Using Acupuncture to Manage Hot Flushes & night sweats in women taking tamoxifen for early breast cancer: two observational studies.

Using Acupuncture to Manage Hot Flushes & Night Sweats in Women Taking Tamoxifen for Early Breast Cancer: Two Observational Studies

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Abstract

Introduction

This research comprises two observational studies investigating the use of acupuncture to manage hot flushes and night sweats that are side effects of tamoxifen as an adjuvant treatment for early breast cancer. Two forms of acupuncture were examined: traditional body acupuncture and ear acupuncture.

Aims of the research

The primary aims of the research were to evaluate the:

- Effect of acupuncture on the frequency of hot flushes and night sweats
- Effect on physical and emotional well-being
- Acceptability of acupuncture to women who have had invasive treatments for early breast cancer.

Design and methods

The research comprised two consecutive single-arm observational studies using before and after measurements with the participants acting as their own controls. Study 1 assessed traditional body acupuncture, using a semi-individualised treatment plan for each participant; Study 2 assessed a standardised ear acupuncture protocol delivered in a group setting.

The research used primarily quantitative research methods, and participants were monitored for 30 weeks. Hot Flush Diaries were used to measure hot flush frequency, and physical and emotional well-being was measured using two validated questionnaires: the Women's Health Questionnaire, and the Hot Flushes and Night Sweats Questionnaire. Qualitative data were obtained from structured questionnaires and from focus groups conducted as a separate sub-study.

Results

Fifty women in each study completed a course of eight acupuncture treatments, given on a weekly basis. The primary outcome was at the end of treatment, and the results suggest that in both studies, hot flush frequency was reduced significantly over baseline. In addition, physical and emotional well-being showed improvements, and women perceived hot flushes to be less of a problem after treatment. The majority of participants found acupuncture an acceptable and beneficial treatment.

Conclusion

These preliminary investigations suggest that acupuncture may be useful for managing menopausal side effects in women taking adjuvant treatments for early breast cancer. The studies allowed thorough testing of recruitment procedures, outcome measures, and analytical approaches. This can inform further investigations, for example, multi-centre randomised controlled trials or further qualitative studies. This research contributes to the evidence base for complementary medicine, and specifically, its use alongside conventional treatments for cancer.

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In memory of

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1918 – 1993

and

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Chapter 1 Introduction

1.1 Synopsis

In this chapter, I introduce the research comprising this thesis and explain the context for its development. After a brief discussion of the research and the questions it explores, I present an outline of the structure of this thesis. I then present the key question that motivated this programme of study, and describe how this research project came into being. Following a discussion of the use of the first person in writing this thesis, I introduce the context of the study, the personnel involved in its execution, and my role and responsibilities. I then discuss the acupuncture styles used in this research, setting out a number of concepts of Chinese medical theory, and explaining the choice of terminology used in this thesis. I conclude with a discussion about the place of this research within the wider context of the relationship between complementary and orthodox medicine.

1.2 Introduction to the research

This thesis investigates the use of acupuncture to manage the hot flushes and night sweats that are a side effect of adjuvant treatments for early breast cancer. The main research questions are:

1. Can acupuncture be used to manage the hot flushes and night sweats that are a side effect in women taking tamoxifen as an adjuvant treatment for early breast cancer?

2. Does acupuncture affect the overall physical and emotional well-being of the recipient? If so, is it possible to measure this?
3. Is acupuncture acceptable to women who have had invasive treatments for breast cancer?

To answer these questions, I conducted two consecutive studies. These studies used two different forms of acupuncture and explored two different delivery methods. The work evolved over time, and the second study grew out of the first. My aim in performing two studies was to explore questions about the application of acupuncture theory. Two questions of specific interest from an acupuncturist's perspective are:

1. Can the theories of traditional acupuncture used to treat the symptoms of natural menopause be applied to manage pharmaceutically induced menopause symptoms?
2. Is there any difference in the results of using semi-individualised body acupuncture treatments and standardised ear acupuncture treatments?

As an initial investigation into the latter question, this thesis compares the results of the two studies. This provides a preliminary indication of how the two types of acupuncture, with their distinctive methods, compare.

Study 1 (called Study 1: TA in this thesis) explored the use of traditional acupuncture (TA). Drawing on traditional theories of Chinese medicine (CM), it used a semi-individualised acupuncture point protocol and included points for the individual. Participants received treatment using

traditional acupuncture points on the body, in one-to-one practitioner-participant sessions.

Study 2 (called Study 2: NADA[1]) explored the use of ear acupuncture using a standardised protocol. All participants in Study 2 received the same treatment, delivered in small group clinics with about five women per group.

Both studies used the same overall design, which was a prospective single-arm observational approach using before and after measurements, with the participants acting as their own controls. In each study, 50 women received a course of acupuncture consisting of eight treatments, delivered once a week. Monitoring participants for 30 weeks provided data on short-term and longer-term results.

This thesis discusses research that was positivist in its methodology. The project focused primarily on collecting quantitative data using hot flush diaries and a selection of validated outcome measures. Some qualitative data were also collected, using structured questionnaires. Qualitative research methods in the form of focus groups were a separate aspect of the research conducted independently of this thesis.

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[1] NADA stands for the National Acupuncture Detoxification Association, whose ear acupuncture protocol I used for Study 2. I discuss this in detail in Chapter 7 of this thesis.

These studies enabled exploration of a number of practical aspects of conducting research. These included testing the recruitment procedures, scheduling appropriate clinic times, and determining whether participants found the "burden" of filling in questionnaires acceptable. Above all, they provided the opportunity to assess whether women treated for early breast cancer would find acupuncture acceptable in managing their treatment side effects. Furthermore, data analysis has provided a first measure of results in a field where, at the outset of this research, little information existed about the possible effects of acupuncture on this condition. In addition, the studies were an opportunity to begin to assess the possible demand for acupuncture treatment by women treated for early breast cancer.

The findings from these studies contribute to the evidence base for complementary medicine. They have the potential to inform further research into the use of acupuncture in supportive care for people living with cancer. Dissemination to the acupuncture profession, as well as to cancer service professionals and providers, may help to improve the care of women receiving adjuvant treatment for early breast cancer. In addition, acupuncture may increase the range of choices women have for managing their side effects.

1.3 Structure of this thesis

This thesis explores whether acupuncture can be a viable treatment option for women experiencing menopause-like side effects of taking tamoxifen as an adjuvant treatment for early breast cancer.

Chapter 1 introduces the research and sets the scene.

Chapter 2 explains the background to breast cancer and its treatments. It discusses the use of tamoxifen as an adjuvant treatment for breast cancer, and introduces the problem of hot flushes and night sweats as a side effect. In this chapter, I explore the literature relating to the use of acupuncture to treat hot flushes in natural menopause and discuss the literature related specifically to the use of acupuncture to manage hot flushes associated with treatments for breast cancer. This literature informed the design of the research.

Chapter 3 presents the design and methodology that is common to both studies. It details the history of the study design, and explains the rationale for conducting single-arm observational studies. It also describes the design decisions, methodology, and outcome measures, as well as the setting, participants, and recruitment procedures used in both studies.

Chapter 4 focuses on the statistical methods and analysis. It details the data collection and management procedures, including the handling of

missing data. I discuss the approach and rationale for analysing the hot flush frequency data, as well as the data from the validated questionnaires.

The following two chapters focus on Study 1: TA. **Chapter 5** explains the methods specific to this study. I discuss how the traditional acupuncture protocol was developed, and how I administered the treatments during the course of the study. **Chapter 6** reports the results of using this approach. I present the data detailing the changes in hot flush frequency and emotional and physical wellbeing in the participants. I also explore whether the participants found traditional acupuncture an acceptable way to manage their symptoms.

The next two chapters focus on the Study 2: NADA. **Chapter 7** presents the rationale for using ear acupuncture to manage hot flushes, and I examine the relevance of using a standardised protocol called the NADA protocol. I also detail how I administered the treatments during the course of the study. **Chapter 8** reports the results of using this approach, and I present the data detailing the changes in hot flush frequency and emotional and physical wellbeing in the participants. I also explore whether the women found having ear acupuncture in small group clinics acceptable.

Chapter 9 compares the results of two studies to identify if there are significant differences in the effects of the two approaches to treatment.

Chapter 10 discusses the findings of this research and concludes with recommendations for further developments in this area.

1.4 The story behind this research

Can acupuncture benefit people who have cancer? This question haunted me as I worked with in-patients at the North Middlesex University Hospital in north London, as the aromatherapist in the multi-disciplinary hospital-based Macmillan Oncology and Palliative Care team. At the time, I was completing my acupuncture studies. Filled with the zeal of the enthusiastic student, I felt that acupuncture should be able to help people living with cancer. However, as I massaged the emaciated, bruised limbs of the oncology in-patients, and observed the ravages of cancer and its treatments, I wondered how to apply acupuncture in this situation.

Opportunity knocked, or so I believed, when I accepted a part-time role as Complementary Therapy Co-ordinator at the Lynda Jackson Macmillan Centre (LJMC). This cancer information and drop-in centre associated with Mount Vernon Hospital in northwest London offers complementary therapies to patients attending for treatment at the hospital. I hoped to introduce acupuncture as a service to outpatients. However, as time progressed and there were no signs of this service coming into existence, I came to understand that there were concerns about introducing acupuncture. Managers worried about having a practitioner who was not medically trained offering an "invasive" treatment

using needles. They also were reluctant to offer a therapy that claimed therapeutic benefits; the general view was that the complementary therapies on offer at the LJMC were "feel-good" interventions that had few specific benefits beyond relaxation. After some discussion, the medical director proposed that I carry out an assessment of acupuncture. This was a challenge: a research project was born!

Discussion with key staff quickly revealed that tamoxifen-related hot flushes were the problem raised most frequently by women visiting the LJMC. Could acupuncture deal with these? This thesis attempts to begin to find answers to this question. It is also the very personal journey of a modern traditional acupuncturist practising in the UK, seeking to understand many of the contemporary issues currently surrounding acupuncture in the West. What is the role of research in relation to clinical practice? What are appropriate design methodologies for researching complementary medicines such as acupuncture? How can research benefit the acupuncture profession? Is individualised treatment really better than standardised protocols? These are just a few of the issues that this research allowed me to explore. At the heart of this, however, was always the key question: can acupuncture benefit people living with cancer?

1.5 Conventions used in this thesis

1.5.1 Using the first person to report this study

Historically, use of the third person characterises the writing of positivist quantitative research. It emphasises the detachment and objectivity of the scientific observer (Bryman 1988) and suits the presentation of quantitative data. Following this convention, this thesis should adopt the third person voice; however, I choose to present the thesis predominantly in the first person. Style is one of the two main reasons for this; style guides increasingly encourage the use of the first person. This applies across a number of fields, including science and technology (Kirkman 1992), nursing (Webb 1992), and academia (Giltrow 1995). In addition, prestigious medical journals such as the *British Medical Journal* specify use of the first person in their house style (Cooter 1999). Style experts argue that writing in the first person promotes clear and accurate communication (Kirkman 1992). (Similarly, they encourage the use of active rather than passive verbs, and I strive to implement this style as far as possible.) Through adopting these recommendations, I aim to increase the clarity of the writing in this thesis.

The second reason for using the first person is to ensure transparency of responsibility and ownership. The traditional use of third person serves to distance the researcher from the research. Striving for objectivity denies the involvement of the researcher in the thought processes needed for research, implying that the researcher was not active in the work (Webb

1992). As practitioner-researcher in this project, I was involved at every stage, from shaping the design of the studies, through developing the acupuncture approaches, to analysing the statistics. I interacted fully with the participants, recruiting them to the studies, administering questionnaires, and giving them acupuncture treatment. To present this in the voice of an objective third person would give a false impression of this work. Thus, in this thesis, I intend to make it clear where I have been the main person responsible for any decision, action, interpretation, or observation by using the first person singular.

It is nevertheless important to acknowledge that this work is the result of team effort. A research project can be a complex activity requiring access to a wide range of skills, knowledge, and experience. I am grateful to the colleagues listed below (see Table 1 on page 14) whose expertise contributed to the development and execution of this research. Where decisions, actions, interpretations or observations were the result of team effort, I will make this clear by using the first person plural "we". I will also aim to clarify who was involved in particular aspects of the research activities.

1.5.2 Format for terms used in Chinese Medicine

Many of the translated terms used in Chinese medicine (CM) equate to terminology used in Western medicine. As the meanings are different, it is a common convention for writers on CM to capitalise the Chinese terms, to distinguish them from their Western meanings (Kaptchuk 2000, Maciocia 1989, Hicks et al. 2004, Ross 1995). For example, the "Kidney"

in CM has very different functions and meaning to the "kidney" in Western thought.

However, some writers on CM opt to keep capitalisation to a minimum (Deadman et al. 1998), and some journals, such as the *European Journal of Oriental Medicine* actively discourage the capitalisation of CM terminology. The terms used in this thesis refer almost exclusively to CM equivalents; therefore, I have chosen to use this latter convention and keep capitalisation to a minimum. In circumstances where confusion may arise, I will seek to distinguish between CM and Western medical meanings to ensure clarity for the reader.

1.5.3 Hot flushes and night sweats

To avoid repetition of a long phrase, I use the term "hot flushes" to denote both hot flushes and night sweats. Where I discuss these as separate items, I will make this clear in the text.

1.6 Introducing the context and the team

1.6.1 The context

This research took place at the Lynda Jackson Macmillan Centre (LJMC), which is part of the Cancer Treatment Centre (CTC) at Mount Vernon Hospital (MVH) in Northwood, Middlesex. The MVH is an integral part of the Mount Vernon Cancer Network, which serves a population of about 2 million residents, mainly in Bedfordshire and Hertfordshire. Its serves 15 district general hospitals in the area. Treating most cancer tumour types,

the network provides radiotherapy for about 4,500 new patients per year and chemotherapy treatment for about 1,500 new patients annually (Mount Vernon Cancer Network Website Development Team 2005).

The LJMC opened in 1993 in response to research investigating what patients really want when they receive a diagnosis of cancer (Bradburn et al. 1992). Recognition of the psychosocial impact of cancer and its treatments was one factor identified by the research, and the LJMC was one of the first centres in the UK to respond to this by offering information, counselling and complementary therapies to people living with cancer and to their carers. In addition, the Supportive Oncology and Research Team (SORT) is a department at the LJMC specialising in research into aspects of supportive care for patients. The research presented in this thesis is one of SORT's many investigations. Others include involvement in a randomised controlled trial of aromatherapy massage for anxiety and depression in cancer patients, as well as collaboration with Southampton University on a Department of Health funded study investigating cancer patients' reasons for using complementary and alternative medicine (Yardley et al. 2005).

Nationally recognised, the LJMC has received a number of prestigious awards. In 1999, it won a Nye Bevan award for its work in the field of cancer support and information. This award recognises NHS teams who make outstanding contributions to excellence and innovation in the treatment and care of patients. The Prime Minister, Mr Tony Blair,

commended the LJMC for its innovation and best practice in health care. Furthermore, the Centre's resources are widely accessed: over 6,000 patients and their carers "drop-in" to the Centre annually; over 5,000 use the telephone help-line; and about 4,000 health professionals use the services available (unpublished data supplied by the Supportive Oncology Research Team, LJMC).

The work presented in this thesis was underway as a research project before it became a doctoral study. As mentioned, it stemmed from my interest in investigating how acupuncture might be used for people with cancer. From its inception in 1999 though to autumn 2003, the research developed solely at the LJMC. During this time, my role transformed from Complementary Therapy Co-ordinator to Research Acupuncturist. I worked with colleagues at the LJMC to develop the design and methodology. Dr Myra Hunter was our external consultant, providing expertise on menopausal symptoms and use of the Women's Health Questionnaire (WHQ) and the Hot Flushes and Night Sweats Questionnaire (HFNSQ).

Thames Valley University (TVU) accepted this work as appropriate for a doctoral thesis in 2003. This gave birth to an important collaboration between an academic institution and the National Health Service (NHS) - the collaboration between the Centre for Complementary Healthcare and Integrated Medicine (CCHIM) at TVU and the Supportive Oncology Research Team (SORT) at the LJMC. This collaboration provided the

range of support needed to continue the study, including academic, statistical, and medical expertise. It also contributed much of the financial support needed for the academic aspect of this work.

1.6.2 Introducing the team

Table 1 below lists the individuals involved throughout this study, specifying their roles and affiliations.

Table 1 Personnel involved in this research

Name	Role	Affiliation
Richard Atkins	Statistical Consultant	TVU
Ann Ashton	Research Assistant	LJMC
Beverley de Valois	Research Acupuncturist	LJMC & TVU
Dr Myra Hunter	External Consultant	St Thomas's Hospital
Rosemary Lucey	Research Sister	LJMC
Prof E J Maher	Medical Director	LJMC
Dr C McCourt	Academic Advisor	TVU
Prof N Robinson	Academic Advisor	TVU
Teresa Young	Research Co-ordinator	LJMC

1.6.3 My role within this collaboration

I collaborated with these individuals, drawing on their expertise to enrich and inform this research. Within this collaboration, it is necessary to identify the areas of the research I initiated, and the work that I specifically carried out. Although I identify these at the relevant points in the thesis, I will summarise them here.

Responsible for the following activities, I:

- Proposed the model for using traditional acupuncture, and convinced managers at the LJMC to accommodate this model (as opposed to investigating Western medical acupuncture)
- Prepared all submissions to the Local Research Ethics Committee, and defended the proposals at ethics committee meetings
- Designed all the documentation (questionnaires, diaries, and patient information sheets)
- Researched and developed the protocol used in the traditional acupuncture study, and developed the arguments supporting its theoretical relevance to this condition
- Conceived the idea of using ear acupuncture, and in particular I identified the NADA protocol, and conducted the mapping exercise to support its theoretical use in treating tamoxifen-induced hot flushes.
- Recruited all the participants in both studies, ensuring they met the inclusion/exclusion criteria, and I treated all the patients in both studies (with the exception of five clinics out of approximately 130 in the NADA study, when I was on holiday or ill)
- I administered all the paperwork for short term and long term follow-up
- I input all the data for Study 1: TA, and trained the Research Assistant to input the data for Study 2: NADA.

Regarding the statistical aspects of this study, I studied statistics so I could understand the statistical processes involved in this research (discussed in Chapter 4 starting on page 118). The Research Co-ordinator developed the process for summarising hot flush diary data into

a single summary value allowing for missing data, and carried out the initial analyses on the data for Study 1:TA for dissemination (using simple 't' tests on incomplete data sets, see the abstracts in Appendix 30). However, I repeated the analyses on complete data sets for Study 1: TA, and was entirely responsible for the analysis of the data for Study 2: NADA. I carried out all the calculations using log transformations (see section 4.8 starting on page 135) following a consultation with the Statistics Consultant, as well as the final analyses for the Women's Health Questionnaires and Hot Flush and Night Sweats Questionnaires. I present the results of these final analyses in this thesis. I also analysed the written data submitted by the participants in the end of treatment and follow-up questionnaires.

In addition, I:

- Conducted all the literature searches relating to this research
- Disseminated the findings on an ongoing basis through conference presentations and publications (see Appendices 31 and 32)
- Critically evaluated the data and findings, for presentation in the discussion of this thesis (see Chapter 10 starting on page 331).

1.6.4 Funding

Dr Richard Ashford, Consultant Clinical Oncologist at the Cancer Treatment Centre, Mount Vernon Hospital, funded the clinical phases of both studies. The West Hertfordshire NHS Trust Research and Development Fund contributed funding towards Study 2: NADA. A number of private individuals made donations as well. TVU and the

LJMC also supported the project financially, largely in providing salaried time and training for the academic aspects of this research.

1.7 Definition of acupuncture

Acupuncture may be defined as a therapeutic technique that comprises a family of procedures used to stimulate specific anatomical sites on the body, known as acupuncture points (National Center for Complementary and Alternative Medicine 2004). Needling is perhaps the most common and well-known means of stimulation used in acupuncture, and involves the insertion of thin, solid, metallic needles under the surface of the skin. These needles are sometimes stimulated manually or with electrical currents (electroacupuncture). Other techniques used to stimulate acupuncture points include:

- Moxibustion, a process which involves the burning of the herb *artemesia vulgaris*, commonly known as mugwort, to warm and stimulate
- Cupping, which uses cup-like devices to create a vacuum on the skin's surface
- Acupressure, which uses finger pressure rather than needles to stimulate the acupuncture points
- Other techniques, such as laser beams, pressure bands, and heat lamps (National Cancer Institute 2005, National Center for Complementary and Alternative Medicine 2004).

This thesis focuses on the use of acupuncture needling.

1.8 Brief history of acupuncture

Acupuncture is part of traditional Chinese medicine, whose medical theories have been under continuous development for over 3,000 years. Acupuncture itself may have emerged during 200 to 100 BCE (Birch and Felt 1999). Evolving over many centuries, its practice spread to neighbouring countries including Japan, Korea, Viet Nam, and Taiwan, where it was adapted to suit local conditions. It first appeared in the West as early as the mid-seventeenth century, but it was not until President Nixon's visit to China in 1972 that it caught the interest of Western healthcare practitioners and began to take root. Today, acupuncture is practised and is gaining acceptance worldwide. The World Health Organisation recognised the "promising potential" of acupuncture for relieving pain and nausea (2003), and the National Institutes of Health (NIH) concluded that there were promising results for the efficacy of acupuncture in post-operative and chemotherapy nausea and vomiting, as well as indications for its use in a range of other conditions (1997). In the United Kingdom, the House of Lords Committee on Science and Technology included acupuncture as one the "Big Five" principle disciplines in their classification of complementary and alternative medicines (2000).

As previously noted, acupuncture practice has adapted as it crossed national boundaries, making it a richly diverse practice. In the West, a number of styles are practised, including Traditional Chinese Medicine (TCM) which is derived from contemporary clinical practice in China;

Japanese acupuncture (or meridian therapy); Korean acupuncture (or constitutional acupuncture); Five Element acupuncture (also known as English acupuncture), and western medical acupuncture (National Cancer Institute 2005).

1.9 Contemporary acupuncture in the UK

This richly diverse range of styles makes it difficult to discuss acupuncture practice in general terms. However, I will attempt a brief exploration of what may be regarded as two of the main models of acupuncture practised in the UK. These are "traditional" or "professional" acupuncture and "Western medical" acupuncture.

Traditional acupuncture stems from theory and practice originating in the Orient, primarily, though not exclusively, in China. Generally referred to as "Chinese medicine" (CM), it is based on the "qi paradigm" (Birch and Felt 1999). As I discuss later in this chapter (see section 1.10 starting on page 21), it has a complete vocabulary of specialised terms and concepts, and it differs substantially from Western biomedical models of anatomy, physiology, and pathology. As noted above, there are many different schools of acupuncture: although based on the qi paradigm, they have differing theoretical frameworks, terminology, and reference systems. (I discuss two of these theoretical frameworks in section 1.10) Many of these styles derive from acupuncture practices from countries including China, Japan, Korea, and Viet Nam, and they undergo further adaptation in the West. In the UK, many of these diverse styles come

together under the umbrella of the British Acupuncture Council (BAcC), the professional body representing what it terms "professional acupuncturists" (BAcC no date). These acupuncturists are, in general, not medical professionals and they practise forms of acupuncture based on the "qi paradigm".

Acupuncture practised by "professional acupuncturists" differs from that used by the majority of medical professionals who administer acupuncture in the UK. Western medical professionals have not embraced the complex and foreign concepts associated with CM and the qi paradigm. They prefer to find alternative explanations for the phenomena of acupuncture. This is exemplified by Dr. Felix Mann's book *Reinventing Acupuncture* (2000), in which the author rejects traditional models of CM and sets out a theoretical framework based on scientific models acceptable to the Western biomedical school of thought. Members of the British Medical Acupuncture Society (BMAS), the professional organisation founded by Dr. Mann, see acupuncture as a process that stimulates the nerves (rather than qi), and increases the release of endorphins and serotonin to modify the brain's reception of pain (Livingstone 2005). Although this system uses some of the acupuncture points used in CM (called "classical points" in this context), it draws mainly on "trigger points". These are areas under the skin where degeneration of muscle tissue causes chronic pain (Birch and Felt 1999). Thus, medical acupuncture focuses primarily, although not exclusively, on managing pain.

Medical acupuncture differs significantly in its theory and application from styles of acupuncture based on the qi model. The form of acupuncture found commonly in the National Health Service (NHS), its practitioners generally regard the qi models of acupuncture as lacking scientific basis. I include it in this discussion to illustrate the diversity of acupuncture, and to highlight the attitudes that dominate the environment in which this research project took place.

1.10 Acupuncture used in this study

In this section, I explain the style of acupuncture I use, which informs the design of Study 1: TA. This discussion introduces fundamental concepts of CM and summarises the theoretical frameworks that are the basis for this style of acupuncture.

1.10.1 Two theoretical frameworks of acupuncture

The style of acupuncture I practise is "integrated acupuncture". Taught at the College of Integrated Medicine in Reading, Berkshire, it brings together two different frameworks of acupuncture theory: eight-principles (sometimes called yin/yang theory) and Five Element Constitutional Acupuncture (College of Integrated Chinese Medicine 2002). Both theoretical frameworks have distinctive models for the aetiology, diagnosis and treatment of disease, as well as their own interpretation of the functions of the acupuncture points. However, there are concepts common to both. I will outline these shared concepts before explaining the distinctive features of these two theoretical frameworks.

1.10.1.1 Shared Concepts

Three of these shared concepts are "qi", the "organ system", and "yin and yang". It is important to note that what follows is a simplified discussion of very complex concepts.

Qi

"Qi" is translated as "energy", although most acupuncture commentators agree that this is an inaccurate description (Birch and Felt 1999, Maciocia 1989, Kaptchuk 2000). The Chinese character for qi shows the vapour or steam produced when rice is cooked (Birch and Felt 1999): this simultaneously expresses the non-material (steam) and the material (rice) aspects embodied by the concept of qi (Hicks et al. 2004, Maciocia 1989). Figure 1 below illustrates this concept: the star-like figure in the lower left of the character symbolises uncooked rice; the vertical and horizontal strokes in the remainder of the character indicate steam.

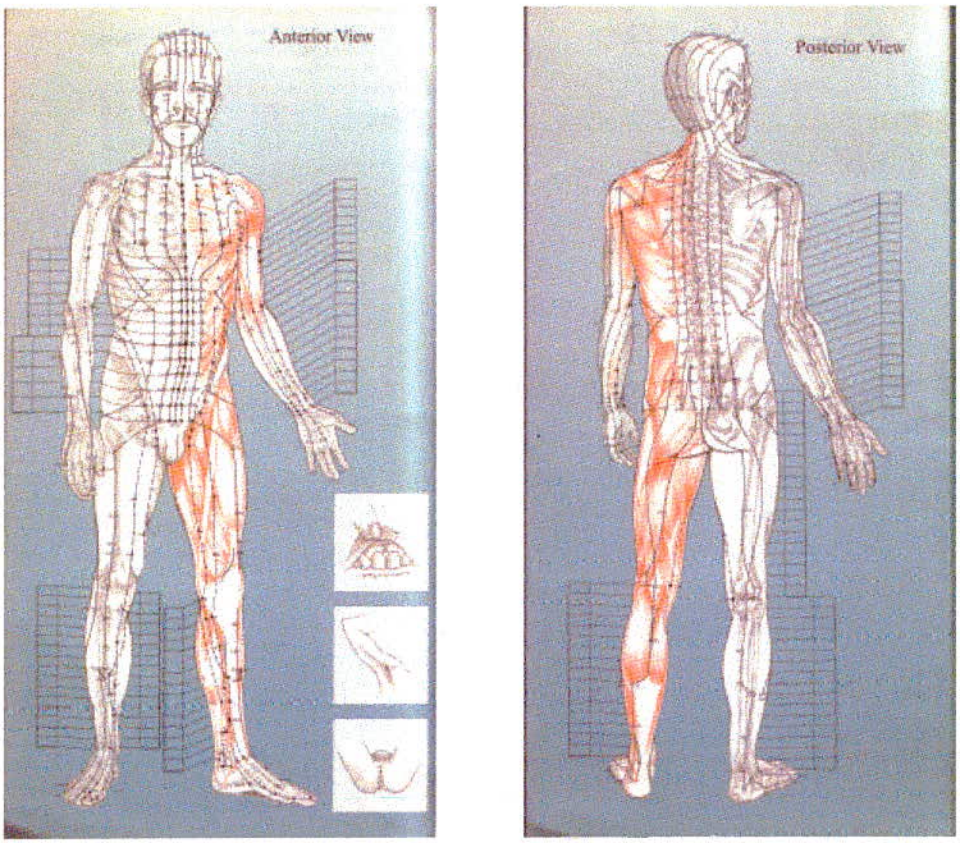
Figure 1 The Chinese symbol for qi

This embodiment of two apparently contradictory concepts (the material and the non-material) can be regarded as a characteristic of Chinese

thought (Nisbett 2005). With regard to qi in the clinical sense, it embodies the idea that we are unable to see qi itself (because of its non-material nature). However, we can see the manifestations of qi in many aspects of a patient's demeanour, including their complexion, their eyes, and their outward behaviour, and feel it in the qualities of the pulse. In this sense, qi is rather like the wind: we cannot see the wind itself, but we can see and feel its manifestations when it blows.

Chinese philosophers throughout the ages regarded qi as present in all things, whether animal, vegetable or mineral. In CM theory, there are many forms of qi in the body; it manifests on physical and spiritual levels; and is in a constant state of flux (Maciocia 1989). It circulates through the jing-luo, or channels of the body, represented in Figure 2 below.

Figure 2 The channels on the anterior and posterior aspects of the body (© College of Integrated Chinese Medicine. Used with permission.)



The channels are not physical entities (Kaptchuk 2000). However, they are a fundamental component of acupuncture theory, for it is along these channels that acupuncture points lie (Birch and Felt 1999). These are places where qi gathers and where the insertion of acupuncture needles can influence its behaviour. Thus, a very simplified explanation of how acupuncture works is as follows: qi flows through the body, and if it circulates smoothly, the individual feels well. If something happens to disturb the flow of qi, the qi stops flowing smoothly. This disruption manifests in symptoms of ill health in the individual. Poor nutrition, pent-up emotions, and overwork are just some examples of conditions that can

disrupt the flow of qi. Acupuncture needles influence this flow, helping to restore its balance and improve the health of the individual.

The organ system

As mentioned previously, qi flows through the channel system. The theory of the organs and their associated network of channels is complex, and as with the discussion of qi, what follows is a simplified discussion. Understanding the organs and channels, as well as their functions and inter-relatedness, forms the basis for the understanding of disease, its diagnosis and treatment in CM.

In CM, there are twelve channels; each one connects to an organ of the body. There are twelve organs, and CM theory links them together into six pairs, each comprising a yin and a yang organ (see the discussion of yin and yang below). Table 2 below shows these organ pairs.

Table 2 The organ system in Chinese medicine

Yin	Spleen	Heart	Kidney	Pericardium	Liver	Lung
Yang	Stomach	Small Intestine	Bladder	Triple Burner[2]	Gall Bladder	Large Intestine

Detailed theories underpin the organ system and each organ has specific functions. For example, every yin organ is associated with each of the following: a vital substance, a tissue, a sense organ, a part of the body,

[2] The triple burner does not exist as an organ, but functions as a pathway between the lungs, spleen, kidney, small intestine and bladder (Kaptchuk 2000). As such, it works to regulate fluids and yang (Larre and de la Vallee 1994). Such a concept does not exist in Western biomedical models of physiology.

and a mental/spiritual aspect (Hicks 2005). An example of this is the kidney: it stores "essence" (a vital fluid) and governs birth, growth, reproduction and development; it manifests in the hair (a tissue); it opens into the ears (a sense organ); it controls the lower orifices (the body parts the urethra and anus); and it houses the will power (a mental/spiritual aspect) (Maciocia 1989).

Overall, the organ system is responsible for the assimilation, production, distribution and storage of qi (Birch and Felt 1999). The way the organs perform affects the qi, which in turn affects the health of the individual. Acupuncture influences the organs: inserting needles on appropriate points along the organ's channel, or the channel of its paired organ, rebalances the flow of qi related to that organ.

Yin and yang

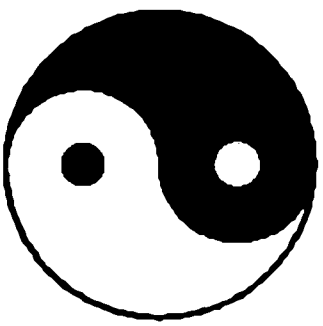
Yin and yang is the third shared concept to discuss. It is the fundamental underpinning theory of CM, and the basis for all diagnosis (Maciocia 1998, Kaptchuk 2000). The Chinese character for yin is the shady side of the mountain; that for yang is the sunny side of the mountain. Table 3 below lists the correspondences of yin and yang, showing the opposing characteristics of these two forces.

Table 3 Some properties of yin and yang

Yin	Yang	
Interior	Exterior	**The eight-principles**
Cold	Hot	
Empty	Full	
Dark	Light	
Wet	Dry	
Water	Fire	
Winter	Summer	
Passive	Active	
Descending	Ascending	
Below	Above	
Feminine	Masculine	
Front	Back	
Contraction	Expansion	

However, as well as being opposite, yin contains elements of yang, and yang contains yin. Figure 3 below shows this embodiment: the dark yin area of the circle contains a circle of white yang, and vice versa.

Figure 3 Symbol of yin and yang



This embodiment of opposites is challenging to Western models of thought, which sees contraries in opposition to each other. In Chinese thought, yin and yang are relative forces and only exist in relation to each other. For example, my knee is more yang than my foot (which is located lower on the body than the knee), but it is more yin than my chest (which is located higher on the body than the knee). Furthermore, yin and yang

are interdependent and cannot exist without each other. As such, they hold each other in a state of dynamic balance through continuous adjustment, and they transform into each other, as night transforms into day. The forces of yin and yang are dynamic, constantly changing, and at the heart of diagnosis and treatment in CM.

Clinically, an acupuncturist assesses the relative state of a patient's yin and yang, and develops a treatment plan to address this. For example, excessive yang activities (such as too much exercise, hard work, sex, worry, or substance misuse) may deplete the yin energy (Maciocia 1989). In women, such a depletion of yin can manifest in symptoms of heat, especially around the time of the menopause. Hot flushes are often the result.

1.10.1.2 Distinctive features

I will now discuss the distinctive features of the two theoretical frameworks that comprise the "integrated" style: eight-principles acupuncture and Five Element Constitutional Acupuncture (FECA).

Eight-principles acupuncture

Qi, the organ system, and yin and yang are concepts that underpin "eight-principles acupuncture", an approach that forms the foundation of CM (Maciocia 1998, Kaptchuk 2000). Diagnosis identifies the imbalances in the flow of the qi according to four pairs of opposing principles: yin/yang, interior/exterior, hot/cold, and full/empty (as shown in Table 3 above). Treatment principles determine the acupuncture points to use to restore

balance. Birch and Felt describe the treatment principles as "direct" (1999): if the condition is hot, cool it; if it is cold, warm it; if empty, tonify it; if full, drain or disperse it.

This theory is the basis of a method of diagnosis that is fundamental to the practice of CM (Maciocia 1989, Kaptchuk 2000). This identifies imbalances in specific organs in terms of patterns; patterns are overall pictures of signs and symptoms associated with the underlying disharmony. It brings together the concepts of the vital substances such as qi, the organs, and the eight-principles to describe the imbalance. For example, "kidney yin deficiency" is a pattern in which the yin (in this case, a form of qi) of the kidney (the organ) is deficient (or, "empty" according to the eight-principles). Clinical manifestations of this pattern include poor memory, night sweats, feelings of heat (especially in the evening), and aching bones (Kaptchuk 2000, Maciocia 1989, Ross 1995). Descriptions of the patterns might list these clinical manifestations, providing the pathology or explanation of how the manifestations arise in terms of CM theory, the aetiology or cause of the pattern, and the treatment (including the acupuncture points and the rationale for their use).

Part of the eight-principles approach is pulse and tongue diagnosis. CM theory advocates that both the pulse and the tongue provide a "snapshot" of the energy state of the person. For instance, the person with kidney yin deficiency might display a red tongue with no coating, and with many cracks; the pulse might be rapid. Eight-principles acupuncturists learn to

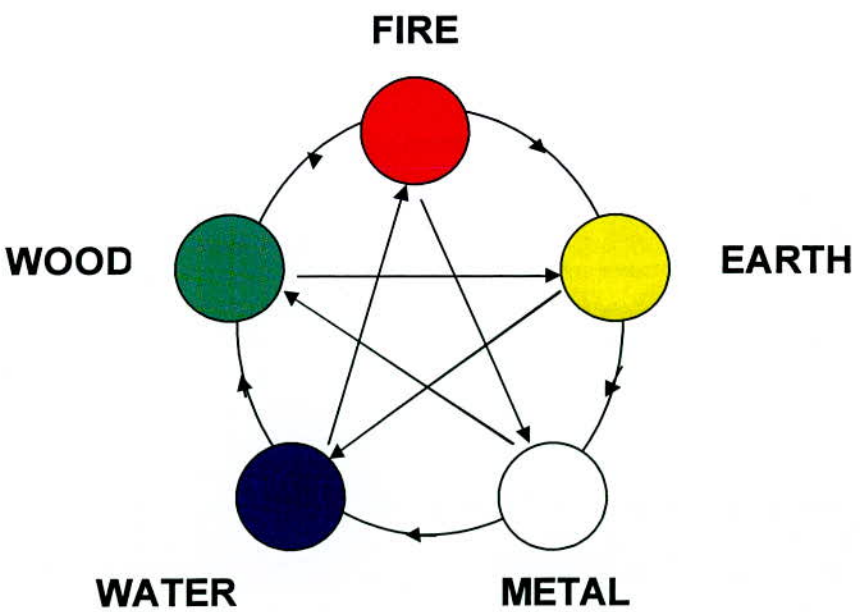
read the signs on the tongue as well as learning a specific system of pulse taking, and they use these readings to confirm the pattern diagnosis.

Treatment strategies derive from the theoretical framework. For example, the treatment principle for kidney yin deficiency is "nourish kidney yin" and the practitioner uses acupuncture points that fulfil this function to rebalance the disharmony.

Five Element Constitutional Acupuncture (FECA)

Five Element Constitutional Acupuncture differs substantially from the eight-principles approach. It is based on the theory of the five elements or five phases, which are water, wood, fire, earth, and metal, as shown in Figure 4 below.

Figure 4 The five elements or five phases



This theory derives from Daoist and Naturalist thought, in which all nature is seen to be governed by yin and yang and the five elements (Hicks et al. 2004). Like yin and yang, the force of the five elements is dynamic, in a constant state of flux, and the elements exist in relation to each other (as indicated in Figure 4 above). Each element has its own particular type of qi, characterised by comparisons with nature, particularly the changing seasons. Table 4 below lists some of the five element correspondences as they relate to CM, in particular the relationship of the elements to the organ system. Although this theory informs most styles of CM, in Five Element acupuncture it is the central focus.

Table 4 Some five element correspondences

Element	Water	Wood	Fire	Earth	Metal
Season	Winter	Spring	Summer	Later Summer	Autumn
Colour	Blue-black	Green	Red	Yellow	White
Sound	Groan	Shout	Laugh	Sing	Weep
Emotion	Fear	Anger	Joy	Worry	Grief
Odour	Putrid	Rancid	Scorched	Fragrant	Rotten
Yin Organ	Kidney	Liver	Heart/ Pericardium	Spleen	Lung
Yang Organ	Bladder	Gall Bladder	Small Intestine/ Triple Burner	Stomach	Large Intestine

Furthermore, the concept of a "constitutional imbalance" underpins this style. This is the idea that one of the five elements may be out of balance in an individual, leading to symptoms of ill health on the levels of body, mind, and/or spirit. Treatment on the imbalanced element, or the "constitutional factor" (CF) restores balance to the individual. Diagnosis

focuses on identifying characteristics of colour, sound, emotion, and odour (CSEO) in the patient, as presented in Table 4 above.

Clinically, a Five Element acupuncturist uses interaction with the patient to assess the CF, looking for signs of the CSEO to derive this. For example, a patient with an imbalance in the Water element might display some blue-black colouring around the mouth and eyes. Their voice might have a groaning quality to it, and they might give off an odour described as "putrid", which is like stagnant water or stale urine. They might display a pattern of intense fear and crave reassurance, or they may display an absence of fear. Signs of the CSEO are subtle, and diagnosis and treatment rely heavily on the practitioner's intuitive ability and sensory perceptiveness (Hicks et al. 2004). After identifying the CF, treatment proceeds according to treatment principles and point usage specific to this style of acupuncture.

The FECA style is a distinctly western adaptation of acupuncture, and is seen as particularly appropriate for the treatment of "longer-term chronic problems with a mixture of physical and spirit-level issues" which exist widely in modern western culture (Hicks et al. 2004, p xi).

1.10.2 The integrated approach

The integration of eight-principles and FECA styles equips the acupuncture practitioner with a wide range of diagnostic approaches, treatment principles, and interpretations of the functions of the acupuncture points. Hicks (1988) maintains that eight-principles

acupuncture enables the acupuncturist to deal with acute conditions, and the use of tongue diagnosis increases the means to identify imbalances in the individual. The organ system is fundamental to diagnosis and the understanding of imbalance. By contrast, FECA endeavours to address the "whole person", looking beyond the physical symptoms to address mental, emotional, and even spiritual aspects of well-being (Hicks 1988). Together, they offer the practitioner a range of tools that facilitate a flexible approach to dealing with the healthcare of the individual, in a manner tailored to the individual's specific requirements.

Integrated acupuncture embraces a number of fundamental concepts that characterise contemporary acupuncture practice in the UK (Eckersley et al. 2006). As noted in the previous discussion, qi plays a central role in the philosophy and conduct of acupuncture treatment. There is a holistic view of healthcare, which sees the body, mind, and spirit as interrelated entities. The acupuncturist addresses these entities in treatment, tailoring treatment to the individual patient and his or her particular needs. The practitioner respects the dynamic nature of health, healing and change, adapting treatment as appropriate to the patient's changing state throughout treatment. This form of practice recognises and accepts that diagnoses are subjective, based on the practitioner's individual experience of observation, pulse taking and tongue diagnosis and on their individual relationship with each patient. Communication and interaction are highly prized; establishing good rapport with the patient enables practitioners to obtain better quality information, which in turn

improves diagnosis and leads to improved treatment for the individual. In summary, this style honours the artistry of practice, while recognising the need to build the knowledge and research base for contemporary acupuncture (Eckersley et al. 2006). This contrasts with Western medical acupuncture, which tends to view acupuncture as a medical technology based on the insertion of needles, and seeks to find standard point prescriptions to apply to conditions identified by a Western medical diagnosis. It focuses on symptoms, rather than the "whole person".

1.10.3 Notes on terminology

I call the style of acupuncture used in the first study in this research "traditional" acupuncture. This is partly to differentiate it from medical acupuncture, the style practised more widely in orthodox medical settings. I also chose the term "traditional" in preference to "integrated" acupuncture to avoid confusion with the current movements to "integrate" complementary medicine into mainstream medicine. In seeking to name the style of acupuncture, I rejected the BAcC's term "professional", as this did not seem appropriate for use in an NHS environment.

In addition, I would like to emphasise that I do not equate this "traditional" or "integrated" style with the commonly used term "Traditional Chinese Medicine" (TCM). While there are few generally accepted definitions of acupuncture styles within the acupuncture community, I concur with Birch and Felt (1999), who define TCM as "the synthesis of internal medicine and biomedicine currently taught in Chinese medical schools to which modern Chinese acupuncture has conformed". This describes a

paradigm shift that started under Mao Tse-Tung in which the culture of biomedicine dominates, and often seeks to replace, traditional concepts. While this model sits comfortably with those who prefer a paradigm that conforms to biomedical models, it does not encompass the aims of many contemporary professional acupuncture practitioners in the UK. Hicks et al (2004) discuss the adaptation of CM to make it more suitable to the needs of Western patients and practitioners. They argue that whilst acupuncture in China focuses on acute and short-term health problems (with the aim of getting people back to work as rapidly as possible), acupuncture in the West often seeks to deal with long term chronic ailments, that combine physical, emotional, and spiritual issues. This approach seems particularly suitable for the care of people dealing with a chronic, potentially life-threatening disease such as cancer. Consequently, I endeavoured to make these values integral to my work with women undergoing treatment for early breast cancer.

1.11 This research in the wider context of CAM and orthodox medicine

It may be interesting to discuss this study in the wider context of the relationship between CAM and orthodox medicine. Saks (2003) characterises "medical orthodoxy" by its political legitimacy, contrasting it with alternative medicine, which is characterised by its political marginality. However, he acknowledges that (perhaps like the relationship of yin and yang) these positions are relative, and may fluctuate over time and in relation to wider socio-economic influences.

This research took place during a time of significant events that influenced the status of CAM in the UK, either directly or indirectly. These include the publication of the House of Lords (HoL) Select Committee *Sixth Report on Complementary and Alternative Medicine* (2000), as well the Medical Research Council's (2000) acknowledgement of the unique challenges involved in researching complex interventions. However, these examples support the argument that the political and medical establishments are the predominant controllers of the status of CAM, in spite of the swelling consumer demand for complementary medicine (Saks 2006). Furthermore, attitudes about CAM therapies are not straightforward: for example, the House of Lords' report classified "acupuncture" as one of the five principle therapies in Group 1 (for which, they said, there may be a convincing evidence base), and "traditional Chinese medicine" in Group 3a (which, they said, lacks a credible evidence base). This system of classification is somewhat confusing for traditional acupuncturists like me, and again it underlines the status quo by suggesting that medical acupuncture is "okay", whilst traditional acupuncture is not.

The research presented in this thesis took place in the NHS, and it simultaneously attempted to change orthodox perceptions of traditional acupuncture, whilst conforming to the expectations of the orthodox medical environment. Thus, this research attempts to contribute to the evidence base for CAM in an orthodox way: the research is primarily

quantitative in nature, and the methodology responds to NHS constraints on resources and its rationing of CAM therapies. In effect, this research attempts to change perceptions from within, rather than overtly challenging established orthodoxy.

In this sense, the medical establishment in the Mount Vernon Hospital (MVH) Cancer Treatment Centre (CTC) acted as gatekeepers to allowing the existence of traditional acupuncture in their environment. The LJMC works hard to engender good relations with the oncology consultants at the CTC, and only offers services approved by these medics. Managers at the LJMC are careful not to challenge these relationships. Thus, the set-up of this study depended on the consultants' acceptance of an acupuncture service. Furthermore, it was made clear to me that any research methods involving medical tests would not be possible, as this would interfere with consultants' time and cost the CTC money. The project could exist, so long as it remained polite, well-mannered, and made no demands on the established order.

In addition, attitudes at the LJMC reflect the general attitudes to CAM in the world of oncology. Generally, "complementary" therapies are defined as those used in conjunction with conventional medicine, whilst "alternative" therapies are used instead, or independently, of orthodox medicine (British Medical Association 1993, cited in Tavares 2003, National Cancer Institute 2006). In cancer literature, these definitions are extended. Complementary therapies (such as aromatherapy,

acupuncture, reflexology, and meditation) are acceptable so long as they are used to relieve symptoms and side effects, and make no claims to treat cancer itself. Alternative therapies (such as shark cartilage, laetrile (apricot seeds), and special diets such as the Gerson diet[3]) are regarded as dangerous, unscientific, and lacking evidence for their safety or effectiveness. By contrast, conventional medical treatments (such as surgery, radiotherapy, and chemotherapy) are promoted as evidence-based treatments, proven to be safe and effective at treating cancer (Cancer Research UK 2006, The Cancer Council Australia 2005).

These messages are devised in order to protect patient safety, but they are also value-loaded, and deliver strong messages to those whose lives are affected by cancer. My observation of attitudes of medical professionals over the decade I have worked in the field of cancer care is that CAM therapies are generally held in contempt. Alternative therapies are seen as nothing short of dangerous; complementary therapies are tolerated, but those who practise or use them are regarded as "flaky".

These attitudes permeate the medical profession and are strong influences on the agenda for CAM in cancer care. In understanding this, one can understand the reasons for the conservative attitudes in cancer

[3] For an example of the controversy and strong feelings around alternative medicine in cancer care, one need only examine the numerous articles in the media and in medical publications that were printed as a result of Prince Charles' reference to the Gerson diet at a conference on CAM and cancer in June 2004.

centres such as the LJMC, and the challenges involved in attempting to introduce new CAM therapies into such environments.

A further powerful influence in this arena comes from the medical acupuncturists, and the position statements of the British Medical Acupuncture Society (BMAS). Although relations between the BMAS and British Acupuncture Council (BAcC) have become more cordial over the past decade, BMAS members exert considerable power over the CAM agenda with regard to acupuncture. Their strong message, delivered publicly, is that acupuncture approaches that do not involve a conventional diagnosis are "potentially dangerous" (Filshie 2001), and non-medical acupuncturists are safe as long as they work "in close communication and co-operation with a patient's regular medical attendant" (Livingstone 2005). These messages persist in spite of recent studies reporting the general safety of both medical and traditional acupuncture approaches (White et al. 2001, MacPherson et al. 2001), which went some way to dispelling the strong feelings between the two groups. BMAS members hold positions of power in oncology organisations and have great influence over the use of acupuncture in this sphere. Thus, they function to maintain orthodox control over the agenda and contribute to keeping traditional acupuncture on the margins.[4]

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[4] It is interesting to note that at the time of writing, BMAS members are working to raise concerns about the safety of ear acupuncture in the treatment of cancer patients, presumably in response to the popularity of the use of ear acupuncture in cancer treatment centres.

In spite of the challenges of orthodox attitudes, this research project has been the catalyst for some changes within the establishment. Attitudes within the LJMC have changed considerably: in 1999, acupuncture was regarded with suspicion, and LJMC staff were not allowed to recommend acupuncture to patients seeking information about suitable CAM therapies. Today, the LJMC recommends acupuncture, distributes BAcC leaflets to patients, and has started an ear acupuncture service to manage hot flushes. This influence has rippled outward into the wider medical community, with oncologists and General Practitioners associated with the MVH CTC showing an active interest in the study and in acupuncture in general. The model of this research (particularly the use of the NADA protocol) has inspired several cancer treatment centres in the UK to set up similar services. Medical professionals have recognised my work as an example of CAM research that is rigorous and sound, and the BAcC regard it as an important study that will help the profession in its progress towards regulation and professionalisation.

These are some of the positive wider influences of this research. There is also an interesting irony to observe. When I joined the LJMC in 1999, I was unable to practise acupuncture because the managers had anxieties about allowing a non-medically trained acupuncturist to deliver an "invasive" therapy. Today, the managers enthusiastically promote the NADA ear acupuncture protocol, specifically because personnel who are

not acupuncturists, and who may or may not be medically trained, can deliver it!

1.12 Conclusion

In this chapter, I introduced the background and context to the development of this research project. I laid out the fundamental questions behind the research, and provided an initial description of the two studies. The discussion of contemporary acupuncture in the UK and the fundamental concepts of Chinese medicine give non-acupuncturists an insight into the theories, concepts and environment of acupuncture practice, as well as its complexity. I have endeavoured to express the philosophy and principles underpinning my training as an integrated acupuncturist, and to relate the relevance of this style to treating people with cancer. I have also attempted to position this study within the wider context of CAM and orthodox medicine. Having provided this background, I will turn my attention to the discussion of breast cancer, tamoxifen and hot flushes in the next chapter.

Chapter 2 Breast Cancer, Tamoxifen & Hot Flushes

2.1 Synopsis

In this chapter, I examine the subject of hot flushes that are a side effect of tamoxifen, and provide the context for this health care issue. I begin by exploring the incidence and prevalence of breast cancer, and then provide a brief overview of cancer generally, explaining what early breast cancer is. I discuss the treatments for this disease, focusing on the use of tamoxifen as an adjuvant treatment and its resulting side effects. Hot flushes and night sweats are a major side effect, and I discuss these as they occur both in natural menopause and because of cancer treatment. I explore the range of treatments for managing hot flushes, covering pharmacological products, CAM (complementary and alternative medicine) treatments, and lifestyle advice. I then focus on the use of acupuncture, again examining its use in natural menopause, as well as in managing tamoxifen side effects. I conclude by examining the literature providing evidence for the use of acupuncture to manage tamoxifen-related side effects. This discussion demonstrates the magnitude of hot flushes as a side effect, and supports the argument for focusing on this condition as an important health care issue for women.

2.2 Introduction to breast cancer

2.2.1 Incidence and prevalence of breast cancer[5]

2.2.1.1 Incidence in the UK

Cancer is the second most common cause of death in England and Wales (Office for National Statistics 2006). In the UK, breast cancer is the most commonly occurring cancer, accounting for 15% of the 275,280 cancer diagnoses in 2002 (Cancer Research UK 2006). Although it affects men, 99% of diagnoses relate to women, with 42,023 new cases of female breast cancer diagnosed in 2002. It is the most commonly occurring cancer in women, accounting for 31% (almost one in three) of all female cancers in the UK (see Figure 5 below). The risk of diagnosis during a woman's lifetime (the "lifetime risk") is one in nine.

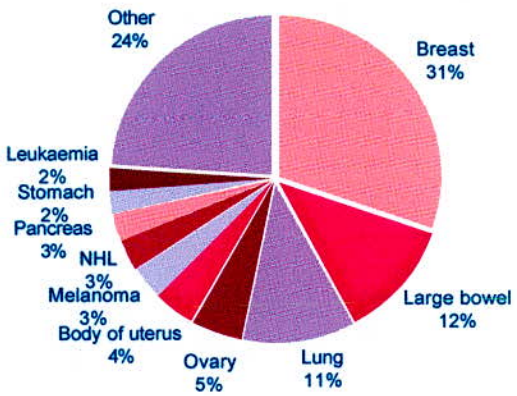
[5] All statistics are taken from Cancer Research UK (2006), unless otherwise indicated.

