حالت تهوع و یا سنگینی معده (دل آشوبی) داشته ام.	7 مرتبه یا بیشتر	5 تا 6 مرتبه	3-4 مرتبه	1-2 مرتبه	هیچگونه
8	در 12 ساعت گذشته من.....حالت اوغ زدن یا حالت بالا آوردن بدون اینکه چیزی بالا بیاورم داشته ام.	هیچگونه	1-2 نوبت	3-4 نوبت	5-6 نوبت	7 نوبت یا بیشتر

سئوال28: آیا امروز از داروهای ضد تهوع و استفراغ (که توسط پزشکتان تجویز گردیده است) استفاده کرده اید؟

بلی [ ] خیر[ ] اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

نام داروی ضد تهوع و استفراغ	لطفا علامت بزنید	مقدار مصرف	تعداد دفعات	تعداد قرص های مصرف شده	زمان استفاده
اوندانسترون (زوفران) Ondansetron (Zofran TM)					
گرانیسترون (کتریل) Granisetron (KytrilTM)					
دگزامتازون Dexamethason					
متوکلوپرامید Methocolopramide					
Aprepitant (Emend)					

سئوال 29: آیا امروز به صوتی که برای شما در نظر گرفته شده گوش دادید؟

بلی [ ] خیر[ ]

اگر پاسخ شما بلی است لطفا جدول زیر را تکمیل فرمایید.

تعداد دفعات	ساعت شروع	ساعت پایان	مدت زمان گوش دادن
1			
2			
3			
4			

سئوال 30: بنظر شما گوش دادن به این صوت امروز تا چه میزان بر روی کاهش تهوع و استفراغ تاثیر داشته است؟ لطفا دور عدد مورد نظر را خط بکشید.

1 2 3 4 5

هیچگونه تاثیری نداشته است **کاملا موثر بوده است**

سئوال31: آیا گوش دادن به این صوت امروز برای شما با عوارض جانبی همراه بود؟

بلی [ ] خیر [ ]

اگر پاسخ شما بلی است لطفا این عوارض را توضیح دهید

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سئوال32:تجربه شخصی شما از شرکت در این تحقیق و قرار داشتن در این گروه چیست؟

سئوال 33: مدت زمان پاسخگویی به سوالات و تکمیل پرسشنامه در هر روز برای شما چقدر بود؟

سئوال34:لطفاً اگر پیشنهاد یا انتقادی نسبت به این تحقیق دارید ذکر نمایید.

لطفاً پس از تکمیل این پرسشنامه آنرا به مسئول مربوطه تحویل و یا به آدرس ذیل ارسال فرمایید.لطفاً از پاکت نامه که هزینه آن قبلا پرداخت شده است استفاده فرمایید.

مشهد- خیابان کوهسنگی فلکه الندشت بیمارستان امید مرکز تحقیقات سرطان- مربوط به طرح تحقیقاتی Nevasic

Appendix 13: Study Inspection

Ref : 462110 شماره

Date : 7 FEB 2012 تاریخ

Mashhad University of Medical Sciences

معاونت پژوهشی
Vice Chancellor for Research

To Whom It May Concern,

This is to certify that research study entitled "Management of chemotherapy-induced nausea: A pilot randomised controlled trial using Nevasic audio programme" conducting by Dr. Mohammad Ghavam Nasiri and Saeed Moradian has been evaluated by MUMS Clinical Trial/Study Report on January 16, 2012. The report has confirmed that:

- The conduct of the trial has been in compliance with the protocol that was approved by MUMS Ethical Committee on 12th March 2011 and the amendments that have been made to the study in November 2011.
- The clinical trial has been conducted in accordance with the ethical principles. In obtaining and documenting informed consent, the investigators, or persons designated by the investigators, have complied with Good Clinical Practice standards and the applicable regulatory requirements.
- Quality management of data handling ensured that data have been processed correctly. Accessing to the data has been limited to the authorised individuals by the security system. An unambiguous identification code has been used that allowed identification of all the data reported for each subject.
- No unexpected (serious) adverse event has been identified/ reported in subjects.

Yours sincerely,

Dr. Mohsen Tafaghodi
Vice Chancellor for Research

Appendix 14: Permission to use and translate the Rhodes INVR

Rhodes, Verna [RhodesV@health.missouri.edu]

Inbox

08 December 2010 13:41

Dear Mr.Saeedd Moradian'
Your proposed study in the in a population from Iran is of special interest. Since the translation is needed, I suggest you read, in the event you have not, the puplication on translating the INVR by Dr, Mei Fu. I am sending her a copy of our communication. Any translated insturments should always indicate the original authorship and then transkated by------. I am attaching a copy of the INVR and instructions for administration.

Best wishes on your continued scientific study.

Sincerely,
Verna Adwell Rhodes, RN EdS FAAN

Saeed Moradian

Sent Items

08 December 2010 09:34

Dear Professor Rhodes,

I am a Ph.D.(in nursing) student at the University of Manchester. My PhD entitled '' Management of chemotherapy -induced nausea: A pilot randomised controlled trial using Nevasic audio programme". To attain the required information for the effectiveness of the intervention, I need a tool to be able to accurately measure the symptoms (nausea, vomiting and retching) in a reliable manner. The Rhodes Index of Nausea, Vomiting, and Retching (INVR) have chosen for this study. As the setting of research is a cancer centre in Iran and the INVR has not been translated to Farsi (Iranian language), it is required to translate for the use of this study. I would be grateful if you could please let me have your permission to translate and use the tool for my study. Thank you in advance.

Saeed Moradian