Figure 5 The 10 most common cancers diagnosed in women, UK, 2002 excluding non-melanoma skin cancer (NMSC) (Cancer Research UK, 2006)

THE TEN MOST COMMON CANCERS DIAGNOSED IN FEMALES, UK, 2002

Breast	41,724
Large bowel	16,175
Lung	15,195
Ovary	6,959
Body of uterus	5,600
Melanoma	4,530
NHL	4,444
Pancreas	3,647
Stomach	3,193
Leukaemia	3,049
Other	32,750
All cancers (exc NMSC)	137266

Figure 4.1 The 10 most common cancers in females, UK, 2002



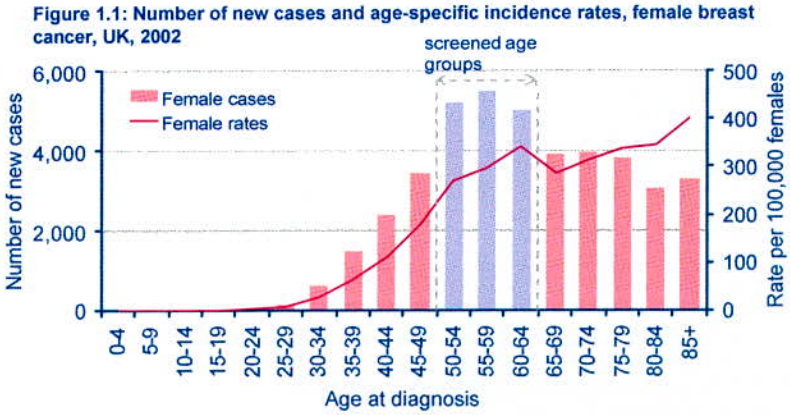
Risk is related to age, with more than 80% of cases occurring in women over 50 years old. As the greatest rate of increase occurs in the 50 – 54 age group, there appears to be a link with hormonal status. Figure 6 below shows that the 50 – 64 age group has the highest number of diagnoses, with few cases in women under 20.

Figure 6 Number of new cases and age-specific incidence rates, female breast cancer, UK, 2002 (Cancer Research UK, 2006)

BREAST CANCER INCIDENCE 2002

	Female cases	Female rates
0-4	0.0	0.0
5-9	0.0	0.0
10-14	0.0	0.0
15-19	0	0.0
20-24	29	1.6
25-29	133	7.1
30-34	609	27.0
35-39	1461	61.7
40-44	2365	109.7
45-49	3415	178.2
50-54	5212	268.3
55-59	5481	297.1
60-64	5022	340.8
65-69	3909	287.0
70-74	3974	311.8
75-79	3803	338.7
80-84	3042	347.2
85+	3269	402.3

Figure 1.1: Number of new cases and age-specific incidence rates, female breast cancer, UK, 2002



2.2.1.2 Worldwide incidence

Worldwide, there are over a million diagnoses of female breast cancer annually, accounting for 10% of all new cancers, and 23% of all female cancers.

Incidence varies according to geography: the developed world has the highest rates, while Africa and Asia have the lowest. There are about 361,000 new cases annually in Europe and 210,000 in the USA. The UK has the fifth highest incidence (after the USA, France, Denmark and Sweden) but the third highest mortality rates (after the Netherlands and Denmark). Japan and China have the lowest rates of incidence in the world. However, migrants from low to high-risk countries acquire the host country risk within two generations.

Incidence rates have been on the increase in developed countries for many years. In the UK, the rate increased by 45% in the twenty years from 1983 – 2002. Even in areas with historically low incidence, such as Eastern Europe and the Far East, rates are rising rapidly.

2.2.1.3 Prevalence in the UK

With this high incidence, and five-year survival rates reaching more that 75%, there are many survivors of breast cancer. Current estimates suggest that about 172,000 women are alive in the UK who have been diagnosed with breast cancer.

2.2.2 Summary

The high incidence and prevalence figures for the UK and worldwide demonstrate that breast cancer is a widespread problem, currently affecting many women and predicted to affect many more. This suggests that any problems relating to the disease and its treatment will also be widespread in contemporary society.

2.3 Breast cancer treatment in the UK

2.3.1 Brief introduction to cancer and its terminology

There are over 200 different types of cancer (Cancer Research UK 2006), a general term that describes a malignant tumour. Malignancy means that the tumour (usually called the primary tumour or primary site) is invasive, that it is capable of progressive, rapid growth, and that it may be capable of spreading via the lymphatics or bloodstream to other sites of the body. This process, called "metastasising", establishes secondary deposits of the tumour called "metastases" (Underwood 1996, p 251, Macpherson 1995, p 78). This process of spread is a factor that makes cancer so difficult to treat with a view to cure.

Tumours are classified according to their "histogenesis", that is, the specific cell of origin (whether from epithelial cells, connective tissue, or lymphatic or blood systems). For example, breast cancer originates in the epithelial cells, and broadly speaking it is a "carcinoma". Malignant tumours are "graded" according to the degree to which they resemble the

cells or tissue of their origin. Well-differentiated cells closely resemble the parent tissue, and usually indicate slow proliferation, while poorly-differentiated cells are more primitive than their origin, and indicate that a tumour is "aggressive" or proliferates rapidly (Macpherson 1995). Differentiation is important as it correlates with prognosis (patient survival) and indicates the appropriate treatment (Underwood 1996).

Just as there are many types of cancer, there are many different breast cancers, including ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), inflammatory carcinoma, Paget's disease of the breast, bilateral breast cancer, and male breast cancer (Neal and Hoskin 2003). Each of these has its own pathology, pattern of spread and rate of progression, and each will have a different set of treatment regimes and prognoses.

2.3.2 Early and late stage breast cancer

"Staging" is the medical process used to measure the extent of the tumour locally and the degree to which it has spread. Staging indicates the likely prognosis, helps determine the best treatment, and provides a baseline against which to assess response to treatment (Neal and Hoskin 2003).

In breast cancer, staging is an important indicator for prognosis and treatment. Oncologists use a formal, internationally accepted system, the TNM Staging System, for breast cancer assessment. It uses the following components to measure the anatomical spread of the disease:

- T for the primary tumour
- N for the regional lymph nodes
- M for distant metastases (Neal and Hoskin 2003).

Within this scheme, there are four stages. Stages I, II, and III are called primary or early stage breast cancer. Stage IV is called secondary or metastatic breast cancer, and indicates that the cancer has spread to other body organs or to lymph nodes beyond those in the armpit (Cancer Research UK 2006). Stage IV breast cancer is incurable (Neal and Hoskin 2003, p 80).

This differentiation between early and secondary breast cancer is important in terms of this thesis, as the research focuses on women with early stage breast cancer, and specifically excludes those women with advanced breast cancer (see exclusion criteria in section 3.10.2 on page 113).

2.3.3 Treatment of early breast cancer

2.3.3.1 Local and systemic adjuvant treatments

Generally, treatment of early breast cancer consists of a combination of local treatment (surgery, radiotherapy) and systemic adjuvant treatment (chemotherapy, hormonal therapy).

Surgery removes the primary tumour, and allows further pathological tests on the tumour and regional lymph nodes (for example, to measure the spread of the cancer, and to determine the hormone receptor status).

Radiotherapy often follows surgery. This is the use of radium or other radioactive material such as X-rays (Macpherson 1995, p 433) to ensure that any cancer cells in the remaining breast tissue are destroyed.

Systemic adjuvant therapy complements these local treatments. *Systemic* treatments typically use a drug to affect the entire body, rather than the local area; *adjuvant* means the prophylactic use of a treatment to prevent recurrence. In treating early breast cancer, chemotherapy aims to destroy any cancer cells ("micrometastases") that have travelled beyond the tumour and regional lymphatics into other areas of the body. Hormonal therapies slow or stop the growth of breast cancer cells, and help to prevent recurrence of breast cancer. Hormonal therapies may be given instead of, or as well as, chemotherapy.

Treatment for the individual depends on a number of factors, including the stage, grade, and size of the tumour, the woman's age and menopausal status, and the hormone receptor status (discussed below) (cancerBACUP 2003). This is an important concept for this study: the participants had different types of breast cancer, and had undergone a variety of different treatment regimes. The only factors that all participants had in common were that they had a diagnosis of early breast cancer at the time of joining the study and that they were receiving tamoxifen as adjuvant hormonal therapy.

2.3.3.2 The importance of determining hormone receptor status

Hormone receptor status is an important indication for hormonal therapy, and determines the type of hormonal therapy used. After surgery on a primary breast cancer tumour, tests of the cells confirm the presence and type of hormone receptors on the cell surface. Oestrogen and progesterone, the female sex hormones, may stimulate these receptors, causing the cancer cells to grow and multiply. Consequently, the goal of hormonal treatment is to prevent these hormones stimulating cell growth.

Cells can be oestrogen-receptor-positive (ER+), progesterone-receptor-positive (PR+), oestrogen-receptor-negative (ER-), progesterone-receptor-negative (PR-), or of "unknown" status. About 75% of breast cancers are ER+ (of which 65% are also PR+); about 25% are ER- and PR- or of unknown status; about 10% are ER+ and PR-; and about 5% are ER- and PR+ (Breastcancer.org 2006). Current UK national guidelines for treating breast cancer specify that ER+ cancers should be treated with hormone therapy, whilst ER- breast cancers should be treated with chemotherapy (Cancer Research UK 2006). However, hormone therapy is administered to PR+ breast cancers that are ER-, and some patients receive both hormone therapy and chemotherapy.

2.3.3.3 Hormonal therapies for treating ER+ early breast cancer

There is a range of hormonal therapies used in treating early breast cancer, and these work in different ways. Anti-oestrogen drugs, or selective oestrogen receptor modulators (SERMs), inhibit oestrogen reception in breast cells, thus prohibiting cell proliferation in the breast

(National Cancer Institute 2006). Tamoxifen is a SERM, and I will discuss it below. Whereas SERMs block the reception of oestrogen in the cell, aromatase inhibitors (AIs) block the production of oestrogen, thus reducing overall oestrogen levels in the body. Common AIs include anastrozole (Arimidex), letrozole (Femara), exemestane (Aromasin), and formestane (Lentaron) (cancerBACUP 2003). Progestogens such as megestrol (Megace) and medroxyprogesterone (Provera) are also used, although it is not clear how they work (cancerbackup 2006, Neal and Hoskin 2003). Pituitary down-regulators such as goserilin (Zoladex) lower the production of luteinising hormone by the pituitary gland, thus reducing oestrogen production in the body (cancerbackup 2006).

2.3.3.4 Treating pre- and post-menopausal women

These hormonal therapies are administered in different situations. For example, AIs are licensed for use in the UK for treating early breast cancer in post-menopausal women only, whilst pituitary down-regulators are used to treat pre-menopausal women. In some cases, particularly in pre-menopausal women, multiple hormonal therapies comprise the treatment regime (for example, Zoladex and tamoxifen may be prescribed simultaneously).

As discussed below, until the introduction of AIs in 2005, tamoxifen was the gold standard treatment for all women with early breast cancer, regardless of their menopausal status. With the introduction of AIs, there is now a wider choice of treatments for post-menopausal women, which includes, but is no longer limited to, the use of tamoxifen. However,

tamoxifen remains part of the treatment regime for pre-menopausal women.

2.3.3.5 A note on adjuvant treatments for early breast cancer

During the course of this study, treatment of early breast cancer with hormonal therapies began to change. At the outset of this research, tamoxifen was the gold standard treatment, used for the majority of women with early breast cancer to prevent recurrence. In 2005, anastrozole (brand-name Arimidex) was licensed in the UK to treat early breast cancer in post-menopausal women (Fleming 2005, Breast Cancer Care 2005), and promoted as a treatment with fewer side effects, especially hot flushes (Breastcancer.org 2006). However, we received many referrals to our study of women taking anastrozole, and in 2004, we opened the study to these women as well as those taking tamoxifen (see section 7.3.8 on page 261). Nevertheless, tamoxifen remains the adjuvant treatment of choice for pre-menopausal women with early breast cancer, and many consultants prefer it as it confers health benefits that are not available with anastrozole (Bilimoria et al. 1996; Maher, J, personal communication, 23 January 2003).

2.4 Tamoxifen as an adjuvant treatment

2.4.1 Introduction

Tamoxifen is the hormonal treatment of choice for the adjuvant treatment of early oestrogen-receptor-positive (ER+) breast cancer in post-menopausal women (Joint Formulary Committee 2003, p 432). It

maintained its status as the 'gold standard' treatment for twenty-five years (Buzdar 2002), although this is starting to change due to the introduction of aromatase inhibitors, as noted above. This status was largely due to tamoxifen's effectiveness in delaying metastases and increasing survival (Early Breast Cancer Trialists' Collaborative Group 2001, Henderson 1996). The odds of recurrence in women with ER+ breast cancers reduce by approximately 40% after five years of tamoxifen treatment, and the risk of developing contralateral primary breast cancer reduces by half for up to ten years (Neal and Hoskin 2003, p 79).

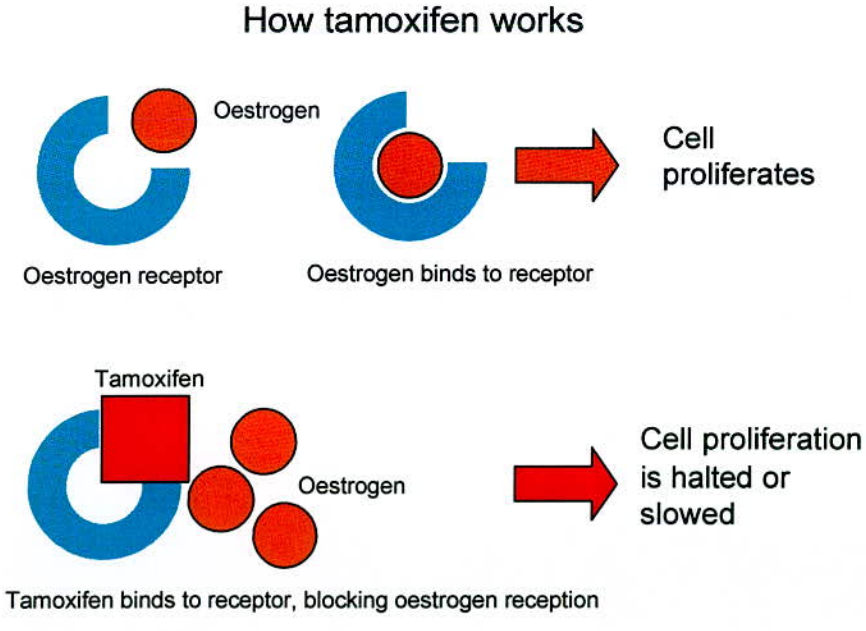
2.4.2 What is tamoxifen?

Tamoxifen is the generic name for an anti-oestrogen drug, also marketed under the trade names Nolvadex, Nolvadex-D, and Tamofen in the UK. As mentioned above, tamoxifen is a selective oestrogen receptor modulator (SERM). It selectively stimulates or inhibits the oestrogen receptors of different target tissues (National Cancer Institute 2006). This means that while tamoxifen inhibits oestrogen receptors in breast cells, it stimulates these hormone receptors in uterine endometrial cells. This ability to select oestrogen receptors in the breast and interfere with their proliferation was discovered in the 1970s, leading to clinical studies of its effectiveness in both advanced and early breast cancers (Jordan 1996). (It is worth noting that this selective aspect of tamoxifen's action results in its major serious side effect, the proliferation of oestrogen receptive cells in the uterus, which may increase the risk of uterine cancer (National Cancer Institute 2006).)

2.4.3 How does tamoxifen work?

A simple way to understand how tamoxifen works is to compare its action to a lock and key (cancerBACUP 2003). The cell's receptors are the lock, whilst the sex hormones act as the key. When oestrogen contacts the receptors, it "unlocks" or activates them, stimulating cell proliferation. Tamoxifen mimics the action of oestrogen, but while it fits into the lock like a key, it does not "turn", and this "blocks" the power of the hormones to stimulate cell growth. Another way to describe this is to say that tamoxifen binds to the oestrogen receptor, and blocks its activity (Neal and Hoskin 2003). This interference stops the oestrogen's ability to stimulate cell proliferation, thus halting or slowing the spread of cancer. Figure 7 below illustrates this.

Figure 7 How tamoxifen works



2.4.4 Treatment regime

Tamoxifen is usually taken in tablet form or as syrup for people who experience difficulty taking tablets. The tablet, taken once daily, comes in dosages of 10 mg, 20 mg and 40 mg, with 20 mg regarded as the optimum dose. Much research has been done on the optimum duration of treatment (Early Breast Cancer Trialists' Collaborative Group 2001), and this is currently considered to be five years (Joint Formulary Committee 2003, Neal and Hoskin 2003).

2.4.5 Side effects and hot flush incidence

As with many pharmaceutical preparations, side effects are possible. Severe side effects of tamoxifen include increased risk of thromboembolism (blood clots) (AstraZeneca UK Limited 2003) and of uterine cancer (National Cancer Institute 2006, Assikis and Jordan 1996), making it unsuitable for women who are at high risk for these conditions (Joint Formulary Committee 2003, p 433, Barakat 1996).

Less severe side effects that are commonly cited include hot flushes, indigestion or nausea, sweats, vaginal dryness, vaginal discharge, weight gain, and changes in menstrual patterns in premenopausal women (Joint Formulary Committee 2003, AstraZeneca UK Limited 2003, cancerBACUP 2003, Neal and Hoskin 2003). Of these, hot flushes are among the most frequently occurring (Langer 1996, Love et al. 1991). Statistics for the incidence of hot flushes vary according to the group studied (whether pre- or post-menopausal, and whether being treated for

early or late breast cancer). In addition, many studies do not focus on tamoxifen alone and often group all cancer treatments together. However, results from the National Surgical Adjuvant Breast and Bowel Project NASBP-14 study (which monitored nearly 3,000 women with early breast cancer) indicate that 910 of 1424 (63.9%) participants taking tamoxifen reported hot flushes, as opposed to 685 of 1420 (47.6%) taking placebo (Jordan 1996, p. 206, Micromedex (R) Healthcare Series 2004). Canney and Hatton's (1994) study of 108 women under the age of 65 who had been treated for early breast cancer shows 20% of the participants who had no adjuvant treatment reporting menopausal symptoms, compared with 69% who were treated with tamoxifen. Similarly, Ganz et al (1998) monitored 1096 women, and report hot flushes in 40% (n = 265) of participants not taking adjuvant treatment, compared with 60.7% (n = 356) taking tamoxifen, and 72% (n = 295) treated with both tamoxifen and chemotherapy. The Ganz study measured night sweats separately, reporting their occurrence in 33.3% of the participants not taking adjuvant treatment, compared with 47.2% (n = 356) taking tamoxifen, and 52.4% (n = 295) treated with both tamoxifen and chemotherapy.

These studies demonstrate an apparent relationship between hot flushes and night sweats and tamoxifen, and provide an indication of how widely these side effects affect the women who take tamoxifen as adjuvant treatment for early breast cancer.

2.5 Hot flushes

2.5.1 What are hot flushes?

Hot flushes (also called hot flashes in America) and night sweats, collectively known as vasomotor symptoms, are associated with natural menopause. However, these phenomena affect women undergoing treatment for breast cancer, men undergoing hormonal treatments for prostate cancer, women who have undergone oophorectomy (removal of one or both ovaries), or who are undergoing treatment for infertility or endometriosis (National Institutes for Health 2004), as well as people undergoing substance detoxification (Brumbaugh 1994).

Hot flushes are experienced as a sensation of spreading warmth that may vary in intensity and duration according to the individual. Physical symptoms that may accompany them include sweating, flushing or redness, palpitations, dizziness, feelings of suffocation, nausea, tingling sensations in the hands, and chills before or after the flush. Emotional symptoms such as anxiety, feelings ofpanic, irritation, annoyance, frustration, depression, and even suicidal feelings may be experienced (Kronenberg 1990, Northrup 2001, Kaufert and Syrotiuk 1981). Night sweats (also called nocturnal hot flushes) may disturb sleep patterns, leading to fatigue and irritability (Kronenberg 1990, Couzi et al. 1995, Erlik et al. 1981, Dennerstein et al. 2000). Women often experience hot flushes and night sweats as disabling and socially embarrassing, and the

phenomenon can seriously affect quality of life (Kronenberg 1990, National Institutes for Health 2004).

2.5.2 Hot flushes in natural menopause

Hot flushes and night sweats are the most commonly reported symptom of the menopause transition (Kronenberg 1990, National Institutes for Health 2004). They are widespread: in her seminal paper, Kronenberg (1990) reports prevalence from 24% to 93% for post-menopausal women in the USA and Northern Europe, and estimated that in 2000, between four and five million women in the USA alone would experience this phenomenon. In spite of this prevalence, the causes are unknown. Various theories of endocrinology implicate oestrogen withdrawal or reduction, changes in gonadotrophin levels, and the action of catecholamines, but study results are contradictory and no clear causes have been identified (National Institutes for Health 2004, Kronenberg 1990, Dormire 2003). In addition, cultural factors, environment, and stress may play a role, adding levels of biological and psychological factors to the physiological triggers (Kronenberg 1990, Hunter and Liao 1995, Swartzman et al. 1990).

Furthermore, the wide variability in the way these symptoms manifest makes it difficult to identify general patterns. Some women experience few, if any symptoms during the menopause transition; others experience severe symptoms that may continue for many years. Frequency and severity of flushes vary from woman to woman, as well as for the individual, and they may change as the individual woman progresses

through the various stages of menopause. Hot flush frequency may range from less than one per week to as many as one or more per hour, and women may experience flushes for as little as two years to as long as 16 years or more after the menopause (Kronenberg 1990). Measuring these variable and subjective symptoms is also problematic, and the National Institutes for Health (NIH) in the USA has launched a consensus development programme to determine how best to manage menopause-related symptoms (National Institutes for Health 2005) and how to assess and improve measures of hot flushes (National Institutes for Health 2004).

2.5.3 A note on definitions of stages of menopause

In this thesis, I use the definitions defined by the World Health Organisation and the Stages of Reproductive Aging Workshop (STRAW). Menopause is:

> "The permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognised after 12 consecutive months without menstrual periods that are not associated with a physiologic (e.g. lactation) or pathologic cause" (National Institutes for Health 2005).

The STRAW working group recognises the difficulty of defining menopause, and recommends a complex staging system. Simplified, it defines the following three phases of reproductive aging, which are being validated (Soules et al. 2001):

1. Reproductive stage: from menarche to the beginning of perimenopause (when cycles become variable).
2. Menopausal transition: the time of increased follicle-stimulating hormone and increased variability in cycle length, 2 skipped menstrual cycles with 60 or more days of amenorrhea (absence of menstruation), or both. This phase concludes with the final menstrual period (FMP) and the beginning of postmenopause.
3. Postmenopause: begins with the FMP, and recognised only after 12 months of amenorrhea (National Institutes for Health 2005).

Although the STRAW group does not recommend using the term "perimenopause" for scientific papers, they recognise that it is commonly used, and define it as the time immediately prior to menopause and the first year after menopause. It includes the menopausal transition and overlaps the first 12 months of postmenopause (Soules et al. 2001).

2.5.4 Hot flushes as a side effect of tamoxifen

Previously, I discussed the incidence of hot flushes and night sweats as side effects of tamoxifen (see section 2.4.5, starting on page 55). While these symptoms are not life threatening, they cause considerable distress and inconvenience to those women who experience them. Carpenter et al (2002, 1999) report that breast cancer survivors experience hot flushes more frequently than women in natural menopause, and that these cancer-related flushes may be more severe, distressing, and of greater duration.

The onset of hot flushes and night sweats can occur regardless of the woman's natural menopause status. Thus, young women who are pre-menopausal may experience these symptoms prematurely; women whose cancer diagnosis coincides with their natural menopause may experience exacerbated symptoms; and post-menopausal women may experience an unwelcome recurrence of symptoms they thought they had left behind.

Women are often advised that the severity of their tamoxifen-related hot flushes will diminish over time (Love and Feyzi 1993). However, Hunter's (2004) cross-sectional study of 113 women taking tamoxifen shows that 80% of the sample were still experiencing an average of 20.3 hot flushes per week (range 0 – 140) at a mean time of 2.8 years after starting tamoxifen therapy. This is more than halfway through the typical five-year duration of tamoxifen therapy, and indicates that even if the problem diminishes, it remains at noticeable, if not unacceptable, levels.

2.6 Treatments for menopausal hot flushes

2.6.1 Managing symptoms in natural menopause

2.6.1.1 Hormone Replacement Therapy (HRT)

Hormone Replacement Therapy (HRT) is considered the most effective treatment for managing menopausal symptoms: a Cochrane systematic review reports results equivalent to a 75% reduction in frequency (95% CI

64.3 to 82.3) for HRT relative to placebo (MacLennan et al. 2004). However, its use is controversial, with fears that its long-term usage may lead to increased risk of breast cancer, thromboembolism, and endometrial cancer (Hickey et al. 2005, Ringa 2000). The premature closure in 2002 of the Women's Health Initiative, a study designed to investigate the health benefits and risks of HRT, stimulated controversy and confusion about the safety of HRT use (National Electronic Library for Health 2003, National Electronic Library for Health 2004, Neves-e-Castro et al. 2002). There are now conflicting messages: the North American Menopause Society (NAMS) recommend that oestrogen-based products should remain "the therapeutic standard for moderate to severe menopause-related hot flashes" (2004, p. 11), whilst a Cochrane review concludes that HRT is not indicated for "routine management of chronic disease" (Farquhar et al. 2005, p 2). In the light of this, many medical professionals and women are keen to seek alternatives (Hickey et al. 2005, Neves-e-Castro 1999).

2.6.1.2 Pharmacological alternatives to HRT for natural menopause symptoms

Influenced by such publicity and uncertainty, many women choose not to use HRT (Neves-e-Castro 1999), fearing that its risks outweigh its benefits. Alternatives are under investigation. Pharmacological preparations for managing hot flushes and night sweats include Tibilone, a synthetic prohormone with weak oestrogenic action; antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs) such as Venlafaxine (Barton et al. 2002), Paroxetine, fluoxetine; Gabapentin, an

anticonvulsant; and antihypertensives such as Clonidine and Methyldopa (The North American Menopause Society 2004, Hickey et al. 2005, Shanafelt et al. 2002).

2.6.1.3 CAM alternatives to HRT for natural menopause symptoms

Non-pharmacological solutions including complementary and alternative medicines are also of interest to women and their health care professionals (Kessel and Kronenberg 2004, Philp 2003). These include Western herbal preparations such as red clover (*Trifolium pratense*) and black cohosh (*Cimicifuga racemosa* syn. *Actaea racemosa*), while traditional Chinese herbal preparations include dong quai (*Angelica sinensis)*, ginseng (*Panax ginseng*), liquorice (*Glycyrrhiza glabra*), and herbal mixtures (The North American Menopause Society 2004). Vitamin E, evening primrose oil (Chenoy et al. 1994), and topical wild yam and natural progesterone creams are often recommended, as is homeopathy. As is so often the case with complementary medicines, scientifically acceptable evidence is sparse: results of the few clinical trials on these substances may be inconclusive, research methodologies may be unsound or inappropriate, or there are safety concerns (Kessel and Kronenberg 2004, Kronenberg and Fugh-Bergman 2002). (However, these comments also apply to evidence for the pharmacological preparations mentioned above (National Institutes for Health 2005).)

2.6.1.4 Lifestyle changes for managing natural menopause symptoms

Lifestyle changes are also promoted, especially when symptoms are mild (The North American Menopause Society 2004). Women may be advised to dress in layers to keep cooler, use a fan, consume cold rather than hot drinks, increase exercise, avoid obesity and smoking, practise relaxation techniques, and avoid triggers such as alcohol and spicy food (if they are able to identify these) (Neves-e-Castro 1999, Hickey et al. 2005, Philp 2003).

2.6.2 Managing tamoxifen-related hot flushes

2.6.2.1 Hormone Replacement Therapy (HRT)

For women with breast cancer, using HRT to manage menopause symptoms is even more controversial. The HABITS (HRT after breast cancer – is it safe?) study, a Swedish RCT that randomised 434 women with a history of breast cancer to HRT and non-HRT groups, was halted when interim analysis showed high levels of recurrence in the HRT group (Holmberg and Anderson 2004). These findings may have led to the premature closure in 2004 of the clinical study of HRT in Women Being Treated for Breast Cancer, funded by Cancer Research UK.

In fact, the HRT controversy affected this acupuncture research project. I wrote the first protocol for Study 2: NADA in 2002 (see Appendix 6) to accommodate the UK HRT study, stating that the NADA study was suitable for women randomised to the non-HRT arm in the UK HRT

study. However, on extending the protocol in January 2004 to include women taking Arimidex, the LREC asked us to remove the references to the HRT study, because Mount Vernon Hospital had withdrawn due to concerns raised by the HABITS study (Brown, A, personal communication by letter, 27 February 2004).

Because of the controversy about the safety of HRT, it is not recommended for women who have breast cancer. It is usual practice to advise women diagnosed with breast cancer to stop taking HRT (Hickey et al. 2005), and many women stop taking HRT voluntarily when they receive a breast cancer diagnosis (Biglia et al, cited in Hickey et al. 2005, p. 412).

2.6.2.2 Pharmacological alternatives to HRT for tamoxifen-related symptoms

For women with breast cancer, the alternatives to HRT are similar to those for healthy women, as discussed above. A number of studies specifically investigating the effects of the pharmacological preparations on breast cancer patients include research into oral Clonidine (Pandya et al. 2000), transdermal Clonidine (Goldberg et al. 1994), Venlafaxine (Loprinzi et al. 2000) and megestrol acetate (Loprinzi et al. 1994). Further recommendations include prescribing SSRIs, albeit only to patients for whom hormonal options are not viable and when non-pharmacological options have failed (Stearns and Hayes 2002).

2.6.2.3 CAM alternatives to HRT for tamoxifen-related menopause symptoms

Many women choose complementary medicine because they do not wish to experience further side effects of pharmacological preparations for hot flushes (Hunter et al. 2004), or they do not wish to take medication in addition to tamoxifen. Examples of studies of complementary medicines to manage menopausal symptoms in women with breast cancer include an observational study of homeopathy (Thompson and Reilly 2003), a cross-over RCT of Vitamin E (Barton et al. 1998), an RCT investigating black cohosh (Jacobson et al. 2001), and RCTs of soy phytoestrogens (Quella et al. 2000, Van Patten et al. 2002). In many of the CAM studies, there is no strong evidence that the therapy is effective over and above placebo (Quella et al. 2000, Van Patten et al. 2002, Jacobson et al. 2001). Others show statistical significance, but no clinical significance (Barton et al. 1998), or are exploratory studies preliminary to conducting an RCT (Thompson and Reilly 2003). Furthermore, the safety of many CAM therapies is as controversial as the safety of HRT: black cohosh, red clover, and soy phytoestrogens are amongst the subjects of complex arguments about whether supplements stimulate growth of cancer cells (de Lemos 2002, National Centre for Complementary and Alternative Medicine 2006, Philp 2003). Consequently, women with breast cancer are often advised to avoid these substances until more is known about their effects on breast tissue (National Centre for Complementary and Alternative Medicine 2006).

2.6.2.4 Lifestyle changes for managing tamoxifen-related menopause symptoms

As with the management of symptoms of natural menopause discussed in section 2.6.1.4 above, lifestyle advice is often prescribed to breast cancer patients by medical professionals and advisors on cancer care (Lynda Jackson Macmillan Centre 1998).

2.7 Using acupuncture to treat hot flushes

In section 5.6.1, starting on page 155, I discuss the literature pertaining to the use of traditional acupuncture to treat hot flushes that informed the design and methodology for Study 1: TA. That discussion covers literature available at that time (1999 to 2001), and in this section, I will provide a brief review of literature published more recently.

The most important publication to emerge is Wyon et al's (2004) three arm RCT comparing electro-acupuncture, minimal needling, and oral estradiol. Forty-three out of 45 women completed a 12-week course of treatment, with a six-month follow-up period. All groups responded well, with statistically significant reductions in hot flush frequency, leading the investigators to conclude that electro-acupuncture is a viable alternative treatment to estradiol. They also conclude that minimal acupuncture is not an inactive control treatment.

Cohen et al's (2003) smaller RCT compared two acupuncture arms. One received an "experimental" acupuncture treatment using points

selected for their affect on menopausal symptoms according to traditional Chinese Medicine (CM) theory; the other received treatment described as a "general tonic". Seventeen women completed the course of six treatments delivered over nine weeks, and they were monitored over four months. The authors claim superior results from the experimental acupuncture procedure, although it appears that both groups had reduced severity. Sleep disturbances and mood changes were also monitored, and again, the authors claim superior results from the menopause-specific treatment.

A third study by Dong et al (2001) measured the effects of acupuncture on quality of life and hormone secretion in eleven women. The participants received ten acupuncture treatments based on principles of CM over five weeks, with follow-up three months after the end of treatment. The authors claim significant improvement in vasomotor symptoms, which are maintained at follow-up, improvements in physical symptoms, but not in psychosocial aspects (measured by the Menopause Specific Quality of Life Questionnaire (MENQuoL)), and variable changes in the levels of follicle-stimulating hormone but no other hormones.

All three studies suggest that acupuncture may be beneficial in the management of menopausal hot flushes. Both Cohen and Dong conclude that further research is warranted.

2.8 Literature review

During the course of this research, I carried out a number of literature searches on the subject of using acupuncture to treat hot flushes related to cancer treatments, especially tamoxifen (and Arimidex). In 2005, CAMEOL (Complementary and Alternative Medicine Evidence OnLine) published *Acupuncture for hot flushes as a result of cancer treatment: a systematic literature review* (Smith J. et al. 2005). This reviewed the literature relating to the use of acupuncture to manage hot flushes in women with breast cancer and men with prostate cancer. It found no systematic reviews, three RCTs (of which two were unpublished, and in abstract form only), no controlled clinical trials, nine uncontrolled studies, and one qualitative study.

Four of CAMEOL's uncontrolled studies were the abstracts from Study 1: TA (de Valois et al. 2003, de Valois et al. 2003), and Study 2: NADA (de Valois et al. 2004, de Valois et al. 2005), available in Appendix 30. The systematic review also lists a qualitative study, which is the focus group study carried out on the TA group in this research project (Walker et al. 2004). In section 5.7.3.4 (starting on page 173) and section 5.7.4 (starting on page 174), I discuss aspects of four of the other uncontrolled studies reviewed by CAMEOL. These were available during the set up of my two studies. They include: Porzio's (2002) pilot study using traditional acupuncture to treat 15 women taking tamoxifen; Tukmachi's (2000a, 2000b) case series of 22 women treated with acupuncture, diet and lifestyle; Cumins and Brunt's (2000) uncontrolled trial of 26 patients

(abstract only); and Towlerton's (1999) uncontrolled trial of 12 women taking tamoxifen, treated with semipermanent indwelling studs. The systematic review lists an RCT comparing minimal and traditional acupuncture by Davies (2001); this is an abstract only, and was unknown to me at the time of setting up my studies.

The CAMEOL report identified a further study, published during my Study 2: NADA, which was an uncontrolled pilot study of 13 patients (male and female) treated with electroacupuncture according to traditional Chinese medicine (TCM) (Johnstone 2003). It also identified two on-going RCTs of acupuncture on female breast cancer patients, on which there were no publications. These are a NCCAM sponsored study of 70 breast cancer patients (National Centre for Complementary and Alternative Medicine 2005), and Cohen's ongoing study on which there is no published information (Smith J. et al. 2005). (One further study identified focused on hot flushes in prostate cancer patients, and is not directly relevant to my current research.)

From October to December 2005, I carried out a literature search, seeking to update the CAMEOL findings and to focus on tamoxifen-related hot flush studies. Appendix 1 contains details of the search criteria I used. This search identified one new publication regarding studies of acupuncture for the management of vasomotor symptoms in women treated for breast cancer (Nedstrand et al. 2005). This was a small, preliminary RCT (n = 38) comparing electro-acupuncture with

applied relaxation. Thirty-one women completed twelve weeks of treatment and six months of follow-up, and both groups showed reductions in flushes after four weeks of treatment, with change lasting at the three and six month follow-up periods. The authors conclude that further evaluation is warranted into both applied relaxation and electro-acupuncture for controlling vasomotor symptoms in post-menopausal women with breast cancer.

In addition to finding this paper, I subsequently contacted several of the authors listed above for updates of their studies. The NCCAM RCT was awaiting finalisation of long term follow-up of two patients in June 2006, with the data analysis phase planned to follow shortly (Vickers, A, personal communication by email, 21 June 2006). Filshie, Bolton et al published the results of an audit of acupuncture and self-acupuncture (2005). This was a retrospective audit of the records of 194 breast and prostate cancer patients, treated using a number of acupuncture approaches. The audit leads to a recommendation for the use of self-acupuncture for maintenance in these patients. I did not identify any further new work in this area.

2.8.1 Summary of the literature

At the time of planning Study 1, there was very little literature on the use of acupuncture for the treatment of hot flushes related to treatments for breast cancer. I used the available studies to inform the design of Study 1: TA.

In addition, literature searches conducted during the design phase of Study 2: NADA did not identify any studies or literature on using ear acupuncture or the NADA protocol to manage hot flushes related to tamoxifen or cancer treatments generally. In fact, although there are claims that the NADA protocol reduces hot flushes in addiction detoxification, there does not appear to be any literature documenting this in other than anecdotal reports (Brumbaugh 1994, Peckham 2002).

I was aided by the CAMEOL systematic review, but this did not identify any significant literature to supplement my earlier findings. Personal contact with authors identified one new publication in 2005, and the promise of further publications, possibly in 2006. My literature search also identified one preliminary study comparing electro-acupuncture with applied relaxation. Thus, it is appropriate to say there is very little published about the use of acupuncture in the management of hot flushes. However, of the papers available, there are promising signs that it may be an effective treatment, and most investigators conclude that further research in this area is warranted (Smith J. et al. 2005).

2.9 Conclusion

In this chapter, I have endeavoured to provide the reader with a comprehensive background to understanding breast cancer, tamoxifen and hot flushes, and introduced the concept of using acupuncture to manage tamoxifen side effects. I have discussed the incidence and prevalence of cancer, explored its treatments, and introduced hot flushes

and night sweats, the major side effect of adjuvant tamoxifen. The discussion of hot flushes, both in natural menopause and as a side effect of tamoxifen treatment, highlights that this is a serious healthcare issue for women. This leads to an exploration of the methods used to manage these phenomena, and some of the challenges of finding effective treatments. Acupuncture lends itself as a possible means for treating menopausal symptoms, and I examine the literature relating to this. After attempting to replicate and update an existing systematic review of acupuncture to manage hot flushes resulting from cancer treatment, I conclude that there is very little evidence for its use, but that initial investigations show promising results and justify further research. Having fully explored this background, in the next chapter I turn my attention to the overall design and methodology used in the research that comprises this thesis.

Chapter 3 Overall Design and Methodology

3.1 Synopsis

In this chapter, I present the design structure that is generic to Study 1: TA and Study 2: NADA. This covers the study design, its history and rationale, as well as the outcome measures, measurement points, and follow-up. I also describe the methodology pertaining to the recruitment of study participants. In this discussion, I present the challenges involved in creating this design, and the rationale for the decisions made by the design team.

3.2 Introducing the design team

The team involved in developing the overall design for these studies included the following personnel from the Lynda Jackson Macmillan Centre:

- Myself, as Research Acupuncturist
- Teresa Young, Research Co-ordinator
- Rosemary Lucey, Research Sister
- Jane Maher, Medical Director.

Dr Myra Hunter of the Cancer Research UK London Psychosocial Group, Institute of Psychiatry, King's College London, was our external consultant.

In this chapter, the word "we" refers to this team.

3.3 Introduction to study design

I conducted two single-arm observational studies, using before and after measurements (Deeks et al. 2003), in which the participants acted as their own controls. The studies were consecutive, and each used a different type of acupuncture and delivery method. Study 1 used traditional acupuncture (TA), and participants received semi-individualised treatments (using acupuncture points on the body) on a one-to-one participant/practitioner basis. Study 2 used a standardised ear acupuncture protocol, and all participants received the same treatment in small group clinics with minimal participant-practitioner interaction.

The results and the experience gained from Study 1 informed the approach adopted in Study 2. However, both studies adhered to the same overall design: they used the same outcome measures, measurement points and follow-up, inclusion and exclusion criteria, and statistical methodology. This chapter details this overall design and methodology. I discuss details that are specific to each of the studies (such as the acupuncture protocols and changes in delivery method) in Chapter 5 and Chapter 7. I present the details of the data handling and statistical methodology in Chapter 4.

3.4 Purpose of the studies

Our purpose in carrying out these studies was to explore the question "can acupuncture offer a means of managing the hot flushes and night

sweats that are a side effect in women taking tamoxifen as an adjuvant treatment for breast cancer?" As discussed in Chapter 2, there was very little information in the literature on this subject when we began this project. My first task was to gather data to see if there could be any possible benefits from using acupuncture to address this condition. We also had questions about whether women treated for breast cancer would choose to have acupuncture, an intervention using needles, after having considerable exposure to needles in the course of their cancer treatment. We needed to know if we could recruit enough participants to carry out a successful study. Furthermore, we needed to test whether our chosen outcome measures were acceptable to the participants, and whether they would provide meaningful information and be sensitive to change.

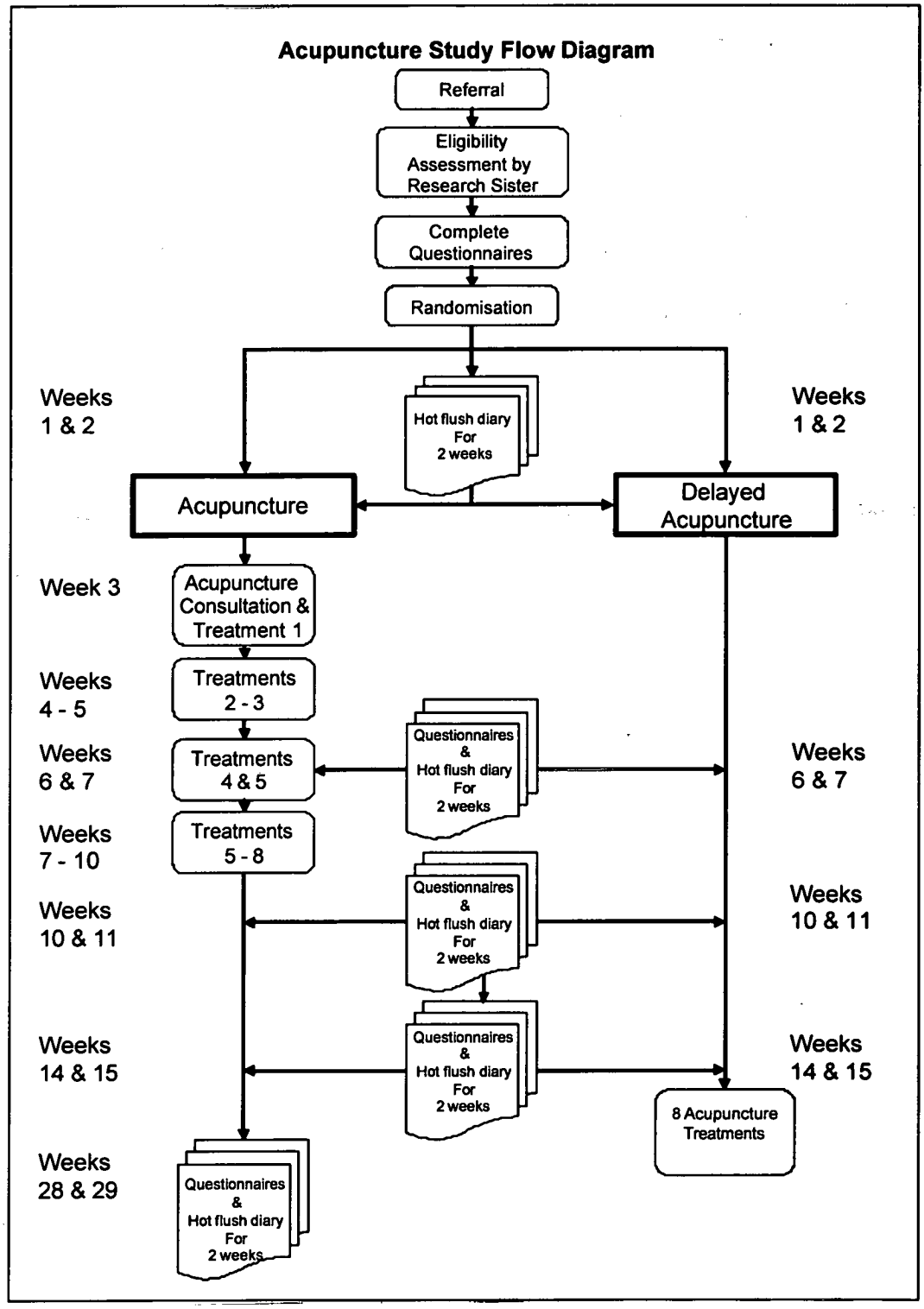
In this situation, it seemed that exploratory studies would provide valuable basic data. Although these studies would provide indicative, rather than definitive evidence, our experience and findings would have the potential to inform further studies (Thomas and Fitter 2002, White and Ernst 2001).

3.5 Brief history of study design

Our choice to carry out single-arm, exploratory studies was not straightforward. There is enormous pressure, especially in the NHS, to conduct randomised controlled trials (RCTs), regarded as the "gold standard" in medical research (Concato et al. 2000, Greenhalgh 2001, House of Lords Select Committee on Science and Technology 2000). This pressure also exists in the CAM community, with influential figures

pushing the RCT research agenda (Ernst 2005, Ernst 1995, House of Lords Select Committee on Science and Technology 2000, section 7.19). Thus, our first study design was for a two-arm, randomised controlled trial. Figure 8 below illustrates this design. The intention was to compare participants undergoing "standard" treatment(s) for their hot flushes (as discussed in section 2.6.2 starting on page 64) with those in the intervention arm, who would receive a course of acupuncture in addition to "standard" treatment. At the time, we called these the "Acupuncture" and "Delayed Acupuncture" arms, as the participants in the non-intervention arm would receive a course of acupuncture late in the study. In fact, the terms "Standard Treatment plus Acupuncture" and "Standard Treatment" would have been more accurate, as participants in both arms would be having some form of "standard" treatment for their flushes.

Figure 8 Proposed design for a randomised controlled trial



This type of research design can be classified as a "pragmatic clinical trial" (Thomas and Fitter 2002). (Our variation was to allow participants randomised to the "standard treatment" arm the option to have acupuncture after the primary endpoint measurement, and this we called "Delayed Acupuncture". We did this as a reward to these participants for completing the study paperwork.) Pragmatic studies aim to evaluate an intervention as conducted in everyday clinical practice, or "normal" conditions, as opposed to experimental studies that focus on establishing the efficacy of an intervention, usually in carefully controlled, "laboratory" conditions (Thomas and Fitter 1997). This allows the practitioner to individualise treatment and adapt it to the changes in the participant. Pragmatic studies focus on packages of care, rather than seeking to separate out the individual components of the intervention (such as participant/practitioner interaction). They compare two treatments (in this case, standard treatment for hot flushes with standard treatment plus acupuncture), rather than comparing the intervention with placebo. They are not blinded, they aim to optimise non-specific effects, and offer long-term follow-up (MacPherson et al. 2004).

Pragmatic studies have been discussed in the literature since the late 1960s (Swartz and Lellouch 1967) and they are increasingly regarded as an appropriate research design for CAM studies (Verhoef et al. 2005). In recent years, a number of studies looking at the use of CAM for chronic conditions have used this design (Meade et al. 1990, Vickers et al. 1999, MacPherson et al. 2004). However, at the time of our application to the

Local Research Ethics Committee (LREC), pragmatic studies were relatively rare. We also lacked sufficient knowledge to defend successfully our design in a culture that insisted on classic randomised placebo controlled trials. Consequently, we were disappointed to have our study rejected: the Mount Vernon & Watford Hospitals LREC was concerned that there was no placebo arm, and that there was a risk of the Hawthorne effect (the acupuncture group would show an improvement simply because there was an intervention) (Neal, D, personal communication by letter, 26 January 2001). They insisted that the control group receive a placebo.

3.5.1 Identifying an appropriate control arm

Anxious to save our study, we examined a number of possibilities for a control arm. The LREC had suggested playing a music tape as a basic form of relaxation therapy, but we felt this was inappropriate given the context and problems facing women with hot flushes. The possibilities we explored included lifestyle advice, lifestyle advice plus lying down to music, foot massage, weekly music-listening sessions, one relaxation class followed by self-managed listening to a relaxation tape, regular relaxation classes, visualisation, Venlafaxine, and Clonidine. I rejected using sham acupuncture, as discussed below in section 3.5.2, page 82.

We questioned the effects that each of these approaches might have, and their validity as a placebo control arm. Taking advice from specialists in a number of these therapies, as well as specialists in CAM research, we concluded that none of these interventions was an appropriate

placebo. There was insufficient research on each of these interventions to indicate whether they might be effective or ineffective in their own right, a situation common to CAM therapies (Ernst 2004). Consequently, introducing any one of these into the study would require us to change our basic research question (Hart 2001) to one that questioned whether acupuncture was more or less effective than a comparative therapy. Such a change would have redefined the study as either an equivalence or non-inferiority trial. Due to the lack of available evidence about the efficacy of acupuncture for tamoxifen-related hot flushes, these designs would have been inappropriate (Ernst 2004, Nahin and Straus 2001). At this stage, we needed to conduct an exploratory study to gather evidence about whether acupuncture could have any effect at all in treating tamoxifen-related hot flushes.

A key issue in this debate is how to control for the non-specific effects of complex treatments such as acupuncture, where it is difficult to separate out the effect of the needle intervention with other effects such as those relating to the patient-practitioner intervention. There has been a strong call for studies that make this separation. Recently, however, experts in research methodology have argued for study designs that include the "holistic" or non-specific effects of CAM (Mason et al. 2002, Hawe et al. 2004, Paterson and Dieppe 2005, Long 2001).

With regard to our study, our external consultant, Dr Hunter, advised us that it would be difficult to identify a control arm for the non-specific

effects of TA that would appear relevant to the symptoms experienced by the participants. This relevance was important when taking account of the burden of time, travel and commitment that participation in a study entails. She also suggested that taking part in a study, completing questionnaires, being monitored, and knowing someone is interested in your problem are all strong contributors to the placebo effect, without the need of additional factors (Hunter, personal communication, 1 February 2001). This advice helped us to confirm our decision to resist the pressure to introduce a control arm, as requested by the Ethics Committee.

3.5.2 A note about sham acupuncture

We also rejected the option of introducing a sham acupuncture arm. "Sham" refers to a range of techniques used as a placebo control in randomised controlled trials of acupuncture. These techniques include needling of non-acupuncture points; needling points considered to be ineffective for the condition treated; using specially designed placebo needles to replicate acupuncture needling without piercing the skin; needling superficially, known sometimes as minimal needling; and using techniques other than needles, such as inactivated laser and TENS machines (White 2002, Dincer and Linde 2003).

Dincer and Linde's (2003) systematic review of sham interventions shows that such techniques have been widely accepted as placebo control methods. It also demonstrates the complex and widely misunderstood issues surrounding use of sham acupuncture. One example is the use of

minimal acupuncture. White (2002) stipulates that an essential feature of a good sham intervention is that it does not obtain needling sensation (this is called *deqi* in CM, and this term usually describes sensation(s) felt by the patient when being needled (Bovey 2006)). However, whilst Chinese-style and Western medical acupuncture often stress the importance of obtaining deqi, Japanese-style acupuncture uses superficial needling techniques that do not seek to obtain this sensation (Yamashita and Tsukayam 2001, Bovey 2006). This raises a question about the validity of minimal needling as an inert, placebo control technique.

This example is indicative of the wider issues about the use of sham methodologies. Many specialists in acupuncture research methodology acknowledge that sham techniques have their place in answering specific questions about specific acupuncture techniques, and caution that care must be taken in matching the sham technique to the question asked. They also argue that it is misleading to regard them as placebo treatment (Birch 2004, Dincer and Linde 2003, White et al. 2001). Sham techniques are thought not to be physiologically inert (Linde et al. 2005, White and Lewith 2003), and may actually "activate physiologic nonplacebo non-specific effects" as well as activating specific effects (Birch 2004, p 489)[6].

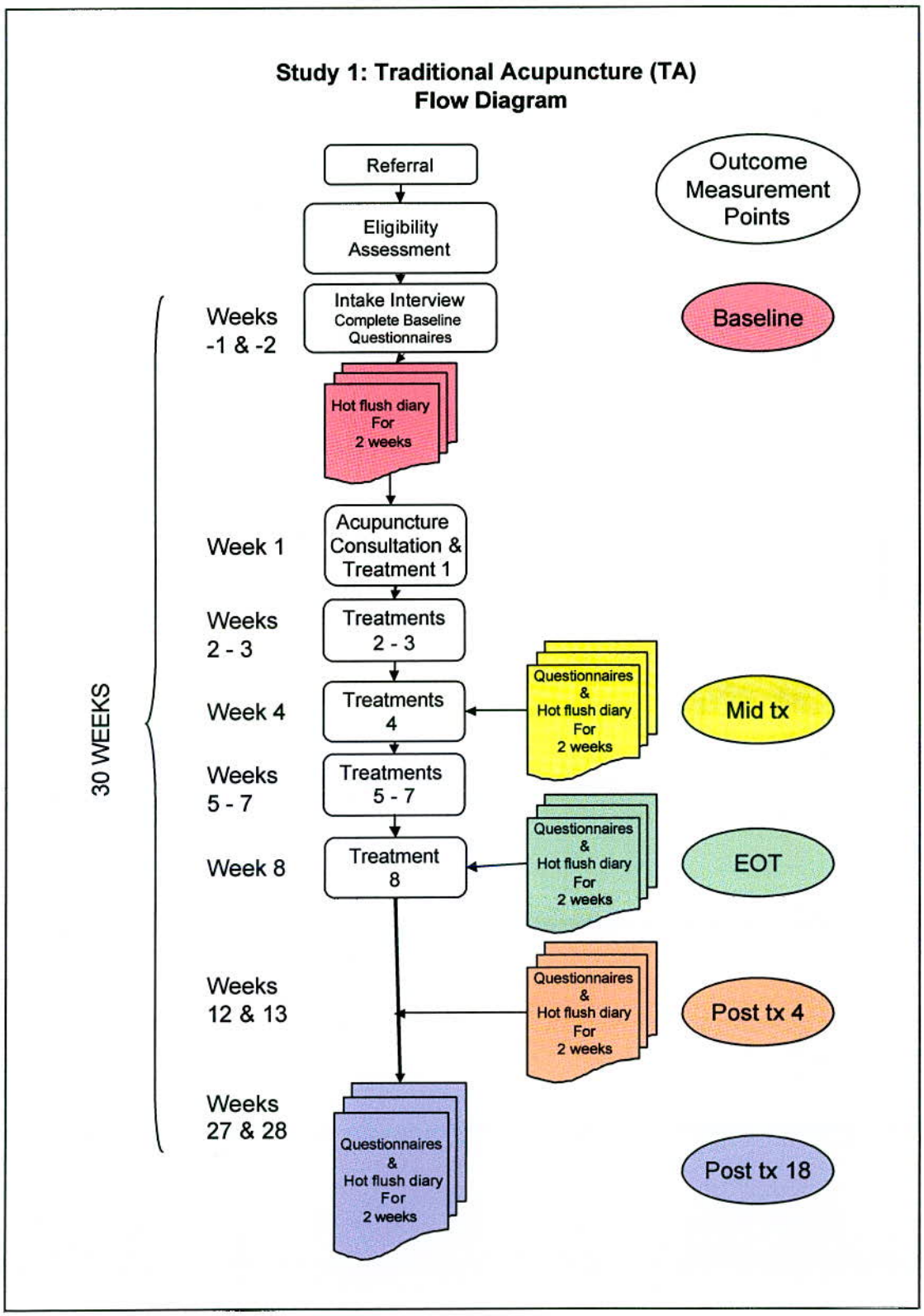
[6] For a discussion on the subject of placebo and non-specific effects, see Paterson and Dieppe (2005).

However, these discussions were not clearly articulated in the literature when we designed our study. As a traditional acupuncturist with an awareness of the diversity of acupuncture styles, I resisted the idea of a sham intervention. If energy is affected by superficial needling, it may well be influenced by the sham techniques in vogue at the time, such as cocktail sticks, guide tubes, pressing the skin with a fingernail or the blunt end of a needle (White 1996, White et al. 2001).

3.6 Rationale for single-arm observational studies

Our decision not to conform to the LREC's requirements meant we were unable to carry out a randomised controlled trial. After prolonged discussion with the LREC, all parties agreed that it would be acceptable to carry out a single-arm pilot study. Figure 9 on page 85 shows this new design for the traditional acupuncture (TA) study. Study 2: NADA follows this design, and Figure 35 on page 255 illustrates this. (I used coloured paper to differentiate the paperwork for each measurement point of the study as discussed in section 4.4.1 on page 120, and Figure 9 reflects this colour coding.)

Figure 9 Design for a single-arm observational study for traditional acupuncture



In some ways, this decision posed serious disadvantages. Non-randomised uncontrolled studies are lower in status than RCTs (Hart 2001, Greenhalgh 2001). Consequently, it is more difficult to obtain funding as well as to find journals willing to publish findings of non-RCT studies. However, in retrospect, it is clear that this was the correct and appropriate course of action for our work at that stage. The Medical Research Council (MRC) has published guidelines for the development and evaluation of RCTs for complex interventions (2000). These stress the importance of preliminary investigative work prior to developing an RCT, and the exploratory work presented in this thesis corresponds with aspects of the first three phases of the MRC's continuum of increasing evidence. I will discuss these correspondences, starting on page 86 below.

3.6.1 Pre-clinical phase (theory)

This phase "explores relevant theory to ensure best choice of intervention and hypothesis" as well as predicting "major confounders and strategic design issues" (Medical Research Council 2000, p 4). Consulting the literature confirmed a lack of high quality literature and the need to undertake original research in this area. Chapter 5 of this thesis discusses the need to explore whether traditional acupuncture was an appropriate treatment for menopausal symptoms resulting from a pharmacological intervention. Furthermore, we based the power calculations for the RCT design on a "best-estimate" available from one experienced acupuncturist, as this was all that existed at the time. We

needed to gather more data in order to carry out some of the basic activities required for good study design, conduct and analysis.

3.6.2 Phase I (modelling)

The purpose of this phase is to "develop an understanding of your intervention and its possible effects" (Medical Research Council 2000, p 4). As an acupuncturist, I had to learn about the changes that participants undergoing acupuncture treatment might experience. Would the protocol I designed reduce hot flush frequency? If hot flushes changed, in what way did they change? How quickly did change happen? How much did they change? What other conditions changed or did not change? How long would any effects of treatment last? In terms of conducting a study, we needed to know whether the outcome measures were appropriate. Would the participants fill in the hot flush diaries? Was the Women's Health Questionnaire, designed for women undergoing a normal menopause transition, an appropriate measure for women with cancer? Did it capture the changes in overall health and well-being that an acupuncturist would expect to observe in patients undergoing acupuncture treatment? It was essential to gather data to answer these and other questions before launching into a definitive study, and we have achieved this by using the observational studies and conducting focus groups, as recommended by the MRC.

3.6.3 Phase II (exploratory trial)

The MRC describes this as the crucial step prior to a main RCT, when the evidence gathered to date is tested. This phase involves experimenting

with the intervention (Medical Research Council 2000, p 4). In our studies, we experimented with a number of aspects of clinical delivery. These include the mode of acupuncture (firstly investigating TA, and then ear acupuncture), the question of individualised treatment and standardised treatment, the methods of delivery (one-to-one sessions and small group clinics), and the ratio of practitioner-participant involvement. We extensively tested our chosen outcome measures, and we have accumulated data about how women treated for breast cancer feel about having acupuncture as a treatment for their hot flushes.

Furthermore, we have gathered much information about the experience of having hot flushes in the context of early breast cancer. We learned a great deal about managing the data and the challenges of statistical analysis. By not locking ourselves into a fixed protocol, we could adapt our approach, applying what we learned as we developed the studies. This approach also allowed us to think, observe and reflect on the various components of the study and their impact on the studies as a whole.

3.6.4 Summary of the rationale for a single-arm observational study

In summary, at the outset of our study, there was insufficient data to carry out a properly designed RCT. The MRC framework confirms that choosing to conduct single-arm observational studies was an appropriate and, for us, a necessary course of action. Furthermore, organisations such as the National Centre for Complementary and Alternative Medicine

(NCCAM), part of the National Institutes for Health (NIH) in the USA recognise the appropriateness of observational studies, in such situations as described above (Nahin and Straus 2001).

The single-arm observational design enabled us to focus on gathering information relating to our main questions. These included the main study question, which was "Can traditional acupuncture be used to manage tamoxifen-related hot flushes and night sweats?" Specifically, could it help to reduce the frequency and/or severity of these symptoms? It was also important to see if the treatment could have further effects on emotional and physical well-being in the participants.

Furthermore, this type of study enabled us to test the appropriateness of our outcome measures (see section 3.9, page 98), whilst also allowing us to collect data on the numbers of hot flushes women taking tamoxifen typically experience. In addition, we would be able to assess whether the medical professionals at MVH and more importantly, whether women who had undergone treatment for cancer would find acupuncture an acceptable intervention for managing their treatment side effects. Finally, as an acupuncturist, this would give me, in the first instance, insight into the effect of using traditional theory to manage a modern-day problem (discussed in Chapter 5).

3.7 Design decisions

Figure 9 (above) presents the agreed design for Study 1: TA and Study 2: NADA also followed this overall design (see Figure 35 on page 255). The basic structure comprises establishing a baseline measurement, followed by eight acupuncture treatments administered on a weekly basis. The study monitored participants for a period of 30 weeks, with short and longer-term follow-up. This section describes how the design team arrived at this design.

Our aim was to ensure the study was pragmatic, in the sense of being practical and reflecting "real-life". This meant that the study, taking place in the context of the LJMC, needed to conform to the standards, policies and procedures of the Centre. It also needed to be relevant to the women attending Mount Vernon Hospital (MVH) and the LJMC for breast cancer treatment, and acceptable to the consultants responsible for the medical care of these women. I will now discuss some of the major decisions taken.

3.7.1 Establishing the need

It was essential to investigate the potential demand for acupuncture treatment, and we surveyed users of the LJMC and medical healthcare professionals associated with MVH.

In late 1999 to early 2000, we surveyed women attending the LJMC who experienced hot flushes resulting from treatment for breast cancer. This

informal survey (see Appendix 2) provided preliminary data about the frequency and nature of this condition. It also indicated that many women attending the Centre were interested in taking part in an acupuncture research project. This survey also provided a useful insight into the challenges of collecting hot flush data, and we used this experience to inform our later work.

We also surveyed health professionals at MVH to ask if they would refer patients to an acupuncture service (see Appendix 3). Of the ten oncologists and breast care nurses surveyed, seven responded, and four of these indicated that they would refer three or more patients a month. Many volunteered additional comments, which we took into account in the study design. For example, two respondents voiced concerns about needling into the arm on the side of the surgery (refer to section 5.13.2.3 on page 197 for a discussion of lymphoedema); others indicated the great need for a service to treat hot flushes.

3.7.2 Establishing treatment time

At the LJMC, patients having complementary therapy treatment receive this once a week, in treatment sessions usually lasting one hour. Our study design, especially that of Study 1: TA, adhered to this delivery model.

3.7.3 Establishing the "dose"

How many acupuncture sessions comprise a course of treatment? In Study 1 and Study 2, participants received eight sessions of acupuncture

as a course of treatment. We vigorously debated the number of sessions, especially as there were no guidelines in the literature for frequency and duration of treatment. (Proving the adequacy of the test treatment, with particular reference to the number of treatments required, is a problem that is well documented (Birch 2004, Lewith et al. 2002).)

A general rule of thumb for gynaecological conditions is to continue treatment for at least three months, before expecting to see significant changes in the condition (Maciocia, G, personal communication, 1998). I attempted to apply this "rule" to the original study design, stipulating that participants should receive 12 or 13 treatments on a weekly basis. This was at variance with the LJMC policy on the number of CAM treatments patients should receive. The Centre's research on its complementary therapies indicated that four treatments was the optimum number. This is a balance of a number of factors, including the patient's willingness or ability to attend, waiting lists, resources, and therapeutic benefit (Kite 1998). (It is widespread practice in the NHS to set limits on the number of CAM treatments, which are often set to between four and six. This rationing is due to a number of factors, including lack of evidence of the effectiveness of CAM therapies, lack of evidence of cost-effectiveness, and limited resources (House of Lords Select Committee on Science and Technology 2000, Thomson 2005, Smallwood and FreshMinds 2006). In some instances, such as in palliative and supportive care in cancer, there is evidence that patients may be unable or unwilling to attend for more than a minimum number of sessions (Kite et al. 1998).)

Convinced that four acupuncture treatments were insufficient to affect a problem as seemingly intractable as tamoxifen-related hot flushes, I argued determinedly for more treatments. We reached a compromise, agreeing, in the first instance, to test the effect of eight acupuncture sessions as a course of treatment.

3.7.4 Establishing the measurement points

Timing of the outcome measures was the subject of further debate. As appropriate for a before-and-after study, where outcomes are measured before and after an intervention (Deeks et al. 2003), we endeavoured to ensure appropriate baseline and end of treatment (EOT) measurement. The baseline measurement was a fortnight-long period, commencing on the day of joining the study (see Figure 9 above); the EOT measurement was the fortnight-long period commencing on the day of the eighth and last acupuncture treatment. This was the primary outcome measurement point.

We also wanted to measure any possible changes at the following points:

- Mid-treatment (Mid-tx) – as LJMC policies usually restricted CAM treatments to four sessions, it therefore seemed important to carry out measurements after the fourth treatment. This could provide data to help determine dose: if the change after four treatments was similar to that at EOT, there would be a potential rationale for reducing the number of sessions.

- Short-term follow-up – we wanted to see if changes, should there be any, had any lasting effect, both in the short and longer terms. Thus, we chose to apply the outcome measures again one month after the end of treatment. We hoped that this would measure whether the treatment had any short-term lasting effect, and we called this measurement point "Post tx 4".
- Long-term follow-up – this final measurement point, called "Post tx 18" was set at 18 weeks after the end of treatment. Again, in lieu of better data, this positioning was purely arbitrary. We were concerned that participants would lose their motivation to complete questionnaires as time from EOT increased. Our aim was to collect as much usable data as possible; hence, we chose not to have long-term measures six or twelve months after EOT. In addition, I was cautious about the length of time any changes would last. I hypothesised that acupuncture was a management intervention rather than a "cure". As long as the participants were taking tamoxifen, the hot flushes would continue. Thus, any alleviation of symptoms that occurred at EOT would be highly likely to return as time from EOT increased.

3.7.5 Establishing the number of participants

Although 20 participants is regarded as sufficient for an observational study (Sloan et al. 2001), we opted to recruit 50 participants. We did this because we wanted to gain as much experience as possible in recruiting participants, as well as to obtain a body of information about their opinions about having acupuncture treatment for their hot flushes. Furthermore, from my point of view as an acupuncturist, I wanted to

observe as many women as possible, to increase my clinical experience and understanding of hot flushes and how to treat them using acupuncture.

3.7.6 Summary of major decision points in the design

In this discussion, I have shown that we were required to make a number of design decisions based on little, or no, available evidence. Thus, we had to take risks. Some decisions, such as the number of acupuncture treatments, were a compromise between LJMC resource and policy restrictions and the ideals of best practice in acupuncture. We based other decisions, such as where to set measurement points, on experience of participation in other trials and our best guess of how long participants would remain interested in completing outcome measures. Only the experience of running the studies and evaluating the data would confirm the appropriateness of these decisions.

3.8 Methodology

This section discusses the overall methodology in terms of the practical clinical aspects of the two studies. I discuss details of certain specifics of each study (such as rationale for the style of acupuncture used, the acupuncture points used, and the delivery method) in Chapter 5 and Chapter 7. I discuss the statistical methodology in Chapter 4.

3.8.1 Protocol, ethics approval and funding

I submitted full protocols, conforming to NHS standards, to the Local Research Ethics Committee (LREC) for both studies, and attended LREC

meetings to defend the proposed studies. Table 5 below lists the documents supplied with each protocol, as appropriate to each study, and shows where to refer to these in the appendices.

Table 5 Documents submitted for each LREC application

Document Title	Study 1: TA	Study 2: NADA	In Appendix:
Protocol	X	X	4, 6
Patient Information Sheet	X	X	5, 7
Consent Form	X	X	8
Letter to Consultant and GP	X	X	9
Case History Questionnaire	X		24
Hot Flush Diary	X	X	pocket
Women's Health Questionnaire	X	X	10
Questionnaire: Subjective Measures of Hot Flushes and Night Sweats (subsequently known as the Hot Flushes & Night Sweats Questionnaire)	X	X	11
Follow-up letters and questionnaires (End of Treatment, 4 weeks and 18 weeks post- treatment)		X	14, 15, 16

I began recruitment to the studies after receiving approval from the LREC.

Dr Richard Ashford, Consultant Oncologist at the Cancer Treatment Centre at Mount Vernon Hospital, funded the clinical phases of both studies.

I provide further details about ethics approval and funding in the chapters describing the individual studies (Chapter 5 and Chapter 7).

3.8.2 Timing of the studies

The clinical phase of Study 1: TA ran from April 2001 through September 2002. The clinical phase of Study 2: NADA ran from September 2003 through December 2004.

These timings do not include preparation time (which started in 1999 for the TA study) or time for data input and analysis.

3.8.3 Research methodologies

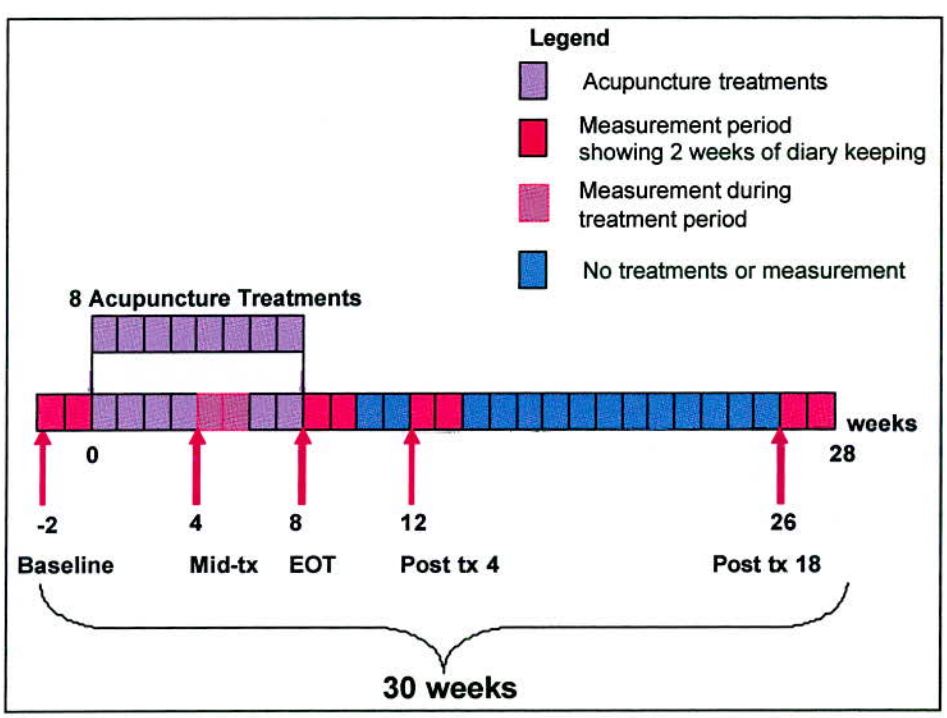
The overall acupuncture project used both quantitative and qualitative methods. This thesis focuses on the quantitative methodology and the results thereof. (As part of this study, I collected qualitative type data from participants using structured questionnaires. However, I did not apply a formal qualitative research methodology to the collection and analysis of this data. I plan to address this shortcoming in future studies.)

It is also usual LJMC research procedure to conduct qualitative research in the form of focus groups. Two colleagues from the Supportive Oncology Research Team (SORT) at the LJMC conducted focus groups for each of the study phases. The purpose was to gather qualitative data on participant perspectives of having acupuncture and taking part in a trial of acupuncture. I do not discuss the methodology of these focus groups in this thesis. However, I include the publication of the data from one of these focus groups in Appendix 31.

3.9 Outcome measures

We administered the outcome measures five times throughout the 30 weeks of the monitoring period for both studies. As previously discussed, the measurement points were at baseline, mid-treatment (Mid-tx, after the fourth treatment), at end of treatment (EOT), four weeks after EOT (Post tx 4) and 18 weeks after EOT (Post tx 18). Figure 10 below illustrates this sequence, and shows how the measurement points relate to the treatment period.

Figure 10 Diagram showing treatments and measurements over 30 weeks



3.9.1 Measuring hot flush frequency with diaries

The primary outcome measure was hot flush frequency and we chose to use paper-based hot flush diaries to collect this data. This section describes the diary, and discusses the rationale for its use.

3.9.1.1 Description of the hot flush diary

The diary, designed at the LJMC, takes the form of an A5 size booklet (see the example in the pocket at the back of Volume II). It allows for 24 hour-a-day recording, for a period of 14 days per diary. Each participant completed five diaries during the course of the study, potentially providing a total of 70 days of hot flush records per participant for analysis. To facilitate ease of input, we divided each day on the diary form into 12 two-hour intervals. An additional reason for this design was to collect data about the relationship of hot flush frequency to circadian rhythms, a sub-project we wish to conduct in the future (Carpenter et al. 2001, Freedman et al. 1995, Molnar 1981, Albright et al. 1989). Directions in the diary instruct the participant to denote each hot flush or night sweat with a tick mark in the relevant space for the day and time.

We also wanted to collect data on hot flush severity, and asked participants to give each incident a severity rating, using this code:

1. Mild
2. Moderate
3. Severe

The participants provided their own definition of these ratings, recording them on the second page of the diary. This practice of allowing participants to define subjectively the severity of their hot flushes has been used in several cancer-related hot flush studies (Sloan et al. 2001, Finck et al. 1998). The reliability of this method is a subject of debate

(National Institutes for Health 2004); our data will allow future comparison with other studies (Finck et al. 1998).

In addition, we asked participants to denote, on a weekly basis:

- Any out of the ordinary events during this period, such as holiday, illness, bereavement, change of circumstances, etc.
- Exposure to any temperature changes in this period, such as weather, living or work environment, holiday, etc.

We included these questions to monitor if there was any relationship between hot flush frequency and out of the ordinary events, or weather changes.

Finally, participants could record any additional comments on the back page of the diary.

3.9.1.2 Rationale for using diaries

A major debate in researching hot flushes focuses on how best to measure a phenomenon whose mechanisms are poorly understood, and whose manifestations are poorly defined (National Institutes for Health 2004). Researchers debate whether objective measures provide data that are more accurate than that from subjective self-reports (Carpenter 2004). Examples of objective measures include measuring finger temperature or sternal skin conductance to register elevations in temperature during hot flushes (Carpenter et al. 1999, Erlik et al. 1981, Freedman 1989). Webster (2004) also lists tests that measure respiratory exchange ratios, skin temperature, core body temperature,

and sweat rates as possible objective measures. However, these tests require equipment that is often expensive, and they require use in a controlled, laboratory environment. This restricts the monitoring time, and while these tests may provide accurate indications of hot flush frequency during time spent in the laboratory, they do not give information about "real-life" circumstances or longer-term patterns of flushing. Consequently, researchers are seeking to develop tools that allow "ambulatory monitoring", the ability to capture hot flush data as subjects go about their normal life activities (National Institutes for Health 2004, Carpenter et al. 1999).

"Self-reported" hot flush monitoring is a method that can be used in lieu of potentially expensive technological solutions. This requires study participants to count, or estimate, the number of hot flushes experienced in a given period. Self-reports are perceived by some to be inaccurate (Stone et al. 2002). Carpenter (1999) reports a 31-33% false-positive rate in subjective reporting of hot flushes when compared with objective (sternal skin conductance) measures, and she notes the problems with incomplete self reports at night as well as during waking hours (2004). On the other hand, researchers who conducted seven clinical studies into hot flushes at the Mayo Clinic argue that daily diaries exhibit consistency and reliability, with few missing data (Sloan et al. 2001).

Given the controversy in this area, and the "lack of standard, well-characterized instruments to collect self-reported data on hot flushes"

(National Institutes for Health 2004, p 23), we opted to use the self-report option of paper-based diaries. We investigated using Minidoc® electronic diaries, but these proved too expensive for our limited resources. In addition, Newton (2004) reports that (as of 2004) there was no published literature on using this type of technology for vasomotor symptoms, although an investigation into using this device for overactive bladder research demonstrated it was easy to use, comparable to paper diaries, and the data were quick to analyse (Quinn et al. 2003).

Once again, there is variation in the design of paper-based diaries. Some diaries ask subjects to summarise data at the end of the day, thus reducing the burden of paperwork (Sloan et al. 2001). Hunter's Hot Flush and Night Sweat Questionnaire (HFNSQ) asks subjects to estimate the number of vasomotor incidents in the past week (Hunter and Liao 1995). This leads to questions about the accuracy of recall (Newton 2004, Stone et al. 2002), and our experience of using this tool suggests that there is a discrepancy between the number estimated on the HFNSQ and the hot flush diaries, at least at baseline. We designed our diary to be completed at the time of each hot flush (categorised by Thurston as "ecological momentary assessments" because they are recorded in real time, in the subject's normal environment (National Institutes for Health 2004)). This raised concerns with our LREC about the burden of paperwork for participants. While many of our study participants found this method tedious, they also reported that this method helped them to better

understand their flushes, identify triggers, and monitor changes (Walker et al. 2005).

3.9.1.3 Defining the length of each measurement period

Another important design decision was the length of time the diary should cover. Again, there was little in the literature to inform our decision, and subsequent publications show a wide variety of opinions. Sloan and Loprinzi (2001) cite a one-week baseline period, and suggest that it may even be appropriate to use a single day of hot flush data to establish the baseline. This relies on having a relatively large number of participants (which they do not specify) in the study group, and they discuss the problems of demonstrating a reduction if a participant does not register any hot flushes on the day of baseline measurement. On the other hand, Dr Hunter, our external consultant, suggested that participants in hot flush studies have demonstrated a preference for constant monitoring (personal communication, 22 November 2000). After discussion with Dr Hunter, we chose to design the diaries to cover a two-week period, and observe participant compliance and reactions to this approach.

3.9.1.4 Summary of hot flush diary design

There were considerable challenges in choosing and designing an appropriate method to collect data about hot flushes, in a situation where the only agreement amongst researchers is that there is no validated instrument for this purpose (National Institutes for Health 2004, Sloan et al. 2001). I have discussed the decisions we made, and the rationale for

taking these decisions. Our next step was to test the design of the diary and evaluate how well it worked.

3.9.2 Measuring physical and emotional well-being

Secondary outcome measures focused on physical and emotional well-being. We used two questionnaires to collect these data: the Women's Health Questionnaire (WHQ) and the Hot Flush and Night Sweats Questionnaire (HFNSQ). This section describes these questionnaires, and discusses the rationale for their use.

3.9.2.1 Description of the Women's Health Questionnaire

The WHQ (see Appendix 10) is a validated health-related quality of life measure, designed to assess physical and emotional well-being in women from the ages of 45 – 65 going through the normal menopausal transition (Hunter 2003). The questionnaire is self-administered and takes about five minutes to complete.

The thirty-six statements of the WHQ fall into the following nine domains (the number of questions or items follows in brackets after the domain):

- Depressed mood (6 items)
- Somatic symptoms (7 items)
- Anxiety/fears (4 items)
- Vasomotor symptoms (2 items)
- Sleep problems (3 items)
- Sexual behaviour (3 items)
- Menstrual symptoms (4 items)

- Memory/concentration (3 items)
- Attractiveness (3 items).

It asks respondents to indicate their agreement with the statements using a four-point Likert scale:

- Yes, definitely
- Yes, sometimes
- No, not much
- No, not at all.

The responses are calculated according to the methods described in Section 4.9.5 on page 147. This results in a scoring system based on a ten-point scale from 0.00 to 1.00. Lower scores indicate better quality of life, and higher scores indicate symptoms that are more serious.

Test-retest reliability (0.78 to 0.96 across the nine domains) suggests that the WHQ is reliable across a two-week time interval. The Depressed Mood domain was validated against the General Health Questionnaire and the SF36 (mental health and vitality scales). The WHQ is sensitive to change, and Hunter proposes a meaningful clinically significant change on the sub-scales would be a difference of 0.10 to 0.20 (Hunter 2003).

The WHQ has been widely used since its development in the 1980s, in national and multi-national clinical trials, as well as studies of CAM. It is currently available in 27 country-specific versions, and allows for cross-cultural comparisons of menopausal experience (Newton 2004).

3.9.2.2 Rationale for using the WHQ

We selected the WHQ in preference to other available questionnaires for measuring health related quality of life during the menopause transition (Zollner et al. 2005). I assessed that its 36 questions, which cover a broad range of symptoms, correlate with changes an acupuncturist might expect to observe in a patient undergoing treatment for menopausal symptoms. Acupuncture patients often report that symptoms other than their main complaint improve with treatment. Consequently, they experience improved well-being (British Acupuncture Council 1999), and they "feel better in themselves" (Hicks et al. 2004, p. 337). It was our objective to collect data on a wide range of symptoms, and identify whether, and in what ways, this concept applied to women whose main complaint was hot flushes and night sweats.

In addition, its widespread application would give us data against which to compare our results.

3.9.2.3 Description of the Hot Flushes & Night Sweats Questionnaire

We used a validated questionnaire developed by Hunter and Liao (1995) to measure the subjective responses of women to their hot flushes and the impact of these incidents on their daily lives. In 2004, Dr Hunter named this the Hot Flushes and Night Sweats Questionnaire (HFNSQ) (Hunter et al. 2004); prior to that it had various appellations. During Study 1: TA, it was titled "Questionnaire: Subjective Measures of Hot Flushes & Night Sweats"; during Study 2: NADA, it was "Questionnaire: Hot Flush and Problem Rating Scale" (see examples in Appendix 11). I

will refer to it by its current name the Hot Flush and Night Sweats Questionnaire (HFNSQ) in the remainder of this thesis.

The questionnaire uses seven questions to examine three factors: frequency, problem, and coping/control. The frequency factor is the respondent's estimate of the number of hot flushes and night sweats (per day or per week) experienced over the previous week (questions 1 and 2). The problem factor (questions 3, 4, and 5) measures how much of a problem women see their vasomotor symptoms posing in their lives. Using ten-point scales, participants rate how much they regard their hot flushes and night sweats as a problem (problem), how much distress they cause (distress), and how much they interfere with daily life (interference). This provides the problem rating scale (PRS), which is the mean of the sum of these three scales. The coping/control factor (questions 6 and 7) measures how well women feel they are coping with their symptoms, and how much control they feel they have over them.

Test-retest reliability on the frequency and problem factors is highly reliable across a two to three week interval, with frequency measuring r = .82 ($p < 0.001$) and problem factors measuring r = .79 ($p<.01$) (Hunter and Liao 1995). The coping/control factor was unreliable ($r = -.01$, not significant) (Hunter and Liao 1995) and disappeared from Hunter's subsequent studies (Hunter and Liao 1996, Hunter et al. 2004).

3.9.2.4 Rationale for using the HFNSQ

Hunter uses the HFNSQ as a companion questionnaire to the WHQ, to collect hot flush frequency data and to determine the problem rating scale (PRS). As we used the diaries to gather frequency data, our interest was in the PRS. These data provide insight into how troublesome women find their hot flushes. Sensitive to change, the PRS would provide another measure of potential change in the study participants (Hunter and Liao 1995). The data can be compared with other studies that have used this measure (Hunter and Liao 1995, Hunter et al. 2004, Hunter and Liao 1996).

3.9.3 Additional questionnaires

I administered the hot flush diaries, WHQ and HFNSQ in "packages" that participants completed at each of the five measurement points of the study. I used additional questionnaires on a one-off basis. These included two questionnaires administered at baseline:

- Baseline Medical Questionnaire (BMQ) (Appendix 12)
- Sociodemographic Questionnaire (SDQ) (Appendix 13)

Three other questionnaires elicited end of treatment and follow-up information, and were the:

- Exit Questionnaire (EQ) administered at EOT (Appendix 14)
- Follow-up Questionnaire 1 (FQ1) administered at Post tx 4 (Appendix 15)
- Final Follow-up Questionnaire 2 (FFQ) administered at Post tx 18 (Appendix 16).

We designed these questionnaires in-house at the LJMC, based on questionnaires used in other research projects in which SORT was involved. They are not validated.

3.9.3.1 Baseline Medical Questionnaire (BMQ)

The BMQ collected information (including dates) about the participant's cancer diagnosis, treatments, tamoxifen regime, and history of Hormone Replacement Therapy (HRT). It recorded other health issues, as well as medications (both prescribed and over-the-counter) other than tamoxifen. Details of the participant's oncology consultant and their general practitioner were also recorded here.

3.9.3.2 Sociodemographic Questionnaire (SDQ)

I based the SDQ on similar questionnaires used in other studies carried out at the LJMC. It recorded data about the participant's marital status, employment status, education, and dependents. Home and car ownership were also recorded.

The BMQ and SDQ provided data about the profile of the participants. In addition, as a practitioner I used the information collected on the BMQ to gain insight into each participant's cancer background and to gain a better understanding of her experience.

3.9.3.3 End of treatment and follow-up questionnaires

I used three questionnaires to collect qualitative data written by the participants themselves. They were administered as part of the packages delivered at EOT (the EQ), Post tx 4 and Post tx 18 (the FQ1

and FFQ). The design included both closed and open-ended questions, to elicit feedback about how the women felt about having acupuncture, as well as to monitor their impressions of the effect of the acupuncture treatment on their hot flushes as well as their general health. These questionnaires also provided a means of identifying whether participants had changed their medication during the follow-up period, and whether they had opted to have further acupuncture treatment, either for their hot flushes or for other health conditions.

3.10 Setting and participants

This study focused on women who had treatment for early breast cancer at the Cancer Treatment Centre (CTC) at Mount Vernon Hospital (MVH), or at one of the 15 district general hospitals associated with the CTC at MVH (as discussed in section 1.6.1 starting on page 11). It reflects the responses of the women in this geographic area, and thus the findings may not be generalisable to a wider population (see the discussions in section 6.3.1.1 on page 202 and section 8.3.1.1 on page 275). We also designed the study to meet the available resources and the needs of the LJMC, which had a focus on using complementary therapies in the supportive care of cancer patients.

3.10.1 Inclusion criteria

Within this context, we recruited women to the study as they presented, provided they met the inclusion and exclusion criteria. Participants needed to meet the following inclusion criteria:

- Be female, minimum age 35

- Be in otherwise good health
- Have a prognosis of at least six months
- Have been taking tamoxifen for a minimum of six months as an adjuvant treatment for breast cancer
- Be six months since completing active anti-cancer treatment for breast cancer (e.g. surgery, adjuvant chemotherapy, or radiotherapy)
- Have been experiencing hot flushes and/or night sweats for a minimum of three months, and to be self-reporting at least four in a 24-hour period (irrespective of the time of day)
- Have had no change in medication (including over-the-counter medicines) aimed at controlling menopausal-like side effects in the previous 3 months. This includes remedies such as low-dose progesterone, Clonidine, homeopathic remedies, herbal remedies such as agnus castus, black cohosh, sage, dong qua, and liquorice, and natural remedies such as evening primrose oil
- Be able to speak, read and understand English
- Read and sign the informed consent form after the nature of the study has been fully explained.

3.10.1.1 Rationale for the inclusion criteria

We set these criteria to establish as stable a basis as possible from which to measure any effects of the acupuncture treatment. Thus, we felt it was important for participants to recover from the demands of active cancer treatment (surgery, radiotherapy, and/or chemotherapy) before joining the study. In addition, we felt it important that potential participants had taken tamoxifen for a period of time: women are often advised by their

healthcare professionals that the hot flushes will diminish over time (Love and Feyzi 1993). We judged that six months was a reasonable time for the flushes to settle.

We did not exclude women who were already taking medications for their hot flushes. Instead, we endeavoured to create a stable basis, to ensure that any changes occurring during the course of study were attributable, as far as is possible, to the acupuncture treatment. Thus, we set three months as a duration we thought was reasonable for the effects of a medication to take effect and stabilise. We set the same time length of three months for women who had ceased taking medications, in order to ensure a generous washout period.

The hot flush count of four per 24-hour period was based on patient self-report, prior to taking the baseline measurement.

It was essential that women had been under the care of an oncology consultant who had a base at the MVH CTC, although the women may have received all or part of their cancer treatment elsewhere within the Mount Vernon Cancer Network.

It is important to note that although we stipulated that participants be "in otherwise good health", we did not exclude women who had other health issues. Thus, the studies included women with a range of chronic and complex health conditions, including cardiovascular disease, stroke,

clinical depression, chronic fatigue, and bladder problems. This reflects a "real-world" situation, where women with breast cancer have other (often pre-existing) health conditions (Greenhalgh 2001, pages 61 - 62). In addition, many participants also had interventions such as breast reconstruction or bladder surgery during the course of their acupuncture treatment, another "real-life" factor in treating patients with complex, chronic medical conditions.

3.10.2 Exclusion criteria

At the outset, we thought women experiencing any of the following were unsuitable for the study:

- A history of prolonged blood clotting times, for example, taking anti-coagulants or very low platelet counts
- Needle phobia
- Pregnancy.

3.10.2.1 Comments on the exclusion criteria

In fact, these criteria were inappropriate. Anti-coagulants are not a contraindication for acupuncture, although care must be exercised when needling patients taking such medications (Wheeler and Werth 2006, Filshie 2001, Tavares 2003, Sciammarella 2006). Low platelet counts were unlikely in the women with early breast cancer for whom this study was intended. Furthermore, pregnancy is not a contraindication for

acupuncture[7] and few of the women considered for our study were likely to be, or become, pregnant. As for needle phobia, women whose fear of needles was problematic either excluded themselves, or attempted to overcome their apprehension.

These criteria were included because of the nervousness of medical professionals about the invasiveness of acupuncture. In fact, it would have been more appropriate to state clearly that advanced, metastatic breast cancer was an exclusion criterion.

3.11 Recruitment and consent

3.11.1 Recruitment channels

We recruited participants via a number of channels. Oncology consultants, breast care nurses, or other health care professionals within the Mount Vernon Cancer Network could refer patients, as could staff at the LJMC. In addition, women could self-refer. I also contacted the women who completed the survey on hot flushes in 1999 (as discussed in section 3.7.1, page 90 above) and who expressed an interest in having acupuncture to invite them to participate.

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[7] Acupuncture is generally regarded as a safe procedure during pregnancy, provided the acupuncturist is properly trained and qualified. See Betts, D (2006) *The essential guide to acupuncture in pregnancy and childbirth.* Hove: The Journal of Chinese Medicine Ltd. and West, Z (2001) *Acupuncture in pregnancy and childbirth.* Edinburgh: Churchill Livingstone.

At the outset of each study, I wrote to the oncology consultants at MVH and to the breast care nurses in the district general hospitals informing them of the study and inviting them to refer any patients who met the entry criteria. I included a Patient Information Sheet (see Appendix 5 and Appendix 7), a package of leaflets advertising the study (the leaflet for Study 2: NADA can be found in the pocket at the back of Volume II), and a laminated "quick guide" to the inclusion/exclusion criteria. I provided LJMC staff with "Screening Checklist" forms (see Appendix 17) so that they could assess a woman's eligibility before referring her to the study.

3.11.2 Initial screening of prospective participants

Upon receiving a referral, I contacted the potential participant, usually by telephone. I assessed (or reassessed) her eligibility using the Screening Checklist, and explained the study. If she expressed interest in participating, I made an appointment for an intake interview, and sent a confirmation of this appointment along with a Patient Information Sheet. I asked her to read this before coming for her appointment.

We did not provide incentives for taking part, nor were consultants or any other person given any reward for referring women into the study.

At the intake interview, I reviewed the study with the potential participant, answering any queries she might have. Once any questions and concerns were addressed, and it was clear the woman understood the study, I asked her to sign a consent form (Appendix 8). Once I obtained consent, I assigned a study number to that participant. I then gave her

the first package of questionnaires, of which she filled in the Sociodemographic Questionnaire, the WHQ and the HFNSQ in private. I collected the data for the Baseline Medical Questionnaire by asking the participant the questions. After explaining how to fill in the Hot Flush Diary, I made the appointment for the first session in two weeks time. The woman departed with her diary, which she would fill in during the intervening fortnight. I sent a letter informing of her participation in the study to her oncology consultant, with a copy to her GP (see Appendix 9).

This process completed the Referral, Eligibility Assessment, and Complete Questionnaires stages of the study as shown on the Acupuncture Study Flow Diagram in Figure 9 on page 85 above.

3.12 Conclusion

In this chapter, I presented the overall design of the two studies. I discussed the history, including the initial design for a randomised controlled study, and the challenges we faced in attempting to conduct such a study. Drawing on the Medical Research Council's guidelines, I set out the rationale for conducting single-arm observational studies in the early stages of evaluating complex interventions. I have discussed a number of decisions that the design team had to make, including number of treatments. In lieu of existing evidence, these decisions were often the result of practical considerations, compromise, or best judgement based on previous similar experience.

I have also discussed the outcome measures used, and the rationale for their selection for these studies. The setting for the study and the recruitment and consent procedures are also explained. This chapter focused on the design of the study, and aspects of the methodology for recruitment. I provide details of the methodology for the acupuncture treatments and their delivery in Chapter 5 and Chapter 7. In the next chapter, I discuss the methodology for collecting, inputting, and analysing the data.

Chapter 4 Statistical Methods and Analysis

4.1 Synopsis

In this chapter, I present the methodology used for handling quantitative data and the subsequent statistical analysis. I explain the processes used for collecting, inputting and preparing the data for analysis, and discuss the methods for handling missing data. I then discuss the challenges we faced in developing an appropriate statistical approach, explaining the rationale for analysing the data. The data from each of the outcome measures required different strategies for analysis, and I detail the approaches used for the hot flush frequency data, the Women's Health Questionnaire (WHQ) data, and the Hot Flushes and Night Sweats Questionnaire (HFNSQ) data.

4.2 Introduction

In a quantitative research project, statistical analysis plays a major role. In this chapter, I focus on the statistical analysis used to handle the data gathered in this study. I would like to emphasise that I am not a statistician, and the following discussion lays out my learning process in handling this aspect of the research.

4.3 The data management team

The team involved in the data handling and analysis processes included myself, the research co-ordinator (Teresa Young from LJMC), the statistical consultant (Richard Atkins from Thames Valley University), and

the research assistant (Ann Ashton from the LJMC). I refer to the activities for which each individual was responsible in the discussion below. I use "we" to denote actions or decisions taken jointly, and this usually refers to the research co-ordinator and me.

4.4 Data collection

Each of the 50 participants who completed the course of treatment in each study was required to complete a total of 20 diaries and questionnaires during the study. This resulted in the collection of over 1,000 documents for each study. Table 6 shows the questionnaires administered to each participant.

Table 6 Questionnaires administered per participant

Questionnaire	No. administered
Baseline Medical Questionnaire (BMQ)	1
Sociodemographic Questionnaire (SDQ)	1
Hot Flush Diary	5
Women's Health Questionnaire (WHQ)	5
Hot Flush & Night Sweat Questionnaire (HFNSQ)	5
Exit Questionnaire (EQ)	1
Follow-up Questionnaire 1 (FQ1)	1
Final Follow-up Questionnaire (FFQ)	1
Total questionnaires per participant	**20**

To manage this large dataset, we employed a variety of administration and collection strategies, which I will now describe.

4.4.1 Colour coding the questionnaires

I adopted a colour coding scheme to ensure the questionnaires from each measurement point were easily differentiated. This made it easier to manage and administer the large numbers of documents. I printed questionnaires and diaries for each measurement point on coloured paper, as denoted in Table 7 below.

Table 7 Colour coding of questionnaires

Measurement point	Colours for Study 1: TA	Colours for Study 2: NADA
Baseline	Pink	Light blue
Mid tx	Yellow	Light green
EOT	Light green	Dark green
Post tx 4	Peach	Dark blue
Post tx 18	Lilac	Orange

I have also noted this colour coding on the flow diagrams for the two studies, in Figure 23 on page 180 and Figure 35 on page 255.

4.4.2 Collecting the baseline data

I administered the Baseline Medical Questionnaire (BMQ) first, completing this in discussion with the participant at the intake interview. I then left the participant to complete the Sociodemographic Questionnaire (SDQ), as well as her first Women's Health Questionnaire (WHQ) and Hot Flushes and Night Sweats Questionnaire (HFNSQ) on her own. The participant took away her first hot flush diary, which she filled in during the fortnight between the intake interview and the first treatment. At that first treatment, after some discussion with the participant about the nature and

pattern of her hot flushes, I filed the diary in the participant's notes, where it remained until the data input stage.

4.4.3 Collecting the mid-treatment data

At mid-treatment, the participant took the WHQ and HFNSQ home for completion, along with her second hot flush diary. She returned the WHQ and HFNSQ at the next treatment (Treatment 5). She returned the diary at the appointment following its completion. In the TA study, I asked participants to return these at the treatment a fortnight after it was administered (Treatment 6). This meant that, in most cases, the final day was not completed. In the NADA study, I adjusted this slightly to allow for completion of the 14th and final day, and participants returned it at the session three weeks from the start of keeping that diary (Treatment 7). Again, I filed these documents in the participant's file until the data input stage.

4.4.4 Collecting EOT data

At the end of the eighth and final treatment, I gave the participant her end-of-treatment (EOT) questionnaires and diary. I advised her that this package included a new, extra questionnaire (the Exit Questionnaire). I included a stamped addressed envelope (SAE), and gave instructions to post these back to the LJMC when completed. I also discussed the remaining measurement points, to remind the participant that monitoring her flushes was an ongoing process over the next 20 weeks.

At this treatment, I also gave participants the British Acupuncture Council's leaflet "How can acupuncture help you?" (in the pocket at the back of Volume II), along with instructions on how to find a qualified acupuncturist should they wish to have further treatment. I asked participants not to seek further acupuncture treatment until they had completed and returned the package of questionnaires delivered at four weeks after EOT (Post tx 4). This meant there would be a six-week period during which no further acupuncture treatment would take place. (In developing the design, we discussed asking participants to refrain from having acupuncture until the end of the total follow-up period, that is, until the end of Post tx 18. However, as hot flushes cause such distress, we felt it important that participants were free to find relief for their discomfort, using acupuncture if that was their choice. Follow-up questionnaires monitored whether participants chose to have further acupuncture treatment, and I report this in section 6.6.2.1 starting on page 229, and section 8.6.2.1 starting on page 301).

4.4.5 Collecting follow-up data

I posted the two follow-up packages (Post tx 4 and Post tx 18) of questionnaires at the appropriate times, enclosing an SAE and a covering letter specifying when to start keeping the diary and how to return the questionnaires. For Study 1: TA, the SAE was addressed to the Research Sister; in Study 2: NADA, the SAE was addressed to the Research Assistant. In practice, however, I collected the returned items and filed them in the participant's notes, keeping a log of all the returned and non-returned items. In the event that questionnaires were not

returned or missing, I followed-up with the participants in Study 1, and the research assistant followed up missing documents in Study 2.

4.4.6 Notes on completing the questionnaires

4.4.6.1 Hot flush diaries

The diaries collected the data for the primary outcome measure, hot flush frequency. Thus, they were the most important tool for data collection used in the study, and it was important that participants complete them correctly. At the intake interview, I took care to talk participants through the instructions, to ensure that they understood clearly how to complete the diaries.

I modified the diary design slightly for Study 2. As well as improving the layout of the diary, I adjusted the instructions to ask participants to mark any two-hour periods in which they did not experience a vasomotor incident with a "0". This was to facilitate data entry, making it clear to the research assistant that the participant had a flush-free period, and had not merely forgotten to record incidents during that time. This also provided a useful visual aid for identifying flush-free periods, facilitating quick identification of any changes in the flushing frequency or pattern.

4.4.6.2 The WHQ and HFNSQ

In Study 2, I explicitly instructed participants that the WHQ was double-sided, as some Study 1 participants had neglected to fill in the final page of the questionnaire.

I modified the layout of the HFNSQ for Study 2 to make it easier for participants to follow the instructions and use the 10-point scales (see Appendix 11).

4.5 Data transfer and preparation

This section describes the process of data entry and the three stages of transformation: from raw data to untransformed summary data (USD) to transformed data.

4.5.1 Roles and responsibilities

I entered all data for Study 1 except the Exit Questionnaire (EQ), Follow-up Questionnaire 1 (FQ1) and the Final Follow-up Questionnaire (FFQ). The research co-ordinator felt that this was a useful learning experience for me, to develop my understanding of the data transfer process, as well as to identify any patterns in the participants' hot flushes. I conducted this data input activity some months after the end of the Study 1 clinical phase. The research assistant entered all the data for Study 2, as well as the questionnaires I did not enter for Study 1, as listed above.

In both studies, the research co-ordinator supervised the data entry. We discussed any ambivalent items to identify the most objective approach for handling these. She also carried out random checks to verify the accuracy of the data input. We used coding to identify missing data:

- "99" denoted that data were missing from questionnaires received (for example, a participant not recording some flushing incidents,

perhaps due to illness or forgetfulness; or a participant neglecting to fill in the last page of the WHQ)

- "88" denoted that a participant had formally withdrawn from a study and had therefore not completed questionnaires.

4.5.2 Managing the "raw data" for hot flush frequency

We collected a huge volume of data, especially from the diaries. The diary was designed to collect data by two-hourly intervals over 14 days, and was administered five times for each participant. This amounted to a potential 840 entries of hot flush frequency data for each participant, with a total of over 45,000 pieces of this type of data for each of the two studies (Walker et al. 2005). I refer to these data as "raw data".

We transferred this raw data to computer using forms designed by the research co-ordinator in Microsoft Access 2000. She then exported the data to the software package SPSS (Statistical Package for the Social Services) for data cleaning and analysis. Interim analyses used SPSS version 11; final analyses used version 13.

4.5.3 Creating untransformed summary data (USD)

The research co-ordinator carried out various interim analyses for dissemination at conferences (see abstracts in Appendix 30). For these, she generated summary data variables. These were a single value summarising the number of flushes per day for each fourteen-day period for each participant (mean and median). She based all analyses on

these means and medians, and we refer to these data as "untransformed summary data" (USD).

4.5.4 Creating transformed data

Under the supervision of the research co-ordinator and the statistical consultant, I executed the final quantitative data analysis presented in this thesis. The consultant identified that the USD were not normally distributed, and advised that it was appropriate to perform "log transformations" to normalise the data and allow for parametric testing. I discuss this below (see 4.8.2 Logarithmic transformations), and refer to this data as "transformed data".

4.6 Handling missing data

Although we collected large amounts of data, there were incidents where individual data items from returned questionnaires were missing, and when entire questionnaires were missing. In Quality of Life studies, the former is termed "item non-response", and the latter is termed "unit (questionnaire) non-response" (Fairclough 2005). It is important to distinguish between these two types of missing data, and to develop appropriate strategies for handling them. This section discusses missing data and the approaches we adopted for dealing with it.

4.6.1 Item non-response: imputing the data

One way to handle item non-response is to impute the missing values (Fayers et al. 2001, Fairclough 2005, Armitage et al. 2002). This process involves "imputing" or estimating the missing value by calculating the

score based on the items that are completed. There are two prerequisites for using this approach.

Firstly, the item non-responses must be missing at random. Fayers et al (2001) argue that it can be difficult to establish whether an item is missing accidentally or for a particular reason (for example, a respondent who feels ambivalent about a particular issue may avoid answering a related question), but they suggest that it is likely that most missing items occur completely at random. Entering the data for Study 1: TA myself provided the opportunity to identify any possible patterns of missing data. My observations, as well as subsequent examination of the missing data at the final analysis stage, suggest that data were likely to be missing at random.

Overall, the participants were diligent in completing diaries and questionnaires, and for Study 1, only 8.4% of hot flush frequency data were missing (Walker et al. 2005). Typically, participants missed entering data if they had an acute illness, were undergoing surgery and were in hospital, or during random incidents of being busy or on holiday. The participant usually signalled these incidents in her diary, explaining the reason. Data missing from the WHQ also appeared to be missing completely at random. Some participants sometimes overlooked a question, and at least one failed to complete the final page of the WHQ in Study 1.

Once we established, as far as possible, that data were missing completely at random, it was possible to impute the missing data variables. Following the precedents used in Quality of Life studies, the research co-ordinator applied the following rule: where at least half of the values are available, the missing values are assumed to have values equal to the mean of those that are completed (Fairclough 2005, Fayers et al. 2001). We discussed this procedure with the statistics consultant, who confirmed that it was appropriate and robust.

In practical terms, this means that for each participant diary, there is a possible fourteen days worth of data. Each day is divided into 12 data points, each of which represents a two-hour period of a 24-hour day. SPSS calculated the number of valid values, with "99" and "88" denoting missing values. Missing values tagged "99" were imputed providing that at least seven of that day's values were present (that is, over half the data for that day, or more than six of the twelve data points). The mean of the existing data points was used to impute the missing data points in the database. In cases where there were six or fewer of the possible twelve data points, the research co-ordinator labelled the corrected mean "99", and it was excluded from the subsequent analyses.

The sum of these results across all twelve two-hour periods for each day gave the "Corrected Daily Total". The fourteen daily totals for each participant were then averaged to provide two important sets of data - the "Corrected Mean per Day" and the "Corrected Median per Day. The

research co-ordinator used these data, the "untransformed summary data" (USD), for all interim analyses of the data. I used the Corrected Median per Day data as the basis for the final analyses. I chose to use the medians, rather than the means, because of the wide standard deviations for the means, as shown in Table 9 on page 132. We discussed this with the statistical consultant, who confirmed that this was appropriate.

The research co-ordinator did not apply these calculations to missing values labelled "88". These generally denoted participants who had withdrawn from the study. Thus, entire questionnaires were missing at any given measurement point, and these are handled as unit (questionnaire) non-response.

4.6.2 Unit (questionnaire) non-response

The next stage was to establish the strategy for dealing with unit (questionnaire) non-response. In Study 1, four of the initial 54 recruits did not complete the study, and of these, only two completed the baseline data. Six of the remaining 50 participants failed to complete all the questionnaires at every measurement point, with a total of ten of their diaries missing. Similarly, in Study 2, four of the 54 recruits did not complete the study. Thirteen of the remaining 50 participants failed to complete all questionnaires, with 17 of their diaries missing. Some of these missing data were coded "88" to denote that entire questionnaires were missing because the participants had formally withdrawn from the study. Others were coded "99" because the questionnaires were missing

for some other reason (often, participants failed to return the final set of questionnaires). In these situations, we could not impute the missing data.

We decided to apply the following rules to the data:

- The primary outcome measurement point was the change between baseline and EOT, as proposed in the initial protocols
- We would monitor the longer-term effects of treatment at Post tx 4 (four weeks after EOT) and Post tx 18 (18 weeks after the end of treatment). However, we formulated our hypotheses on the EOT results; the data from these longer-term measurement points would be indicative only.

Our next step was to decide on the number of participants on which to base the analysis. Should we focus only on the participants whose data sets were complete across all five-measurement points? Alternatively, should we analyse the maximum number of participants at each time point, regardless of their missing data at other time points?

We decided to use the maximum data possible for the primary measure (that is, EOT) and chose not to exclude participants whose data might be missing at the other measurement points. We analysed each of the other measurement points using all available valid data for that measurement point, whether or not data was missing for a particular participant at a different measurement point.

This course of action is justified if there are no significant differences at baseline between the data for participants with complete sets of frequency data for all five measurement points and the data from participants with missing data at particular measurement points. To establish this, we compared the baseline frequencies for participants having all diaries present with the frequencies for those with some diaries missing. We conducted unpaired t tests, and as Table 8 below shows, there were no significant differences between those with complete or incomplete sets.

Table 8 Unpaired t tests for participants with all diaries and those with diaries missing

Study	t =	df	p = *
Study 1: TA	1.2	50	0.25
Study 2: NADA	-0.4	49	0.72

* Significance (2-tailed)

The impact of this decision is that there are minor variations in the descriptive data. This varies according to the number of participants used in a particular calculation (as seen in the data presented in Table 9 on page 132). However, we believe the impact of these discrepancies is very small.

4.7 Describing the data

After establishing the strategies for dealing with missing data, the next step was to describe the data. I explored the data in SPSS to determine statistical information including the means, medians, confidence intervals, standard deviations, minimum and maximum values, and range for each

measurement point in each of the two studies. Table 9 below presents these data for hot flush frequency, showing hot flush frequency at baseline and EOT for both studies.

Table 9 Descriptive statistics for Studies 1 & 2 showing Baseline and EOT

	Study 1: TA				Study 2: NADA			
	Baseline (n = 52)		EOT (n = 48)		Baseline (n = 51)		EOT (n = 47)	
	Statistic	Std Error	Statistic	Std Error	Statistic	Std Error	Statistic	Std Error
Mean	10.35	.89	6.48	.77	10.66	.68	7.68	.69
95% CI Lower	8.56		4.93		9.29		6.30	
95% CI Upper	12.33		8.03		12.03		9.06	
Median	9.00		4.75		10.00		6.50	
Std Deviation	6.41		5.34		4.88		4.71	
Minimum	2.5		1.00		2.0		1.0	
Maximum	35.0		21.00		23.0		19.0	
Range	32.5		20.00		21.0		18.0	
Skewness	1.67	.33	1.38	.34	0.65	.33	.89	.35

As well as showing the means and medians for each measurement point, this descriptive information presents interesting data about the minimum and maximum number of flushes recorded at each point. Additionally, it shows there is a positive skew to the data, and this is the first indication that the distribution of the data is not normal. This was a major factor in determining how to analyse the data.

Figure 11 and Figure 12 below display histograms confirming this skew. They show that the hot flush frequency data for Study 1 do not follow a symmetrical, or normal, distribution curve. The smooth line on each diagram shows the curve a normal distribution would follow.

Figure 11 Histogram showing distribution of frequencies at baseline (TA)

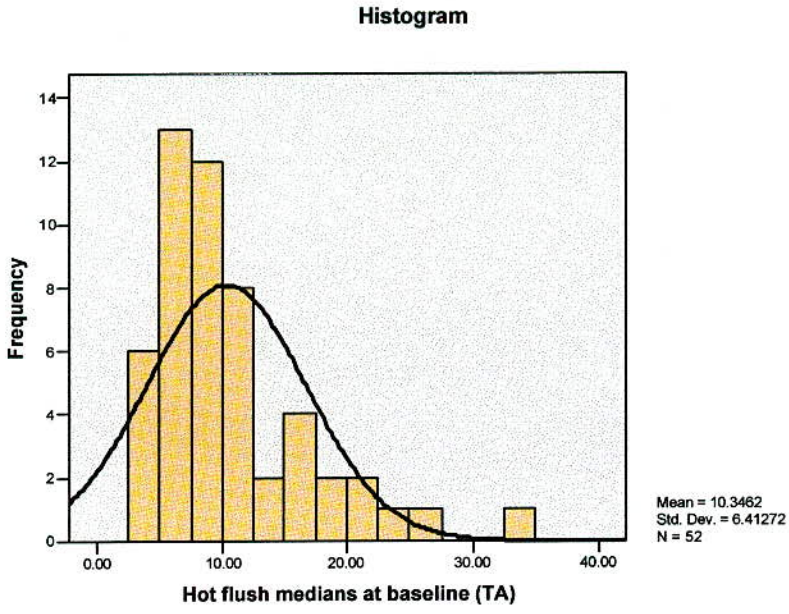


Figure 12 Histogram showing distribution of frequencies at EOT (TA)

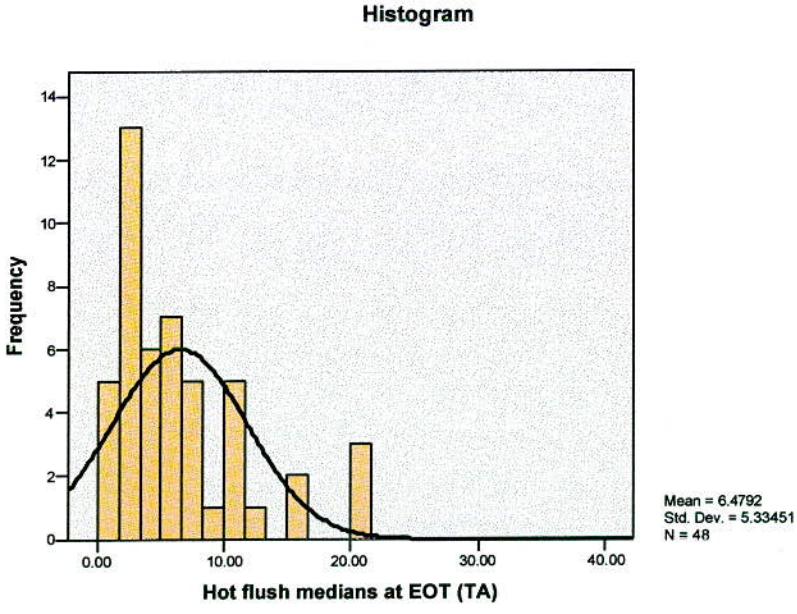


Figure 13 and Figure 14 below display a similar situation with the data for Study 2. Although the data at baseline (Figure 13) corresponds more closely with a normal distribution, they are skewed at EOT (Figure 14).

Figure 13 Histogram showing distribution of frequencies at baseline (NADA)

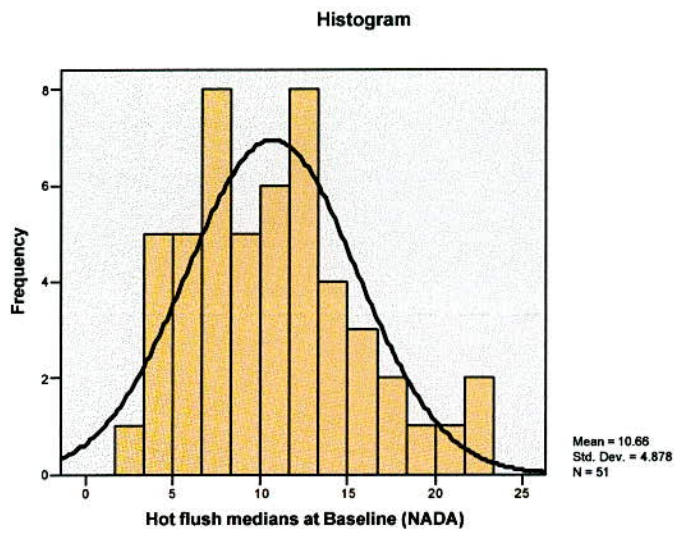
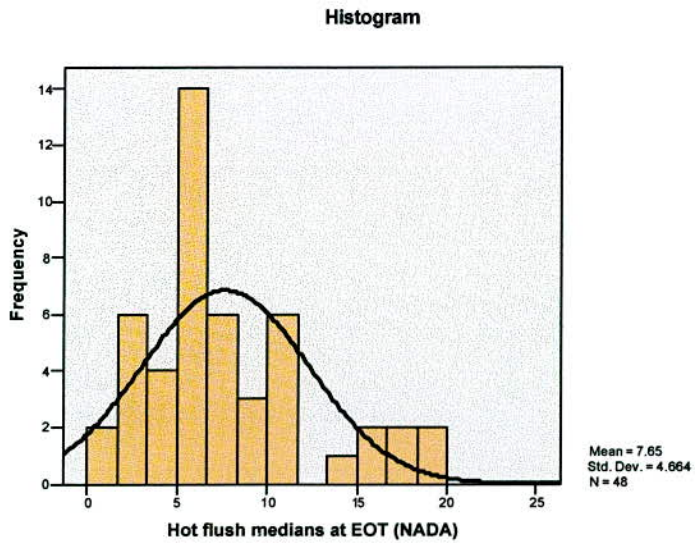


Figure 14 Histogram showing distribution of frequencies at EOT (NADA)



Overall, the distributions are positively skewed, meaning that most of the data values, including the median, fall to the left of the mean (Jaisingh 2000). This type of distribution requires that data are analysed using non-parametric tests. These are less robust than parametric tests and provide a less satisfactory statistical analysis than does working with observations that follow a normal distribution curve and can be analysed using parametric tests (Gore 1982, Greenhalgh 2001, Hill and Lewicki 2006). Therefore, it is desirable to find a way to "normalise" the data and so facilitate the use of parametric testing.

4.8 Developing the strategy for analysing the data

For early dissemination of the results, the research co-ordinator carried out interim analyses using the means and non-parametric testing (see abstracts in Appendix 30). Subsequent consultation with the statistical consultant helped us to understand better how to handle the data to obtain the most meaningful and robust results.

Firstly, the consultant identified the raw data as "rate data" (Atkins, personal communication, 13 June 2005). This is defined as the "*number of times* that an *event* happens in a *fixed period of time*" (Harris and Taylor 2004). Applying this definition to the hot flush frequency data, we can see that the diaries recorded the *number of times* that *hot flushes* (an event) happened in a *two-week period* (a fixed period of time). By definition, rate data follows a skewed distribution. In our study, the distribution is likely to be positively skewed: hot flush frequency data is

restricted to positive values (that is, a woman cannot record a negative event) that vary over a wide range, for example, from 0 to 40 per day in Study 1, as shown in Table 10 below (Armitage et al. 2002).

Table 10 Hot flush frequencies at baseline (raw data)

Study	N =	Minimum	Maximum	Range
Study 1: TA	52	0	40	40
Study 2: NADA	51	0	27	27

4.8.1 Identifying the appropriate transformation

Skewed data can sometimes be transformed to give a normal, smooth distribution curve, and thereby facilitate parametric testing (Greenhalgh 2001; Atkins R, personal communication by letter, 14 January 2005, Gore 1982). Thus, the consultant conducted a number of exploratory plots on the data in order to identify an appropriate transformation. Using Q-Q (quantile-quantile) plots allows distribution of a given variable (in this case, hot flush frequency) to be compared with a theoretical normal distribution (Archambault 2000). From the shape (see Figure 15 and Figure 16 below on page 138), the consultant identified the data to be a lognormal distribution (Atkins, R, personal communication by letter, 14 January 2005).

4.8.2 Logarithmic transformations

Given this situation, it is statistically appropriate to analyse the data after performing a process called logarithmic (or log) transformation (or transform) (Armitage et al. 2002). This valid process normalises datasets with a lognormal distribution (Harris and Taylor 2004,

Greenhalgh 2001). Its logic is that "when numbers are multiplied together, their logs are added" and "when a series of numbers increases by a constant multiplying factor, their logs must increase by a constant difference" (Armitage et al. 2002). This means that although the median data have a positive skew, using the logarithms of the variables will result in a normal or symmetric distribution. This allows parametric tests to be conducted on the data. (Refer to Appendix 18 for a detailed explanation of logarithms).

The Q-Q plots on the following page illustrate this. Looking at data from Study 1, the baseline (Figure 15) and EOT (Figure 16) plots show that the measurements do not follow the theoretical normal distribution, indicated by the straight line in each plot.

Figure 15 Q-Q Plot showing hot flush frequency distribution at baseline (TA Study)

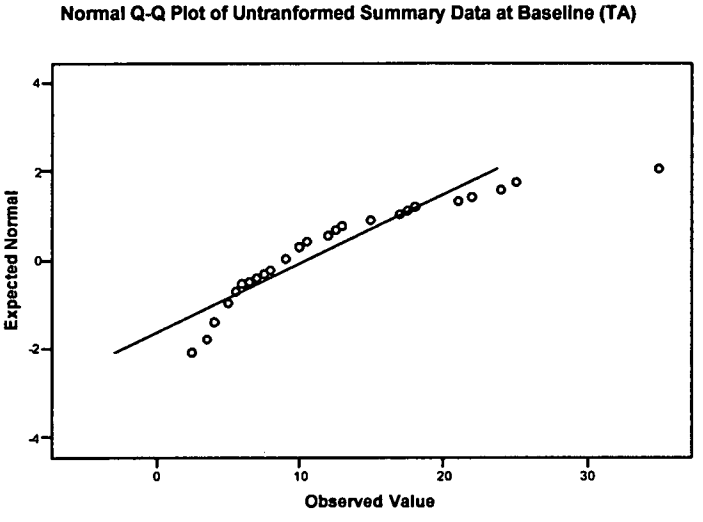
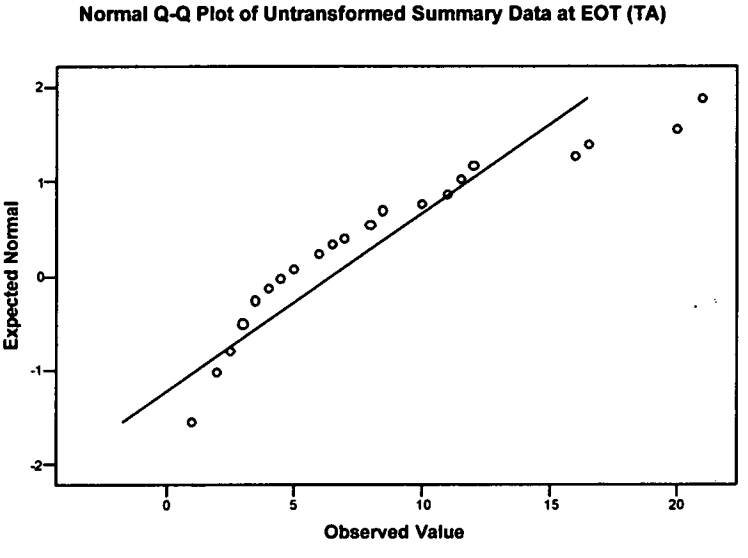


Figure 16 Q-Q Plot showing hot flush frequency distribution at EOT (TA Study)



If we compare these two plots with Q-Q plots showing these data after they have been log transformed (Figure 17 and Figure 18 below), we see how the log transformation normalises the data. The results in these plots cluster quite neatly along the line indicating normal distribution.

Figure 17 Q-Q Plot showing log transformed data at baseline (TA Study)

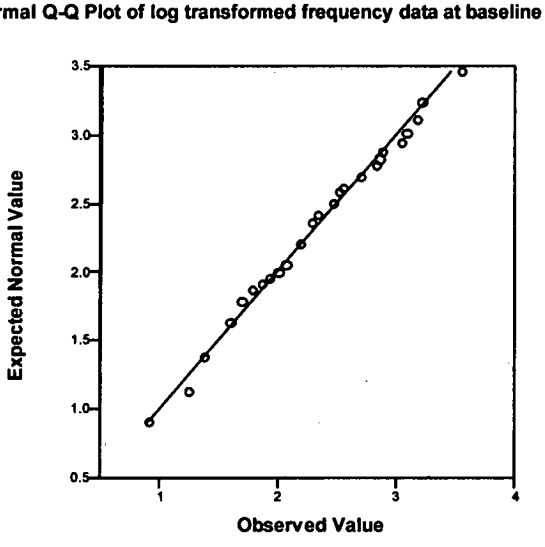
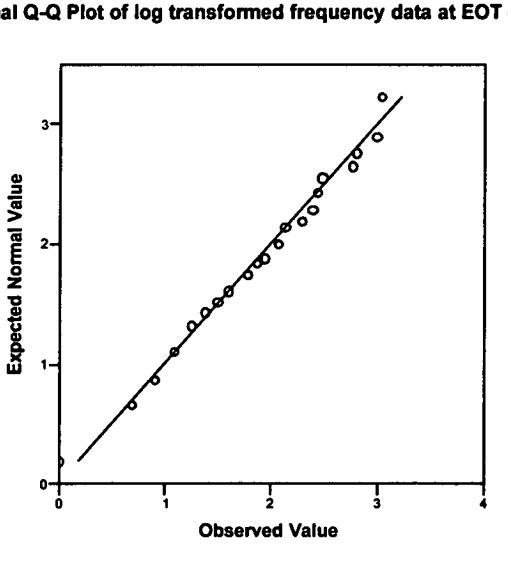


Figure 18 Q-Q Plot showing log transformed data at EOT (TA Study)



Thus, we can see graphically how log transformations normalise the data.

4.8.2.1 Further rationale for using log transformations

As well as being mathematically and statistically correct, there is another reason for using log transformations. This relates to the most useful way to present the data – both statistically and clinically. Our interim analyses used untransformed summary data (USD), and provided results in terms of overall average reduction in the score. For example, Study 1: TA, showed a reduction of a mean number of flushes from 10.75 per day at baseline to 6.5 per day at EOT (de Valois et al. 2003), while Study 2: NADA showed a reduction from a mean of 10.3 at baseline to 7.2 at EOT (de Valois et al. 2004). Whilst statistically correct, these figures do not provide helpful clinical data. Knowing that she can expect an average reduction of four or three hot flushes per day is not particularly helpful to the woman who suffers 20 or 30 daily incidents. Nor is it appropriate to a woman who experiences fewer than four or three per day at baseline (it is impossible for her to have a negative number of hot flushes!). Thus, a method that allows presentation of percentage reductions compared to baseline provides a more meaningful and clinically useful way of talking about the results, whilst remaining statistically robust (Atkins, R, personal communication by letter, 14 January 2005).

Using log transformations facilitates this approach. In mathematical terms, this shifts the interpretation from an arithmetic to a geometric reduction. This allows us to look at the change in hot flush frequency scores in relation to the baseline scores. It provides a proportional representation that shows the geometric reduction in relation to the

baseline scores, rather than reducing the figure to a simple arithmetic figure for all women regardless of their baseline frequency score (Atkins, R, personal communication by email, 16 June 2005).

Interestingly, this geometric analysis accords more closely to the goals of traditional acupuncture, which seeks to see each patient as an individual. The possibility of discussing a patient's possible prognosis in terms of a percentage reduction that relates to her particular number of flushes helps to "individualise" the statistics and may make them more relevant to the individual patient as well as the practitioner.

4.8.2.2 Further analysis

Further analysis of the data is possible, and this requires advanced levels of statistical training, which are outside of the scope of this thesis. Pending the availability of this level of statistical expertise (as well as the necessary funding), we would seek to apply these advanced techniques to the data. For example, it is appropriate to perform repeated measures (also known as longitudinal or serial data) analysis on this type of data. The hot flush data were collected successively on the participants, and the objective of the measurement points was to show change over time. However, repeated measures analysis is highly complex (Armitage et al. 2002). After initial investigation on our part, we agreed that this was beyond the range of skills available for this study. With sufficient resources, we would seek to use this method for future research in this area.

4.8.3 Analysing the hot flush frequency data

We established the nature of the data, and identified the data to analyse. The next step was to carry out the analysis. I have discussed the rationale for log transforming the data, and I will now describe the process.

In carrying out the log transformation, I used the SPSS "COMPUTE" function to calculate the log (mean) at baseline and each of the other four time points for each participant. I then ran paired samples t tests using the transformed data.

I manually back transformed the resulting means and their confidence intervals, using the "antilog" features on a scientific calculator. I then used these figures to calculate the proportional result, using the following equation:

$$\%\ change\ at\ EOT = \left[1 - \frac{1}{Baseline / EOT}\right] \times 100$$

The resulting figure is the proportional reduction in hot flushes that a participant might expect from her baseline score, and I report these in section 6.4.1.6 on page 210 and section 8.4.1.6 on page 283.

4.8.4 Analysing the hot flush severity data

Severity data is lacking in studies of the use of acupuncture to manage hot flushes related to cancer treatment (Smith J. et al. 2005). We collected these data in our studies, but did not use them during the

interim analyses. Resource constraints including time, money, and access to appropriate statistical expertise made it difficult to deal with this data in-house. Collaboration with the Psychology Department at the University of Hertfordshire provided the opportunity to access a resource and appropriate expertise to analyse this data. This work is ongoing as a separate project and will be reported outside of this thesis.

4.9 Analysing the WHQ data

4.9.1 Background to the analyses of the WHQ data

The MAPI Research Institute[8] publishes a user manual giving instructions on how to manage and analyse data from the Women's Health Questionnaire (Girod et al. 2004). We followed these instructions for the final analysis of the WHQ data presented in this thesis.

However, these were not available for the earliest interim analysis of the data for Study 1 (de Valois et al. 2003), which we analysed following Hunter's early instructions (Hunter 1992). (For consistency, we used these early instructions for the interim analyses of the WHQ data for Study 2 (de Valois et al. 2005).) This particularly affects the handling of missing data. In the interim analyses, the research co-ordinator imputed the missing data according to the procedures described above for hot flush frequency. The *WHQ User Manual* prescribes a different process,

[8] The Mapi Research Institute, an international company based in Paris, specialises in the linguistic validation of patient-reported and clinical assessments to promote their international use. Refer to the MAPI website at <http://www.mapi-research.fr>.

which we used for this final analysis and which I discuss below. However, the difference in the results was minimal.

4.9.2 Description of the WHQ

As discussed previously in section 3.9.2.1 starting on page 104, the WHQ comprises nine domains, covering 37 items. Table 11 provides a brief overview of the items in each domain, as well as the number of items per domain. It also summarises the content of each item. Refer to Appendix 10 for the full questionnaire.

Table 11 Summary of items in each domain of the WHQ

Domain	Code	No. of items	WHQ Item No.	Item content (Hunter 1992)
Depressed mood	DEP	7	3	Miserable and sad
			5	Loss of interest
			7	Lack of enjoyment *
			8	Life not worth living
			10	Loss of appetite *
			12	Irritability
			25	Reduced well-being *
Somatic symptoms	SOM	7	14	Headaches
			15	Tiredness
			16	Dizzy spells
			18	Backache/pains in limbs
			23	Sickness/nausea
			30	Pins and needles in hands and feet
			35	Urinary frequency
Memory/concentration	MEM	3	20	Clumsiness
			33	Difficulty in concentrating
			36	Poor memory
Vasomotor symptoms	VAS	2	19	Hot flushes
			27	Night sweats
Anxiety/fears	ANX	4	2	Panicky feelings
			4	Anxiety leaving the house
			6	Palpitations
			9	Tension
Sexual behaviour	SEX	3	24	Loss of interest
			31	Dissatisfaction * [a]
			34	Vaginal dryness [a]
Sleep problems	SLE	3	1	Early wakening
			11	Restlessness
			29	Insomnia
Menstrual symptoms	MEN	4	17	Breast tenderness
			22	Abdominal cramps
			26	Heavy bleeding [a]
			28	Bloatedness
Attractiveness	ATT	2	21	Not lively *
			32	Feeling unattractive *

- * Denotes items that are reversed for scoring. See the discussion on item reversal that follows
- [a] Denotes items that are omitted if the symptom does not apply to the respondent's condition

The WHQ has undergone development and refinement during the time of this study. Consequently, there are some minor disparities in publications about the number of items in the WHQ in total, and the number of items in some of the sub-scales, in particular depressed mood and attractiveness. Although the WHQ is generally reported to have 36 items, it actually comprises 37 items (Hunter 1992, Girod et al. 2004). Item 13 ("I worry about growing old") is not factored into the scoring (Hunter 1992, Girod et al. 2004), nor is Item 37 which asks respondents to identify

which, if any, of the symptoms presented on the questionnaire they find it difficult to cope with. Therefore, the scoring is based on 35 questions in total. There are also some disparities in the numbers of items in each sub-scale. In her early work, Hunter analyses depressed mood using six items, and attractiveness relies on two items (Hunter 1992); in later work, depressed mood still uses six items but attractiveness uses three (Hunter 2003). However we have followed the instructions in the *WHQ User Manual*, which lists seven items for depressed mood, and two for attractiveness (Girod et al. 2004).

4.9.3 WHQ data preparation

As previously noted, I input the WHQ data for Study 1, and the research assistant input the data for Study 2. We used forms designed by the research co-ordinator in Microsoft Access 2000. The research co-ordinator exported the data into SPSS, which we used for the analyses.

4.9.4 Handling missing data

The *WHQ User Manual* prescribes the procedures for handling missing data (Girod et al. 2004). It provides a score table for each domain, and identifies the number of items needed to calculate the score for that domain. For example, the domain "depressed mood" comprises seven items; a score cannot be calculated if responses to more than two of the items are missing. I used these instructions to prepare the data for the final analysis presented in this thesis.

4.9.5 Scoring the WHQ

4.9.5.1 WHQ scoring system

Responses to the WHQ are based on a four-point Likert scale, with the following values:

1. Yes definitely
2. Yes sometimes
3. No, rarely
4. No, not at all.

Scoring the WHQ involves reducing these scales to binary options (0/1). "Yes definitely" and "yes sometimes" are scored as 1; "no not much" and "no not at all" are scored as 0. The item scores are grouped into their relevant domains, as indicated in Table 11 above.

4.9.5.2 Item reversal

Table 11 also shows the items for which scores need to be reversed, as some items on the questionnaire are worded to avoid the over-use of negative phrasing. In Study 1, we handled this reversal at data entry, when I reversed the scores for the relevant questions as I entered them. In Study 2, the research assistant entered the scores as they appeared on the questionnaires, and we reversed these scores when we prepared the data.

4.9.5.3 Calculating the score per domain

Data preparation for the WHQ consists of reducing and grouping the data, ensuring the relevant items are reversed, and handling missing

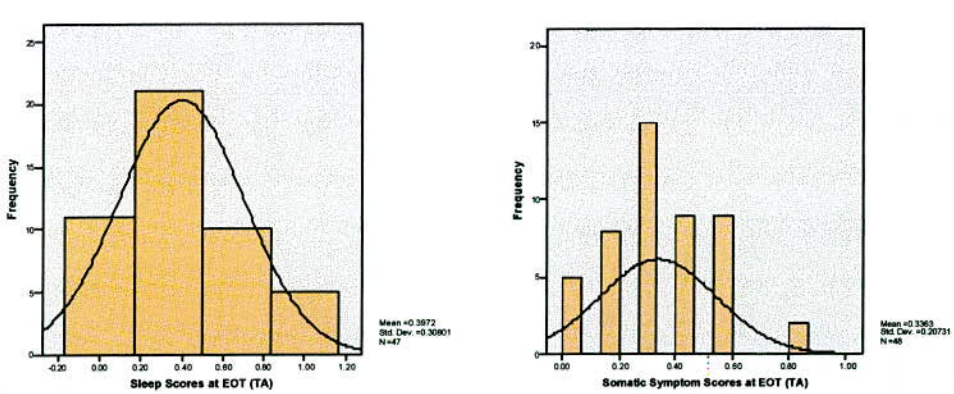
data. On completion of these procedures, the data scores are calculated according to the following equation:

$$Domain\ Score = \frac{Sum\ of\ the\ reduced\ items}{Total\ number\ of\ items\ in\ the\ Domain}$$

4.9.5.4 Identifying the distribution

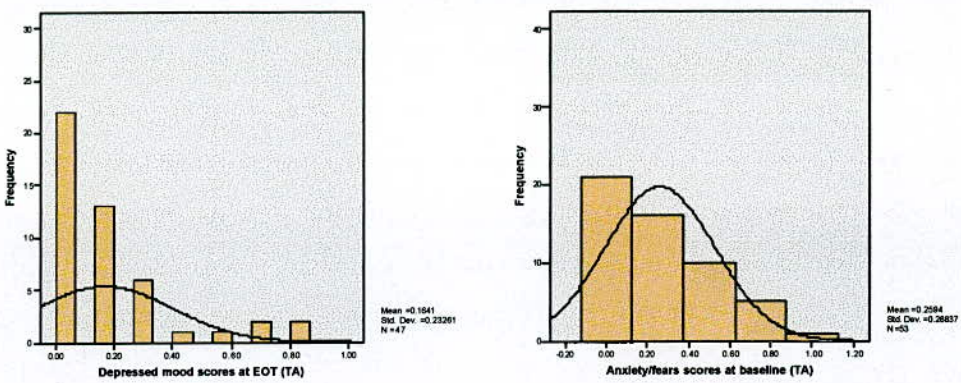
As discussed previously, it is important to identify the distribution of the data in order to determine the appropriate statistical tests. After cleaning and scoring the data, and handling missing data according to the procedures discussed above, I explored the data in SPSS. I produced histograms for each domain to ascertain the distribution of the scores over the five measurement points. The histograms showed a variety of normal and skewed results. For example, histograms for Somatic Symptoms and Sleep (Figure 19 below) displayed normal or near-normal distribution curves.

Figure 19 Histograms showing near normal distributions of WHQ scores



Other histograms showed skewed distributions, as in the Depressed Mood and Anxiety/fear scores in Figure 20 below.

Figure 20 Histogram showing skewed distribution of WHQ scores



Theses variations in distributions posed the question of how best to analyse these data.

In Hunter's development of the WHQ, she found that scores for depressed mood and sexual behaviour were slightly skewed, but that analysis of log transformations for these scales gave similar results to non-transformed scores (Hunter 1992). Thus, her analyses use non-transformed scores and parametric tests.

One of our aims was to be able to compare WHQ data with results from the numerous studies using this questionnaire. For this reason, we wanted to analyse the data following the methodology used in these other studies. To check the appropriateness of this for our data, we ran parametric and non-parametric tests on the untransformed WHQ data for Study 1 and Study 2. Our results (in Appendix 19) showed these two approaches produced different results for only one domain in one of the

studies. This was Depressed Mood at EOT in Study 1: TA. Consequently, we proceeded to use parametric tests for our analyses.

4.9.5.5 Somatic Symptoms sub-analysis

We presented our data to Dr Hunter for comment. She suggested that we conduct a sub-analysis of the items in the Somatic Symptoms domain. This would identify any specific symptoms that the treatment appeared to help reduce. I present the results of this sub-analysis, as well as those of the WHQ as a whole, in section 6.5 starting on page 212 and in section 8.5 starting on page 285.

4.10 Analysing the HFNSQ data

As discussed previously in section 3.9.2.3, starting on page 106, the Hot Flushes and Night Sweats Questionnaire (HFNSQ) has had a number of name changes over the years during which this study has been in progress. Changing titles notwithstanding, the questionnaire examines three factors: frequency, problem, and coping/control.

The frequency factor is based on the respondent's *estimate* (my italics) of the number of hot flushes and night sweats (per day or per week) experienced over the previous week. The problem factor is based on the mean of three ten-point scales, rating the extent to which the incidents are seen to be a problem, the distress they cause, and the extent to which they interfere with daily life. The coping/control factor is the mean of two ten-point scales that ask the respondent how well she feels she is

coping with the symptoms, and how much control she feels she has over them.

Of these, we chose to analyse only the problem factor, which gives the problem rating scale (PRS). We excluded the frequency factor, as we felt that the diaries provided more extensive (and possibly more accurate data) about the frequency of vasomotor incidents. However, it may be interesting to analyse and compare the baseline data for the frequency as reported on the HFNSQ and the diaries at a later date. This might provide interesting insights into how many hot flushes and night sweats women *feel* they have (provided by their *estimates* on the HFNSQ) and the number they *actually* experience (recorded on the diaries). It is useful to remember that the baseline measurement is the one time that the participants would fill in the HFNSQ before keeping a diary, so they would have little or no urge to make the frequency counts match at that stage.

We excluded the coping/control factor from the analysis, as its test-retest reliability was unreliable in the validation of the questionnaire. As previously discussed, Hunter uses this factor only in her early work (Hunter and Liao 1995) and not in subsequent or more recent publications (Hunter and Liao 1996, Hunter et al. 2004).

Unlike the WHQ, there is little discussion in the literature about how to analyse the HFNSQ (Hunter 1992). I prepared the data, and calculated the PRS. To do this, I used SPSS to calculate the mean of the 10-point

Likert scales for questions 3, 4, and 5 of the HFNSQ. These questions ask the women to state the extent that hot flushes are a problem, cause distress, and interfere with daily life (see the HFNSQ in Appendix 11). I explored the distribution of the mean scores in SPSS. As in the WHQ, the histograms showed both normal and skewed distributions across the five measurement points. I then applied both parametric and non-parametric tests to the means. The results were similar in all cases (see Appendix 20), and I use parametric tests in the results reported in Table 33 on page 227 and in Table 53 on page 299. Adopting this approach allows for direct comparison with Dr. Hunter's study results.

4.11 Conclusion

In this chapter, I discussed the statistical methodology used to analyse the quantitative data collected in these studies. I described the data collection, administration and preparation processes, as well as the strategies for handling missing data and analysing hot flush frequency. I have presented the rationale for using log transformations to normalise these data and allow for parametric testing. Finally, I have detailed the processes used to analyse the WHQ and HFNSQ data.

In the next chapter, I turn my attention to the specifics of Study 1: TA, where I discuss the traditional acupuncture methodology used in the study.

Chapter 5 Design & Methodology Specific to Study 1: TA

5.1 Synopsis

In this chapter, I discuss the rationale for conducting Study 1: Traditional Acupuncture (TA) and the design and methodology specific to this study. After introducing the study, I discuss the evidence for using acupuncture to treat natural menopause symptoms, and how this informed the development of a protocol for treating tamoxifen-induced symptoms. The chapter details the rationale for developing treatment principles, point selection, and procedures for administering the treatment. Co-interventions, such as moxibustion and lifestyle advice, are covered, as are highlights of the experience developed through treating 50 women using this approach.

5.2 A note on STRICTA reporting guidelines

Although this is not a controlled study, I report the details of Study 1: TA observing the guidelines specified for reporting acupuncture studies in the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (MacPherson et al. 2001). Appendix 21 presents the topics covered by these guidelines. This ensures thorough coverage of important aspects of acupuncture procedure, and makes possible future comprehensive comparison with other acupuncture studies that observe these guidelines.

5.3 Background to Study 1: TA

Study 1: TA was the result of my attempts to introduce an acupuncture service at the Lynda Jackson Macmillan Centre (LJMC), and the medical director's stipulation that new services needed to be evaluated (as discussed in section 1.4, starting on page 7). We identified the need for a complementary therapy service to treat tamoxifen-related hot flushes. In the first instance, personnel working in the LJMC drop-in identified this, reporting that one of the most frequently asked questions by women attending the Centre was how to deal with tamoxifen-related hot flushes. We confirmed this need by conducting an informal survey of women attending the Centre, and by polling medical professionals treating women with breast cancer (as discussed in section 3.7.1 on page 90). Once we identified and confirmed the need, the next step was to establish the rationale for using traditional acupuncture to treat this cancer treatment side effect.

5.4 Funding

Dr Richard Ashford, Consultant Clinical Oncologist at the Cancer Treatment Centre, Mount Vernon Hospital, provided the funding for the clinical aspect of this study. The LJMC funded the development of the study, as well as the analysis of the data. Thames Valley University funded the development of research and academic skills.

5.5 Ethics Approval

The West Hertfordshire Hospitals NHS Trust Local Research Ethics Committee granted ethical approval on 5th March 2001 (Neal D, personal communication by letter).

5.6 Establishing the rationale for using TA

As discussed in section 2.8, starting on page 69, there was scant literature on the subject of using acupuncture to manage tamoxifen-related hot flushes. In this section, I discuss the rationale for using TA for treating these symptoms. Thus, I began investigating the use of TA to treat the hot flushes and night sweats that are a symptom of natural menopause.

5.6.1 Examining the literature for using TA to treat the symptoms of natural menopause

5.6.1.1 Textbooks and journals

Natural menopause is a condition recognised in the canon of Chinese medicine, and many authors discuss using acupuncture to manage the associated symptoms, including hot flushes and night sweats. In his chapter devoted to the treatment of menopausal syndrome, Maciocia (Maciocia 1998) lists seven different syndrome patterns commonly associated with the menopause. Hot flushes manifest in six of these syndromes, and night sweats are associated with five of these. Lyttleton discusses four syndromes associated with the menopause, of which one explicitly cites "flushing in the face (especially after midday) and

sweating" (1990, p 7). Textbooks by Ross (1995), Low (1990), Deadman (1998) and Gascoigne (2001) also discuss the treatment of hot flushes associated with the menopause, whilst several authors cite points for treating night sweats (Deadman et al. 1998 pp 217 - 219, 346 -348, Ross 1995 p 277, Maciocia 1998 p 744).

5.6.1.2 Clinical trials for natural menopause symptoms

Five trials investigating the use of acupuncture to treat symptoms of the natural menopause were conducted and published prior to 1999, and therefore prior to the start of our Study 1 (Acupuncture Research Resource Centre 1999). Of these, three specifically discuss treatment of hot flushes and/or night sweats. Wyon's randomised controlled trial (RCT) comparing electro-acupuncture (n=11) with superficial needling (n=10) yielded a 50% decrease in frequency of flushes in both groups, as well as showing decreased symptoms measured on the Kupperman Menopausal Index (Acupuncture Research Resource Centre 1999). (The paper was published in Swedish (Wyon et al. 1994), and abstracts in English do not discuss the range of hot flushes experienced by the study participants.) Grilli et al (1989) conducted an RCT comparing three groups of 15 women each, with one group receiving acupuncture, the second receiving HRT, and the third receiving no treatment. The study showed comparable changes in the levels of hormones (including an increase in oestradiol) in the acupuncture and HRT groups, with additional hormonal changes in the acupuncture group. The paper, published in a mixture of French and Italian, states that hot flushes ("*vampate*") and sweats ("*sudorazioni*") disappeared, although it does not

discuss the methodology used to measure these. The paper states that the symptoms returned over time and recommends at least monthly treatments to maintain the therapeutic result (Grilli et al. 1989). Di Conchetto's uncontrolled study followed 100 women experiencing hot flushes for two years. Treated with acupuncture and moxibustion (see Glossary) consistently over two years, 85 patients had clinically favourable results, with 20 reporting complete remission of symptoms (Di Conchetto 1989). This paper, published in French, is not explicit about the methods used for measuring outcomes.

Poor reporting of these studies leaves many questions about methods and outcome measures unanswered. This criticism also applies to papers reporting research conducted in China. In a study of 300 cases of menopausal syndrome treated by acupuncture, the authors report "cure" in 153 cases. However, it is difficult to understand the measures used. Although the study mentions night sweat (sic) it does not mention hot flushing, and the outcomes seem to focus on improvements in "psychosis" (Wu and Zhou 1998). Another Chinese study compared a group treated with acupuncture and "ear therapy" (n=30) with a group treated with estriol (n= 26) to manage "menopausal syndrome", which included symptoms such as "afternoon fever" and "profuse sweating". Both groups improved, but the acupuncture group showed greater improvement, it improved more quickly, and did not report any side effects. The authors conclude that the results of this small study merited further research (Ji et al. 1998).

5.6.1.3 Summary and the next question

At the time of setting up Study 1: TA, the evidence for the use of acupuncture to treat symptoms relating to natural menopause was sketchy, but suggested the possibility of positive results. Furthermore, the range of textbooks and authors discussing treatment of this condition suggested that clinically, this was routine treatment. My next question was "is it possible to apply the Chinese Medicine (CM) theories for treating the hot flushes and night sweats associated with natural menopause to those that are pharmaceutically, or more specifically, tamoxifen-induced?"

5.7 Developing the TA protocol

5.7.1 Researching contemporary TA practice

To answer this question, my first step was to contact eminent acupuncturists, mainly in the UK, to ask about their experience of treating tamoxifen-related hot flushes. Several expressed the view that acupuncture would have little or no effect against this drug-induced condition (Hicks, A, personal communication, 9 September 1999). Success would not be good, as tamoxifen was "very powerful" (Mole, P, personal communication, 9 September 1999). As the side effects are "not comparable to a 'normal' menopause", treatment is more difficult because the acupuncturist is "constantly working against something that is negating your treatment" (Maciocia, G, personal communication by email, 26 October 1999).

In spite of these discouraging views, Maciocia predicted that it should be possible to achieve a 50% improvement in seven sessions (personal communication by email, 26 October 1999). Terje Alræk of the University of Bergen suggested several acupuncture points useful in treating hot flushes, based on his experience of treating a small number of patients in Norway (personal communication by email, 22 January 2001).

Thus, in 1999 to 2000, as I was preparing this study, there was little evidence and little encouragement for the success of this venture. Perhaps instinctively, I felt that acupuncture could address this problem. My curiosity was piqued, and I was eager to explore this challenging issue. Clutching the only encouragement I received ("you don't know what you can do until you are doing it!" (Firebrace, P, personal communication, 9 September 1999)), I persevered, and began to develop an acupuncture protocol for treating tamoxifen-related hot flushes and night sweats.

5.7.2 Planning a treatment strategy

5.7.2.1 Overall strategy for the protocol

Experienced acupuncture colleagues took the view that tamoxifen was very difficult to work against. Therefore, I wanted my overall strategy to have at its heart a two-part core protocol. The first part of this core protocol would comprise a standardised treatment, designed to counteract the power of the tamoxifen. The second part would be tailored to meet the needs of the individual.

At the time of designing the study, this seemed like a radical approach. A common expectation in acupuncture research (especially Western medical acupuncture) was to use a standard, or optimum, treatment applying the same acupuncture points ("formula acupuncture") for each patient (Webster-Harrison et al. 2002, Linde et al. 1996, White et al. 2001). The pros and cons of this approach are the subject of continued debate in acupuncture research (Hogeboom et al. 2001, MacPherson 2000), and acupuncture studies are still criticised if they do not adhere to a standardised treatment (Smith J. et al. 2005). However, as a traditional acupuncturist, I valued the concept of individualised treatment, and wanted the protocol to include "points for the patient". This created a tension for me as researcher-practitioner: the researcher was intrigued by the effect a standardised approach might have; the practitioner endeavoured to stay true to the philosophy of individualised treatments. (It is interesting to note that there is a movement towards designing acupuncture research studies to reflect the diversity of the individual acupuncturists and their patients, and even to encompass many styles of acupuncture within one study (MacPherson 2006).)

The intention in my design was to use a core approach to combat the tamoxifen, whilst retaining the freedom to individualise treatment and meet the other specific needs of the patient. This is how I evolved the specifics of the protocol.

5.7.2.2 Main sources

As discussed, at the time of setting up the study, there was little information available about how to treat tamoxifen-related hot flushes and night sweats. I drew on my training as an integrated acupuncturist (see section 1.10, starting on page 21) to develop the protocol. My main sources included the theories of Five Element Constitutional Acupuncture (FECA) as taught at the College of Integrated Chinese Medicine (and subsequently published by Hicks et al (2004), the textbooks of Maciocia (1989, 1998) and Deadman et al (1998), and the practical information I gleaned from personal contact with acupuncturists in the UK, China, and Norway.

5.7.2.3 Identifying the syndromes

Maciocia was my main source for identifying the syndromes relating to tamoxifen-induced hot flushes. His assessment was that tamoxifen side effects could "be assumed to be mostly a Kidney-Yin deficiency and Damp-Heat" (personal communication by email, 26 October 1999). Alræk, speaking from his experience of a small number of cancer patients with hot flushes, identified the presence of Damp and Heat (personal communication by email, 22 January 2001). Beyond this, there was little helpful information. Tukmachi identified deficiencies of liver yin, heart blood, and kidney yin, with the yin deficiencies leading to excess fire and a consequent uprising of liver yang (2000a, 2000b). However, this diagnosis appears to relate to natural menopausal symptoms, rather than being specifically tamoxifen-related.

Armed with this scant information, I investigated the literature relating to hot flushes associated with natural menopause. My primary source, Maciocia, regards kidney essence deficiency as the root of menopausal problems. He identifies kidney yin deficiency, kidney yang deficiency, or a combination of both as common menopausal patterns that manifest hot flushes and night sweats as a symptom (Maciocia 1998). Lyttleton also associates these syndromes with natural menopause, but only cites flushing and sweating as symptoms of kidney yin deficiency and combined kidney yin and yang deficiency (Lyttleton 1990). Wu and Zhu (1998) express a similar view. Zell et al (2000) discuss the prevalence of diagnoses of kidney yin deficiency in postmenopausal women in their small study to evaluate Traditional Chinese Medicine (TCM) methods of diagnosis.

Many papers discussing the use of acupuncture to treat the symptoms of natural menopause do not identify syndromes according to CM. Consequently, it was necessary to rely heavily on texts on CM and on the advice of acupuncturists with experience of treating menopausal hot flushes.

5.7.2.4 Developing the treatment strategy

The information I gathered about treating hot flushes, due to both natural menopause and as a side effect of tamoxifen, informed the treatment strategy I developed. This consisted of:

- A core protocol, comprising two steps:
    - Step 1: Test for and treat Aggressive Energy (administered in

the first treatment)

- Step 2: Treat hot flushes and night sweats (the basis for treatments two through eight)

- Points for the individual.

This approach draws on the theories and practice of both the eight-principles and Five Element Constitutional Acupuncture (FECA) models of acupuncture.

Step 1: Testing and treating Aggressive Energy (the AE Drain)

The first step in my protocol drew on the theory and practice of FECA, and involved clearing a block to treatment called Aggressive Energy (AE). The concept of blocks to treatment plays an important role in Five Element theory, which identifies main four blocks. These are Aggressive Energy, Possession, Husband-Wife Imbalance, and Entry-Exit blocks (Flaws 1988, Hicks et al. 2004). Each of these blocks has its own characteristics, aetiology, pathology, and treatment protocol. However, one important shared characteristic is the concept that their presence can have a "profoundly negative effect on the patient's physical or psychological health unless they are cleared" (Hicks et al. 2004 p. 227). In Five Element theory, blocks impede treatment, and if not cleared, they may cause deterioration in health.

The aetiology of Aggressive Energy indicated that an AE Drain was appropriate as part of a protocol for women experiencing the side effects of breast cancer treatment. A person who has had any of the following may be disposed to having AE:

- Serious or life-threatening illness
- History of intensive drug therapy
- Intense emotions over a period of time (Hicks et al. 2004).

These predisposing factors are all likely to be present in women undergoing treatment for breast cancer, which is obviously a serious, life-threatening disease. Regardless of their treatment regime, these women will have had some intensive exposure to pharmaceutical drugs – from the anaesthetics and antibiotics for surgery through chemotherapy drugs and the related steroids to tamoxifen itself (as well as anti-depressants and other pharmaceuticals in many cases). Furthermore, as one of the Western world's most feared diseases, patients are likely to experience many intense emotions from the time of diagnosis, including shock, fear, worry, anxiety, grief, and anger (Drew and Fawcett 2002, Regnard and Kindlen 2002, Sawyer 2000). CM theory classifies these emotions as internal causes of disease; when intense or prolonged they can lead to imbalances in health and well-being (Hicks et al. 2004, Maciocia 1989, Ross 1995).

In terms of practice, FECA practitioners commonly perform an AE Drain as a first treatment (Gordon 1998, Hicks et al. 2004). This is because AE may be present without manifesting signs and symptoms, and from a FECA perspective, it makes sense to test for AE (and clear it if it is present) before commencing further treatment. This eliminates the possibility of AE being a block to further treatment. As discussed, the

participants were predisposed to the factors contributing to AE, and this indicated that an AE Drain was an appropriate and vital part of a protocol for treating women experiencing tamoxifen side effects.

Having chosen this procedure as the first step of the treatment, I went on to develop the strategy to counteract the effects of tamoxifen itself.

Step 2: Treating hot flushes and night sweats due to tamoxifen

As mentioned previously, I drew on the information I gathered from textbooks and practitioners to develop the protocol. The second step of the core protocol focused specifically on counteracting the hot flushes and night sweats. I based my approach on Maciocia's advice that kidney yin deficiency was the underlying cause of tamoxifen-related hot flushes (see section 5.7.2.3, page 161). As most women experience nocturnal hot flushes, it seemed appropriate to include a strategy to counteract night sweats. Both Maciocia and Alræk identified Damp and Heat as conditions present in tamoxifen-related hot flushes, and I incorporated these in my treatment strategy. Thus, my core protocol for treating tamoxifen-related hot flushes and night sweats comprised the following treatment principles:

- Nourish kidney yin
- Stop night sweats
- Drain heat
- Resolve damp.

I discuss the points I selected to support these treatment principles in section 5.7.3, page 166 below.

Treating the patient

The final part of the treatment strategy was to treat the patient, according to her individual presenting condition. This aspect of the strategy complied with the need to treat each patient as an individual, rather than apply a "one-size-fits-all" standardised approach to each woman. It was impossible at the outset to anticipate the type and range of conditions that participants might present. My strategy was to draw on FECA principles where possible, to treat each participant according to her Constitutional Factor (CF). If I was unable to make a confident CF diagnosis, I would draw on the appropriate eight-principles theories and practices to treat the participant's condition. This reflected the approach I would normally adopt in clinical practice, and it seemed appropriate to apply it in this situation.

5.7.3 Selecting the points

Once I devised the treatment principles and strategy, the next step was to select the appropriate points for the standardised core protocol.

5.7.3.1 Points for the AE Drain

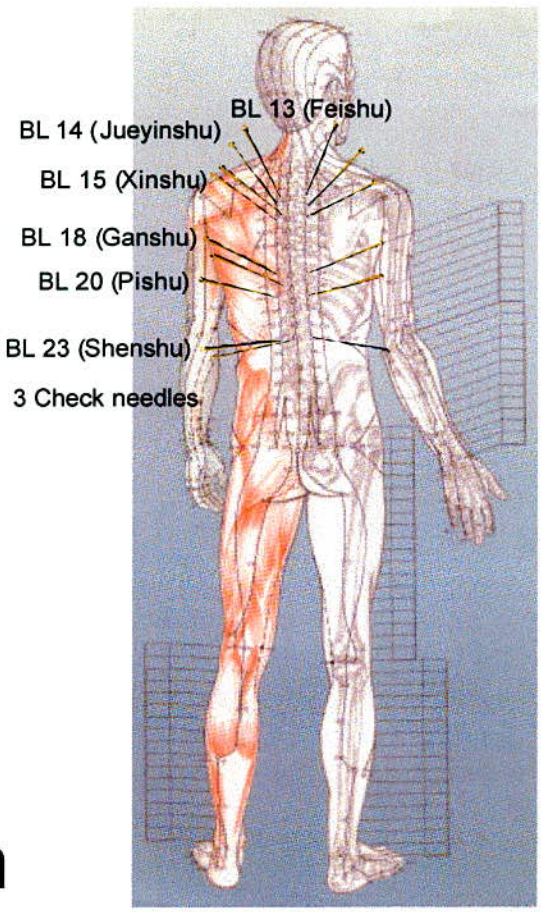
The points used to drain AE are prescribed, and comprise the back shu points of the yin organs of the body (Hicks et al. 2004). The back shu, or transporting, points are twelve points located along the bladder channel on the back, and they correspond to the twelve organs or zangfu in CM theory (Deadman et al. 1998, Maciocia 1989). Table 12 below lists these points and the organs to which they relate.

Table 12 Back shu points and their related organs

Point number	Point name	Yin Organ
Bladder (Bl) 13	Feishu	Lung
Bl 14	Jueyinshu	Pericardium
Bl 15	Xinshu	Heart
Bl 18	Ganshu	Liver
Bl 20	Pishu	Spleen
Bl 23	Shenshu	Kidney

Figure 21 below shows the locations of these points. In an AE drain, three additional needles are inserted into the muscle, rather than acupuncture points, as check needles. I discuss the purpose of these check needles under the procedures below.

Figure 21 Back shu points used for the AE Drain (used with the permission of the College of Chinese Integrated Medicine)



AE
Drain

5.7.3.2 Selecting points to treat hot flushes and night sweats

I drew heavily on Maciocia's work to select the points for the standardised portion of the core protocol. This was the basis for the remaining seven treatments of the study.

Points to nourish kidney yin

As the starting point for this protocol, I chose to nourish kidney yin by using an "extraordinary vessel" called the ren mai or conception vessel. The extraordinary vessels (of which there are eight) act as reservoirs of energy, and they have strong links with the kidney essence (Maciocia

1989). The ren mai connects to the kidney essence, and serves to nourish yin and reduce symptoms of empty heat that result from yin deficiency. As such, using the ren mai is particularly useful in treating menopausal symptoms (Maciocia 1998). The points to open the ren mai are Lung 7 (Lieque) and Kidney 6 (Zhaohai).

Amongst its many functions, Ren 4 (Guanyuan) is a principal point to benefit essence and nourish kidney yin (Deadman et al. 1998, Maciocia 1998). Maciocia (1998) strongly recommends its use in conjunction with the ren mai for a range of gynaecological problems. This combination, which nourishes kidney yin and blood and regulates the uterus, is particularly indicated for menopausal problems.

Spleen 6 (Sanyinjiao) is another point strongly indicated for gynaecological problems (Deadman et al. 1998). Like Ren 4, it acts to nourish blood and yin and regulate the uterus (Deadman et al. 1998, Maciocia 1989). It is positioned at the meeting point of the three yin channels of the leg (spleen, liver, and kidney); thus, it has a powerful and wide-ranging effect on the yin energy.

In addition, I drew on my clinical training at the Zhejiang College of Traditional Medicine in Hangzhou, China. Dr Chen Hua-De, in his lectures on treating gynaecological disorders, advised that Ren 4 and Spleen 6 should always form part of a core protocol, with additional points

added according to the specific nature of the condition being treated (personal communication, 8 October 1998).

I chose these points because they offered a powerful and elegant combination to nourish kidney yin. I discuss their additional wider ranging benefits below.

Stopping night sweats

Heart 6 (Yanglao) and Kidney 7 (Fuliu) are both indicated for controlling sweating (Deadman et al. 1998), and are often combined to treat night sweats due to deficiency of kidney yin (Ross 1995, Maciocia 1989). Maciocia advises the use of these points in combination with Lung 7, Kidney 6, and Ren 4 to treat menopausal imbalances that present with pronounced hot flushes, night sweats and anxiety (Maciocia 1998).

Drain heat

I chose to use Large Intestine 11 (Quchi) as the point to drain heat. It is an important point for treating heat in the body (Deadman et al. 1998, Maciocia 1989, Ross 1995). Both Ross (1995) and Alræk (personal communication by email, 22 January 2001) indicate its use for treating menopausal flushes.

Resolve damp

I did not choose points specifically to resolve damp, although Spleen 9 and Stomach 40 are arguably the most powerful points for treating this condition (Maciocia 1989, Deadman et al. 1998). A characteristic of elegant point selection is to use the minimum number of points to achieve

the maximum effect (Peter Mole, personal communication, no date). Thus, I drew on the functions of the points that were already present in my protocol to carry out this treatment principle. Spleen 6 is a main point for resolving damp (Ross 1995, Maciocia 1989, Deadman et al. 1998), and Kidney 7 is also indicated for clearing damp (Maciocia 1989, Deadman et al. 1998). Maciocia also cites Large Intestine 11 for treating a range of manifestations of damp and damp-heat. Thus, the points already selected appeared to have ample power to treat the damp that Alræk and Maciocia advised was the result of tamoxifen.

Summary of the protocol to treat hot flushes and night sweats

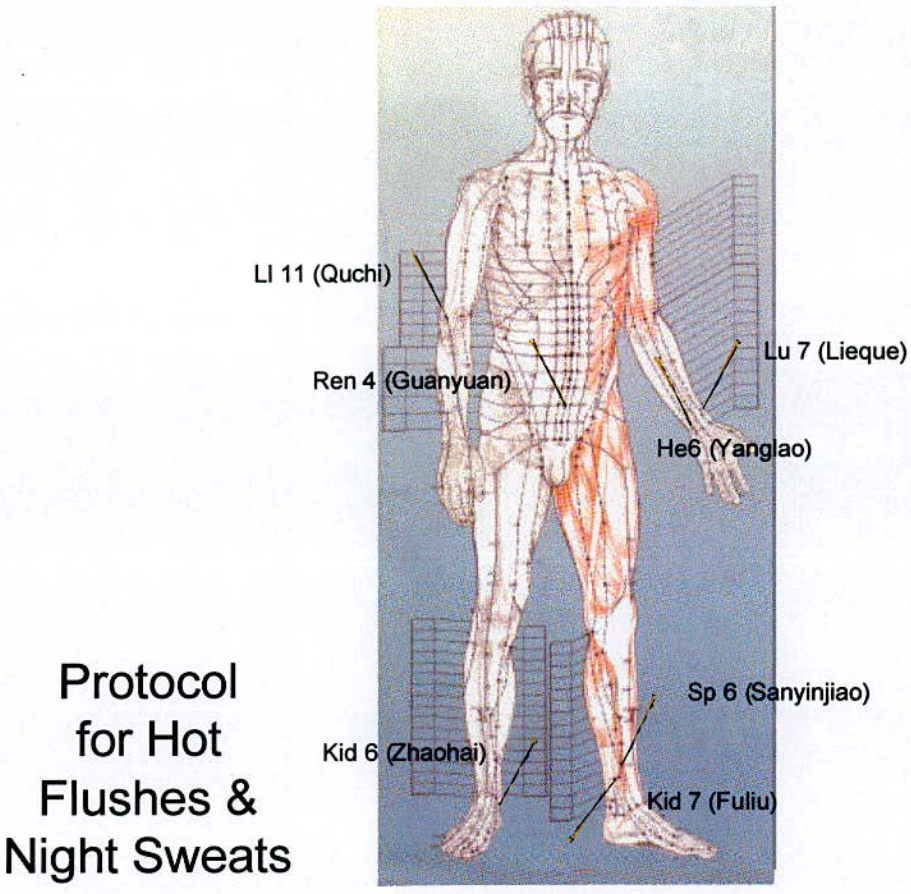
Table 13 below summarises the treatment principles at the heart of this part of the core protocol, and the points selected.

Table 13 Acupuncture points used in the core protocol

Treatment principle	Points selected
Nourish kidney yin	Open Ren Mai: Lung 7 (Lieque), Kidney 6 (Zhaohai) Ren 4 (Guanyuan) Spleen 6 (Sanyinjiao)
Stop night sweats	Heart 6 (Yanglao) Kidney 7 (Fuliu)
Drain heat	Large Intestine 11 (Quchi)
Resolve damp	Spleen 6 (Sanyinjiao) Kidney 7 (Fuliu) Large Intestine 11 (Quchi)

Figure 22 below shows the locations of these points.

Figure 22 Illustration of points used to treat hot flushes and night sweats (used with the permission of the College of Chinese Integrated Medicine)



5.7.3.3 Selecting "points for the patient"

As previously mentioned, it was impossible to predict the range of conditions the participants would present. Thus, this area remained undefined, and I allowed myself the freedom of the full range of acupuncture points to apply as appropriate to each woman and her condition(s). As appropriate for my training, the rationale for the use of these points followed eight-principles and/or FECA schools of theory and application.

5.7.3.4 Checking the protocol

I checked the logic of my protocol with members of my acupuncture supervision group. This was a group of practitioners trained in both eight-principles and Five Element acupuncture styles, but with no specific experience in treating tamoxifen-related hot flushes. My colleagues considered the theory of the point selection sound, and agreed that only by testing it in practice would I gather evidence of its effectiveness.

I also compared the points I selected in my protocol with points used in other studies available in the literature. The four papers citing specific points that were available at the time were by Cumins and Brunt (2000), Porzio et al (2002), Towlerton et al (1999), and Tukmachi (2000a). None of these papers discusses the treatment principles used, or the rationale for point selection. However, Table 14 below presents the range of points used in these small studies, and the points most frequently used.

Table 14 Variety of points used in studies available in the literature

Channel	de Valois	Cumins & Brunt	Porzio et al	Towlerton et al	Tukmachi
Stomach (St)		St 36			St 36
Spleen (Sp)	**Sp 6**	**Sp 6**	**Sp 6**	**Sp 6**	**Sp 6**
Heart (Ht)	Ht 6		Ht 5		Ht 7
Small Intestine (SI)					
Bladder (Bl)			Bl 23		Bl 62
Kidney (Ki)	Ki 6 Ki 7		Ki 6		Ki 3
Pericardium (P)		P 6			
Triple Heater (TH)					TH 6
Gall Bladder (GB)			GB 35	GB 20 GB 34	
Liver (Liv)		Liv 3		Liv 3	Liv 14
Lung (Lu)	Lu 7				
Large Intestine (LI)	LI 11	LI 4			LI 4 LI 11
Ren	**Ren 4**		**Ren 4**	**Ren 4**	
Du					Du 20
	Plus AE Drain and points for the individual		Plus other points not listed		

This table shows the range of points used in various studies. It is interesting to note how frequently Spleen 6 and Ren 4 are used, as well as the range of other points selected by various researchers.

5.7.4 Establishing the dose and frequency

Participants received eight sessions of acupuncture, on a weekly basis. The sessions lasted one hour each. I discussed the rationale for this in sections 3.7.2 and 3.7.3, on page 90.

Comparing this with the other studies available in the literature at the time shows the range of frequencies and treatment lengths. Table 15 below shows this range.

Table 15 Comparing treatment regimes for contemporary studies

	de Valois	Cumins & Brunt	Porzio et al	Towlerton et al	Tukmachi
Number of participants	50	26	15	Not specified	22
Number of sessions	8	Not specified	Weekly for 3 months	4	6 – 14 [3]
Frequency	Weekly	Not specified	Weekly	Weekly	Twice weekly
Appointment duration	1 hour	See Notes [1]	Not specified	Not specified	20-30 minutes
Follow-up treatments	None	Not specified	Monthly maintenance	See notes [2]	None specified
Protocol	Semi-individualised	Formula	Formula	Formula	Unclear

[1] Needles left in for 10 minutes at first session, 20 minutes at subsequent sessions.

[2] Patients continuing to have severe hot flushes were given semipermanent needles at Sp 6. This treatment continued for 4-36 months (mean 13 months).

[3] Positive response expected after 4-6 sessions. Treatment discontinued if no improvement after 8 sessions.

This table shows the range of approaches used to address the problem of tamoxifen-related hot flushes, as well as the variance in reporting details of treatment. As discussed previously, the treatment regime I adopted in Study 1: TA was based on pragmatic considerations specific to the LJMC, and our intention was to measure and observe the results.

5.8 Acupuncture procedures

5.8.1 Administering the AE Drain

Needles for the AE Drain are inserted bi-laterally, with superficial insertion and no attempt to obtain deqi (needle sensation). The order of insertion is Bladder (Bl) 13, Bl 14, Bl 18, Bl 20, Bl 23. Three "check" needles are

inserted into the muscle, one at each level of points (that is, one at the level of BI 13, BI 14, another at the level of BI 18, BI 20, and the final at the level of BI 23). The purpose is to identify erythema, or redness appearing around the needles, which indicates the presence of AE. The purpose of the check needles is to determine whether redness around the needles is due to skin sensitivity: if AE is present, erythema will only appear around the needles in the points, and not around the check needles.

BI 15 is needled only if erythema appears around BI 14, or around BI 13 and BI 23 together.

It is standard procedure to leave the needles in place for 10 to 20 minutes, or until the AE is drained (that is, until the erythema disappears, or the patient shows signs of change in colour, sound, emotion, odour). An AE Drain is usually administered once, unless AE is present, in which case it is advisable to repeat the procedure at the next treatment.

I used 34 gauge ½-inch stainless steel disposable needles manufactured by Carbo.

5.8.2 Administering the protocol to treat hot flushes and night sweats

I usually administered this step of the protocol for treatments two to eight.

I began the protocol by opening the ren mai, needling Lung 7 first, followed by Kidney 6 in the contralateral ankle. Maciocia's procedures for opening the ren mai in women prescribe using Lung 7 in the right arm, and Kidney 6 in the left ankle (1998, p 134). However, because of medical concerns that needling in the limb on the side of the affected breast could exacerbate lymphoedema (see 5.13.2.3, page 197), I was limited to using the arm on the unaffected side. Maciocia confirmed that this was an acceptable adaptation of the procedure, given the circumstances (personal communication, 17 January 2000).

Immediately after opening the ren mai, I needled the remaining points, usually in this order: Heart 6, Kidney 7, Large Intestine 11, Sp 6, and Ren 4. All the points of the arm (Heart 6, Large Intestine 11, as well as Lung 7) were needled in the arm on the side of the unaffected breast. The leg points were distributed across both legs. The needles stayed in place for 20 minutes from the insertion of Kidney 6. I removed the needles in reverse order of their insertion, ensuring Kidney 6 was the penultimate needle removed, and Lung 7 the last (as per Maciocia's protocol for opening the ren mai (1998, p 134)).

Figure 22 on page 172 shows the locations of these points, all of which I needled unilaterally. In this figure, LI 11 appears on the right arm, but in practice, all arm points were needled in the same arm, as discussed above. (In addition, the figure shows a male figure, because of the impossibility of finding good point location charts using female figures.)

I used 34 gauge stainless steel disposable needles manufactured by Carbo, in ½, 1 and 1½ inch lengths, according to the area of the body needled (that is, shorter needles on areas with less flesh covering; longer needles on fleshier areas). I used "even" technique for all needles, which means I inserted them perpendicular to the channel. I aimed to obtain deqi, and did not use any manipulation.

5.8.3 Administering points for the patient

I inserted any additional individualised points after administering the core protocol. Techniques varied according to the style of acupuncture used: when using an eight-principles approach, I generally inserted the needles along with the core protocol, leaving the needles for the 20-minute period; when using a FECA approach, I needled the points after removing all the needles for the core protocol. In these cases, I inserted the needles to obtain deqi, and then removed them immediately. I used 34 gauge Carbo needles as per the core protocol discussed above.

5.8.4 Safety procedures

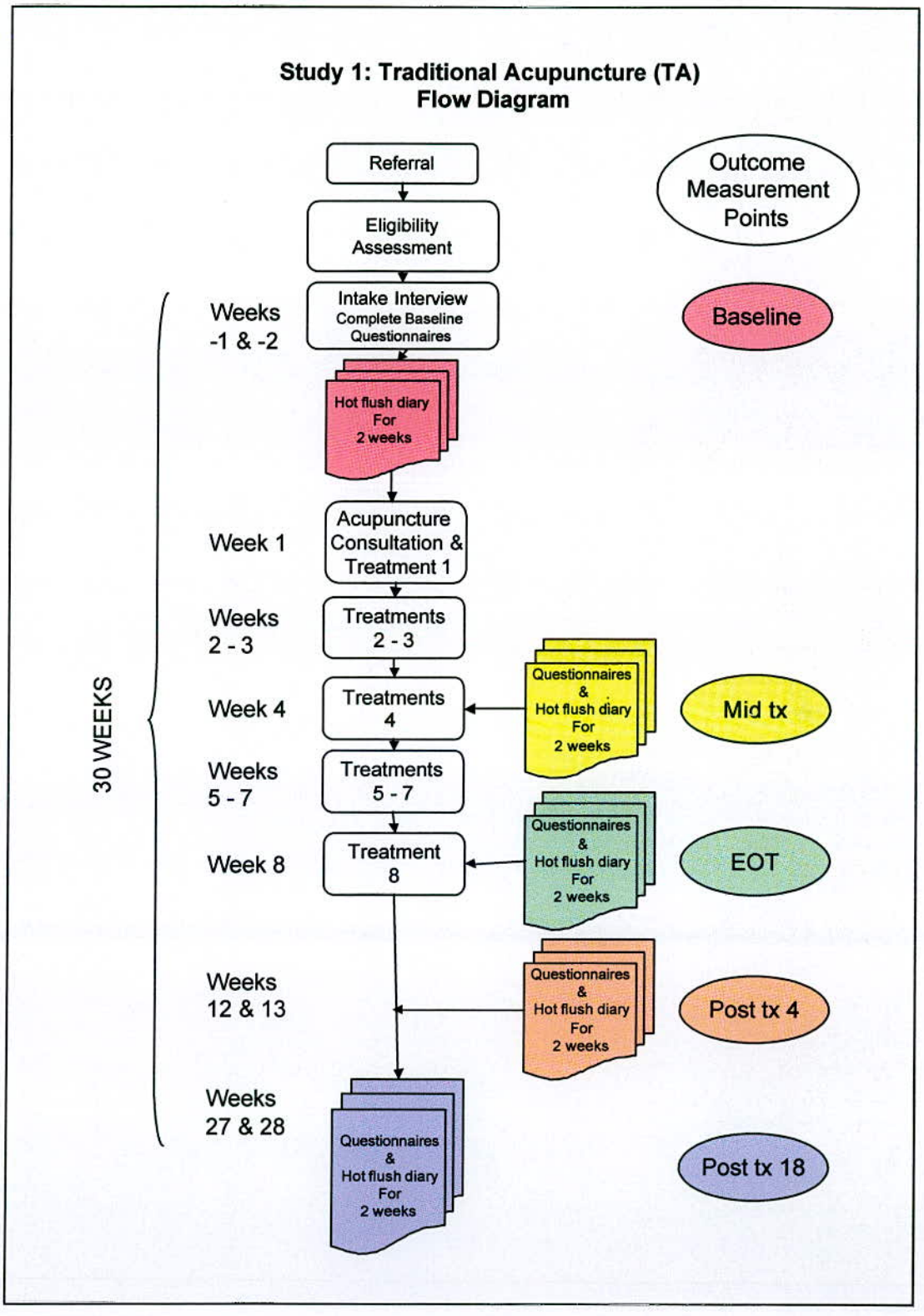
All needles were standard sterilised needles, inserted using guide tubes, and discarded after single use. I recorded all the needles inserted on a record sheet, and counted the needles on removal. Needles were disposed of in sharps boxes, and subsequently destroyed as per Mount Vernon Hospital procedures for dealing with sharps. I staunched any bleeding with sterile cotton wool, and disinfected the site with sterile antiseptic wipes (Sterets pre-injection swabs).

I recorded the patient feedback, treatment principles and points, pulse and tongue pictures, and any other comments on a Daily Treatment Sheet (see Appendix 23). I summarised the treatment principles and points used for each treatment on the Acupuncture Treatment Record (also in Appendix 23). I filed these documents in the participant's files.

5.9 Design of Study 1: TA

This study followed the design and methodology described in Chapter 3 and Chapter 4. Figure 23 below illustrates the stages of the study. Appendix 22 presents a map of the documentation associated with each stage of the study.

Figure 23 Flow diagram of Study 1: TA



5.10 Methodology

5.10.1 Referral, recruitment, and the intake interview

I carried out the recruitment, consent, and intake interview (including administration of the diaries and questionnaires) as described in section 3.11, starting on page 114.

5.10.2 Acupuncture consultation and treatment 1

5.10.2.1 Purpose of this session

Participants received their first treatment at the end of the two-week baseline measurement period. They returned their first hot flush diary at this session, which lasted for two hours. The session was divided between taking the "traditional diagnosis" (TD), and administering the first treatment (the AE Drain).

5.10.2.2 The Traditional Diagnosis (TD)

The TD is a consultation during which the practitioner gathers information about the main complaint, the patient's medical and family history, their systems (the 'Ten Questions'), and information about lifestyle and circumstances (including the emotions). In eight-principles acupuncture, this provides the information to identify the patterns or syndromes (Maciocia 1989). In FECA, this is the time to establish rapport and to assess the patient's Constitutional Factor (CF), which is the basis for FECA style treatment (Hicks et al. 2004).

The TD comprises many aspects, including diagnosis by looking, by smelling and hearing, by asking, and by feeling (Maciocia 1989). Pulse and tongue diagnosis are important aspects of "feeling" and "looking", and the "Ten Questions", the questioning of the systems of the body, are the essentials for "asking". Maciocia (2004) attributes the Ten Questions to the Chinese practitioner Zhang Jing Yue (1563 – 1640), and despite modifications over the centuries, they remain the core of a TD. The Ten Questions cover the topics of sleep, food and taste, thirst and drink, stools and urine, sweating, temperature preferences, head and body, eyes and ears, thorax and abdomen, and pain, with an additional category for women (Maciocia 2004, Maciocia 1989, Hicks et al. 2004). Although called the Ten Questions, each topic is an area comprising many specific questions. Consequently, taking a TD is a thorough process that involves detailed questioning and note taking, and may be time-consuming.

I recorded the information gathered during the TD on the Case History Questionnaire (see Appendix 24), which shows the depth, range and complexity of the consultation. I also used this form to develop the treatment principles for the individualised portion of each participant's treatment plan. I took the pulses, and examined the tongue, a process many participants found novel! (Tongue diagnosis is an essential feature of eight-principles acupuncture, as the tongue is believed to reflect the health of other parts of the body, and especially of the internal organs (Maciocia 1987).)

5.10.2.3 Treatment 1

After completing the TD, I proceeded with the first treatment, as described in section 5.8.1, page 175.

5.10.3 Subsequent treatments

Treatments two through eight lasted one hour each. I began each of these treatments by asking the participant how she was, and what changes she noticed since the last session. This allowed me to monitor how the treatment was progressing, identify what factors might be affecting the participant, and continue to build rapport. I examined the tongue at each session, and took pulses frequently throughout the treatment.

At the second session, I briefed the participant about the characteristics of "needle sensation", the sensations associated with obtaining deqi when needling (Bovey 2006). I then administered the protocol to treat hot flushes and night sweats as described in section 5.8.2, page 176 above.

At subsequent sessions, I continued to deliver this core protocol, tailoring it to the individual's condition. Some participants found acupuncture uncomfortable or painful, and for these women, I restricted the points used to the core protocol. Other participants, with complex health conditions and greater tolerance to needling, received treatments using points in addition to the core protocol.

During the sessions, I gave the participants the option of resting quietly while the needles were in place or of continuing to interact. I also gave lifestyle information during these sessions, as described in section 5.10.4.2, page 186.

5.10.4 Co-interventions

5.10.4.1 A note on moxibustion

Moxibustion (or moxa) is the practice of burning the herb *Artemesia vulgaris latiflora* (commonly called "mugwort") (Hicks et al. 2004) to warm, nourish or move energy, or reduce excess (Abbate 2002). Its practice is entwined with that of acupuncture: the Chinese term for acupuncture "*zhen jui*" specifically means "needling and moxibustion" (Birch and Felt 1999). In China, "acumoxa" is the name for applying the two methods together, and in current practice in the West, it is common to apply the two modalities together in treatment. This intimate intertwining of two techniques raises a question about its absence in the protocol I developed for treating tamoxifen-related hot flushes and night sweats. I omitted it for the following reasons.

Firstly, contemporary teaching focuses on moxa's warming nature, contraindicating its use in hot conditions such as excess heat or yin deficiency with heat and fire (Abbate 2002). Both eight-principles and FECA styles of acupuncture adhere to these principles: Maciocia (1989, 1998) and Abbate (2002) do not advocate the use of moxa for any conditions of yin deficiency (except in mixed yin/yang conditions, where

yang deficiency is the prominent condition), while Hicks et al specifically cite hot flushes as a contraindication for its use (2004, p. 267). (These contraindications are not universally agreed, however: Abbate (2002) argues that moxa is appropriate for yin deficient conditions that do not manifest heat symptoms, whilst the Classical Five Element school of J R Worsley only contraindicates the use of moxa on specific points and in cases of hypertension (Gumenick and Worsley 2006).) These contraindications were part of my training in the art of moxibustion, and I applied them to the treatment of hot flushes. With a protocol based on the premise that tamoxifen-induced hot flushes are the result of kidney yin deficiency (discussed above in section 5.7.2.3), it seemed that moxa was an unnecessary and inappropriate intervention.

Practicality was another issue. Burning moxa has a rich, pervasive odour that lingers, making its use difficult in some circumstances – especially on hospital wards and in clinics. In addition, it is only suitable for use where heat, rather than smoke, detectors are in place, as the smoke triggers fire alarms. As moxa appeared to be inappropriate for treating hot flushes, I did not think it worth the effort of introducing its use in the NHS setting. Furthermore, there was considerable challenge in introducing acupuncture into this setting. Therefore, I anticipated that introducing the concept of using of a smouldering herb for therapeutic purposes had the potential to cause problems with managers, ethics committees, and other medical practitioners.

Thus, I omitted moxa from the protocol. (However, my experience in treating the 50 women on the study has changed my view. I now believe that moxa may be appropriate for many women with hot flushes, and I would like to investigate this in future work.)

5.10.4.2 Lifestyle advice

Acupuncturists vary in their approach to suggesting their patients change negative habits to positive ones (Birch and Felt 1999); however, lifestyle advice is an important part of the integrated style of acupuncture. This stresses the acupuncturist's responsibility to encourage patients to make changes in their lifestyle, empowering them to take charge of their physical and emotional well-being, with the purpose of ensuring long and happy lives (Hicks 2001, Hicks et al. 2004). This relates to the causes of disease in Chinese Medicine, which lists such things as emotions, climate, diet, exercise, physical and mental overwork, excessive sexual activity as disease aetiologies (Maciocia 1989, Hicks et al. 2004).

It was important for me, as a practitioner, to be able to offer lifestyle advice to the participants in this study. This engendered considerable debate with my colleagues at the LJMC, who argued that this individualised advice would confound the results. However, I argued that traditional acupuncture is a package of care, rather than merely an intervention with needles, and therefore lifestyle advice is a vital part of patient care and empowerment (MacPherson 2000).

Consequently, part of my treatment was to offer appropriate lifestyle advice to individual participants. I drew on my acupuncture training, as well as Angela Hicks' written text on the subject (Hicks 2001), to inform my handling of this aspect of the protocol. Complete details of the range of advice given would form a lengthy discussion; therefore, I present the two most common areas I dealt with in Study 1.

Dietary advice

Guidelines for healthy eating are a major aspect of lifestyle advice in the practice of acupuncture, as poor, irregular diet is an important cause of disease in CM theory (Maciocia 1989, Birch and Felt 1999, Hicks et al. 2004). Chinese culture has many guidelines about maintaining good dietary habits (Hicks 2005, Hicks 2001, Hicks et al. 2004). The subject is complex, and I will only deal with one aspect here, which is eating breakfast.

It is common, as a practitioner, to encounter patients who skip breakfast. This is particularly frequent in patients who believe they are overweight, and the majority of participants in this study expressed their belief that taking tamoxifen added at least half a stone to their weight. The importance of eating breakfast in CM relates to the energy of the spleen and stomach, or Earth element. In the CM twenty-four hour biorhythmic clock, stomach qi is dominant from 7 to 9 a.m., and this is the optimum time to nourish this energy (Hicks et al. 2004). Eating breakfast regularly during this time strengthens the stomach, the most important of the yang organs, whose partnership with the spleen is responsible for the

production of all qi and blood during a person's life (Maciocia 1989). The importance of healthy stomach and spleen qi is central to CM theory; classically, its strength was a prognostic factor for disease, and preserving the stomach qi was an important method of treatment (Maciocia 1989). Following this logic, I encouraged all participants who skipped breakfast, were irregular about eating breakfast, or who ate poor quality food at this meal to improve their diet by having a healthy, nourishing breakfast on a regular basis.

Rest

The balance of work and rest is another important tenet of CM theory; excess activity is another cause of disease, as it depletes the qi (Maciocia 1989, Birch and Felt 1999, Hicks et al. 2004). Modern lifestyles encourage long working hours, and discourage taking time out to rest. Overactivity for long periods depletes the qi, and in contemporary Western societies, it is not restored by rest and proper diet. Furthermore, the concept of recuperation after serious disease has disappeared from our culture. Thus, cancer patients often strive to "get back to normal" without taking time to allow their bodies, or qi, time to recover.

Thus, it is important to encourage cancer patients to adopt the habit of taking regular rest. For women with yin deficiency hot flushes, I consider it an essential practice. Overactivity is a characteristic of yin deficiency; and continued overactivity further depletes the yin, resulting in a downward spiral effect that exacerbates yin deficiency symptoms, including hot flushes and night sweats. Following this logic, I encouraged

participants to take a 10 to 20 minute rest each day, ideally between the hours of one and three p.m. I instructed them to lie down, and to avoid watching television or reading during this period. It was not necessary to sleep, but to allow the body to rest. In CM theory, this nourishes the qi and blood, which in turn nourishes the yin, and consequently has a beneficial effect on hot flushes (Hicks 2001). Many participants were reluctant to take time out of their busy schedules to rest; many saw napping during the day as a sign of weakness or inadequacy. However, those who adopted this habit reported, over time, changes in their energy levels, quality of sleep, and most importantly, the frequency and nature of their hot flushes.

5.10.5 Practitioner background

I administered all of the treatments in Study 1. I qualified as a licensed acupuncturist (Lic. Ac) in May 1999, and became a member of the British Acupuncture Council, the professional body representing professional (traditional) acupuncturists. I trained at the College of Integrated Chinese Medicine (CICM) in Reading, Berkshire, England, which is accredited by the British Acupuncture Accreditation Board (BAAB). I also studied at the Zhejiang College of Traditional Chinese Medicine in Hangzhou, People's Republic of China in 1998.

At the beginning of the clinical phase of Study 1, I had nearly three years of general clinical experience. I had five years experience of working as an aromatherapist in a hospital setting with people with cancer, both in-

patients and outpatients. I had no specific experience of treating menopause-like hot flushes and night sweats.

5.10.6 Control interventions

5.10.6.1 Intended effect of the control intervention

The women acted as their own controls, and there were no additional control interventions. This was appropriate for a before-and-after study design, as discussed in section 3.7.4, starting on page 93.

5.10.6.2 Explanations given to the patients of treatment

All potential participants received the Patient Information Sheet (see Appendix 5), which detailed the study and its aims, acupuncture and the treatment sessions, and the requirements of participants in the study. At the intake interview, I encouraged potential participants to ask any questions they had about the study or about having acupuncture. For Study 1, I told all participants that we had no information about how effective this treatment would be for their hot flushes and night sweats, and that it was only through their participation that we would gather this information.

5.11 Data input and analysis

I entered all the data from this study, for the reasons discussed in section 4.5.1, starting on page 124. The research co-ordinator carried out random checks for accuracy of input. We conducted the analysis as discussed in Chapter 4.

5.12 Summary of STRICTA reporting

I have endeavoured to present these acupuncture details according to the STRICTA guidelines (MacPherson et al. 2001). Table 16 below presents a summary of the STRICTA categories, showing where I have discussed these aspects in the text. Refer to Appendix 21 for a copy of the complete guidelines.

Table 16 Using the STRICTA guidelines to report Study 1: TA

STandards for Reporting Interventions in Controlled Trials of Acupuncture		
Category	**Category description**	**Where discussed in text**
Acupuncture rationale	Style of acupuncture	The style of acupuncture used is the integrated style, which draws on the theory and practices of eight-principles and Five Element Constitutional Acupuncture (as discussed in section 1.10, page 21).
	Rationale for treatment (e.g. syndrome patterns, segmental levels, trigger points) and individualisation if used	Discussed in sections 5.6, page 155, and 5.7, page 158 and 5.7.2.3, page 161.
	Literature sources to justify rationale	
Needling details	Points used (unilateral/bilateral)	Discussed in sections 5.7.3, page 166 and 5.8, page 175.
	Numbers of needles inserted	
	Depths of insertion (e.g. cun[9] or tissue level)	
	Responses elicited (e.g. deqi or twitch response)	
	Needle stimulation (e.g. manual or electrical)	
	Needle retention time	
	Needle type (gauge, length, and manufacturer or material)	
Treatment regimen	Number of treatment sessions	Discussed in section 5.7.4, page 174.
	Frequency of sessions	
Co-interventions	Other interventions (e.g. moxibustion, cupping, herbs, exercises, life-style advice)	Discussed in section 5.10.4, page 184.
Practitioner background	Duration of relevant training	Discussed in section 5.10.5, page 189.
	Length of clinical experience	
	Expertise in specific condition	
Control interventions	Intended effect of control intervention and its appropriateness to the research question, and if appropriate, blinding of participants (e.g., active comparison, minimally active penetrating or non-penetrating sham, inert)	Discussed in section 5.10.6, page 190.
	Explanations given to patients of treatment and control interventions	
	Details of control intervention	Discussed in section 3.6, page 84.
	Sources that justify the control.	

[9] "Cun" or "body inch" is a measure used in acupuncture that is individual for each person (Birch and Felt 1999). It is used to locate acupuncture points on the body, or to measure the depth of needling.

5.13 The learning process & adapting the protocol

Study 1: TA was a learning experience in how to treat hot flushes in women with breast cancer, and how to manage the process of conducting this type of clinical research. I used my observations and growing experience to improve these aspects during the course of the study, and I allowed myself the freedom to adapt and improve my approach. I discuss some of the significant features of this below.

5.13.1 Managing expectations

Setting participant expectations was an important learning experience. Women coming into the study expected immediate results. When the hot flushes did not immediately disappear, they either expressed disappointment with the treatment, or "performance anxiety", which they expressed by concerns that they were somehow abnormal, or doing something wrong.

5.13.1.1 How change happens

It was only when I gained experience in how change manifested that I could manage these expectations, and reassure anxious participants that they were "performing normally". By about one third of the way through the study, the patterns of change became clearer to me. The treatment did not "switch off" the flushes immediately, and changes were gradual. They manifested differently according to the individuals: some women saw a gradual decline in frequency and/or severity of their flushes; others reported no change for several sessions, and then suddenly experienced a dramatic decrease in symptoms. For some women, other symptoms

showed improvement before the flushes changed. However, overall I learned that some noticeable change should occur by the fourth treatment, and if the participant arrived for her fifth session with no change, it was important to examine why this was so (see section 5.13.2.1, page 195).

5.13.1.2 Setting treatment priorities with the participant

As well as demonstrating performance anxiety, many participants focused solely on their hot flushes and night sweats. My training and experience as an acupuncturist taught me that many symptoms change during acupuncture treatment, not just the main complaint. I felt it was important for participants to be open to any wider changes that might occur. In view of this, and as part of the evolving participant management strategy, I implemented the practice of asking participants to prioritise the changes they wished to see in their overall well-being during the course of their acupuncture treatment.

This was part of my learning curve, and I implemented it about halfway through Study 1. Then, as part of the consultation, I asked participants to articulate three aspects of their health and well-being in which they would like to see improvements. I reviewed these from time to time during the eight weeks, with a final review at the last treatment. This strategy helped participants to see the wider changes that acupuncture may or may not have facilitated; it also helped to manage performance anxieties in those women whose flushes were slow to change.

5.13.2 Adapting the protocol to the individual

5.13.2.1 The importance of clearing blocks to treatment

Tukmachi categorised his study participants as "responders" and "non-responders" according to the change, or lack of change, in symptoms during treatment (personal communication, no date). As an acupuncturist, I was intrigued by why some patients showed no change by the fifth treatment, and I sought to identify reasons for this. In Study 1, I drew on the theories of clearing blocks to treatment to explore this phenomenon. I found that several participants who showed no change with repeated applications of the "core protocol" could experience substantial change after I cleared a block to treatment. I could then resume applying the core protocol, and thereby improve their condition.

The energy block procedures I used to most dramatic effect were:

- Repeating the AE Drain
- Possession (internal or external dragons).

I have discussed the rationale for AE Drain above, and noted that there are instances where it should be repeated (see section 5.8.1, page 175).

In Five Element theory, possession is another block to treatment that may arise when the person has underlying poor physical or psychological health, has experienced emotional shock, or has experienced physical shock (including surgery). It manifests with a range of symptoms, including intense dreams or fantasies that are frightening, obsessive behaviour, or relapses or failure to progress with acupuncture treatment.

Its key sign, however, is that "something about the patient is extremely unusual" (Hicks et al. 2004, p 239). I encountered several participants who manifested these symptoms, and I learned that applying the appropriate protocols for clearing "internal" or "external" dragons often had a remarkable and beneficial effect. Encouraged by these effects, I gained confidence in applying these procedures as needed during the course of treatment, adapting the overall protocol to accommodate these interventions.

5.13.2.2 Treating acute conditions

In line with practising as I would in a normal clinic situation, I adapted the protocol where necessary to accommodate acute conditions. This was particularly relevant when participants presented with colds (invasions of wind-cold or wind-heat of the lungs, in CM terminology). In such circumstances, it is common practice to expel the acute condition before resuming treatment of the underlying chronic condition (Ross 1995, p 50, Maciocia 1989, p 318). This is also regarded as appropriate practice in Five Elements Constitutional Acupuncture, where it is advisable to stop constitutional treatment when there are acute conditions (Hicks et al. 2004, p 365).

When participants presented with acute conditions, I adapted the treatment principles as discussed above. In these situations, I used the treatment session to clear the condition, and resumed treating the hot flushes at the next appointment.

5.13.2.3 Lymphoedema

Lymphoedema is a condition that may occur in women who have had lymph nodes removed as part of their breast cancer treatment. The condition is serious and difficult to treat. In view of this, most breast cancer patients are advised to avoid any intervention on the arm on the side of the breast surgery. This includes injections, insect stings, gardening wounds, excessive exertion, and even having blood pressure monitored.

Women are often advised to avoid acupuncture needling as well. This is a difficult area: most medical professionals advise this (Tavares 2003, Filshie 2001), whilst experienced acupuncturists maintain that it is not necessary to avoid needling (Maciocia, G, personal communication by email, 17 January 2000; Lampert, G, personal communication, 2000). I opted to conform to the conventional medical restrictions, and thus adapted the protocol to avoid needling the arm on the side of the breast surgery.

However, two of the 50 women treated in this study had bilateral mastectomies, which meant that I could not needle in the arms at all. For these women, I had to abandon the core protocol, and devise a treatment strategy and point combination that avoided using points in the arms.

5.13.3 Summary of the learning process

Learning about how to manage participants, and how the treatment effects manifested was an on-going process. I used my evolving experience to improve and explore treatments as the study progressed. The impact of this is that participants may not have been treated consistently. However, this exploratory trial was intended to be a learning process. As such, I consider the developments justified, as my aims as an acupuncturist were to deliver the best care possible to the women in this study, and remain true to the flexible and adaptive nature of the integrated style of acupuncture.

5.14 Conclusion

This chapter presented the rationale for using traditional acupuncture to treat tamoxifen-induced hot flushes and night sweats. Given the paucity of evidence on this subject, I drew on the theories for treating symptoms of natural menopause and applied them to these side effects of tamoxifen treatment. I have reported the specifics of how I developed and administered this treatment, along with some of the observations and experience gathered through treating the participants in this study. In the next chapter, I report the results of using this approach.

Chapter 6 Results of Study 1: TA

6.1 Synopsis

In this chapter, I present the results of Study 1: Traditional Acupuncture (TA). I report recruitment, losses to follow-up, sociodemographic data, and baseline medical data. I then present the data related to the three main topics comprising this thesis: hot flush frequency, emotional and physical well-being, and the acceptability of acupuncture as a treatment. Hot flush frequency presents the results of analysing the Hot Flush Diaries. Emotional and physical well-being includes the results of the Women's Health Questionnaire (WHQ), the sub-analysis of the Somatic Symptoms category of the WHQ, and the results of the Hot Flushes and Night Sweats Questionnaire (HFNSQ). Finally, I discuss the participants' feedback on whether they found receiving traditional acupuncture to manage their hot flushes acceptable.

6.2 Recruitment and losses to follow-up

Of 54 women recruited to Study 1: TA, 50 completed the course of eight traditional acupuncture treatments. Reasons for non-participation included one participant stopping tamoxifen immediately after her intake interview, thus invalidating her inclusion; one received a study number in error before consenting to the study. Two participants withdrew from the study after starting treatment: one withdrew after three treatments, citing transportation problems as the reason; one stopped attending after her sixth treatment and ceased to communicate with the study.

6.3 Demographic data for the TA study

The sociodemographic and baseline medical information reported below reflects the 52 participants who completed these questionnaires at baseline. It includes data concerning the two participants who withdrew before completing the course of treatment. It does not include data for the two women who did not proceed beyond the intake interview.

6.3.1 Sociodemographic data for Study 1: TA

Table 17 below presents the results of the Sociodemographic Questionnaire. Some data are missing for two participants who did not complete the second page of this questionnaire.

Table 17 also presents comparative demographic data for 29 breast cancer patients treated at Mount Vernon Hospital (MVH), and I discuss this below in section 6.3.1.1, page 202.

Table 17 Sociodemographic data for Study 1: TA compared with women attending for radiotherapy at MVH in 2005

	MVH Radiotx Patients n = 29 n (%)	TA at baseline n = 52 n (%)
Marital status		
Single	*4 (14)*	
Married (first marriage)	*18 (62)*	34 (65)
Re-married	*1 (3)*	5 (10)
Living with partner	*1 (3)*	5 (10)
Divorced	*2 (7)*	5 (10)
Widowed	*3 (10)*	3 (6)
Home Situation		
Living with family members or partners	*24 (83)*	45 (86)
Living alone	*4 (14)*	3 (6)
Missing data		4 (8)
Dependents		
No dependents		34 (65)
Children under the age of 18 or adults for whom financially responsible		16 (31)
Missing data		2 (4)
Educational qualifications		
Less than compulsory school education	*4 (14)*	5 (10)
Compulsory school education (e.g. school certificate, CSEs, GCSEs)	*10 (35)*	25 (48)
Post compulsory school education below university level	*8 (28)*	16 (30)
University level	*4 (14)*	4 (8)
Postgraduate level	*2 (7)*	2 (4)
Current employment status		
Retired	*10 (35)*	17 (33)
Not working at present	*5 (17)*	5 (10)
Working part time	*6 (21)*	22 (42)
Working full time	*7 (24)*	8 (15)
Country of birth		
England	*27 (93)*	44 (85)
Scotland		1 (2)
Wales	*1 (3.4)*	3 (6)
Irish Republic		1 (2)
Elsewhere	*1 (3.4)*	1 (2)
Missing data		2 (4)
Ethnic background		
Irish		1 (2)
White British	*27 (93)*	48 (92)
White other	*1 (3.4)*	1 (2)
Missing data		2 (4)
Car ownership		
Household with 1 car	*16 (55)*	14 (27)
Household with > 1 car	*11 (38)*	34 (65)
None	*2 (7)*	2 (4)
Missing data		2 (4)
Home ownership		
Own/buying home		46 (88)
Renting		4 (8)
Missing data		2 (4)

6.3.1.1 How representative is this group?

There is little demographic data available about patients attending Mount Vernon Hospital (MVH) for treatment, or attending the LJMC for supportive care. Contemporary annual reports for the MVH Cancer Treatment Centre (West Hertfordshire Hospitals NHS Trust 2001) and for the LJMC do not provide detailed demographic data for women receiving treatment for breast cancer, although the LJMC report acknowledges that the Centre is used mostly by "white Caucasian people" (Wood 1999, p 4). In attempting to determine whether the participants in the TA study are representative of patients attending MVH and the LJMC, the best data come from a recent Department of Health study examining the use of complementary and alternative therapies among people undergoing cancer treatment (Department of Health 2006, Yardley et al. 2005). Unpublished data provides details of 29 breast cancer patients attending MVH for their first course of radiotherapy during 2005. I present the data on these patients in Table 17 above.

This comparison shows that the two groups are similar, and may be representative of typical breast cancer patients treated at MVH. Both are predominately white-British, born in the United Kingdom, married, and car owners. Both groups have similar education levels, although the TA group has slightly higher levels of compulsory school education, and slightly lower levels of university qualifications. Employment status also shows some differences: more women in the TA group are working (either full or part time) than in the MVH group.

Thus, whilst possibly being representative of patients of MVH and users of LJMC, this group is not representative of a multicultural, diverse socio-economic group, which might typically be found in urban areas throughout the United Kingdom.

6.3.2 Baseline Medical Information for Study 1: TA

The data presented in the tables below relate to cancer diagnosis and treatment, as well as the menopausal status of the 52 participants who completed baseline questionnaires.

Table 18 Age, cancer diagnosis, and tamoxifen history

	All participants at baseline n = 52		
	Mean (sd)	Median	Min-Max (Range)
Age at baseline (years)	54.3 (7.9)	54.5	37 – 68 (31)
Time since cancer diagnosis (years)	1.9 (0.85)	1.7	0.96 – 4.7 (3.7)
Time taking tamoxifen (years)	1.7 (0.85)	1.3	0.48 – 4.6 (4.1)

The mean and median ages presented in Table 18 above accord with the UK incidence statistics, which show that the highest number of new diagnoses of breast cancer are in the 50-64 age group (Cancer Research UK 2006). Comparing the time since diagnosis and the time taking tamoxifen shows that women start taking tamoxifen shortly after their diagnosis. The time taking tamoxifen suggests that, despite medical advice that these hot flushes reduce with time (Love and Feyzi 1993), these women still experience unacceptably high levels of discomfort well into their second year on the treatment. One woman registered symptoms in her fifth and final year (see Table 20 on page 204 for details of the distribution for this group).

Table 19 Distribution of participants showing time since cancer diagnosis

	All participants at baseline n = 52 n (%)			
	6-12 months	1-2 years	3 - 4 years	>4 years
Time since cancer diagnosis	4 (8)	25 (48)	22 (42)	1 (2)

Table 19 above shows that over half of the participants were diagnosed up to two years prior to joining the study, with slightly less than half having been diagnosed three to four years prior to the study.

Table 20 Distribution of participants showing time taking tamoxifen

	All participants at baseline n = 52 n (%)			
	6-12 months	1-2 years	3 - 4 years	>4 years
Time taking tamoxifen	10 (19)	28 (54)	13 (25)	1 (2)

Table 20 above shows that although just under a fifth of the group had been taking tamoxifen for under a year, almost half the group had been taking it for one to two years, and a further quarter of the group have been taking it for between three to four years. Only one woman was in her final year of the five-year treatment period. As mentioned previously, this distribution indicates that for some women, hot flushes continue well into the five-year treatment period, with a considerable proportion experiencing symptoms three to four years into standard five-year tamoxifen regime.

Table 21 Other related treatment and gynaecological information

	All Participants at Baseline n = 52 n (%)
Cancer treatments:	
Surgery	51 (98)
Radiotherapy	46 (89)
Chemotherapy	26 (50)
Participants with history of:	
Taking HRT	34 (65)
Hysterectomy	13 (25)
Treatment for lymphoedema	8 (15)
Menopause status[10]:	
Perimenopause (last period within the previous year)	6 (12)
Menopause (no period within the previous 1-5 years)	19 (36)
Postmenopause (no period in over 5 years)	24 (46)
Missing data	3 (6)

The treatment data presented in Table 21 above confirm that most women with breast cancer have surgery (Cancer Research UK 2006) and radiotherapy, and half of this group received chemotherapy as well. Two thirds of the group had a history of taking Hormone Replacement Therapy (HRT). This has a potential impact on the menopause status, as many women cannot differentiate periods from the bleed associated with some types of HRT (Fallowfield et al. 2001). However, using the STRAW staging system (Soules et al. 2001), it appears that a third of this group (36%) may have been going through the menopause transition, whilst a further 46% were postmenopausal.

[10] Based on the STRAW staging system (Soules et al 2001).

6.4 Hot flush frequency for Study 1: TA

6.4.1 Hot flush frequency

This section presents the results of the analysis of the Hot Flush Diaries, and provides answers to the question "Can traditional acupuncture reduce the frequency of hot flushes and night sweats in women taking tamoxifen as adjuvant treatment for early breast cancer?"

6.4.1.1 Compliance

Compliance in completing and returning the Hot Flush Diaries was high. Table 22 below shows the returns at each measurement period.

Table 22 Return of hot flush diaries at each measurement period

MEASUREMENT PERIOD	Baseline	Mid tx	EOT	Post tx 4	Post tx 18
DIARIES RETURNED	52	48	48	47	47

Of the two participants who withdrew from the study after starting treatment (see section 6.2, page 199), one withdrew before completing the Mid tx diary, and the other withdrew before completing the EOT diary.

6.4.1.2 Hypothesis

Our hypothesis was that TA would reduce hot flush frequency by 50% in one third of the participants at EOT. I discuss the rationale for this hypothesis in section 5.7.1, page 158.

6.4.1.3 Establishing hot flush frequency

As discussed in section 2.4.5, starting on page 55, the there was little information available about the numbers of hot flushes experienced by

women taking tamoxifen. Table 23 and Table 24 below present data reflecting the experience of the participants who completed the baseline and EOT hot flush diaries. Table 23 shows the minimum and maximum number of flushes experienced. The study results are based on comparisons with baseline data that are averaged over a 14-day period for each participant. However, it is also worth reporting the minimum and maximum numbers of flushes reported by participants on single days. These data show the variability and range of hot flush frequency, and supports the decision to measure participants' hot flushes for a period of more than one day.

Table 23 Hot flush frequency at baseline (n = 52)

RANGE PERIOD	Minimum	Maximum	Mean	Std. Dev.
Average per day measured over 14-day baseline period	3.6	33.23	10.4	6.4
Per day	0	40	n/a	n/a

6.4.1.4 Comparing hot flush data: baseline and EOT

Table 24 presents the mean, median and range of hot flushes per day when averaged over the fourteen days at the baseline and EOT measurement periods. These untransformed summary (USD) data reflect the 48 participants who completed and returned hot flush diaries for both measurement points.

Table 24 Hot flush frequency – means, medians and ranges of hot flushes/day over the 14-day measurement periods (using USD)

	Baseline (n=48)	EOT (n=48)
Mean (Std dev)	10.7 (6.5)	6.5 (5.3)
Median (95% CI)	9.0 (8.9 – 12.6)	4.8 (4.9 – 8.0)
Min	3.5	1.0
Max	35.0	21.0
Range	31.5	20.0

6.4.1.5 Establishing change in frequency

Table 23 reports frequencies based on untransformed summary data (USD) and shows the wide range and variable nature of the frequency of hot flushes. Table 24 also shows there is a reduction in hot flushes at EOT over baseline. However, to say that flushes reduce from a mean of 10.7 to 6.5 per day, (or a median of 9 to 4.8 per day) is not necessarily helpful to a patient seeking relief from hot flushes, or to a clinician who needs to know what outcome to expect (as discussed in section 4.8.2.1, starting on page 140). Indeed, many participants were experiencing significantly more or less than 10.7 hot flushes per day at baseline.

Using log transformations normalised the data, and the resulting transformed data provide information that is more helpful in clinical terms. Table 25 below presents the percentage change in hot flush frequency for each of the 48 participants who completed the hot flush diaries at the end of the course of acupuncture treatment. (In the following table, the term "lnBaseline no." refers to this log transformed data.)

Table 25 % change in hot flush frequency/day by participant (log transformed data)

Ranking	Study No.	lnBaseline no.	lnEOT no.	% Change
> 50% reduction				
1	11	15.00	2.00	86.67
2	19	5.50	1.00	81.82
3	2	5.00	1.00	80.00
4	36	5.00	1.00	80.00
5	40	5.00	1.00	80.00
6	50	17.50	4.50	74.29
7	31	7.50	2.00	73.33
8	41	3.50	1.00	71.43
9	46	10.50	3.00	71.43
10	1	9.00	3.00	66.67
11	7	9.00	3.00	66.67
12	47	9.00	3.00	66.67
13	42	18.00	6.00	66.67
14	35	8.00	3.00	62.50
15	54	5.00	2.00	60.00
16	23	5.50	2.50	54.55
17	49	17.00	8.00	52.94
18	52	10.00	5.00	50.00
19	24	4.00	2.00	50.00
20	12	6.00	3.00	50.00
21	53	8.00	4.00	50.00
22	39	12.00	6.00	50.00
< 50% reduction				
23	5	13.00	7.00	46.15
24	17	6.50	3.50	46.15
25	37	12.00	6.50	45.83
26	13	9.00	5.00	44.44
27	51	9.00	5.00	44.44
28	34	6.00	3.50	41.67
29	29	10.00	6.00	40.00
30	10	35.00	21.00	40.00
31	30	4.00	2.50	37.50
32	3	12.50	8.00	36.00
33	22	12.00	8.00	33.33
34	28	24.00	16.50	31.25
35	15	5.50	4.00	27.27
36	16	15.00	11.00	26.67
37	38	4.00	3.00	25.00
38	4	21.00	16.00	23.81
39	21	15.00	11.50	23.33
40	20	25.00	21.00	16.00
41	27	9.00	8.00	11.11
42	48	22.00	20.00	9.09
No change				
43	33	4.00	4.00	0.00
44	45	12.00	12.00	0.00
Increase				
45	26	10.00	11.00	-10.00
46	32	9.00	10.00	-11.11
47	25	7.00	8.50	-21.43
48	9	9.00	11.50	-27.78

This table shows that 22 (45.8%) participants recorded a reduction of 50% or more in their hot flush frequency at EOT over their baseline number. This exceeds our hypothetical estimate of a reduction of 50% or more in one third (or 16.7) of participants.

The table also shows that 20 (41.7%) recorded some improvement in their hot flushes, although this was less than a 50% reduction. Two (4.2 %) participants recorded no change, and four (8.3%) recorded that their hot flush frequency increased.

6.4.1.6 Establishing the proportional change in frequency

The analysis presented in Table 25 above shows the percentage change in frequency per participant. It also gives an indication of how our results measure against our hypothesis. As discussed in section 4.8.2.1, starting on page 140, log transformations provide a proportional measure. This allows us to predict the reduction an individual can expect at the end of eight acupuncture treatments over her baseline frequency (based on the mean of all participants in this study). Table 26 below presents the results of the four measurement points, highlighting the primary outcome measure, which is the EOT over baseline result.

Table 26 Results after log transforming the data

TRADITIONAL ACUPUNCTURE						
Measurement point	**n =**	**Mean % Reduction**	**95% CI Lower**	**95% CI Upper**	**Range (%)**	
					Min	**Max**
lnBase - lnMid	48	40.8%	31.0%	50.0%		
lnBase - lnEOT	**48**	**49.8%**	**40.5%**	**56.5%**	**-28.8**	**86.7**
lnBase – lnPost tx 4	47	41.2%	31.0%	49.5%		
lnBase – lnPost tx 18	47	41.8%	29.1%	49.5%		

This analysis shows that on average, a woman might expect a reduction of almost 50% (that is, 49.8%) of the number of hot flushes she experiences before treatment. The 95% confidence intervals indicate that there is only a 5% chance that the mean reduction will lie outside of the range of a 40.5% - 56.5% reduction.

Table 27 below presents the results of paired samples t tests showing the change at each measurement point compared with baseline, using the log transformed data. **Bold** formatting highlights the statistically significant results ($p < 0.05$). These are the data used to derive the results presented in Table 26 above.

Table 27 Results of paired samples t tests for hot flush frequency (TA) using log transformed (ln) data

	Paired differences					Paired sample t tests		
				95% CI				
	Mean	SD	N =	LL	UL	t =	df	p< *
lnBaseline – lnMid tx	.525	.529	48	.371	.678	6.879	47	.0001
lnBaseline – lnEOT	.678	.538	48	.521	.834	8.717	47	.0001
lnBaseline – lnPost tx 4	.530	.533	47	.374	.687	6.820	46	.0001
lnBaseline – lnPost tx 18	.513	.583	47	.342	.684	6.034	46	.0001

* Significance (2-tailed)

These paired samples t tests on the transformed data show that the mean change from baseline to EOT, the primary endpoint, is statistically significant. The results were $t = 8.72$, $df = 47$, $p < .0001$. The changes at the other three endpoints are also statistically significant.

6.4.1.7 Evaluating the short term and longer term results

In addition to measuring the change in frequency at the primary endpoint (EOT), we were interested in exploring what happened to the effects after treatment ceased. Table 26 above suggests that hot flush frequency rises after treatment ends, and at Post tx 4 this increase is 8.6%. However, frequency levels appear to stabilise and the levels are almost the same at both Post tx 4 and Post tx 18.

6.5 Emotional & physical well-being for Study 1: TA

The Women's Health Questionnaire (WHQ) and the Hot Flushes and Night Sweats Questionnaire (HFNSQ) provided data to answer the question "Does TA affect the overall physical and emotional well-being of the recipient?"

6.5.1 Results of the WHQ

6.5.1.1 Compliance and missing data

As with the Hot Flush Diaries, compliance with completing and returning the questionnaires was high. Table 28 below displays the numbers of returned WHQs at each of the measurement points.

Table 28 Return of Women's Health Questionnaires at each measurement period

MEASUREMENT PERIOD	Baseline	Mid tx	EOT	Post tx 4	Post tx 18
DIARIES RETURNED	53	48	48	47	49

On the returned questionnaires, individual items are missing for a range of reasons. Some participants failed to fill in the last page of the

questionnaire, and some participants missed questions at random. Other data are missing because of the rules for analysing WHQ data, as discussed in section 4.9.4, page 146. These are the reasons for the varying numbers in the data presented in Table 29 below.

6.5.1.2 Hypothesis

Our hypothesis was that overall, emotional and physical well-being would show improvement at EOT, and that symptoms would return as time from EOT increased. We did not predict which specific WHQ domains might change, nor did we predict the degree to which changes might occur. This aspect of the data collection was exploratory, and aimed to collect data to answer this question.

6.5.1.3 WHQ results at the primary endpoint

Table 29 below shows the results for the nine domains of the WHQ, comparing baseline with the primary endpoint, EOT. Data for the means at baseline and EOT show the results for these individual measurement points. Data for the paired differences and the paired samples t tests show the change in each domain over time. **Bold** text highlights the statistically significant results ($p < 0.05$).

Table 29 WHQ results for the primary endpoint (EOT) of the TA study

Seq	Baseline			EOT			Paired differences (Baseline - EOT)					Paired samples t tests		
										95% CI				
WHQ Scale[11]	Mean	SD	N =	Mean	SD	N =	Mean	SD	N=	LL	UL	t =	df	p = *
ANX	0.26	(0.27)	53	0.09	(0.13)	47	0.17	.25	47	.09	.24	4.50	46	**.0001**
ATT	0.57	(0.31)	52	0.48	(0.33)	48	0.09	0.37	47	-.02	.19	1.59	46	.12
DEP	0.21	(0.25)	53	0.16	(0.23)	47	0.06	0.20	47	.00	.12	2.07	46	**.044**
MEM	0.59	(0.35)	52	0.31	(0.33)	48	0.24	0.35	47	.14	.35	4.69	46	**.0001**
MEN	0.33	(0.24)	53	0.17	(0.20)	48	0.15	0.18	48	.09	.21	5.69	47	**.0001**
SEX	0.46	(0.32)	44	0.34	(0.33)	41	0.14	0.31	38	.04	.24	2.82	37	**.008**
SLE	0.65	(0.32)	53	0.40	(0.31)	47	0.25	0.34	47	.15	.35	5.05	46	**.0001**
SOM	0.49	(0.21)	53	0.34	(0.21)	48	0.15	0.22	48	.09	.21	4.88	47	**.0001**
VAS	0.99	(0.07)	53	0.83	(0.26)	48	0.17	0.26	48	.09	.24	4.45	47	**.0001**
* Significance (2-tailed)														

The data indicate that at EOT, the primary outcome point for the study, there is statistically significant change for all WHQ domains except Attractiveness.

6.5.1.4 WHQ results at the secondary endpoints

In line with the exploratory nature of this work, I analysed the nine WHQ domains at the remaining three endpoints: Mid tx, Post tx 4, and Post tx 18. These data are in Appendix 25.

It is important to emphasise that these data are indicative only, as they are the results of multiple tests. To be statistically correct, the p values should be adjusted using a multiplicity correction such as the Bonferroni correction (Campbell et al. 2000, pp 163-166). Making these corrections

[11] ANX = Anxiety/Fears, ATT = Attractiveness, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms

would avert the criticism of data dredging (Armitage et al. 2002, pp 496 - 498). However, in line with the exploratory nature of this work, I present the data in an uncorrected form, and suggest that these data may be useful in developing future studies (Staquet et al. 1996).

6.5.1.5 Comparing the data for all endpoints

Bearing in mind the qualifications made above, it is interesting to examine these data for trends. We can see the general trend or pattern of change more easily when the results appear in bar chart format, comparing the changes in each domain across the five measurement points, as shown in Figure 24 and Figure 25 below. In these figures, I exclude the domain Attractiveness, as it is now the normal practice to omit it (Hunter 2003).

Figure 24 Results for Anxiety/Fears, Depressed Mood, Memory/Concentration and Menstrual Symptoms

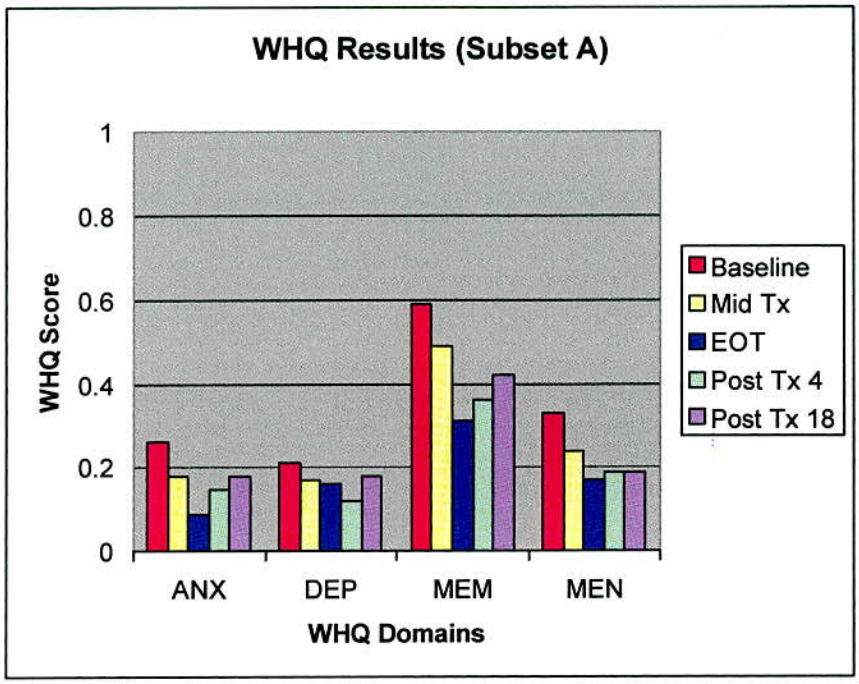
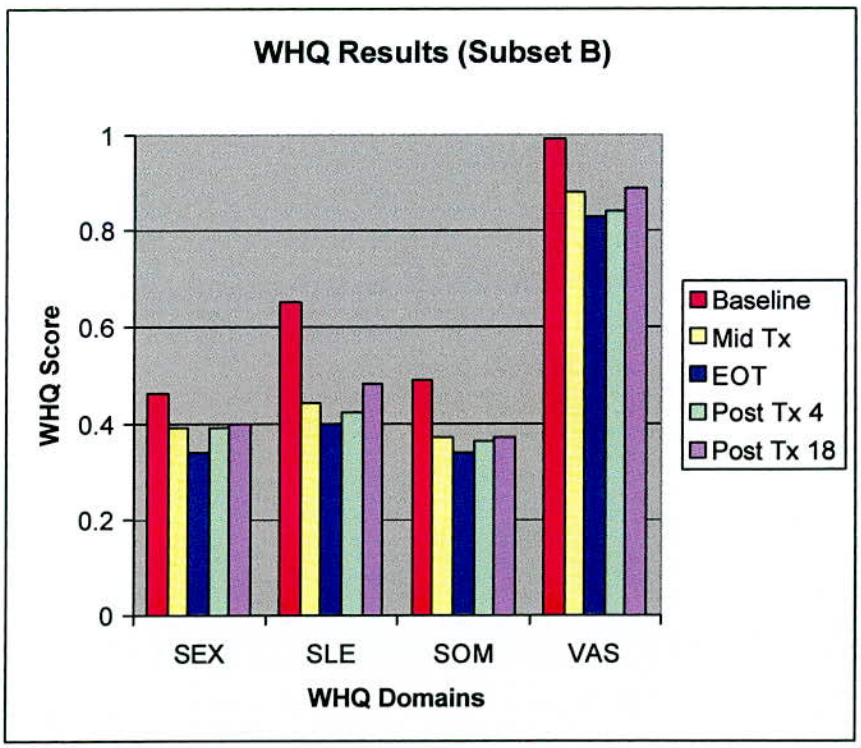


Figure 25 Results for Sexual Behaviour, Sleep Problems, Somatic Symptoms and Vasomotor Symptoms



Guide to abbreviations: ANX = Anxiety/Fears, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms.

Figure 24 and Figure 25 above illustrate the general trend in changes during and following treatment. Overall, symptoms start to recede at Mid tx, and reach their lowest level at EOT. As time from EOT increases, the symptoms begin to return. However, even at the final follow-up (Post tx 18), the symptom scores do not return to their baseline levels. The exception to this pattern is Depressed Mood, which reaches its lowest score at Post tx 4, rather than at EOT as per the other domains. Menstrual Symptoms is also an exception to this pattern, as the Post tx 4 and Post tx 18 scores remain the same, rather than showing an increase at the final measurement point.

This general pattern accords with our hypothesis that emotional and physical well-being would show improvement at EOT, and that symptoms would begin to increase as time from EOT increased.

6.5.1.6 Comparing the data with other studies

Having noted this pattern of change, I will now compare the data with WHQ data from other studies. Figure 26 and Figure 27 below compare the Baseline, EOT, and Post tx 18 results from the TA study with two studies published by Dr Hunter. These are the "norms" derived from the validation of the WHQ showing symptom scores of healthy women (n = 682) undergoing the normal menopause transition (Hunter 1992), and the scores of women with breast cancer (n = 113) (Hunter et al. 2004). In the figures, I refer to the breast cancer group as BCG. Please note that

Hunter does not report data for Memory/Concentration (MEM) and Menstrual Symptoms (MEN) in her breast cancer group (BCG) study.

Figure 26 TA WHQ results compared with norms and breast cancer group (BCG) showing Anxiety/Fears, Depressed Mood, Memory/Concentration and Menstrual Symptoms

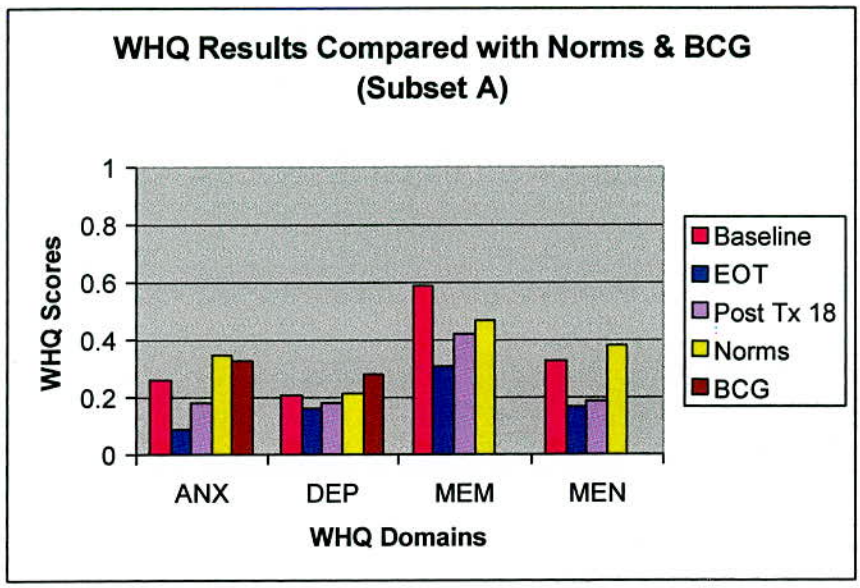
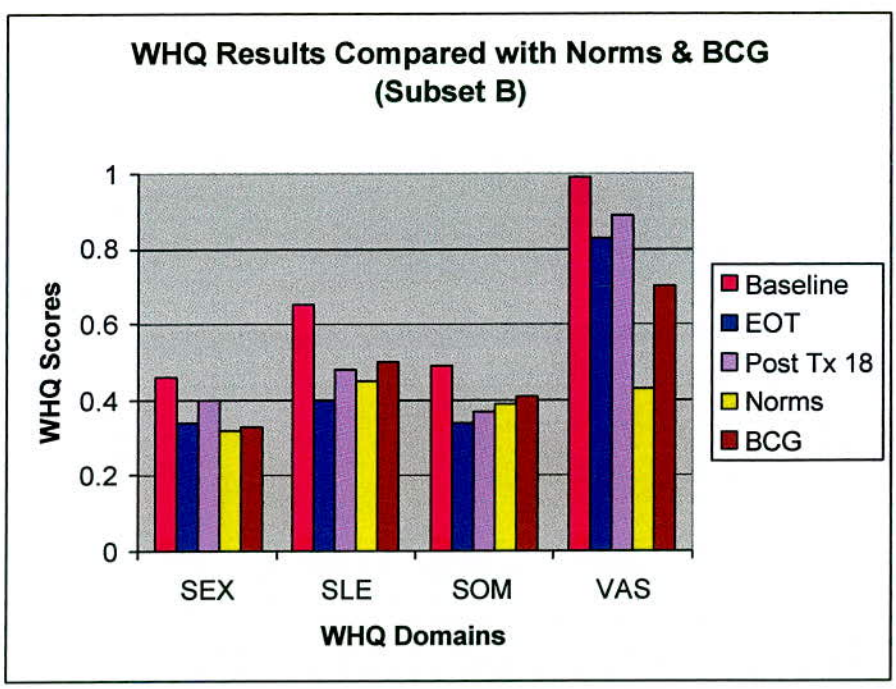


Figure 27 TA WHQ results compared with norms and breast cancer group (BCG) showing Sexual Behaviour, Sleep Problems, Somatic Symptoms, and Vasomotor Symptoms



Guide to abbreviations: ANX = Anxiety/Fears, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms.

This comparison illustrates some interesting patterns. At baseline, the TA group have a higher symptom score than the norms in all domains except Anxiety/Fears and Depressed Mood. This is also the case for comparisons with the scores of the breast cancer group (BCG). At EOT, the TA scores drop below the scores of the norms in all domains except Sexual Behaviour and Vasomotor Symptoms. This is also the case when comparing the TA EOT scores with the BCG scores.

At Post tx 18, the TA group scores remain lower than the norms for Anxiety/Fears, Depressed Mood, Memory/Concentration, Menstrual Symptoms, and Somatic Symptoms. Again, this is the case when comparing TA Post tx 18 scores with the BCG scores, bearing in mind that Hunter (2004) does not report scores for Memory/Concentration and Menstrual Symptoms. At the final follow-up, the TA group scores for Sexual Behaviour have climbed to slightly higher than the norms and BCG score. The score for Sleep Problems has climbed to higher than the norms, but remains slightly lower than that for the BCG. Scores for Vasomotor Symptoms have also increased, and were always higher than the two comparison groups. Overall, there is a tendency for WHQ scores in the TA group at EOT to drop below those for the norms, with the exception of Vasomotor Symptoms.

6.5.2 Somatic Symptoms Sub-Analysis

We explored data relating to "Somatic Symptoms" to determine whether participants experienced benefits in any particular aspect(s) of this domain. The domain comprises seven symptoms including

backache/pain, dizzy spells, frequent urination, headache, nausea, pins and needles, and tiredness.

6.5.2.1 Hypothesis

This sub-analysis was purely exploratory, and we had no hypothesis about the possible result.

6.5.2.2 Somatic Symptoms: results

Table 30 below shows the means and standard deviations for all seven questions at all five measurement points.

It is necessary to highlight that the data from this sub-analysis do not compare directly with the WHQ results. Calculation of the WHQ results accords with the 0 to 1 symptom scale discussed in section 4.9.5, starting on page 147. Calculation of the somatic symptoms data is based on the raw scores (that is, "yes, definitely" (3), "yes, sometimes" (2), "no, not much" (1), "no, not at all" (0), as per the WHQ questionnaire. The vertical axis on Figure 28 on page 224 indicates these.

Table 30 Somatic Symptoms sub-analysis: means and standard deviations (TA)

Seq Symp - tom[12]	Baseline			Mid tx			EOT			Post tx 4			Post tx 18		
	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =
BAC	1.73	.98	48	1.67	.98	48	1.56	1.13	48	1.81	1.01	47	1.58	1.13	48
DIZ	.64	.82	47	.62	.95	47	.38	.76	48	.38	.64	47	.46	.87	48
FRE	1.89	.84	47	1.55	1.1	47	1.39	1.02	46	1.41	1.05	46	1.42	1.05	48
HEA	1.38	.87	48	1.13	.89	48	1.0	.83	48	0.91	.8	47	0.94	.69	49
NAU	.58	.79	48	.46	.77	48	.23	.52	48	.36	.71	47	.41	.81	49
PIN	1.09	.99	46	.85	1.01	46	.87	1.09	46	.96	1.04	45	.91	1.08	47
TIR	2.29	.8	48	1.67	1.1	48	1.48	1.07	48	1.8	1.1	46	1.96	.92	48

Table 31 below presents the results of paired samples t tests showing the results at each measurement point compared with baseline. These data are the results of multiple tests, without a prior hypothesis. As such, they should undergo correction as discussed in Section 6.5.1.4, page 214. Correction for multiplicity is beyond the scope of this thesis, and these data are indicative only.

[12] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness

Table 31 Results of paired samples t tests for Somatic Symptoms (TA)

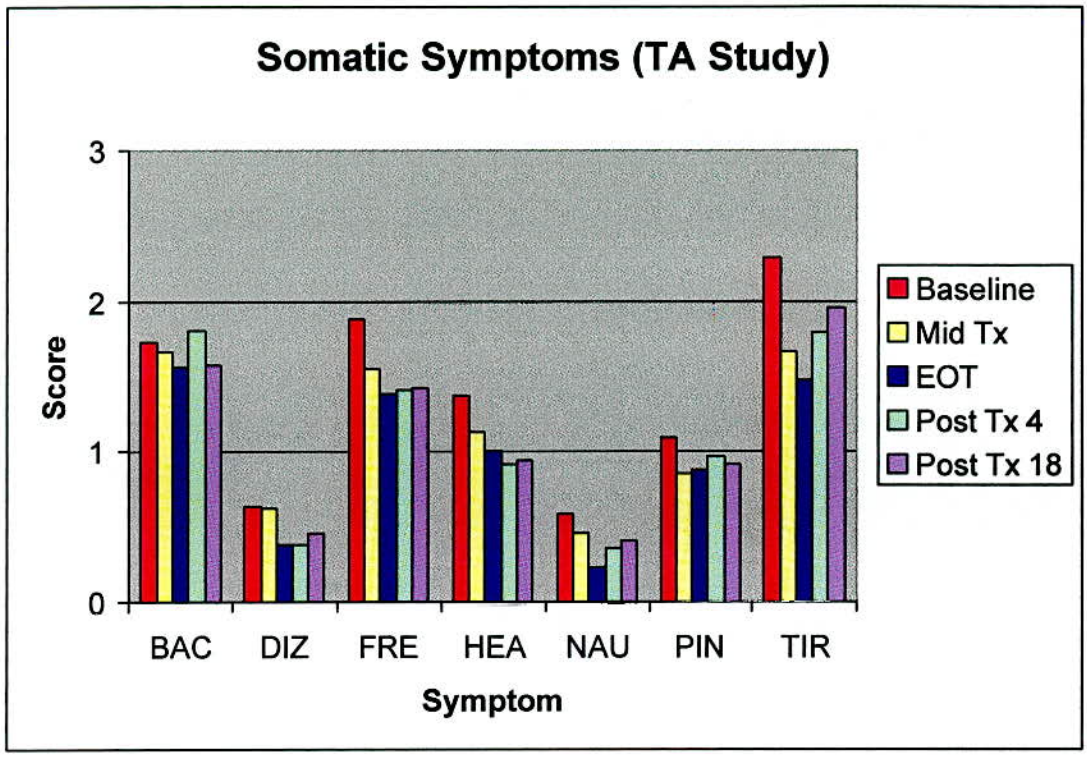
Sym-ptom[13]	Baseline – Mid tx			Baseline – EOT			Baseline – Post tx 4			Baseline – Post tx 18		
	t =	df	p= *	t =	df	p= *	t =	df	p= *	t =	df	p= *
BAC	0.47	47	.64	1.57	47	.12	-.39	46	.7	1.76	47	.09
DIZ	0.15	46	.88	2.01	47	.051	2.04	46	.047	1.48	47	.15
FRE	2.11	46	.04	2.8	45	.008	2.8	45	.008	2.57	47	.013
HEA	1.73	47	.09	2.84	47	.007	3.7	46	.001	3.06	48	.004
NAU	1.03	47	.31	2.89	47	.006	1.77	46	.08	1.43	48	.16
PIN	1.86	45	.7	.94	45	.35	0.14	44	.89	0.81	46	.42
TIR	4.74	47	.0001	5.92	47	.0001	4.16	45	.0001	2.56	47	.014

* Significance (2-tailed)

Bearing in mind the qualifications made above, it is interesting to examine these data for trends. We can see the general trend or pattern of change more easily when the data appear in bar chart format, comparing the changes in each domain across the five measurement points, as shown in Figure 28 below.

[13] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness

Figure 28 Bar chart showing results of Somatic Symptoms[14] sub-analysis



This chart shows that Tiredness is the symptom that shows the greatest change at EOT, followed by Frequent Urination and Headaches.

As with the WHQ results discussed previously, the pattern shows a decline in all categories at Mid tx, with the greatest decrease in symptoms at EOT. Unlike the previous results, the pattern of the return of symptoms is not consistent for all categories, and scores for Backache/pain and Pins and Needles are higher at Post tx 4 than at Post tx 18. However, all measures at Post tx 18 are lower than at baseline, as per the overall WHQ data.

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[14] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness,

6.5.3 Results for HFNSQ: TA study

The Hot Flushes and Night Sweats Questionnaire (HFNSQ) provides the data to calculate the Problem Rating Score (PRS), which indicates how much of a problem women perceive their hot flushes to be in their daily lives.

6.5.3.1 Hypothesis

This exercise was purely exploratory, and we had no hypothesis about the possible result.

6.5.3.2 Results

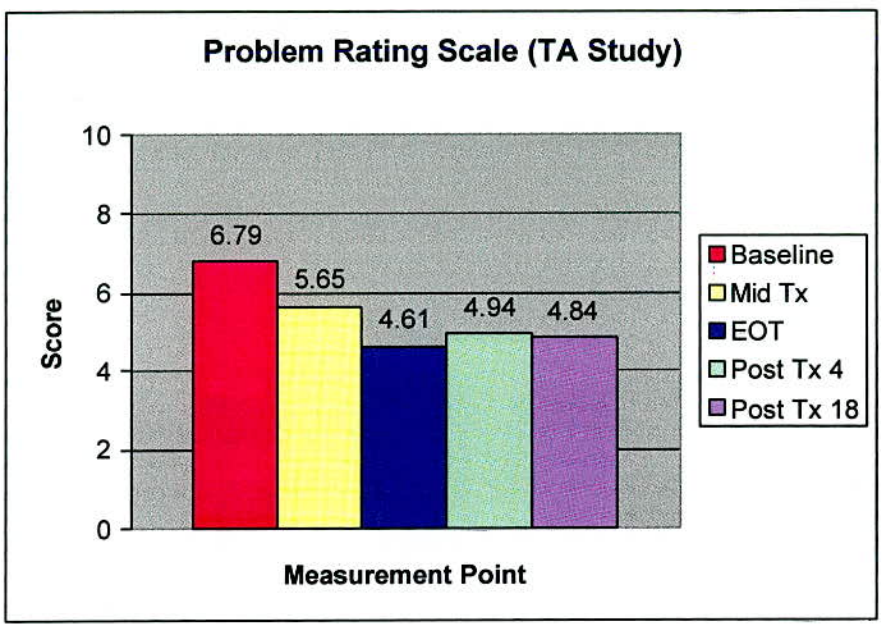
Table 32 below presents the data showing the means and standard deviations for all measurement points.

Table 32 Means and standard deviations for the Problem Rating Score (TA)

Sequence	Mean	SD	N =
Baseline	6.79	1.94	52
Mid tx	5.65	2.32	48
EOT	4.61	2.39	48
Post tx 4	4.94	2.36	47
Post tx 18	4.84	2.11	48

Figure 29 below presents these data in bar chart format, to illustrate the pattern of change over the five measurement periods.

Figure 29 Changes in the Problem Rating Scale (TA)



Once again, we see the relatively high score at baseline dropping to its lowest point at EOT. The rising scores at the two follow-up points are unusual in that Post tx 4 is slightly higher than Post tx 18, but this difference is unlikely to be significant.

Table 33 below presents the results of paired samples t tests showing the change at each measurement point compared with baseline. **Bold** formatting highlights the statistically significant results ($p < 0.05$). (Whilst the previous comments about making corrections for multiple tests apply to these data, all the results are highly significant, and there is less than one in a thousand chances that the results are due to chance. Therefore, it is possible to take these data at their face value, rather than correcting them for multiple testing.)

Table 33 Results of paired samples t tests for PRS data (TA)

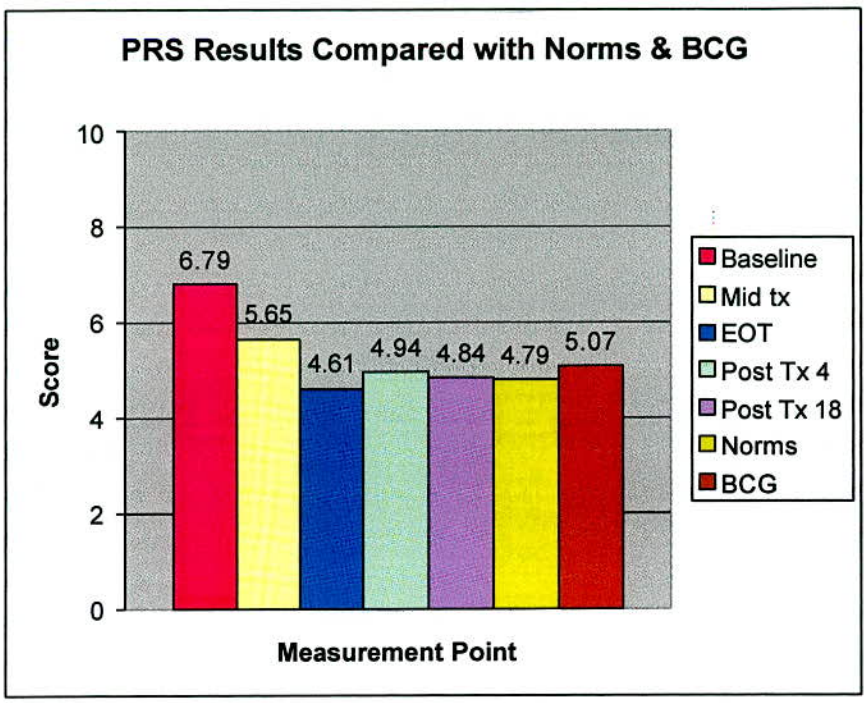
	Paired differences					Paired sample t tests		
				95% CI				
	Mean	SD	N =	LL	UL	t =	df	p < *
Baseline – Mid tx	1.11	1.88	48	0.57	1.66	4.1	47	**.0001**
Baseline – EOT	2.22	2.15	48	1.60	2.84	7.16	47	**.0001**
Baseline – Post tx 4	1.86	2.37	47	1.16	2.55	5.38	46	**.0001**
Baseline – Post tx 18	1.95	2.16	48	1.33	2.58	6.27	47	**.0001**

* Significance (2-tailed)

6.5.3.3 Comparing the data with other studies

As with the WHQ results, we compared the TA results with the two studies reported by Hunter. Figure 30 below compares the TA results at all five measurement points with the "norms" and breast cancer group (BCG) results reported by Hunter (1992, 2004).

Figure 30 Comparison of TA PRS results with Norms and BCG results



The baseline measurement for this group is higher than the norms (n = 682) and the BCG results (n = 113). At EOT, the score descends to a level slightly below those of the comparison groups. Although it rises slightly at Post tx 4, it drops at Post tx 18, and this final measurement point is similar to the comparison groups.

6.6 Acceptability of Traditional Acupuncture

This section presents the results of the following three questionnaires:

- Exit Questionnaire (EQ) administered at EOT
- Follow-up Questionnaire 1 (FQ1) administered at Post tx 4
- Final Follow-up Questionnaire (FFQ) administered at Post tx 18.

The analysis examines selected questions from these questionnaires to answer the question "Is traditional acupuncture acceptable to women who have had invasive treatments for breast cancer?"

6.6.1 Compliance and missing data

Table 34 below presents the numbers of questionnaires returned at each measurement point.

Table 34 Numbers of follow-up questionnaires returned at each measurement point

MEASUREMENT PERIOD	EOT (EQ)	Post tx 4 (FQ1)	Post tx 18 (FFQ)
QUESTIONNAIRES RETURNED	48	47	49

Only one of the 50 women who completed the course of treatment did not return any of the three questionnaires. One participant did not return the EQ and FQ1; another participant's FQ1 was missing. On the questionnaires, data were occasionally missing. Many participants answered the yes/no questions, and chose not to provide further written comments.

6.6.2 Results

6.6.2.1 Analysing the frequencies

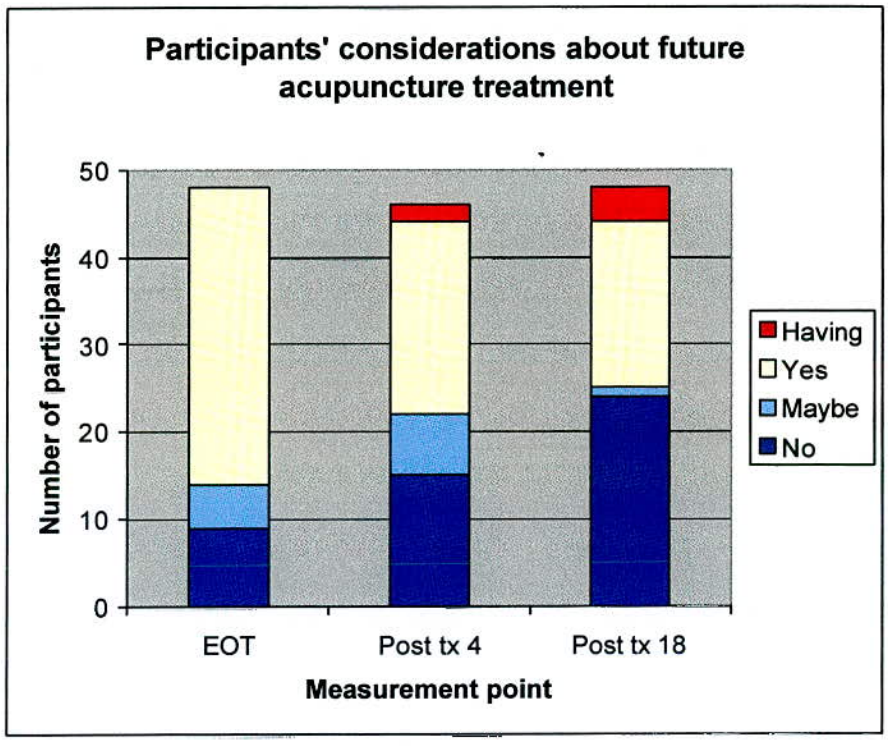
Table 35 below displays the results of the selected questions.

Table 35 Results for acceptability of acupuncture

Exit Questionnaire (EQ) administered at EOT	n=50 (%)
Are you considering having further acupuncture?	
Yes	34 (68)
No	9 (18)
Maybe	5 (10)
Missing	2(4)
Were there any aspects of this study you didn't like?	
Yes	1 (2)
No	47 (94)
Missing	2 (4)
Follow-up Questionnaire 1 (FQ1) administered at Post tx 4	
Are you having further acupuncture treatment?	
Yes	2 (4)
No	45 (90)
Missing	3 (6)
If not, are you considering having acupuncture in the near future to manage your hot flushes and night sweats?	
Yes	22 (44)
Not applicable (having acupuncture)	2 (4)
No	15 (30)
Maybe	7 (14)
Missing	4 (8)
Are you pleased you took part in the study?	
Yes	47 (94)
Missing	3 (6)
Do you regret taking part?	
No	47 (94)
Missing	3 (6)
Final Follow-up Questionnaire (FFQ) administered at Post tx 18	
Have you had any acupuncture for hot flushes and night sweats since finishing your course of treatment here?	
Yes	4 (8)
No	45 (90)
Missing	1 (2)
Have you had any acupuncture for any other health complaints since finishing your course of treatment here?	
No	49 (98)
Missing	1 (2)
If not, are you considering having acupuncture in the near future?	
Yes	19 (38)
Not applicable (having acupuncture)	4 (8)
No	24 (48)
Maybe	1 (2)
Missing	2 (4)
Would you recommend acupuncture to a friend?	
Yes	45 (90)
No	2 (4)
Maybe	1 (2)
Missing	2 (4)

At EOT, there is a great enthusiasm for having further acupuncture treatment, with over three-quarters of participants saying they were considering (68%) or might consider (10%) having further acupuncture. However, this enthusiasm wanes as the time from EOT increases, as Figure 31 below shows.

Figure 31 Changes in participants considering having future acupuncture treatment



The reasons for this decline are not clear. Two participants cited cost as a reason for not having further treatment privately. Some women expressed disappointment that their flushes did not completely disappear, or that they returned as time from EOT increased. These may be reasons that they did not pursue further treatment.

Only one participant said there was an aspect of the study she did not like, and that she "found some of the needles painful". (However, this

participant later volunteered to take part in the NADA user involvement pilot, as described in section 7.3.4 on page 258.) All of the participants who completed questionnaires stated they were pleased to have taken part in the study, and none of the participants expressed regrets.

Most participants said they would recommend acupuncture to a friend. Only 2 (4%) said they would not: one stated "it is something very personal & a decision one would have to make oneself"; another, who was disappointed in the effect on her hot flushes said that "(I) don't feel I could recommend a treatment that didn't work. However I would not be negative about someone trying it."

6.6.3 Analysing written comments: expectations versus experience

The Exit Questionnaire asked, "How did your experience of having acupuncture match your expectations about what acupuncture might be like?" Forty-five participants chose to write a short comment in response. These responses provide further data to answer the question about acupuncture's acceptability to these women. The main themes arising from the comments include expectation; pain, sensation, and apprehension; and relaxation.

6.6.3.1 Expectation

Seven participants volunteered that they had acupuncture previously, so had some idea of what to expect. However, one of these found the experience different, in that "previously I didn't experience sensations as I

did this time". Here she refers to the needle sensation (deqi) that I aimed to obtain when needling, and which was apparently not part of her previous treatment.

Those new to acupuncture expressed a range of expectations. Some came to the study with "no expectations" or "no preconceived idea" about acupuncture, and "had (an) open mind" about what acupuncture would be like. Many said they "didn't know what to expect", and others had some preconception of what it would be like, which matched their experience. Comments that acupuncture "was as I'd imagined" or it "matched up to what I thought it would be like" illustrate this. Some were pleasantly surprised: it was "better than expected", or it "wasn't as bad as (I) thought it would be". One woman said, "It was a far more gentle procedure that I expected and gave me a wonderful sense of well-being".

6.6.3.2 Pain, sensation and apprehension

People who have never had acupuncture often expect it to be painful. Ten participants mention pain, and all but one of them remarked that they found acupuncture "painless". Some expected it to be painful: one woman said she "thought the needles may hurt but they didn't", whilst another "didn't think it would be painful and it wasn't". Four other participants remark on needle sensation. The participant who had previous experience of acupuncture is quoted above, and another said that the "needle sensation (was) more than I expected". Only one participant suggests the experience was painful, but this was not off-

putting: "actual use of the needles didn't worry me, and if one hurt BdV took it out. Wasn't as bad as (I) thought it would be."

Associated with this is the apprehension associated with fear of the unknown. Two participants mention this: one wrote of a "slight fear of the unknown which vanished with (the) first treatment", and the other remarked that acupuncture was "not as scary as (I) thought. After chemo(therapy) needles I was apprehensive." A participant who said she "expected the needles to be larger and more painful" echoes this theme.

6.6.3.3 Relaxation

In spite of any apprehensions, the participants comment frequently on acupuncture being "pleasant & relaxing". For some, this was a surprise: one woman said she "thought it would be more stressful but it was v(ery) relaxing"; another said she was "surprised how relaxing it was" and others remarked that it was "more relaxing than expected". Only one woman said that she "didn't find it as relaxing as I thought it would be".

These comments suggest that many – perhaps the majority – of women taking part in the study found acupuncture acceptable as a form of treatment, and they did not find it unduly uncomfortable. The low number of losses to the study further implies this.

6.6.4 Other indications of acceptability

There is other evidence to support the idea that many women in this study found acupuncture acceptable. In addition to the four participants

who chose to have acupuncture privately, six participants volunteered to take part in a pilot study for the ear acupuncture (NADA) study (discussed in section 7.3.4, page 258). Others expressed interest in taking part in the NADA pilot, but were unable to attend the sessions due to other commitments. Three other women also took part in the NADA study itself (refer to the discussion in section 9.5.1.3, page 323 for how we handled the statistical analysis for these "repeat" participants). The participant who did not return any of her questionnaires referred other women to the studies, and this suggests that she found it acupuncture acceptable enough to recommend to friends.

6.7 Conclusion

In this chapter, I presented the results relating to the three main questions of this study. The data suggest that traditional acupuncture may have an effect on reducing the frequency of hot flushes and night sweats, and that at EOT a woman might expect to have the number reduced by nearly 50% over her baseline frequency. The results of the WHQ suggest that women experience a range of improvements in their physical and emotional well-being, and the Somatic Symptoms sub-analysis suggests that women feel less tired because of treatment. In addition, women seem to see their hot flushes as less of a problem in their daily lives. Finally, the data suggest that the majority of women in this study found traditional acupuncture acceptable as a form of treatment.

Chapter 7 Design & Methodology Specific to Study 2: NADA

7.1 Synopsis

In this chapter, I discuss the rationale for conducting Study 2: NADA[15] and the design and methodology of this phase. After introducing the practice of auriculotherapy, and examining the NADA ear acupuncture protocol, I present the rationale for adopting this approach. In doing so, I evaluate the appropriateness of the NADA protocol for use in managing hot flushes and night sweats, comparing it to the treatment principles used in Study 1: TA. I identify the differences between Study 1 and Study 2, before detailing the NADA specific methodology pertaining to Study 2. I present this according to the guidelines specified by the STRICTA protocol for reporting acupuncture studies.

7.2 Background to Study 2: NADA

7.2.1 Rationale for Study 2

We were encouraged by the results of Study 1: Traditional Acupuncture. At the LJMC, we articulated an aim "to integrate acupuncture into the National Health Service (NHS) as a treatment option for women with breast cancer who suffer from hot flushes and night sweats as a result of

[15] NADA stands for the National Acupuncture Detoxification Association, who developed the protocol used in Study 2. See section 7.2.3 for details.

adjuvant treatment". I disseminated our findings at research and cancer conferences (see Appendix 32), and to acupuncture and healthcare professionals. Medical professionals were generally receptive to the outcomes of Study 1, even though the study was not a controlled trial. However, discussions with medical acupuncturists and some physiotherapists revealed a number of obstacles that could potentially inhibit the widespread implementation of this approach in the NHS.

It became clear that these practitioners did not understand the principles of traditional acupuncture, and therefore were unable to grasp the logic of the core protocol used in Study 1 (see section 5.7, starting on page 158). Thus, they did not understand the concept and techniques involved in opening the ren mai (or directing vessel), which is the basis of the protocol. Many were unfamiliar with some of the points used. Most were not conversant with the needling techniques used in traditional acupuncture. They did not share the view that treatments could be semi-individualised, nor did they expect a course of treatment to be dynamic, and to change in response to the patient's changing condition. Most of all, they rejected the length of time spent on each treatment: it was out of the question to spend an hour with a patient. Although it is easily possible to reduce this appointment time, they said that a protocol that requires needles to stay in place for 20 minutes is impractical for the demands of a busy surgery. It became clear that doctors practising medical acupuncture wanted a treatment that was quick to deliver and

used a standard set of points. Traditional acupuncture, it appeared, was too complex.

Thus, our challenge in Study 2 was to find a mode of acupuncture that could work within the constraints of the NHS. We wanted to develop an approach that is quick, easy and simple to deliver; that requires a minimum of training; and that has the capacity to accommodate potentially large numbers of patients for potentially long periods of time (women take tamoxifen for up to five years). Cost is another important consideration: funding for new NHS services is difficult to obtain. As hot flushes are neither life threatening nor a priority for treatment, a new service needs to be inexpensive if our aim of widespread implementation is to succeed.

It seemed to me that auriculotherapy, or ear acupuncture, might offer a solution, and I began to investigate its possibilities.

7.2.2 What is auriculotherapy?

7.2.2.1 Definition

Oleson (2005) defines auriculotherapy as a therapeutic intervention that uses stimulation of the external ear (or auricle) to alleviate health conditions elsewhere in the body. Stimuli include acupuncture needles (with or without electric stimulation), electro-stimulation (use of an electric probe), laser, press tacks (small semi-permanent needles), ear seeds (*semen vaccaria* or mustard seeds held in place with adhesive plaster), or

magnetic pellets. Special staple guns are also used, as is injection with solutions such as Novocaine, saline, vitamins or herbs (Jia 2003, Oleson 1996, Rubach et al. 2001). Nogier (1998) also recommended cauterisation with the end of an incense stick, although this seems to have fallen from general usage.

Oleson, who is a leading English-speaking authority on auriculotherapy, provides additional definitions (2005). When needles provide the stimulation, the intervention is known as "ear acupuncture" or "auricular acupuncture", whilst the term "auriculotherapy" applies when electro-stimulation with a probe is used. Auricular acupressure or ear reflexology refers to stimulation by manual pressure. In this chapter, I use the term "auriculotherapy" to describe general aspects of ear acupuncture. I use the term "ear acupuncture" when discussing details relating to using the NADA ear acupuncture protocol.

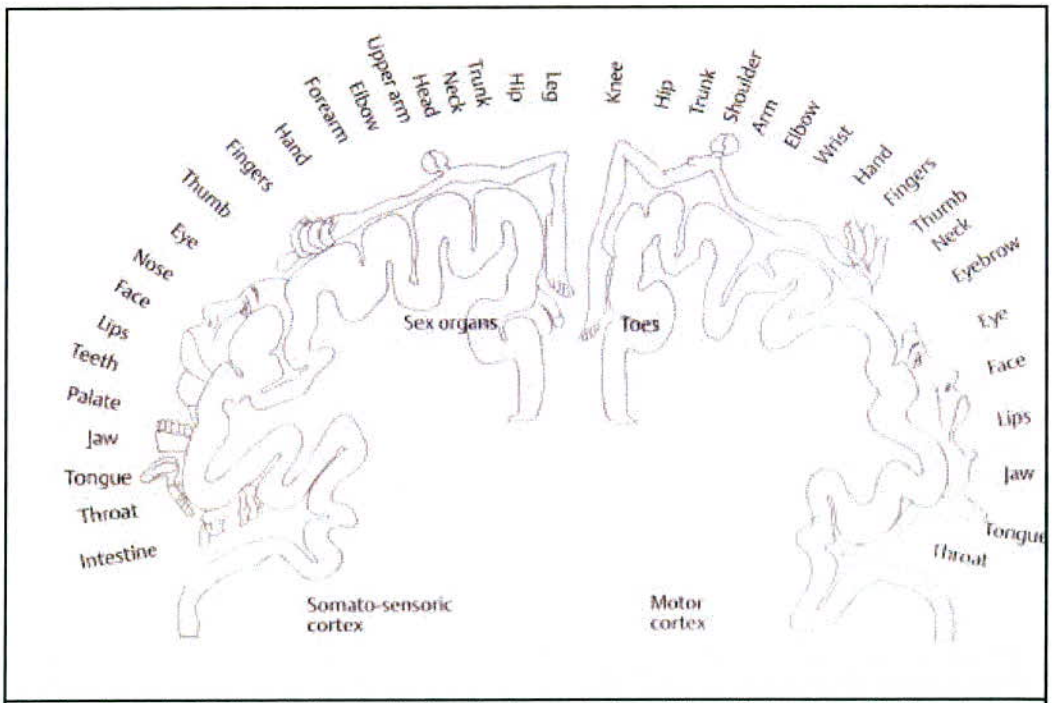
7.2.2.2 Theoretical basis of auriculotherapy

Whatever the mode of stimulation, the underlying theory remains the same. Auriculotherapy uses the concept of the micro-system, in which one part of the body represents the whole body. Reflexology is a well-known micro-system. There are many other types of micro-system: Korean hand acupuncture, Japanese abdominal palpation (Birch and Felt 1999), Chinese ear, scalp and hand acupuncture are some examples (Lewith and Lewith 1983, Hecker et al. 2005). Dr Wan of the Zhejiang College of Traditional Chinese Medicine listed eight micro-systems recognised in modern Chinese clinical practice, including scalp, wrist, ear,

palm, ankle, heel, nose, and eye (Wan, personal communication, 16 October 1998). There are many hypotheses about how these micro-systems work (Jia 2003, Oleson 1996, Oleson 2002); the simplified description that follows is just one of a number of these explanations.

Micro-systems use a somatotopic representation (a "body topography" or map) to link areas of the micro-system with the anatomical arrangement of the entire body. This relates to the neurological reflexes in the brain identified in Penfield and Rasmussen's brain mapping studies (cited by Rubach et al. 2001). This brain mapping, illustrated in Figure 32, is commonly referred to as the "homunculus" or little man (Oleson 1996).

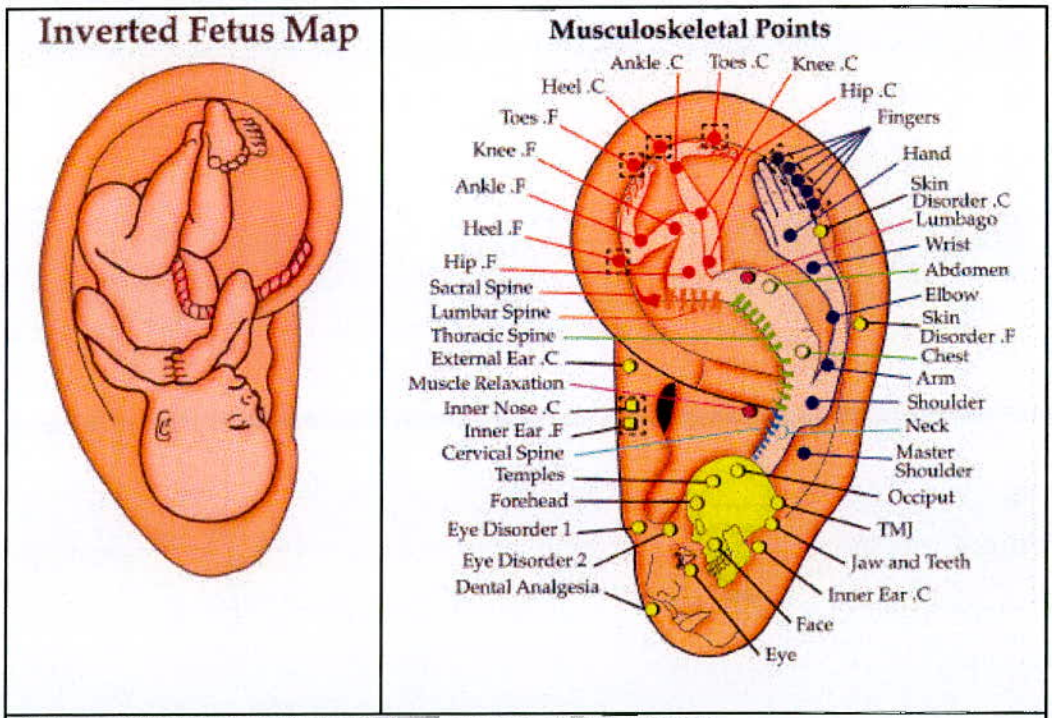
Figure 32 The homunculus



(Rubach et al. 2001 p 8) Used with the kind permission of Axel Rubach and Thieme Publishing Group

In auriculotherapy, the somatotopic map uses the image of an inverted foetus, as shown on the left side of Figure 33 below. In this map, the head areas occupy the ear lobe, the feet occupy the ear apex, and the body lies in between. The diagram on the right of Figure 33 illustrates a more detailed correspondence of the micro-system of the ear to some areas of the body (in this case, the musculoskeletal system). Here the skull is located towards the bottom of the ear, the feet towards the top of the ear, with the torso occupying the space between. The coloured dots on the diagram represent the auricular points used to treat the corresponding area of the body.

Figure 33 The ear showing the mapping of the inverted foetus and the mapping of the musculoskeletal points



(Oleson 1996) Used with the kind permission of Terry Oleson.

These correspondences do not imply a direct connection between the points on the ear and their related anatomical areas. Instead, nerves in

the ear connect to reflex centres in the brain (as represented on the homunculus), which in turn transmit impulses through the neurological system to the related area(s) of the body (Oleson 2005).

7.2.2.3 Diagnosis and treatment

Diagnosis and treatment in auriculotherapy rely on identifying areas of the ear that show changes in colour or skin texture, are tender, or have a high skin conductance when measured with a probe. Generally, the areas of the ear will only show these signs when there is pathology in the related anatomical structure. Treatment involves stimulating these areas using any of the methods listed above (see section 7.2.2, page 238). While there is inconclusive scientific evidence of the validity of the neurological theories of auriculotherapy, there is a growing body of clinical experience and of research investigating this area (Oleson 2002).

7.2.2.4 Brief history of auriculotherapy

The status of auriculotherapy in ancient Chinese medicine is obscure. Writers refer to a passage from *The Yellow Emperor's Canon of Internal Medicine* (*the Huang Di Nei Jing*), which connects the six yang meridians directly to the ear (Rubach et al. 2001, Oleson 2003). It is unclear how ear points were used in practice in ancient China (Oleson 1996), and it is Dr P M F Nogier, a French physician, who is credited with the development of modern auriculotherapy. Observing that patients in the area of Lyon bore a peculiar cauterisation of the auricle, he discovered that the intervention performed by a lay practitioner had relieved sciatic pain. This led him to explore the auricle and its use in pain relief; in 1956,

he presented his theories to a conference in Marseille. Translated almost immediately into German, his work was also translated into Chinese. In 1958, the Nanjing Army Ear Acupuncture Research Team conducted extensive studies on 2,000 patients to verify the clinical accuracy of the "Nogier homunculus". The successful outcome resulted in Mao Tse-tung's adoption of ear acupuncture in his "Barefoot Doctor" programme (Oleson 2003).

Development of Nogier's basic theories has evolved into complex systems, with significant differences between points, correspondences, and nomenclature specific to the French and Chinese systems. Work is ongoing, primarily by the World Health Organisation (WHO) and the University of California, Los Angeles (UCLA) to attempt to standardise these systems to provide a consistent approach that can be understood internationally.

7.2.2.5 Why auriculotherapy was considered for this study

Initially, auriculotherapy looked as if it could work within the constraints of the NHS. Access to the ears is usually straightforward. Recipients do not need to remove clothing, so there is potential to offer treatment in a group setting, rather than on a one-to-one basis. With breast cancer patients, there are no access problems – both ears can be needled without risking lymphoedema (access to acupuncture points was a problem on the TA study, as needling is contraindicated on the arm on the side of the surgery for fear of increasing the likelihood of lymphoedema (see section 5.13.2.3 on page 197).

However, auriculotherapy has its own diagnostic procedures, which require training and experience to use effectively. These include visual assessment of changes on the ear surface (including colouring, skin texture, and appearance of veins, spots or creases), tactile assessment to determine the sensitivity of specific points, and electrical detection using specially designed electrical point finders for the ear (Oleson 2003, Rubach et al. 2001, Nogier 1998, Birch and Felt 1999). In addition, location of the ear reflex points requires skill. The somatotopic charts used for point location indicate an area within which a point may be found, rather than a specific location. The practitioner must identify the "active" point within this area using the assessment techniques discussed in section 7.2.2.3 on page 242.

These characteristics of auriculotherapy suggested it would be more complex to administer than I initially anticipated. Furthermore, there was little research and almost no literature on the use of auriculotherapy to manage hot flushes. Oleson suggested using ear points shenmen, sympathetic, point zero, pituitary, ovaries, uterus, and heat point. He advised that the most effective approach "is to discern the points on the ear that are most electrodermally reactive and tender to palpation, whether or not they are on the list of points ... just mentioned" (Oleson, T, personal communication by email, 23 January 2003). A system requiring the skills to locate points using visual observation of ear colouration or the

use of electrical equipment did not seem to match our requirements for an easy to train, easy to deliver ear acupuncture protocol.

It became apparent that I was looking for an "off-the-shelf" ear acupuncture package, one that came with a history of usage and evidence of its effects. At this time, I was involved in teaching university students on a substance misuse course, and introducing them to the use of NADA ear protocol acupuncture in detoxification settings. In practical, experiential sessions, I observed that recipients experienced profound effects from this treatment, which requires no diagnostic skill, and is simple and quick to administer. I wondered if this was a potential treatment for hot flushes.

7.2.3 What is the NADA protocol?

NADA stands for the National Acupuncture Detoxification Association. Dr Michael O Smith, MD DAc, a psychiatrist and the director of the Lincoln Recovery Centre in the South Bronx, New York City, is credited with developing the five-point ear acupuncture protocol that has come to be known as the "NADA protocol". This was derived from work initiated by Wen and Cheung in Hong Kong in the early 1970s (Wen and Cheung 1973), following Wen's observations of reduced opioid withdrawal symptoms in a patient receiving auricular acupuncture for pain control during surgery (Brumbaugh 1994).

Pragmatic responses to circumstances (particularly budget constraints) played a major role in the development of the NADA protocol.

Experimenting with electro-acupuncture as an alternative to methadone treatment for heroin addicts, Smith and his team discontinued the use of electro-stimulation in favour of manual acupuncture when budgetary constraints prevented replacement of the equipment. They discovered that manual acupuncture was effective, easier to administer and less expensive than electro-stimulation (Brumbaugh 1994). Development of the group clinic approach also stemmed from budget restrictions: funds were simply not available to deliver acupuncture on a one-to-one basis, so Smith introduced the group clinic, which is now an integral feature of the NADA protocol (Kolenda 2000). Successful results with this approach led to the formation of NADA as an organisation in the United States in 1985. NADA remains responsible for developing the protocol, training Addiction Detoxification Specialists (ADS), and disseminating information throughout the world (NADA no date).

7.2.4 Rationale for using the NADA protocol

The spirit of pragmatic response to constraints, and the associated success of the resulting protocol, gives the NADA protocol particular appeal for use in the NHS. Furthermore, the essence of the NADA protocol is its simplicity (Smith 2001b). The five-point protocol described below is standard; no diagnostic skills are required. In Britain, NADA UK has an established training structure, which trains non-acupuncturists to deliver the protocol in less than a week. These non-acupuncturists can deliver the protocol as NADA Addiction Detoxification Specialists so long as they undergo an annual assessment by NADA UK. (Qualified acupuncturists can simply use the protocol as part of their repertoire, or

they may choose to train with and join NADA UK as detoxification specialists.) In addition, using the group clinic approach makes the delivery cost-effective, as there is potential for one practitioner to treat up to 20 patients in an hour and a half (Peckham 2005). Ease of delivery, ease of training, and potential cost effectiveness were attractive features of the NADA protocol. They matched our requirements for a possible approach to managing the problem of hot flushes in women with early breast cancer in the NHS.

Furthermore, as a research acupuncturist, I felt it would be challenging to explore the effects of a standardised protocol. The received wisdom amongst traditional acupuncturists, as well as most CAM therapists, is that individualised treatment is preferable to and more effective than a standard approach. Using the NADA protocol would be an opportunity to begin to investigate this.

However, could an ear acupuncture protocol designed for use in addiction rehabilitation clinics be appropriate for treating side effects of adjuvant cancer treatment? In addition, would British women accept treatment in group clinics, which I had decided would be an essential feature of this delivery method?

7.2.4.1 Evaluating the treatment effects

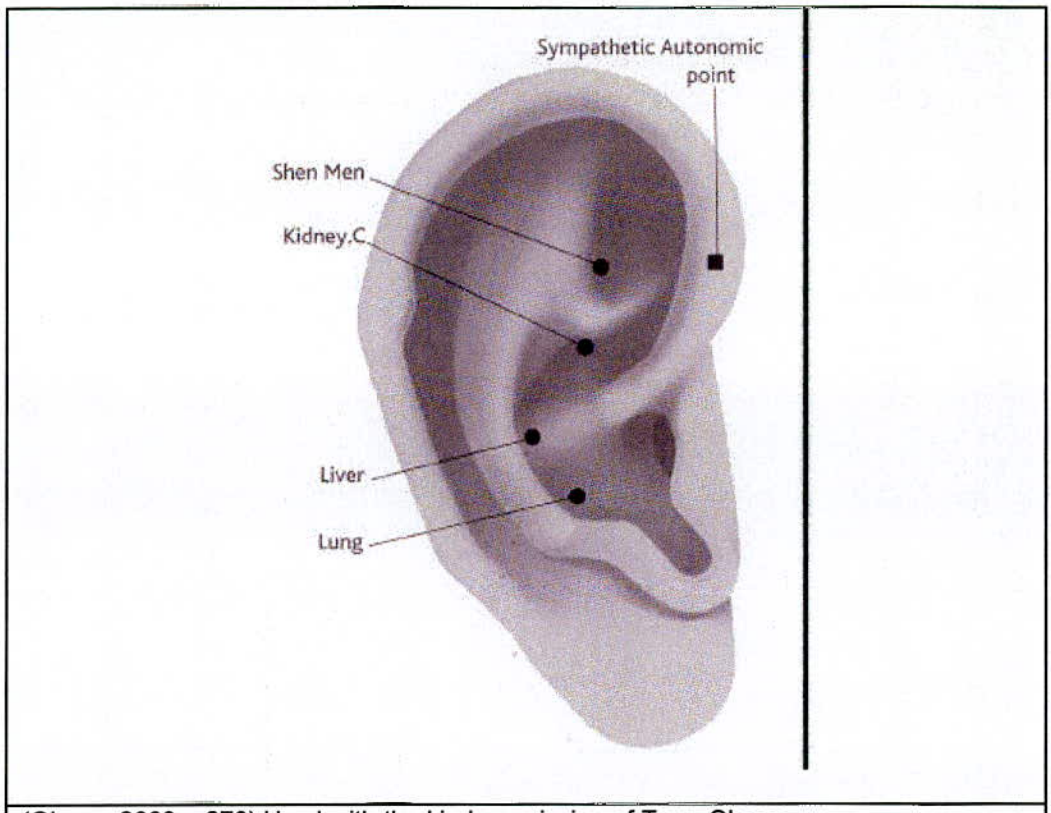
My first task was to examine the treatment effects observed in NADA recipients in its original context, addiction detoxification. Although most reports are anecdotal, a considerable body of clinical observation has

accumulated over the decades of the protocol's use (Brumbaugh 1994, Peckham 2005, Smith 2001b, Voyles 2001, Smith 2001a). Commonly observed effects include "marked relaxation, a feeling of well-being, improved sleep patterns, a clearer mind..., stimulation and strengthening of particular organ systems, especially the kidney, liver, and lungs..." (Taub, cited by Brumbaugh 1994 p 456). Anxiety, insomnia and agitation are also reduced (NADA UK 2004). Furthermore, Smith (2001b) maintains that the points of the protocol are not specific to substance dependency; rather, they promote homeostasis and function to improve an individual's endocrine and autonomic systems. This suggests that women undergoing adjuvant treatment for breast cancer could benefit from receiving the protocol in terms of general health, but to ascertain the potential impact on hot flushes and night sweats, it was necessary to examine the protocol itself.

7.2.4.2 Evaluating the functions of the points

The points comprising the protocol are the ear points shenmen, sympathetic, kidney, liver, upper lung and lower lung. Figure 34 illustrates these points (although it does not distinguish between the upper and lower lung points).

Figure 34 Diagram showing the ear points of the NADA protocol



(Oleson 2003 p 273) Used with the kind permission of Terry Oleson.

Shenmen

Shenmen is the most commonly used point in auriculotherapy, and it is included in nearly every ear acupuncture point prescription (Jia, Y, personal communication, 16 August 2003). It calms the mind and alleviates "stress, pain, tension, anxiety, depression, insomnia, restlessness, and excessive sensitivity" (Oleson, p 56). Smith introduced it into the NADA protocol for its relaxing effects (Kolenda 2000).

In these aspects, ear shenmen functions similarly to the body point shenmen (Heart 7, Spirit Gate), which is the "foremost acupuncture point to calm and regulate the spirit" (Deadman et al. 1998 p. 220). The body

point shenmen is located on the heart meridian; the heart, in Chinese Medicine (CM) is responsible for governing the blood, controlling the blood vessels, and controlling sweat (Maciocia 1989 pp 71 - 76). Sweat is a body fluid, the body fluids have a close relationship to the blood, the heart governs the blood, and so in the logic of CM, the heart relates to sweat. From this relationship, it is possible to extrapolate the possibility that the ear point shenmen may have an influence over sweating and that it would thus be helpful in managing the sweating associated with hot flushes and night sweats. It would also be generally beneficial in managing anxiety and insomnia, symptoms that my experience with the TA group suggests are common in women with early breast cancer.

Sympathetic point

The sympathetic point is also referred to as the autonomic point (Oleson 1996) and the vegetative point (Rubach et al. 2001). It balances the sympathetic and parasympathetic nervous systems. Jia (2003) indicates its use for night sweats, insomnia, and menopause syndrome, and O'Connor and Bensky (1981) cite its usefulness in treating excessive sweating. Smith included it in the NADA protocol after tests of resistance values on numerous ear locations identified this as the most sensitive in his subjects (personal communication by email, 2 February 2006).

Kidney

The kidney ear point has potentially the most direct theoretical connection to the management of hot flushes and night sweats. In CM theory, the kidneys store a vital substance called essence, which controls the stages

in life ranging from birth, puberty, menopause and death (Maciocia 1989). A decline in kidney energy is a natural consequence of aging; there is often a particular tendency towards a decline in kidney yin, which relates to the menopause. As previously discussed, this manifests with symptoms such as hot flushes, night sweating, insomnia, agitation, anxiety (Maciocia 1998 p 31-34, 741-46). Jia (2003) indicates the kidney ear point for gynaecological conditions; Oleson (2003) cites its usefulness in tonifying kidney deficiencies.

Liver

Of all the points in the NADA protocol, it is perhaps most difficult to make a direct connection between the function of the liver ear point and hot flushes and night sweats. Oleson (2003) and Rubach (2001) cite this point for hepatic ailments such as hepatitis, cirrhosis, jaundice, and anaemia. More generally, it is used to improve eyesight, muscular aches and pains, and digestive disorders (Oleson 2003).

From a CM perspective, its usefulness in a protocol for women undergoing cancer treatment may be from the emotional perspective. The liver is responsible for the smooth flow of qi. Maciocia regards this smooth flow as vital to emotional health, stating that a healthy flow of qi ensures a happy emotional life, whilst an impaired flow may give rise to "emotional frustration, depression or repressed anger" (1989 pp 78-79). Smith included it because of its "stress and anger identity" (personal communication by email, 2 February 2006). Brumbaugh also refers to the liver point's relationship to the emotions of anger and determination,

and to its spiritual relationship to hope and despair (1994, p 416). Thus, in managing hot flushes and night sweats, the liver ear point is possibly supportive rather than directly indicated.

Upper Lung and Lower Lung

The final points are the upper and lower lung points. Although two different points, they are grouped together as one point in the "five-point" protocol. Referring to them as lung 1 (contralateral lung) and lung 2 (ipsilateral lung), Oleson suggests that the former is indicated for respiratory disorders and the latter for disorders of addiction (1996 p 96). Nevertheless, he lists relief of night sweats as a function of lung 1. In CM theory, the lungs control the dispersing and descending of body fluids throughout the body, and regulate the opening and closing of the pores and sweating. When there is a lung deficiency, spontaneous sweating may occur (Maciocia 1989 pp 84-85). Upper and lower lung ear points may assist in controlling sweating, and in regulating body temperature (Peckham 2002).

7.2.4.3 Mapping NADA point functions to the TA treatment principles

Examining the functions of the individual points comprising the NADA protocol suggested that many were indicated in the treatment of hot flushes and night sweats. The next step was to map the functions of the ear points to the treatment principles (see section 5.7.2.4, starting on page 162) and body points (see section 5.7.3 starting on page 166) used in the TA study. Table 36 below shows this mapping:

Table 36 Mapping the NADA ear points to the TA treatment principles and body points

Treatment Principles	Points Used in Traditional Acupuncture Protocol[16]	NADA Ear Points
Nourish (Kidney) Yin	Lu 7 *lieque*, Ki 6 *zhaohai* (Ren Mai) Ren 4 *guanyuan* Sp 6 *sanyinjiao*	Heart, Kidney, Lung, Liver
Stop Night Sweats	Ht 6 *yinxi* Ki 7 *fuliu*	Upper Lung, Lower Lung, Sympathetic
Drain Heat	LI 11 *quchi*	Shenmen
Detoxify	AE Drain	Liver
Calm the Spirit (Shen)	Ki 6 *zhaohai* Sp 6 *sanyinjiao* Ht 6 *yinxi* Individualised points	Shenmen Total protocol

The result of this mapping suggested that theoretically, the NADA protocol could fulfil a similar function to the point protocol used in Study 1: TA. It seemed there was a rationale for using the NADA protocol to manage hot flushes and night sweats in women undergoing adjuvant treatment for breast cancer. The next step was to test it out in the study.

[16] Abbreviations of points: Lu = Lung, Ki = Kidney, Sp = Spleen, Ht = Heart, LI = Large Intestine. AE = Aggressive Energy

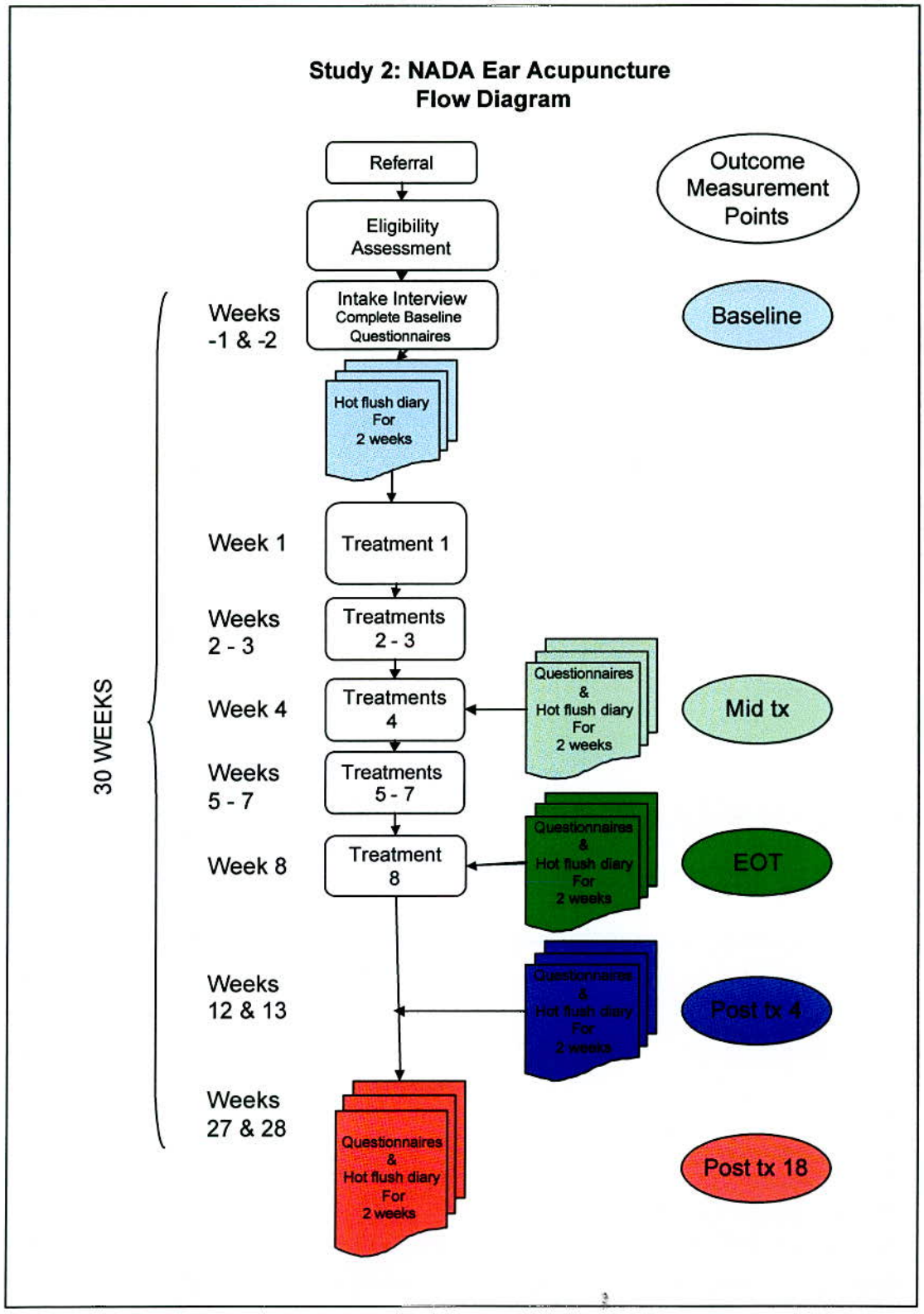
7.3 Relationship to Study 1: TA

7.3.1 Overall design

The design of Study 2: NADA follows the same overall design as Study 1, as discussed in Chapter 3 and Chapter 4. We chose to emulate this design closely to enable us to compare, as accurately as possible, the results of the two studies. We adjusted some of the practical details of the study, based on our discoveries from Study 1: TA, and I discuss these below.

Figure 35 illustrates the stages of the Study 2: NADA. Appendix 26 presents a map of the documentation associated with each stage of the study.

Figure 35 Flow diagram of Study 2: NADA



7.3.2 Significant differences in Study 2

Although the overall design of Study 2 imitated that of Study 1, introducing the NADA protocol resulted in three main differences. These were the use of a standardised protocol (with associated changes in assessing the participant's well-being), the shift to group clinics, and the amount of patient-practitioner contact time.

7.3.2.1 Use of a standardised protocol

Study 2 used a standardised protocol: each of the eight treatments was the same for the individual participants, and every participant received the same treatment. This was a departure, both theoretically and clinically, from Study 1. Theoretically, it challenged the fundamentals of my training, which emphasised the importance of tailoring treatment to the individual's needs, and adapting treatment as the patient changes. Clinically, it meant that I could not deal with acute symptoms that might arise during the course of treatment (such as colds or headaches), nor could I use acupuncture to specifically address wider physical or emotional issues experienced by participants.

As mentioned previously, the application of the NADA protocol does not require a process of diagnosis. Consequently, I did not conduct the full traditional diagnosis (TD) with the NADA group, nor did I examine tongues or take pulses as I had done with the TA study. However, I felt it was important to gain some insight into the participants' symptoms and overall well-being. Consequently, I conducted a "reduced TD" with them at their intake interview. This took between 20 and 30 minutes, and

focused on the participant's experience of having hot flushes, and on sleep, appetite, bowels, urinary habits, headaches, general aches and pains, energy levels, emotional state, and any other issues they wished to discuss. I asked all participants in the NADA study to prioritise the three main areas they would like to see improve as a result of the treatment.

7.3.2.2 Group clinics

The second major change was the shift to group clinics, in which multiple participants received treatment in the same session. Facilities (specifically the small size of treatment rooms) at the LJMC allowed treatment of up to six women simultaneously. In practice, five per clinic was the most comfortable number, both for the acupuncturist and for the participants.

7.3.2.3 Participant – practitioner contact time

The group clinics significantly reduced the time I spent with each patient. I could treat five participants in less than 1½ hours, as opposed to the five hours taken on the TA study. I also aimed to keep my one-to-one contact time to a minimum, and attempted to adhere to the brief time spent per GP consultation in the NHS. This was not rigidly enforced, and I applied it flexibly according to the individual needs of the participants.

7.3.3 Minor adjustments to Study 2

Other minor changes pertained to the time for completing the course of treatment, and changes to communications with the participants' oncologist and GP.

7.3.3.1 Introducing a maximum completion time

Some participants on Study 1 completed their course of treatment over an extended period, resulting in irregular treatment with gaps between sessions. This may have reduced the effectiveness of the treatment. To avoid this in Study 2, I introduced a requirement that women commit to completing their eight treatments in a maximum of 10 weeks. This allowed them to schedule treatment into their weekly routine. It provided flexibility for planned activities such as holidays or medical interventions, as well as unplanned events such as illness or bereavement, and aimed to minimise the possibility of diluting the effectiveness of treatment.

7.3.3.2 Improving communications with medical professionals

In addition, I introduced an administrative change in the form of a follow-up letter to each participant's oncologist and GP at the end of treatment. This informed the medical practitioners that their patient had completed the course of eight ear acupuncture treatments. It also summarised the participant's response to treatment, giving details of the changes the woman reported at her last session. I intended this to give the medical professionals an insight into the changes their patients experienced because of their treatment. I hoped that this would develop relationships with medical practitioners, and improve their understanding of acupuncture and its potential.

7.3.4 User involvement pilot

In line with NHS requirements to involve users in developing research (INVOLVE 2004), I conducted a pilot of the NADA approach prior to

opening recruitment. We invited women who attended the focus groups conducted in July 2003 (see publication (Walker et al. 2004) in Appendix 31) to take part in a pilot of an ear acupuncture study. Six women were able to participate, and they came for a series of three treatment sessions. The aims of the pilot were to test the acceptability of ear acupuncture and of receiving treatment in a group setting. It was not my intention in this pilot to measure effectiveness clinically.

The women completed a questionnaire at the end of the three treatments (see Appendix 28), which asked for their feedback on three areas:

- The experience of having ear acupuncture in small groups
- Their perception of the therapeutic effect of the ear acupuncture
- General comments on any aspect of the ear acupuncture pilot.

Their feedback was positive and contributed to refining the process for the study. The women liked the group setting, although some were initially apprehensive about this. They felt that five to six participants was the correct number of participants per clinic, given the size of the treatment rooms at the LJMC. They appreciated the opportunity to share with others, but missed the one-to-one contact with the acupuncturist that they experienced on the TA study. They appreciated being needled in a private space (as discussed in section 7.4.3.3, starting on page 265 below). They expressed a range of opinions about the sensations of ear acupuncture – one woman found it more painful than the body acupuncture, whilst another woman found it more comfortable than the

body acupuncture, which she had found almost unbearable. This pilot was a useful test of a new approach, and confirmed that this new style of delivery was acceptable and feasible.

7.3.5 Funding

As for the TA study, Dr Richard Ashford provided the funding for the clinical aspect of this study. The West Hertfordshire Hospitals NHS Research & Development Department also contributed funds. The LJMC funded the development of the study, as well as the analysis of the data. Thames Valley University funded the development of research and academic skills.

7.3.6 Ethics Approval

The West Hertfordshire Hospitals NHS Trust Local Research Ethics Committee (LREC) granted ethical approval on 10th June 2003 (Neal, D, personal communication by letter).

7.3.7 National Cancer Research Network involvement

The National Cancer Research Network (NCRN) adopted the study as a research project. The NCRN is a Department of Health initiative to improve the research infrastructure for clinical research in cancer. It aims to improve the quality and integration of research in order to improve patient care (NCRN 2004).

The study was subject to full and proper independent peer review prior to submission. The study design and protocol met the NCRN's standards

and contributed to their portfolio of good quality research. It is listed in the NCRN trials portfolio (http://www.invo.org.uk) in the Breast Cancer Group, under its acronym EATIMS (Ear Acupuncture for Tamoxifen Induced Menopausal Symptoms).

7.3.8 Arimidex sub-project

As discussed in section 2.3.3.5 on page 52, at the time of this study Arimidex was introduced as an alternative adjuvant treatment to tamoxifen. We wished to investigate whether women taking this new treatment experienced hot flushes, and whether these would respond to acupuncture treatment. Consequently, I conducted a literature search to investigate the incidence of hot flushes as a side effect, and then applied for an amendment to the protocol for the NADA study. This was granted by the West Hertfordshire Hospitals NHS Trust LREC (Brown, A, personal communication by letter, 27 February 2004) and I recruited women taking Arimidex to the study. This confirmed that women taking Arimidex experienced hot flushes for which they desired treatment. However, I did not recruit enough of these patients to the study to provide meaningful data. Consequently, I do not discuss any aspects of this sub-project in this thesis.

7.4 Delivering the treatment

7.4.1 Using the STRICTA Guidelines

This section presents the acupuncture-specific details of the study, according to the STRICTA guidelines for reporting acupuncture studies (MacPherson et al. 2001). Refer to Appendix 21 for these guidelines.

7.4.2 Rationale

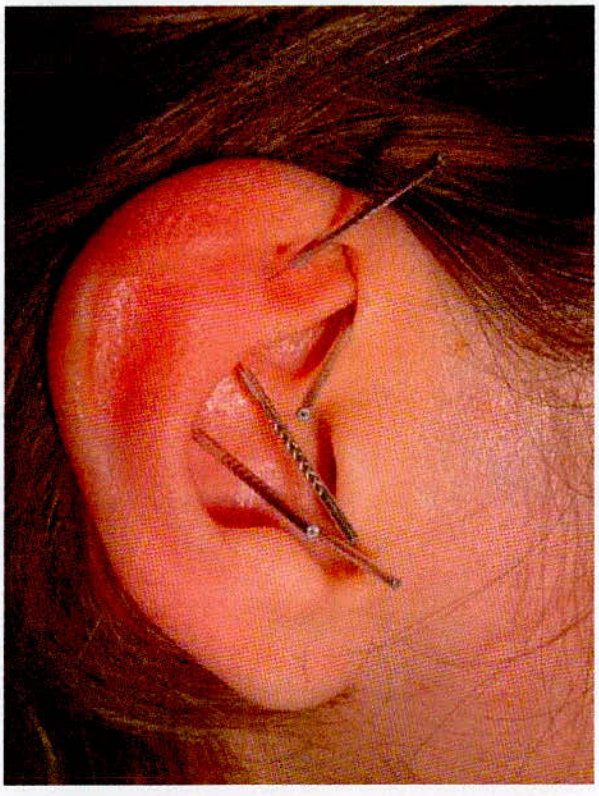
I discussed the rationale for using the NADA protocol in section 7.2.4, page 246 above.

7.4.3 Needling details

7.4.3.1 Points and needles used

The aim was to needle both ears, using five needles in each ear. The procedure started with the right ear, needling shenmen, sympathetic, kidney, liver, and upper lung in this order. I needled the same points in the left ear, using lower lung in place of upper lung. Figure 36 shows the needles in situ.

Figure 36 Photograph of the needles for the NADA protocol in situ



7.4.3.2 Point location procedures

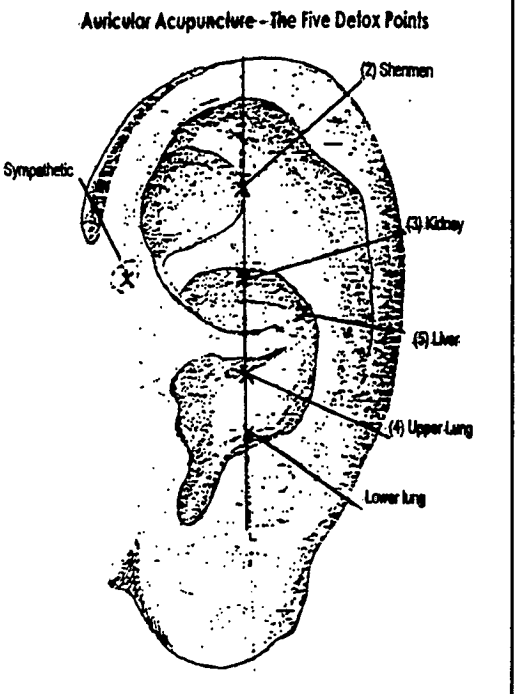
I located the points visually, with the exception of shenmen. For this point, I palpated the area with the blunt end of a needle to ascertain the most sensitive point, and then needled this area of sensitivity (Jia 2003, Oleson 1996). I located the remaining points according to the NADA UK guidelines (Peckham 2002). This situates shenmen, kidney, and upper and lower lungs along an imaginary vertical line running through the midline of the ear, starting from the apex of the superior helix, and continuing to the bottom of the lowest point on the lobe. This locates:

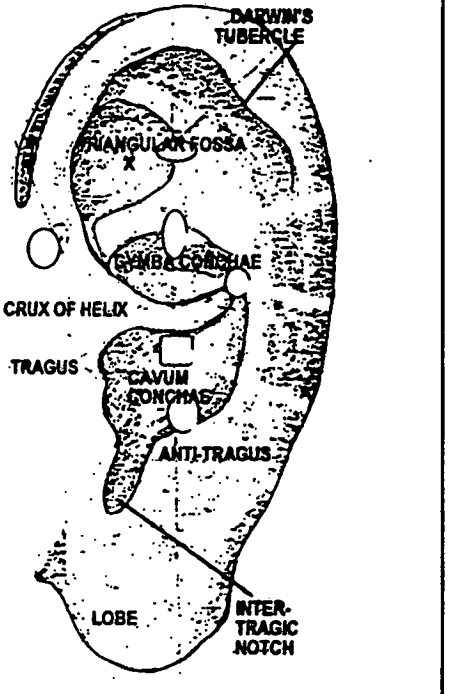
- Shenmen at the outer edge of the triangular fossa

- The sympathetic point at the junction of the antihelix and the inferior crus
- The kidney point in the middle of the inferior edge of the crus of the antihelix on the surface of the cymba concha
- The liver point half-way down the ear on the cymba concha where the crus of the helix joints the antihelix
- The upper lung and lower lung at the top and bottom (respectively) of the peripheral region of the cavum concha.

Figure 37 illustrates these locations.

Figure 37 Illustrations showing ear points and the anatomy of the ear





Used with the kind permission of Rachel Peckham and NADA UK

7.4.3.3 Needling and needle handling techniques

I took special care, especially during the first treatment, to ensure the women were comfortable with the needling procedure, and gave them the option to stop the needle insertions at any time. The majority of women opted to have the full protocol from the start, although a few found the needling sufficiently uncomfortable to ask for the needling to stop. One woman found the lower lung point so uncomfortable that she requested that it be left out of her treatment altogether. However, the majority of women proceeded with the complete protocol for all of their treatments.

I used acupuncture needles specifically made for detoxification protocols. These were 7 mm (0.25 inch) in length and 0.22 diameter (34 gauge) stainless steel needles manufactured by Vinco, and packaged in packs of 10 needles per pack.

I inserted the needles firmly with a slight clockwise twist, penetrating the skin only deeply enough so that the needle stayed in place. There was no further manipulation; electro-stimulation was not used. The needles were retained for 45 minutes. I removed them from the bottom up, in reverse order to their insertion (that is, lung, liver, kidney, sympathetic, and shenmen). This enabled staunching of blood, should bleeding from any point occur. Blood was absorbed using sterilised cotton balls, followed by swabbing with sterile wipes. I disposed of all needles and soiled materials in a sharps container, and these were subsequently disposed of as part of the hospital's clinical waste disposal protocol.

These procedures were in accord with the NADA UK guidelines current at the time of the study.

I needled the participants individually and in private, following a brief (usually no longer than seven minutes) discussion about their condition, symptoms, and any concerns. At the first session, I briefed the participants on what to expect regarding the needling, and reminded them that they could stop the process at any time if they felt uncomfortable. I dealt with any questions or concerns they had about the acupuncture at this time. (This departs from the normal NADA delivery, where needle insertion takes place in the group setting and is usually non-verbal. I chose to do this because I judged that these women would appreciate private space to discuss any issues. I have also noticed elsewhere that in the group situation, participants often follow the lead of the first person needled, and will decide to have as many or as few needles inserted as that person. I was keen to avoid this type of influence. I discussed this approach at length with Rachel Peckham, the trainer for NADA UK, and she agreed that this approach was acceptable in this context.)

During and immediately following needle insertion, I observed the participant carefully to ensure she did not experience any ill effects from the needling (such as feelings of faintness), and then I accompanied her to the adjacent relaxation room. Here I seated her with the other participants in the group, where she remained seated for the duration of the relaxation period of 45 minutes. (Again, this is a departure from usual

NADA delivery, in which participants remain in situ for the needling, relaxation, and needle removal.) During this time, I monitored the relaxation room at periodic intervals, to ensure that no one experienced any ill effects, and to check for any needles that might have fallen out. At the end of this time, I accompanied each participant back into the treatment room to remove the needles. After I double-checked for any bleeding, and again ensured they experienced no ill effects from treatment, the women departed.

7.4.3.4 Guidelines for obtaining optimum benefit from the treatment

I gave the participants the following guidelines to encourage them to obtain the maximum benefit from the yin tonifying nature of the NADA protocol (Peckham 2002, Smith, M, personal communication by email, 2 February 2006, Brumbaugh 1994). I encouraged participants to eat a light meal before treatment. As most of the sessions started at 9.30 a.m., I encouraged those who were not in the habit of eating breakfast to do so before attending clinic. Participants were discouraged from drinking coffee or tea immediately prior to and during the treatment session. During the relaxation period, they were to stay seated and not move too much. Although talking was not banned, I asked participants to use the time to relax and focus inwards, and to conduct any talking in subdued tones. I encouraged them to keep their feet flat on the floor during the retention period, and they could not read or use mobile phones.

7.4.3.5 Safety procedures

I recorded all the needles inserted on a Daily Treatment Sheet (see Appendix 27), and counted the needles on removal. I also noted any bleeding, specifying if this was copious or scant. If needles fell out during treatment, I asked the participant if she wanted it replaced. If she did, I inserted a new replacement needle in situ, without removing the participant from the group. The participants had individual access to sharps boxes, and I briefed them on how to handle any needles that fell out during treatment. I instructed participants not to handle the needles of other participants, and advised them I needed to account for all needles inserted in an individual's ears before she could leave the treatment rooms.

7.4.4 Treatment regime

Study participants had eight NADA treatments, ideally on a weekly basis. To allow for holidays and illness, there was inbuilt flexibility, and participants agreed to complete the eight sessions within a maximum of ten weeks as part of their acceptance of the study conditions.

The number of treatments and frequency was determined by the structure of Study 1: TA, which I was seeking to echo in this study. This weekly treatment frequency is a departure from the daily frequency with which the NADA protocol is commonly delivered in addiction settings. However, as many of the participants were working, had family commitments, and

had to travel to get to the LJMC, I felt that treatment once a week was the most pragmatic approach.

7.4.5 Co-interventions

Life-style advice was the only co-intervention in this study. The reduced level of practitioner-participant interaction in this study meant that I could not explore life-style issues as deeply as in Study 1: TA. However, time allowed some lifestyle advice to be given. This mostly focused on the importance of taking rest periods in the afternoon, and I developed the explanation of this process during Study 2. As in the TA study, I encouraged women to take a 10 to 20 minute rest between the hours of one and three p.m., lying prone, and resting the eyes (see section 5.10.4.2, page 188). To overcome their resistance to resting during the day, I encourage them to "think of yourself as a rechargeable battery, plugging yourself in for a recharge".

Other lifestyle advice focused on the importance of eating breakfast and regular meals, although food issues appeared to be less of a problem with this group of women than the TA group.

Several women appeared to have deeper issues than could be dealt with in the acupuncture sessions. In these cases, I informed the women of the counselling services available at the LJMC and encouraged them to consider using this support. One participant required emergency treatment from the psychiatrist at the LJMC, as she experienced an emotional crisis during one treatment (see "Case 3: June" in the

publication *Serenity, patience, wisdom, courage, acceptance: reflections on the NADA protocol* (de Valois 2006, pp 48-9) in Appendix 31).

7.4.6 Practitioner background

I qualified as a NADA Acupuncture Detoxification Specialist in June 2002 and I administered the majority of the treatments.

Towards the end of the clinical phase, we tested the NADA UK training structure for training non-acupuncturists. Our candidate was a practitioner of complementary medicine (reflexology, reiki, and relaxation techniques), with over 12 years experience of working with cancer patients at the LJMC. She qualified as a NADA Acupuncture Detoxification Specialist in 2004. She delivered treatment to participants whilst I was on a two-week holiday in September 2004, and one day when I was ill.

7.4.7 Control interventions

As in the TA study, the women acted as their own controls, and there were no additional control interventions.

7.4.8 Data input and analysis

The research assistant, a volunteer at the LJMC, input all the data from this study. The research co-ordinator at the LJMC carried out random checks for accuracy of input. I conducted the analysis as discussed in Chapter 4.

7.5 Conclusion

In this chapter, I presented the rationale for conducting Study 2: NADA, and detailed the design and methodology of this phase. I discussed the appropriateness of using the NADA ear acupuncture protocol as a standardised treatment for treating tamoxifen-related hot flushes. This stemmed from the realisation that introducing an acupuncture service for treating hot flushes needed to meet the constraints of the NHS. Consequently, we chose to explore an approach that we assessed would be quick to deliver, easy to train, and could treat potentially large numbers of patients. After analysing the theory of the NADA protocol, I judged it potentially suitable for treating hot flushes. Its introduction necessitated some changes to the details of the design and methodology; however, Study 2 imitated Study 1 in all major aspects, particularly in respect of data collection and analysis. In this chapter, I reported the specifics of how I administered this treatment. In the next chapter, I report the results of using this approach.

Chapter 8 Results of Study 2: NADA

8.1 Synopsis

In this chapter, I present the results of Study 2: NADA Ear Acupuncture. I report recruitment, losses to follow-up, demographic data, and baseline medical data. I then present the data related to the three main topics comprising this thesis: hot flush frequency, emotional and physical well-being, and the acceptability of ear acupuncture as a treatment. Hot flush frequency presents the results of analysing the Hot Flush Diaries. Emotional and physical well-being includes the results of the Women's Health Questionnaire (WHQ), the sub-analysis of the Somatic Symptoms category of the WHQ, and the results of the Hot Flushes and Night Sweats Questionnaire (HFNSQ). Finally, I discuss the participants' feedback on whether they found receiving ear acupuncture and having treatment in small groups acceptable.

8.2 Recruitment and losses to follow-up

Of 54 women recruited to Study 2: NADA, 50 completed the course of eight NADA ear acupuncture treatments. Reasons for non-participation included one participant choosing not to continue after her intake interview, giving no reason for her decision; another suffered repeated bouts of ill health, making it impossible for her to participate. Two participants withdrew from the study after starting treatment: one said, "acupuncture was not the answer" for her after the first treatment; one

withdrew midway through treatment after receiving a diagnosis of liver metastases.

8.3 Demographic data for the NADA study

The sociodemographic and baseline medical information reported below reflect the 52 participants who completed these questionnaires at baseline. It includes data concerning the two participants who withdrew before completing the course of treatment. It does not include data for the two women who did not proceed beyond the intake interview.

8.3.1 Sociodemographic data for Study 2: NADA

Table 37 below presents the results of the Sociodemographic Questionnaire. It also presents comparative demographic data for 29 breast cancer patients treated at Mount Vernon Hospital, and I discuss this below in section 8.3.1.1, page 275.

Table 37 Sociodemographic data for Study 2: NADA compared with women attending for radiotherapy at MVH in 2005

	MVH Radiotx patients n = 29 n (%)	NADA at baseline n = 52 n (%)
Marital status		
Single (never married)	*4 (14)*	3 (6)
Married (first marriage)	*18 (62)*	36 (70)
Re-married	*1 (3)*	3 (6)
Living with partner	*1 (3)*	1 (2)
Divorced	*2 (7)*	6 (12)
Widowed	*3 (10)*	3 (6)
Home Situation		
Living with family members or partners	*24 (83)*	44 (85)
Living alone	*4 (14)*	7 (14)
Living with others (lodgers)		1 (2)
Dependents		
No dependents		36 (69)
Children under the age of 18 or adults for whom financially responsible		16 (31)
Educational qualifications		
Less than compulsory school education	*4 (14)*	4 (8)
Compulsory school education (e.g. school certificate, CSEs, GCSEs)	*10 (35)*	18 (35)
Post compulsory school education below university level	*8 (28)*	11 (21)
University level	*4 (14)*	12 (23)
Postgraduate level	*2 (7)*	7 (14)
Current employment status		
Retired	*10 (35)*	11 (21)
Not working at present	*5 (17)*	16 (31)
Working part time	*6 (21)*	16 (31)
Working full time	*7 (24)*	9 (17)
Country of birth		
England	*27 (93)*	46 (89)
Scotland		1 (2)
Wales	*1 (3.4)*	1 (2)
Northern Ireland		1 (2)
Elsewhere	*1 (3.4)*	3 (6)
Ethnic background		
White British	*27 (93)*	48 (92)
White other	*1 (3.4)*	3 (6)
Indian		1 (2)
Car ownership		
Household with 1 car	*16 (55)*	16 (31)
Household with > 1 car	*11 (38)*	34 (65)
None	*2 (7)*	2 (4)
Home ownership		
Own/buying home		49 (94)
Renting		3 (6)

8.3.1.1 How representative is this group?

As discussed in section 6.3.1.1 (page 202), there is little demographic data available about patients attending MVH for treatment, or attending the LJMC for supportive care. The table compares the NADA group with data collected on 29 consecutive breast cancer patients receiving their first course of radiotherapy at MVH in 2005 (see page 202).

This comparison shows that the two groups are similar, and may be representative of typical breast cancer patients treated at MVH. Both are predominately white-British, born in the United Kingdom, married, and car owners. The NADA group appear to have slightly higher levels of education, with 23% having university level education and 14% having post-graduate qualifications (compared with 14% and 7% in the MVH group). Both groups show the same level of employment, with 48% working either full or part-time. More women in the MVH group are retired (35% compared with 21% of the NADA group).

Thus, whilst possibly being representative of patients of MVH and users of LJMC, this group is not representative of a multicultural, diverse socio-economic group, which might typically be found in many centres in the United Kingdom.

8.3.2 Baseline Medical Information for Study 2: NADA

The data presented here relate to cancer diagnosis and treatment, as well as the menopausal status of the 52 participants who completed baseline questionnaires.

Table 38 Age, cancer diagnosis, and tamoxifen history

	All participants at baseline n = 52		
	Mean (sd)	Median	Min-Max (Range)
Age at baseline (years)	54.8 (7.2)	55.0	38 – 73 (35)
Time since cancer diagnosis (years)	2.2 (1.2)	1.6	0.8 – 5.1 (4.3)
Time taking tamoxifen (years)	1.7 (1.2)	1.2	0.44 – 4.4 (3.9)

The mean and median ages presented in Table 38 above accord with the UK incidence statistics, which show the highest number of new diagnoses of breast cancer are in the 50-64 age group (Cancer Research UK 2006, pp 163 - 166). Comparing the time since diagnosis and time taking tamoxifen confirms that women start taking tamoxifen some time after their diagnosis. The time taking tamoxifen suggests that, despite medical advice that these hot flushes reduce with time (Love and Feyzi 1993), on average these women still experience unacceptably high levels of discomfort. This continues well into their second year on the treatment, with some registering symptoms in their fifth and final year (see Table 40 on page 277 for details of the distribution for this group).

Table 39 Distribution of participants showing time since cancer diagnosis

	All participants at baseline n = 52 n (%)			
	6-12 months	1-2 years	3 - 4 years	>4 years
Time since cancer diagnosis	3 (6)	26 (50)	17 (33)	6 (12)

Table 39 above shows that half of the participants were diagnosed one to two years prior to joining the study, with a further third having been diagnosed three to four years prior to the study.

Table 40 Distribution of participants showing time taking tamoxifen

	All participants at baseline n = 52 n (%)			
	6-12 months	1-2 years	3 - 4 years	>4 years
Time taking tamoxifen	23 (44)	13 (25)	13 (25)	3 (6)

The distribution presented in Table 40 above shows that, although almost half the group had been taking tamoxifen for under a year, a further half had been taking it for between one to four years. A very small number of women were in their final year of the five-year treatment period. As mentioned previously, this distribution indicates that for some women, hot flushes continue well into the five-year treatment period, even into the last year of the standard tamoxifen regime.

Table 41 Other related treatment and gynaecological information

	All Participants at Baseline n = 52 n (%)
Cancer treatments:	
Surgery	52 (100)
Radiotherapy	47 (90)
Chemotherapy	35 (67)
Participants with history of:	
Taking HRT	34 (65)
Hysterectomy	10 (19)
Treatment for lymphoedema	16 (31)
Menopause status[17]:	
Perimenopause (last period within the previous year)	7 (14)
Menopause (no period within the previous 1-5 years)	27 (52)
Postmenopause (no period in over 5 years)	15 (30)
Missing data	3 (6)

The treatment data presented in Table 41 above confirm that most women with breast cancer have surgery (Cancer Research UK 2006) and radiotherapy, and over two-thirds of this group received chemotherapy as well. Two thirds of this group had a history of taking Hormone Replacement Therapy (HRT). This has a potential impact on the menopause status, as many women cannot differentiate periods from the bleed associated with some types of HRT (Fallowfield et al. 2001). However, using the STRAW staging system (Soules et al. 2001), it appears that over half of this group (52%) may have been going through the menopause transition, whilst a further 30% were postmenopausal.

[17] Based on the STRAW staging system (Soules, Sherman et al, 2001).

8.4 Hot flush frequency for Study 2: NADA

8.4.1 Hot flush frequency

This section presents the results of the analysis of the Hot Flush Diaries, and provides answers to the question "Can using a standardised acupuncture protocol (the NADA protocol) reduce the frequency of hot flushes and night sweats in women taking tamoxifen as adjuvant treatment for early breast cancer?"

8.4.1.1 Compliance

Compliance in completing and returning the Hot Flush Diaries was high in the early stages, and diminished slightly at the end of the monitoring period. Table 42 below shows the returns at each measurement period.

Table 42 Return of hot flush diaries at each measurement period

MEASUREMENT PERIOD	Baseline	Mid tx	EOT	Post tx 4	Post tx 18
DIARIES RETURNED	51	51	48	46	40

At baseline, one participant's diary was missing, and thus the baseline figure is 51 although there were 52 participants at this stage. Of the two participants who withdrew from the study after starting treatment (see Section 8.2, page 272), one withdrew from before reaching the Mid tx measurement point and the other left after completing her Mid tx diary.

8.4.1.2 Hypothesis

Our hypothesis was that using the NADA ear acupuncture protocol would reduce hot flush frequency by 33% in one third of the participants at EOT. We based this hypothesis on the results of Study 1: TA (see section

6.4.1.6 on page 210, adjusting the figure downward to reflect our assumption that a standardised treatment that was not specifically designed to treat tamoxifen-related hot flushes would be less effective than an individualised treatment that was.

8.4.1.3 Establishing hot flush frequency at baseline

As discussed in section 2.4.5, starting on page 55, there was little information available about the numbers of hot flushes experienced by women taking tamoxifen. Table 43 and Table 44 below present the data reflecting the experience of the participants in this study. Table 43 shows the minimum and maximum number of flushes experienced. The study results are based on comparisons with baseline data that are averaged over a 14-day period for each participant. However, it is also worth reporting the minimum and maximum numbers of flushes reported by participants on single days. These data show the variability and range of hot flush frequency, and supports the decision to measure participants' hot flushes for a period of more than one day.

Table 43 Hot flush frequency at baseline (n = 51)

RANGE PERIOD	Minimum	Maximum	Mean	Std. Dev.
Average per day measured over 14-day baseline period	3.8	22.4	10.5	5.3
Per day	0	28	n/a	n/a

8.4.1.4 Comparing hot flush data: baseline and EOT

Table 44 presents the mean, median and range of hot flushes per day when averaged over the fourteen days at the baseline and EOT measurement periods. These untransformed summary data (USD)

reflect the 47 participants who completed and returned hot flush diaries for both measurement points.

Table 44 Hot flush frequency – means, medians and ranges of hot flushes/day over the 14-day measurement periods (using USD)

	Baseline (n=47)	EOT (n=47)
Mean (Std dev)	10.7 (4.8)	7.7 (4.7)
Median (95% CI)	10 (9.4 – 12.1)	6.5 (6.3 – 9.1)
Min	3.8	1
Max	22.4	19
Range	18.6	18

8.4.1.5 Establishing change in frequency

Table 43 above presents frequencies based on untransformed summary data (USD) and shows the wide range and variable nature of the frequency of hot flushes. Table 44 above also shows there is a reduction in mean and median hot flush frequencies at EOT over baseline. However, to say that flushes reduce from a mean of 10.7 to 7.7 per day, (or a median of 10 to 6.5 per day) is not necessarily helpful to a patient seeking relief from hot flushes, or to a clinician who needs to know what outcome to expect (as discussed in section 4.8.2.1 on page 140). Indeed, many participants were experiencing significantly more or less than 10.7 hot flushes per day at baseline.

Using log transformations normalised the data, and the resulting transformed data provide information that is more helpful in clinical terms. Table 45 below presents the percentage change in hot flush frequency for each of the 47 participants who completed the hot flush diaries at the end of the course of acupuncture treatment. (In the following table, the term "lnBaseline no." refers to this log transformed data.)

Table 45 % Change in hot flush frequency/day by participant (log transformed data)

Ranking	Study No.	lnBaseline no.	lnEOT no.	% Change
> 33% reduction				
1	26	17.00	2.00	88.24
2	20	5.00	1.00	80.00
3	47	9.00	2.00	77.78
4	51	4.00	1.00	75.00
5	42	8.50	2.50	70.59
6	16	6.00	2.00	66.67
7	22	10.50	3.50	66.67
8	2	7.00	3.00	57.14
9	5	7.00	3.00	57.14
10	13	14.00	6.00	57.14
11	34	13.00	6.50	50.00
12	48	12.00	6.00	50.00
13	49	12.00	6.00	50.00
14	8	11.00	6.00	45.45
15	46	7.00	4.00	42.86
16	10	10.00	6.00	40.00
17	25	12.50	7.50	40.00
18	52	16.50	10.00	39.39
19	41	13.00	8.00	38.46
20	35	16.00	10.00	37.50
21	19	9.50	6.00	36.84
22	15	14.00	9.00	35.71
23	28	6.00	4.00	33.33
24	30	12.00	8.00	33.33
< 33% reduction				
25	29	14.50	11.00	24.14
26	4	23.00	17.50	23.91
27	43	6.27	5.00	20.29
28	39	8.00	6.50	18.75
29	53	7.00	6.00	14.29
30	24	4.00	3.50	12.50
31	32	8.00	7.00	12.50
32	1	22.00	19.50	11.36
33	33	18.00	16.00	11.11
34	11	10.00	9.00	10.00
35	44	21.00	19.00	9.52
36	45	11.00	10.00	9.09
37	40	12.00	11.00	8.33
38	54	15.00	14.00	6.67
39	17	8.50	8.00	5.88
No change				
40	3	6.00	6.00	0.00
41	31	5.00	5.00	0.00
Increase				
42	36	8.50	9.00	-5.88
43	21	14.00	15.50	-10.71
44	12	6.50	7.50	-15.38
45	9	4.00	5.00	-25.00
46	38	13.00	17.00	-30.77
47	18	7.00	11.00	-57.14

This table shows that 24 (51.1%) of participants recorded a reduction of 33.3% or more in their hot flush frequency at EOT over their baseline number. This exceeds our hypothetical estimate of a reduction of 33.3% or more in one third (or 15.6) of participants.

The table also shows that a further 15 (31.9%) recorded some improvement in their hot flushes, although this was less than a 33.3% reduction in frequency. Two (4.3 %) participants recorded no change, and six (12.8%) recorded that their hot flush frequency increased.

8.4.1.6 Establishing the proportional change in frequency

The analysis presented in Table 45 above shows the percentage change in frequency per participant. It also gives an indication of how our results measure against our hypothesis. As discussed in section 4.8.2.1 on page 140, log transformations provide a proportional measure. This allows us to predict the reduction an individual can expect at the end of eight NADA ear acupuncture treatments over her baseline frequency (based on the mean of all participants in this study). Table 46 below presents the results of all the four measurement points, highlighting the primary outcome measure, which is the EOT over baseline result.

Table 46 Results after log transforming the data

NADA Ear Acupuncture						
Measurement point	**n =**	**Mean % Reduction**	**95% CI Lower**	**95% CI Upper**	**Range (%)**	
					Min	**Max**
lnBase - lnMid	50	23.6%	15.3%	31.5%		
lnBase - lnEOT	**47**	**35.9%**	**25.4%**	**45.4%**	**-57.1%**	**88.2%**
lnBase – lnPost tx 4	45	37.5%	25.4%	47.6%		
lnBase – lnPost tx 18	38	37.1%	24.8%	47.4%		

This analysis shows that on average, a woman might expect a reduction of almost 36% (that is, 35.9%) of the number of hot flushes she experiences before treatment. The 95% confidence intervals indicate that there is only a 5% chance that the mean reduction will lie outside of the range of a 25.4% - 45.4% reduction.

Table 47 below presents the results of paired samples t tests showing the change at each measurement point compared with baseline, using the log transformed data. **Bold** formatting highlights the statistically significant results ($p < 0.05$). These are the data used to derive the results presented in Table 46 above.

Table 47 Results of paired samples t tests for hot flush frequency (NADA) using log transformed (ln) data

	Paired differences					Paired sample t tests		
				95% CI				
	Mean	SD	N =	LL	UL	t =	df	p< *
lnBaseline – lnMid tx	.273	.379	50	.165	.381	5.091	49	**.0001**
lnBaseline – lnEOT	.447	.529	47	.292	.602	5.792	46	**.0001**
lnBaseline – lnPost tx 4	.470	.591	45	.292	.647	5.332	44	**.0001**
lnBaseline – lnPost tx 18	.465	.545	38	.286	.644	5.253	37	**.0001**

* Significance (2-tailed)

These paired samples t tests on the transformed data show that the mean change from baseline to EOT, the primary endpoint, is statistically significant. The results were $t = 5.79$, $df = 46$, $p < .0001$. The changes at the other three endpoints are also statistically significant.

8.4.1.7 Evaluating the short term and longer term results

In addition to measuring the change in frequency at the primary endpoint (EOT), we were interested in exploring what happened to the effects after treatment ceased. Table 48 below suggests that the hot flush frequency continues to reduce slightly (by 1.6% to 37.5% reduction) at Post tx 4, and stabilises at that around that level (37.1% reduction) at Post tx 18.

8.5 Emotional & physical well-being for Study 2

The Women's Health Questionnaire (WHQ) and the Hot Flushes and Night Sweats Questionnaire (HFNSQ) provided data to answer the question "Does using the NADA ear acupuncture protocol affect the overall physical and emotional well-being of the recipient?"

8.5.1 Results of the WHQ

8.5.1.1 Compliance and missing data

As with the Hot Flush Diaries, compliance with completing and returning the questionnaires was high at the beginning of the monitoring period, and diminished slightly towards the end. Table 48 below displays the numbers of returned WHQs at each of the measurement points.

Table 48 Return of Women's Health Questionnaires at each measurement period

MEASUREMENT PERIOD	Baseline	Mid tx	EOT	Post tx 4	Post tx 18
DIARIES RETURNED	52	49	48	46	40

On the returned questionnaires, individual items are missing for a range of reasons. Some participants missed questions at random. Other data

are missing because of the rules for analysing WHQ data, as discussed in section 4.9.4 starting on page 146. These are the reasons for the varying numbers in the data presented in Table 49 below.

8.5.1.2 Hypothesis

Our hypothesis was that overall, emotional and physical well-being would show improvement at EOT, and that symptoms would return as time from EOT increased. We did not predict which specific WHQ domains might change, nor did we predict the degree to which changes might occur. This aspect of the data collection was exploratory, and aimed to collect data to answer this question.

8.5.1.3 WHQ results at the primary endpoint

Table 49 below shows the results for the nine domains of the WHQ, comparing baseline with the primary endpoint, EOT. Data for the means at baseline and EOT show the results for these individual measurement points. Data for the paired differences and the paired samples t tests show the change in each domain over time. **Bold** text highlights the statistically significant results ($p < 0.05$).

Table 49 WHQ results for the primary endpoint (EOT) of the NADA study

Seq	Baseline			EOT			Paired differences (Baseline - EOT)				Paired samples t tests		
									95% CI				
WHQ Scale[18]	Mean	SD	N =	Mean	SD	N =	Mean	SD	N=	LL	UL	t =	df	p = *
ANX	0.30	(0.27)	51	0.19	(0.21)	48	0.10	(0.24)	47	.03	.17	2.86	46	**.006**
ATT	0.54	(0.32)	50	0.52	(0.33)	47	0.06	(0.31)	45	-.04	.15	1.22	44	.229
DEP	0.24	(0.22)	51	0.09	(0.12)	48	0.15	(0.24)	47	.08	.22	4.12	46	**.0001**
MEM	0.63	(0.33)	52	0.49	(0.39)	47	0.12	(0.35)	47	.02	.22	2.36	46	**.023**
MEN	0.29	(0.22)	52	0.25	(0.24)	48	0.06	(0.20)	48	-.001	.12	1.97	47	.055
SEX	0.47	(0.34)	37	0.43	(0.33)	36	0.08	(0.26	34	-.01	.17	1.76	33	.088
SLE	0.63	(0.30)	52	0.41	(0.37)	48	0.22	(0.32)	48	.10	.31	4.85	47	**.0001**
SOM	0.45	(0.22)	51	0.34	(0.22)	48	0.12	(0.23)	47	.06	.19	3.68	46	**.001**
VAS	0.98	(0.10)	51	0.74	(0.36)	48	0.23	(0.36)	46	.12	.34	4.29	45	**.0001**

* Significance (2-tailed)

The data indicate that at EOT, the primary outcome point for the study, there is statistically significant change for six WHQ domains. These are Anxiety/Fears, Depressed Mood, Memory/Concentration, Sleep Problems, Somatic Symptoms, and Vasomotor Symptoms.

8.5.1.4 WHQ results at the secondary endpoints

In line with the exploratory nature of this work, I analysed the nine WHQ domains at the remaining three endpoints: Mid tx, Post tx 4, and Post tx 18. These data are in Appendix 29.

It is important to emphasise that these data are indicative only, as they are the results of multiple tests. To be statistically correct, the p values

[18] ANX = Anxiety/Fears, ATT = Attractiveness, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms.

should be adjusted using a multiplicity correction such as the Bonferroni correction (Campbell et al. 2000, pp 163-166). Making these corrections would avert the criticism of data dredging (Armitage et al. 2002, pp 496 - 498). However, in line with the exploratory nature of this work, I present the data in an uncorrected form, and suggest that these data may be useful in developing future studies (Staquet et al. 1996).

8.5.1.5 Comparing the data for all endpoints

Bearing in mind the qualifications made above, it is interesting to examine these data for trends. We can see the general trend or pattern of change more easily when the results appear in bar chart format, comparing the changes in each domain across the five measurement points, as shown in Figure 38 and Figure 39 below. In these figures, I exclude the domain Attractiveness, as it is now the normal practice to omit it (Hunter 2003).

Figure 38 Results for Anxiety/Fears, Depressed Mood, Memory/Concentration and Menstrual Symptoms

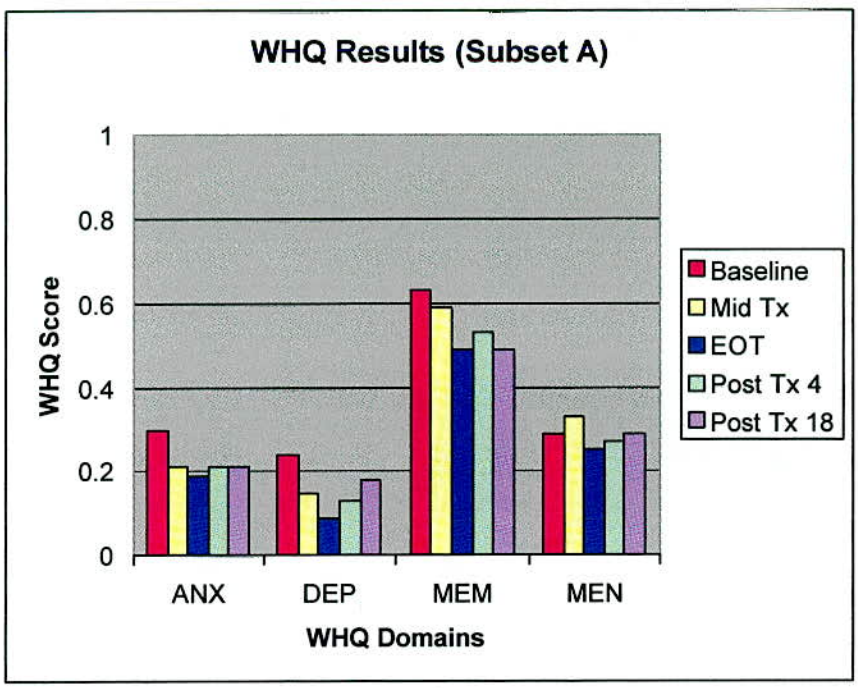
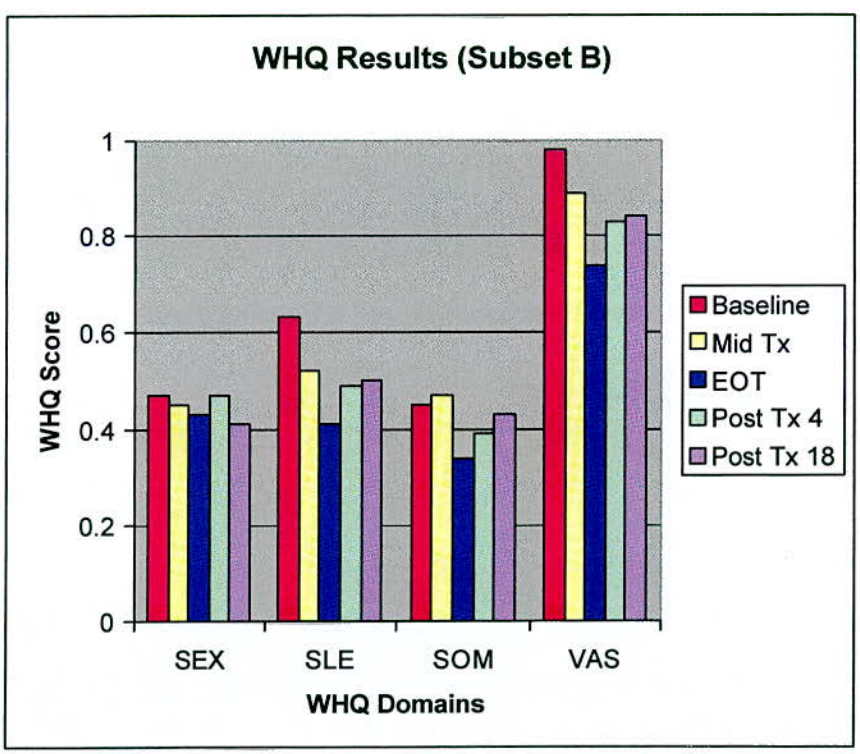


Figure 39 Results for Sexual Behaviour, Sleep Problems, Somatic Symptoms and Vasomotor Symptoms



Guide to abbreviations: ANX= Anxiety/Fears, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms.

Figure 38 and Figure 39 above illustrate the general trend in changes during and following treatment. Overall, symptoms start to recede at Mid tx (with the exceptions of Menstrual Symptoms and Somatic Symptoms), and reach their lowest level at EOT. As time from EOT increases, the symptoms begin to return. However, at the final follow-up (Post tx 18), the symptom scores do not return to their high baseline levels (with the exception of Sexual Behaviour and Menstrual Symptoms).

This general pattern accords with our hypothesis that emotional and physical well-being would show improvement at EOT, and that symptoms would begin to increase as time from EOT increased.

8.5.1.6 Comparing the data with other studies

Having noted this pattern of change, I will now compare these data with WHQ data from other studies. Figure 40 and Figure 41 below compare the Baseline, EOT, and Post tx 18 results from this NADA study with two studies published by Dr Myra Hunter. These studies cite the "norms" derived from the validation of the WHQ showing symptom scores of healthy women (n = 682) undergoing the normal menopause transition (Hunter 1992), and the scores of women with breast cancer (n = 113) (Hunter et al. 2004). In the figures, I refer to the breast cancer group as BCG. Please note that Hunter does not report data for Memory/Concentration (MEM) and Menstrual Symptoms (MEN) in her breast cancer group (BCG) study.

Figure 40 NADA WHQ results compared with norms and breast cancer group (BCG) showing Anxiety/Fears, Depressed Mood, Memory/Concentration and Menstrual Symptoms

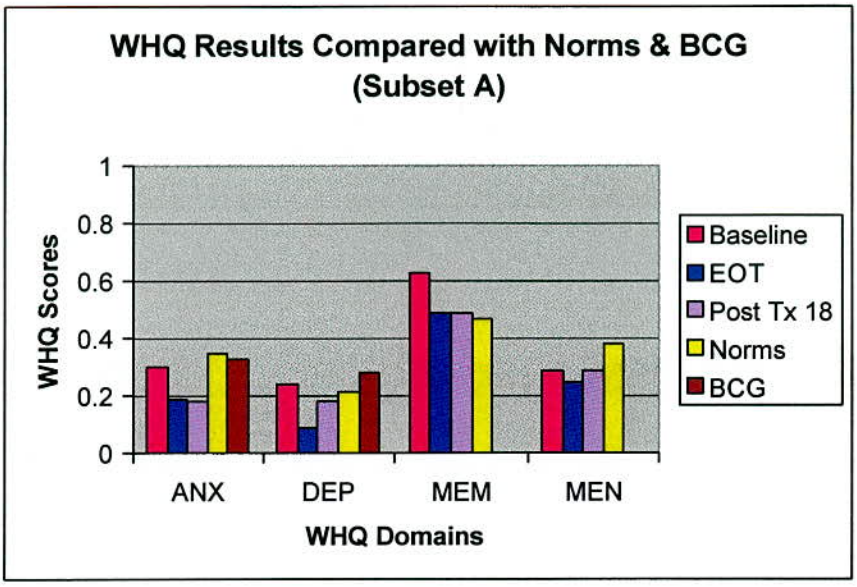
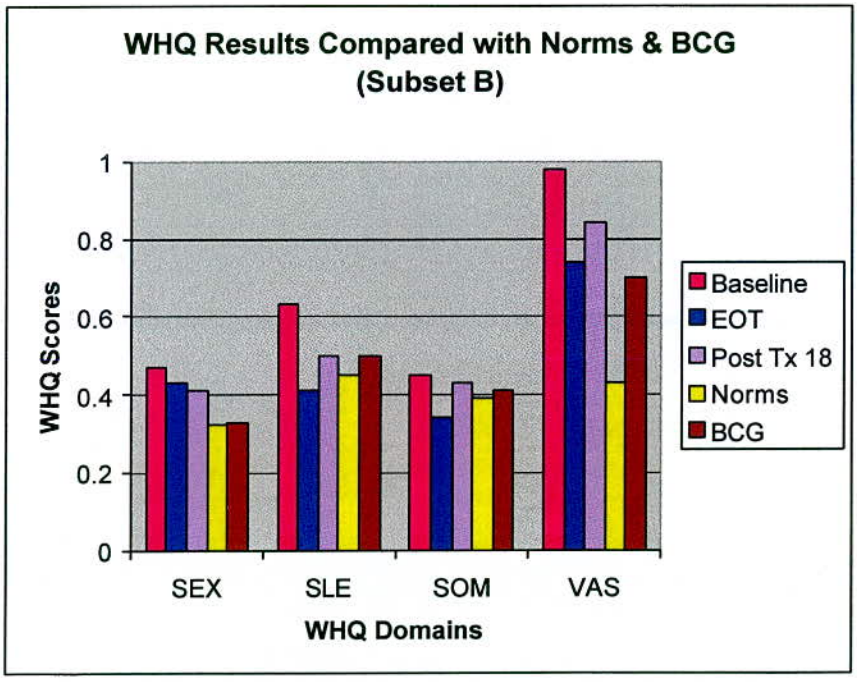


Figure 41 NADA WHQ results compared with norms and breast cancer group (BCG) showing Sexual Behaviour, Sleep Problems, Somatic Symptoms, and Vasomotor Symptoms



Guide to abbreviations: ANX= Anxiety/Fears, DEP = Depressed Mood, MEM = Memory/Concentration, MEN = Menstrual Symptoms, SEX = Sexual Behaviour, SLE = Sleep Problems, SOM = Somatic Symptoms, VAS = Vasomotor Symptoms.

This comparison illustrates some interesting patterns. At baseline, the NADA group have a higher initial symptom score than the norms in all domains except Anxiety/Fears and Menstrual Symptoms. Comparisons with the scores of the breast cancer group (BCG) show the NADA group having higher initial symptom scores for all domains except Anxiety/Fears and Depressed Mood. At EOT, the NADA scores drop below the scores of the norms in all domains except Sexual Behaviour, Memory/Concentration and Vasomotor Symptoms. The NADA EOT scores are lower than the BCG scores, except for the Sexual Behaviour and Vasomotor Symptom domains. At Post tx 18, the NADA group scores remain lower than the norms for Anxiety/Fears, Depressed Mood, Menstrual Symptoms, and Somatic Symptoms. Again, this is the case when comparing NADA Post tx 18 scores with the BCG scores, bearing in mind Hunter (2004) does not report scores for Memory/Concentration and Menstrual Symptoms. At the final follow-up, the NADA group scores for Sexual Behaviour have increased to slightly higher than the norms and BCG score. The score for Sleep Problems has climbed to higher than the norms, but remains slightly lower than that for the BCG. Scores for Vasomotor Symptoms have also increased, and were always higher than the two comparison groups.

8.5.2 Somatic Symptoms sub-analysis

We explored data relating to "Somatic Symptoms" to determine whether participants experienced benefits in any particular aspect(s) of this domain. This domain comprises seven symptoms including

backache/pain, dizzy spells, frequent urination, headache, nausea, pins and needles, and tiredness.

8.5.2.1 Hypothesis

This sub-analysis was purely exploratory, and we had no hypothesis about the possible result.

8.5.2.2 Somatic Symptoms: results

Table 50 below shows the means and standard deviations for all seven questions at all five measurement points.

It is necessary to highlight that the data from this sub-analysis do not compare directly with the WHQ results. Calculation of the WHQ results accords with the 0 to 1 symptom scale discussed in section 4.9.5 starting on page 147. Calculation of the somatic symptoms data is based on the raw scores (that is, "yes, definitely" (3), "yes, sometimes" (2), "no, not much" (1), "no, not at all" (0), as per the WHQ questionnaire. The vertical axis on Figure 42 on page 296 indicates these.

Table 50 Somatic Symptoms sub-analysis: means and standard deviations (NADA)

Seq	Baseline			Mid tx			EOT			Post tx 4			Post tx 18		
Symp-tom[19]	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =	Mean	SD	N =
BAC	1.75	1.08	52	1.50	1.00	51	1.40	0.99	50	1.65	1.04	50	1.90	1.15	46
DIZ	0.71	0.87	52	0.76	0.93	51	0.44	0.78	50	0.53	0.69	48	0.65	0.88	46
FRE	1.76	1.08	52	1.92	1.00	51	1.56	1.06	50	1.67	1.04	48	1.78	1.15	46
HEA	0.98	1.00	52	1.14	0.93	51	0.90	0.99	50	0.93	0.90	48	1.00	0.88	46
NAU	0.57	0.79	52	0.67	0.86	51	0.42	0.78	50	0.59	0.83	48	0.64	0.88	46
PIN	1.31	1.15	52	1.04	1.07	51	0.98	1.13	50	1.07	1.12	48	1.08	1.29	46
TIR	2.21	0.87	52	1.94	0.86	51	1.44	1.06	50	1.83	0.97	48	1.80	1.15	46

Table 51 below presents the results of paired samples t tests showing the results at each measurement point compared with baseline. These data are the results of multiple tests, without a prior hypothesis. As such, they should undergo correction as discussed in Section 6.5.1.4, page 214. Correction for multiplicity is beyond the scope of this thesis, and these data are indicative only.

[19] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness,

Table 51 Results of paired samples t tests for Somatic Symptoms (NADA)

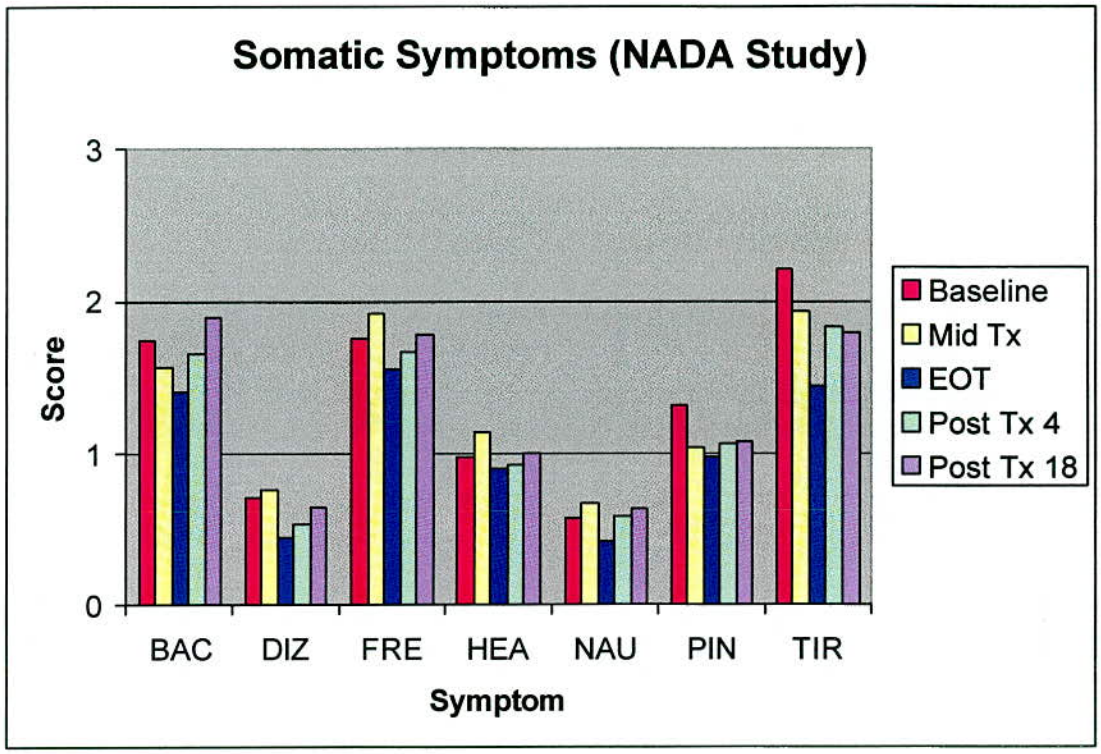
	Baseline – Mid tx			Baseline – EOT			Baseline – Post tx 4			Baseline – Post tx 18		
Sym-ptom[20]	t =	df	p= *	t =	df	p= *	t =	df	p= *	t =	df	p= *
BAC	1.50	47	.141	2.55	46	.014	.797	44	.430	.0001	38	1.0
DIZ	-.62	45	.54	1.95	44	.058	1.55	41	.128	.172	36	.865
FRE	-1.2	47	.254	1.46	46	.11	.781	44	.439	.902	38	.373
HEA	-.76	48	.45	0.61	47	.54	.39	45	.70	-.18	38	.86
NAU	-.93	47	.359	1.10	46	.279	0.00	44	1.0	-.48	37	.64
PIN	2.23	48	.031	3.08	46	.004	2.54	45	.015	2.73	39	.010
TIR	2.62	48	.012	5.12	47	.0001	3.72	45	.001	2.31	39	.026

* Significance (2-tailed)

Bearing in mind the qualifications made above, it is interesting to examine these data for trends. We can see the general trend or pattern of change more easily when the data appear in bar chart format, comparing the changes in each domain across the five measurement points, as shown in Figure 42 below.

[20] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness,

Figure 42 Bar chart showing results of Somatic Symptoms[21] sub-analysis



This chart shows that Tiredness is the symptom that shows the greatest change at EOT, and apart from Pins and Needles, it is the only symptom that does not return to baseline levels at Post tx 18.

For the remaining symptoms, the greatest decrease in symptom levels occurs at EOT, for all categories. The pattern of change at Mid tx is variable, with some symptoms (Backache/Pain, Pins and Needles and Tiredness) decreasing and others increasing (Dizzy Spells, Frequent Urination, Headaches and Nausea). The pattern of the return of

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[21] BAC = Backache/Pain, DIZ = Dizzy Spells, FRE = Frequent Urination, HEA = Headache, NAU = Nausea, PIN = Pins and Needles, TIR = Tiredness,

symptoms is consistent for all categories except Tiredness, with scores increasing progressively as time from EOT increases. At Post tx 18, scores for all domains except Pins and Needles and Tiredness equal or exceed their baseline level.

8.5.3 Results for HFNSQ: NADA Study

The Hot Flushes and Night Sweats Questionnaire (HFNSQ) provides the data to calculate the Problem Rating Score (PRS), which indicates how much of a problem women perceive their hot flushes to be in their daily lives.

8.5.3.1 Hypothesis

This exercise was purely exploratory, and we had no hypothesis about the possible result.

8.5.3.2 Results

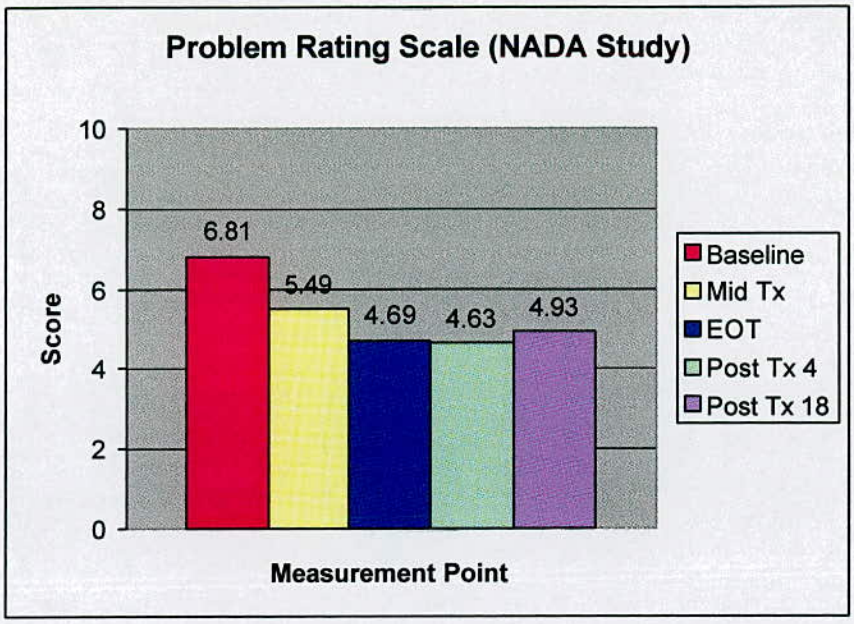
Table 52 below presents the data showing the means and standard deviations for the PRS at all measurement points. **Bold** formatting highlights the data for EOT, the primary endpoint.

Table 52 Means and standard deviations for the Problem Rating Score (NADA)

Sequence	Mean	SD	N =
Baseline	6.81	1.69	52
Mid tx	5.49	1.89	49
EOT	**4.69**	**2.23**	**48**
Post tx 4	4.63	2.09	45
Post tx 18	4.93	2.50	30

Figure 43 below presents these data in bar chart format, to illustrate the pattern of change over the five measurement points.

Figure 43 Changes in the Problem Rating Scale (NADA)



Here we see the relatively high score at baseline dropping to its lowest point at Post tx 4 (although the difference between this and EOT is insignificant). The score rises by Post tx 18, but still remains well below the measurement at baseline.

Table 53 below presents the results of paired samples t tests showing the change at each measurement point compared with baseline. **Bold** formatting highlights the statistically significant results ($p < 0.05$). (Whilst the previous comments about making corrections for multiple tests apply to these data, all the results are highly significant, and there is less than one chance in a thousand that the results are due to chance. Therefore, it is possible to take these data at their face value, rather than correcting them for multiple testing.)

Table 53 Results of paired samples t tests for PRS (NADA)

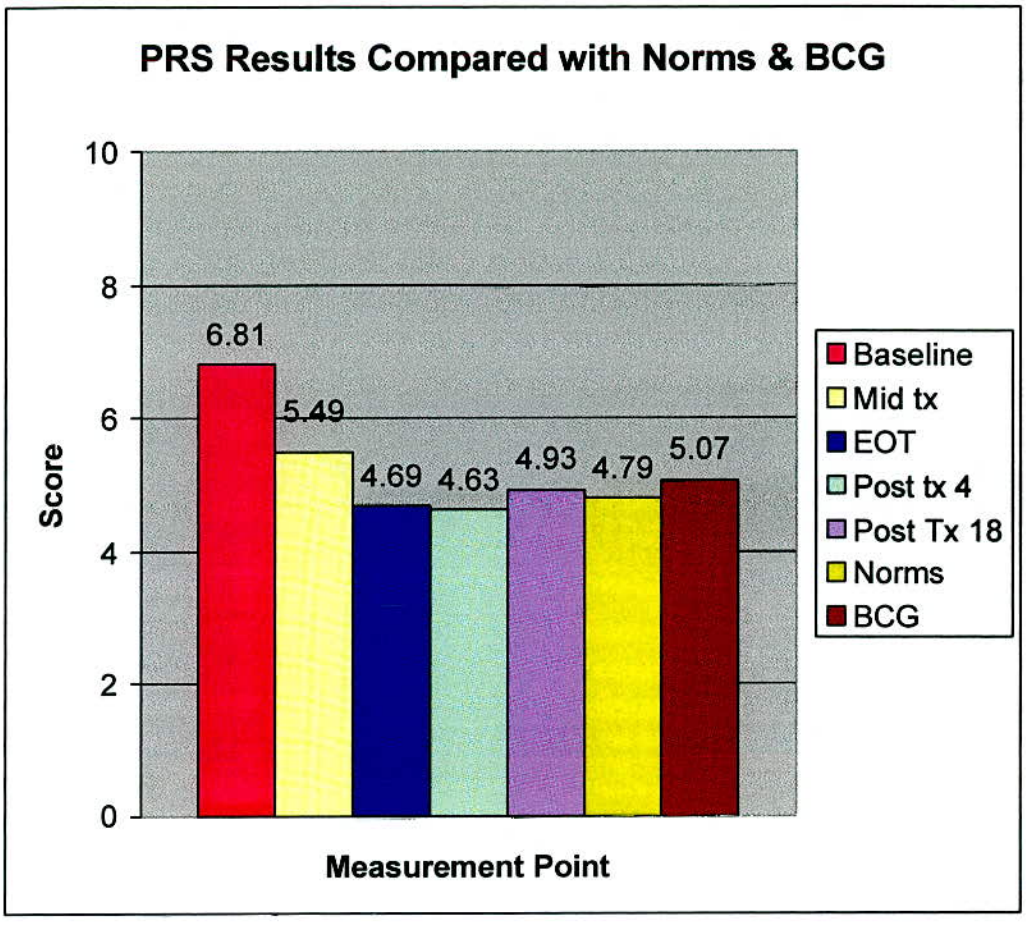
	Paired differences					Paired sample t tests		
				95% CI				
	Mean	SD	N =	LL	UL	t =	df	p < *
Baseline – Mid tx	1.31	1.58	49	0.85	1.76	5.81	48	**.0001**
Baseline – EOT	2.15	2.06	48	1.55	2.74	7.22	47	**.0001**
Baseline – Post tx 4	2.17	1.96	46	1.59	2.75	7.54	45	**.0001**
Baseline – Post tx 18	1.81	1.73	31	1.17	2.44	5.83	30	**.0001**

* Significance (2-tailed)

8.5.3.3 Comparing the data with other studies

As with the WHQ results, we compared the NADA results with Dr Hunter's two studies. Figure 44 below compares the NADA results at all five measurement points with the "norms" and breast cancer group (BCG) results reported by Hunter (1992, 2004).

Figure 44 Comparison of NADA PRS results with Norms and BCG results



The baseline measurement for the NADA group is higher than the norms (n = 682) and the BCG scores (n = 113). At EOT, the score for the NADA group decreases to a level similar to the comparison groups, where it remains at Post tx 4. The score increases slightly at Post tx 18, to a slightly higher level than the norms, but remains similar to the BCG group.

8.6 Acceptability of NADA ear acupuncture

This section presents the results of the following three questionnaires:

- Exit Questionnaire (EQ) administered at EOT

- Follow-up Questionnaire 1 (FQ1) administered at Post tx 4
- Final Follow-up Questionnaire (FFQ) administered at Post tx 18.

The analysis examines selected questions from these questionnaires to answer the question "Do women who have had invasive treatments for breast cancer find the NADA ear acupuncture protocol and delivery method acceptable?"

8.6.1 Compliance and missing data

Table 54 below presents the numbers of questionnaires returned at each measurement point.

Table 54 Numbers of follow-up questionnaires returned at each measurement point

MEASUREMENT PERIOD	EOT (EQ)	Post tx 4 (FQ1)	Post tx 18 (FFQ)
QUESTIONNAIRES RETURNED	48	46	41

Data were occasionally missing on the questionnaires returned. Many participants answered the yes/no questions, and chose not to provide further written comments.

8.6.2 Results

8.6.2.1 Analysing the frequencies

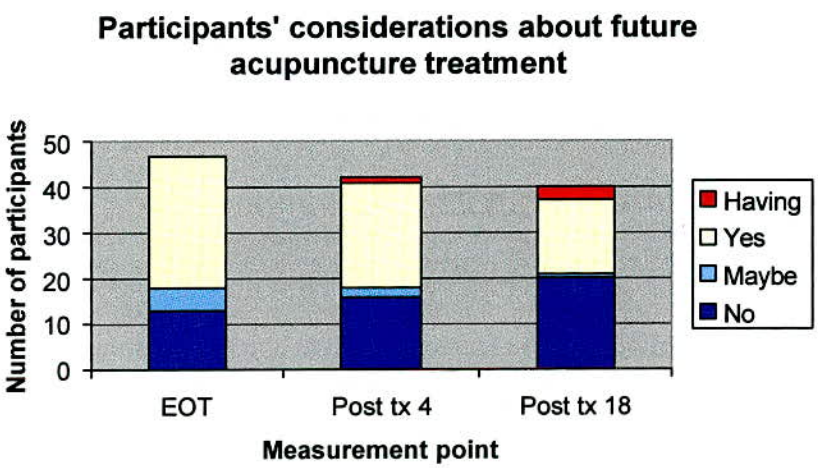
Table 55 below displays the results of the selected questions. The table indicates whether data are missing at random or whether the entire questionnaire is missing.

Table 55 Results for acceptability of NADA ear acupuncture

Exit Questionnaire (EQ) administered at EOT	n=50 (%)
Are you considering having further acupuncture?	
Yes	29 (58)
No	13 (26)
Maybe	5 (10)
Missing (2 questionnaires not returned, 1 missing item)	3 (6)
Were there any aspects of this study you didn't like?	
Yes	9 (18)
No	39 (78)
Missing (2 questionnaires not returned)	2 (4)
Follow-up Questionnaire 1 (FQ1) administered at Post tx 4	
Are you having further acupuncture treatment?	
Yes	1 (2)
No	44 (88)
Missing (4 questionnaires not returned, 1 missing item)	5 (10)
If not, are you considering having acupuncture in the near future to manage your hot flushes and night sweats?	
Yes	23 (46)
Not applicable (having acupuncture)	1 (2)
No	16 (32)
Maybe	2 (4)
Missing (4 questionnaires not returned, 4 missing items)	8 (16)
Are you pleased you took part in the study?	
Yes	45 (90)
Missing (4 questionnaires not returned, 1 missing item)	5 (10)
Do you regret taking part?	
No	45 (90)
Missing (4 questionnaires not returned, 1 missing item)	5 (10
Final Follow-up Questionnaire (FFQ) administered at Post tx 18	
Have you had any acupuncture for hot flushes and night sweats since finishing your course of treatment here?	
Yes	2 (4)
No	39 (78)
Missing (9 questionnaires not returned)	9 (18)
Have you had any acupuncture for any other health complaints since finishing your course of treatment here?	
Yes	2 (4)
No	39 (78)
Missing	9 (18)
If not, are you considering having acupuncture in the near future?	
Yes	16 (32)
Not applicable (having acupuncture)	3 (6)
No	20 (40)
Missing (9 questionnaires not returned, 2 missing items)	11 (22)
Would you recommend acupuncture to a friend?	
Yes	39 (78)
Maybe	2 (4)
Missing	9 (18)

At EOT, enthusiasm for having further acupuncture treatment is highest, with just over two-thirds of participants saying they were considering (58%) or might consider (10%) having further acupuncture. However, this enthusiasm decreases as the time from EOT increases, as Figure 45 below shows.

Figure 45 Changes in participants considering having future acupuncture treatment



The reasons for this decline are not clear. Three participants cited cost as a reason for not having further treatment privately. As in the TA study, some women expressed disappointment that their flushes did not completely disappear, or that they returned as time from EOT increased. These may be reasons that they did not pursue further treatment.

Nine participants said there were aspects of the study they did not like, and of these, four stated they did not like the needles. This aspect was not a complete deterrent: one woman remarked that the needles were off-putting "although not so much that I'd be totally put off having further treatments", and another said she was "not too keen on the needles

going in but OK once they were put in". All of the participants who completed questionnaires stated they were pleased to have taken part in the study, and none of the participants expressed regrets. (Reponses to these questions were missing on one questionnaire).

Most participants said they would recommend acupuncture to a friend, and three volunteered that they had already done so. Only 2 (4%) expressed reservations: one stated "it is difficult to recommend as people's needs are different, but I would be positive about the experience", while the other said "I can't say that the acupuncture helped my hot flushes & night sweats a great deal but it may well help someone else".

8.6.3 Analysing written comments: expectations versus experience

The Exit Questionnaire asked, "How did your experience of having acupuncture match your expectations about what acupuncture might be like?" Forty-seven participants chose to write a short comment in response. The range of responses helps to understand the acceptability of ear acupuncture to these women. The main themes include expectation, pain, and effectiveness of acupuncture. Unlike the feedback on the TA study, there were few remarks about the relaxing nature of the treatment – only two participants commented that the treatment was relaxing.

8.6.3.1 Expectation

Three participants volunteered that they had acupuncture previously, so had some idea of what to expect. Three others were participants in the TA study (refer to the discussion in section 9.5.1.3, page 323 for how we handled the statistical analysis for these "repeat" participants). Their comments suggest that this experience helped them to set expectations about having ear acupuncture, although one wrote that the experience was "much better than I expected...with very good results, much better than I had hoped".

Those new to acupuncture expressed a range of expectations. As in the TA study, some came to the study with "no expectations" or "an open mind" about what acupuncture would be like. A few said they "were not sure what to expect". A large proportion commented that the experience was "as I expected" or "similar to my expectations". Two others commented on aspects that did not match their expectations: one woman wrote that she was "not expecting to have so many needles & expected it to be painless", while another said that she had "expected the procedure of inserting the needles to be more complicated and time consuming" than it was. One participant found the "length of time the needles were left in for" differed from her expectation. (Interestingly, the number of needles in the protocol and the length of time to retain the needles were documented in the Patient Information Sheet, and were explained at the intake interview.)

Many expressed delight that it was "much better than expected". One woman wrote, "I was agreeably surprised that it surpassed my expectations"; for others it was "better than anticipated" or "much more successful than I anticipated". One even found that "it was not as bad as I thought it would be".

8.6.3.2 Pain

Compared with the TA study, there were more comments on the subject of pain. One third of the comments referred to pain. Some participants anticipated pain, and were pleased to find it was "less painful" or "hurt less" than expected. One woman said it was "less painful than I thought, and (I) coped with the needles which I didn't think I would". Others expressed a different view of the experience. Several commented that it was "not as pain free as expected" or it "hurt more than I thought just when the needles were inserted". The experience of pain was not consistent for some participants: one said, "some weeks were more painful than others", and another said it "sometimes hurt a little". Any pain did not seem to last long, and one participant said, "I thought it may be painful in the ear but after a sting which lasted 1-2 seconds it was fine."

8.6.3.3 Effectiveness of acupuncture

Many participants were enthusiastic about the results and expressed this in response to the question about experience versus expectation. Several commented that "the results were better than I expected" or that they were "very surprised" or "very impressed" with the effectiveness of

ear acupuncture. One woman explained "my patterns of hot flushes changed immediately and I felt ...less tired..." This delight was not universal, however, and one participant who found the experience to be "not as pain free as expected" remarked that she "was hoping flushes would reduce more".

8.6.4 Analysing written comments: being treated in a group

One aim of Study 2: NADA was to assess whether women would find treatment in a group acceptable. This section discusses the participants' written remarks about this mode of treatment.

Twenty-four participants commented spontaneously on this topic. Their comments appear in response to a variety of questions, and the data presented below result from analysing the entire questionnaires. Themes that arise include sharing with others, isolation and abnormality, and preference for not sharing.

8.6.4.1 Sharing with others

Many women found it "good to talk" about their problems, whether this focused specifically on hot flushes or related more generally to their experience of having breast cancer and its treatments. For several, this had a therapeutic effect. One woman said, "meeting & talking to other breast cancer patients has helped me with my own feelings"; another wrote, "for the first time I was able to talk about how I felt about the cancer and how it affects me." For others the group provided the

opportunity to "exchange possible solutions". Some of the groups developed a strong identity: one woman commented on the "strong sense of 'group'" that "cohered & formed a unit which was beneficial in itself for group therapy discussions". Others described the group situation as "interesting", "supportive" or "therapeutic".

8.6.4.2 Isolation and abnormality

Arising from these comments is a strong theme of the isolation these women feel in their distress. One woman found that talking to other members of the group "made me realise I wasn't alone with all my problems & didn't feel so isolated". Others spoke of feeling "very alone before the start of the (acupuncture) treatment", or of thinking, "you are the only one" before they joined the study. For some, breaking this isolation to realise that others suffered similarly was liberating. One woman said, "I thought I was slightly abnormal", and another said "I thought I was very peculiar before the study...I was feeling isolated and that nobody cared. I don't feel like that now". This group contact provided some reassurance that these side effects were normal and experienced by others: one participant noted, "the group made me realise it (the hot flushes and night sweats) was normal and not another symptom of illness". For another, the realisation that she was not the only one experiencing side effects meant that that she no longer felt "out of place and can talk about it easier."

For some, this isolation seemed to arise from the responses of the medical professionals to their problems. It suggests that women are not

sufficiently prepared for the experience of tamoxifen. The woman who said, "when I talked to doctors about my problem I got the feeling that they thought I was making a fuss about nothing" also highlighted that she was "totally unprepared for the huge and unpleasant side effects tamoxifen has had on me".

8.6.4.3 Preference for not sharing

Not all of the participants found the sharing beneficial or desirable. Three women commented that they would have preferred silent sessions. One said that although "it was nice to share experience with a small group...I would have benefited from silent meditation while needles were in my ears". Another said it was easier to "de-stress" when the room was quiet: she then felt "more relaxed and the treatment more beneficial as I could concentrate on chilling out". For one woman, the group sessions had the potential to be actually disruptive: she objected to "other participants in the study (who) talked too much". However, the subject of the conversation may have been disturbing: "in some groups there was a lot of talk and negative vibes eg (sic) about hospital treatment, doctors & advice."

One participant initially declined to take part in the group treatment, even though she had read the Patient Information Sheet and consented to the study. At her first treatment, she asked to be treated separately and it was not until after her fourth treatment that she requested treatment with the group. (Refer to the publication *Serenity, patience, wisdom, courage,*

acceptance: reflections on the NADA Protocol (de Valois 2006) in Appendix 31 for details of her story. See Case 3: "June" on pages 48-9.)

8.6.5 Other indications of acceptability

These comments suggest that many – perhaps the majority – of women taking part in the study found ear acupuncture acceptable as a form of treatment. Although many found it somewhat uncomfortable, the low number of losses to the study supports the idea that this was not enough to deter them from completing the course of treatment. The majority of women found the group sessions more than merely acceptable: they found positive benefits in being able to compare their experiences with others in a similar situation.

8.7 Conclusion

This chapter presented the data relating to the three main questions of this study. The results suggest that the standardised ear acupuncture protocol may have an effect on reducing the frequency of hot flushes and night sweats, and that at EOT a woman might expect a reduction in the number of hot flushes by nearly 36% over her baseline frequency. The results of the WHQ suggest that women experience a range of improvements in their physical and emotional well-being, and the Somatic Symptoms sub-analysis suggests that women feel less tired because of treatment. In addition, women seem to see their hot flushes as less of a problem in their daily lives. Finally, the data suggest that the majority of women in this study found ear acupuncture acceptable as a form of treatment. Most participants also found treatment in a group acceptable.

Chapter 9 Comparing the Results of Studies 1 & 2

9.1 Synopsis

In this chapter, I discuss the rationale and methodology for comparing the results of the two studies. I then present the results, first looking at the primary endpoint, which is the change in hot flush frequency at end of treatment (EOT). Comparison of the other measurement points for hot flush frequency follows. I explore the relative changes in emotional and physical well-being, focusing on the comparison of the Women's Health Questionnaire (WHQ) and the Problem Rating Scale (PRS) at EOT.

9.2 Rationale for comparing the two studies

A natural question arising from this work is "how do these two acupuncture approaches compare?" Other questions follow. Is there a difference in the effect of the two treatments? Do the data support the assumption that semi-individualised traditional acupuncture may be more effective than the standardised ear acupuncture? Comparing the results of Study 1: TA and Study 2: NADA may provide some answers to these questions.

9.2.1 Similarities between the two studies

Opportunity for comparison arises from the fact that the two studies share the same design structure, outcome measures, and measurement points. The studies took place in the same environment (the LJMC), with

treatments delivered by the same practitioner. Criteria for participant selection remained the same, as did evaluation of the treatments.

9.2.2 Identified changes since the TA study

Treatment of the participants took place during the four years from 2001 through 2004. Study 1 spanned from April 2001 through September 2002, and Study 2 spanned from September 2003 through December 2004. While diagnosis and treatment of breast cancer may have evolved during this period, it is unlikely that they changed radically. However, we are aware of two changes outside of the study structure.

The first change was the introduction of Arimidex (or anastrozole) as a new adjuvant treatment for post-menopausal women with early breast cancer. It was licensed for use in the UK in June 2005 (Nordqvist 2005), but we had anticipated this change since early in 2004. Although promotions for anastrozole stressed its superiority over tamoxifen, prescriptions for tamoxifen remained the norm during the NADA study. (Our study continued to focus on women taking tamoxifen, although we introduced a small sub-study to include women taking Arimidex.)

Another noticeable change was pharmaceutical practice in dispensing tamoxifen. In 2003, generic brands of tamoxifen became available. They cost less than half the price of the original brand-named product Nolvadex, produced by AstraZeneca (Breastcancer.org 2003), and pharmacies dispensed these generic brands in preference to the more expensive Nolvadex. Thus, during Study 1: TA, women tended to receive

the same brand of tamoxifen for every prescription, while during the NADA study, women reported that the brand could change with every new prescription.

It is difficult to gauge whether or to what extent these changes may have affected the participants. However, within the overall acupuncture project, the conditions for the two studies appeared similar, and we believe they are comparable. It was necessary to test this, however.

The first step was to demonstrate that the two populations were similar in terms of sociodemographic data and baseline medical data. The next step was to compare baseline hot flush frequencies. If these criteria were not significantly different, it would then be appropriate to conduct further comparisons between the two groups.

9.3 Methodology

9.3.1 Independent samples t tests

We used independent groups t tests in SPSS to compare the results of the two studies for hot flush frequency, WHQ, and PRS data. In our earlier analyses of the studies, each participant acted as their own control, and our aim was to measure the mean difference between baseline (before the intervention, or pre-test) and EOT (after the intervention, or post-test) for each participant. The means in such a comparison are "within subject" and are therefore "dependent". It is appropriate to use paired samples t tests to calculate the difference

between pre-test and post test, to ascertain if the mean of these differences is significantly different from zero (Becker 1999).

However, comparing the results of the two studies requires that we examine two different groups (that is, the TA group and the NADA group). Each group is an independent sample; they comprise different participants, and the participants in both groups are not matched or paired (Wielkiewicz 2000). The means are "between subject" and are compared using an independent groups t test (Becker 1999).

As well as establishing that the groups are independent, further criteria for applying independent samples t tests include the following conditions (Archambault 2000):

- The dependent variable is normally distributed.

  In this case, the means are the dependent variables. Our earlier analyses of the hot flush frequency data showed that the untransformed summary data (USD) were not normally distributed, and that the log transformed data were normally distributed. Consequently, we applied the independent groups t tests to the log transformed data. For WHQ and PRS data, we applied the t tests to the data as collected, as per the discussion in section 4.9.5.4 starting on page 148.

- The variance on the dependent variable of the two groups is approximately equal.

  The Levene's Test for Equality of Variance tests this assumption

(Archambault 2000). The null hypothesis for the Levene's test is that the variances between the groups are equal or "homogenous"; in which case the difference is not significant. If the difference is significant, the data are "heterogeneous". Whether the data are homogenous or heterogeneous determines the type of independent samples t test to apply. In the former case, a Student's t test applies; in the latter, a Welch's t test applies (Becker 1999).

SPSS automatically tests and records these results, providing results for both homogenous (Student's t test) and heterogeneous (Welch's t test) data. In practice, however, it is unusual to have a significant difference in the results for these t tests (Wielkiewicz 2000). The example of our t test on Vasomotor Symptoms in Table 56 below demonstrates this:

Table 56 Results of t tests for equality of means for Vasomotor Symptoms

	Levene's Test for Equality of Variances		t test for equality of means		
	F	Sig	t	df	p = Sig. (2-tailed)
Equal variances assumed	6.206	.015	.953	92	.343
Equal variances not assumed			.947	81.5	.346

Here we see that the F is large (6.206), and the significance for the Levene's test is less than .05 (p = .015). This indicates that the variances between the two groups are heterogeneous and that the key principle of the Student t test (homogeneity) is violated (Wielkiewicz 2000). In theory, we would report the data reported for the "Equal variances not assumed". However, in practice, we can see that the differences between the two

sets of reported data for the t test are not vastly different. Thus, it is standard practice in such circumstances to report the results for "Equal variances assumed" and I follow this procedure when reporting the t test results in this chapter. (However, it is important to highlight that in most cases the groups were homogenous.)

9.3.2 Hypotheses

For all the independent samples t tests:

- The null hypothesis is that the means of the two groups are not significantly different
- The alternative hypothesis is that the means of the two groups are significantly different (Archambault 2000).

9.3.3 Comparing categorical values

The sociodemographic data and some of the baseline medical data were categorical variables, and these required different analysis. As the numbers in the two groups were the same (52), we could compare much of sociodemographic data using a simple frequency count.

Of the baseline medical data, cancer treatment and menopause data appeared sufficiently different to warrant further analysis to establish whether this difference was significant. We used chi-square tests to test the association between the categorical values. The null hypothesis for these tests is that there is no difference between the sets of results (Harris and Taylor 2004). We used SPSS to calculate the chi squares.

9.4 Comparing the sociodemographic data

9.4.1 Comparing the sociodemographic data

Table 57 below compares the sociodemographic data for the two studies.

Table 57 Comparing sociodemographic data for Study 1: TA and Study 2: NADA

	TA n = 52 n (%)	NADA n = 52 n (%)
Marital status		
Single (never married)	0	3 (6)
Married (first marriage)	34 (65)	36 (70)
Re-married	5 (10)	3 (6)
Living with partner	5 (10)	1 (2)
Divorced	5 (10)	6 (12)
Widowed	3 (6)	3 (6)
Home Situation		
Living with family members or partners	45 (86)	44 (85)
Living alone	3 (6)	7 (14)
Living with others (lodgers)	0	1 (2)
Missing data	4 (8)	0
Dependents		
No dependents	34 (65)	36 (69)
Children under the age of 18 or adults for whom financially responsible	16 (31)	16 (31)
Missing data	2 (4)	0
Educational qualifications		
Less than compulsory school education	5 (10)	4 (8)
Compulsory school education (e.g. school certificate, CSEs, GCSEs)	25 (48)	18 (35)
Post compulsory school education below university level	16 (30)	11 (21)
University level	4 (8)	12 (23)
Postgraduate level	2 (4)	7 (14)
Current employment status		
Retired	17 (33)	11 (21)
Not working at present	5 (10)	16 (31)
Working part-time	22 (42)	16 (31)
Working full-time	8 (15)	9 (17)
Country of birth		
England	44 (85)	46 (89)
Scotland	1 (2)	1 (2)
Wales	3 (6)	1 (2)
Irish Republic	1 (2)	0
Northern Ireland	0	1 (2)
Elsewhere	1 (2)	3 (6)
Missing data	2 (4)	0
Ethnic background		
Irish	1 (2)	0
White British	48 (92)	48 (92)
White other	1 (2)	3 (6)
Indian	0	1 (2)
Missing data	2 (4)	0
Car ownership		
Household with 1 car	14 (27)	16 (31)
Household with > 1 car	34 (65)	34 (65)
None	2 (4)	2 (4)
Missing data	2 (4)	0
Home ownership		
Own/buying home	46 (88)	49 (94)
Renting	4 (8)	3 (6)
Missing data	2 (4)	0

The two groups are strikingly similar, particularly in terms of marital status, home situation, dependents, ethnic background, and car and home ownership. There are differences in educational qualifications and current employment status. The NADA participants were better educated, with 37% having university or postgraduate qualifications, as opposed to 12% in the TA study. Regarding current employment status, more participants in the TA study were retired (33% compared with 21% in the NADA study), and more were working part-time (42% compared with 31% in the NADA study). More NADA participants were not working at present (31% compared with 10% in the TA study).

9.4.2 Comparing the Baseline Medical Information

We applied independent groups t tests (as discussed above) to compare the following medical characteristics of the two groups: age, time since cancer diagnosis, time taking tamoxifen, and time since last period. There were no significant differences between the groups, as shown in Table 58 below.

Table 58 Results of t tests for baseline medical data

		Group Statistics			Independent Samples Test		
Criteria	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Age	TA	52	54.3	7.8	-.351	102	.73
	NADA	52	54.8	7.2			
***Time on Tamoxifen**	TA	52	87.4	44.2	-.041	102	.97
	NADA	52	87.8	59.6			
***Time since diagnosis**	TA	52	100.9	44.0	-.996	102	.32
	NADA	52	111.5	63.4			
***Time since last period**	TA	50	352.6	376.0	1.12	97	.27
	NADA	49	273.5	323.6			

***Time in weeks**

We compared cancer treatment data, and noted a difference in the number of women who had chemotherapy. In Study 1: TA, 26 (50%) had chemotherapy, compared with 35 (67%) in Study 2: NADA. We carried out a chi-square test to test the null hypothesis that the proportion of participants treated by chemotherapy was the same for both groups. The test indicated that there was no significant difference between the groups ($\chi^2 = 3.21$, $df = 1$, $p = .073$).

We also compared the menopause data and noted a difference between the numbers who were menopausal and post-menopausal, as shown in Table 59 below.

Table 59 Comparison of menopause data for both studies

	All Participants at Baseline n = 52 n (%)	
	TA	**NADA**
Menopause status[22]:		
Perimenopause (last period within the previous year)	6 (12)	7 (14)
Menopause (no period within the previous 1-5 years)	19 (36)	27 (52)
Postmenopause (no period in over 5 years)	24 (46)	15 (30)
Missing data	3 (6)	3 (6)

We carried out a chi-square test to test the null hypothesis that the proportion of menopausal and postmenopausal participants was the same for both studies. The test indicated there was no significant difference between the groups ($\chi^2 = 3.46$, $df = 1$, $p = .063$).

[22] Based on the STRAW staging system (Soules et al 2001).

Thus, we established that no significant differences existed for the two study populations on the variables that we measured. We proceeded to compare the hot flush frequency results.

9.5 Comparing hot flush frequency

9.5.1 Comparing hot flush frequency for the primary endpoint

9.5.1.1 Hypothesis

My hypothesis was that TA would show a greater effect on reducing hot flushes at end of treatment (EOT) than the NADA treatment. EOT is the primary endpoint. This means that the null hypothesis is that there is no difference between the groups (Harris and Taylor 2004).

9.5.1.2 Process and results

Step one was to compare the baseline hot flush frequency for all participants in both groups to establish whether there was any significant difference in their baseline hot flush counts. We compared the log transformed data (as discussed in 9.3.1, page 313 above). Table 60 below presents the result, which shows there was no significant difference between the groups at baseline.

Table 60 Comparing log hot flush frequency for both groups at baseline (all participants)

		Group Statistics			Independent Samples Test		
Log of frequency at baseline	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
	TA	52	2.18	.57	-.756	101	.45
	NADA	51	2.26	.50			

Sig. (2-tailed)

Having established that there was no difference in the frequency of hot flushes between the two groups at baseline, the next step was to compare only those participants who had complete baseline and EOT data. Again, we compared the log transformed data. Table 61 below presents the result, which shows there was no significant difference between the two groups when comparing all participants who have complete baseline and EOT data.

Table 61 Comparing log hot flush frequency for both groups at baseline (participants with complete data for baseline and EOT)

		Group Statistics			Independent Samples Test		
Log of frequency at baseline	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
	TA	48	2.221	.551	-.540	93	.591
	NADA	47	2.277	.454			

Sig. (2-tailed)

Having established that there was no significant difference between the TA and the NADA participants in terms of their hot flush frequency at baseline, we then compared the log of the change from baseline to EOT. We used data for participants who had complete baseline and EOT data. Table 62 below presents the result.

Table 62 Independent t test result on the change from log baseline – log EOT

		Group Statistics			Independent Samples Test		
	Study	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Log (baseline) – log (EOT)	TA	48	.678	.538	2.104	93	**.038**
	NADA	47	.447	.529			

Sig. (2-tailed)

This test showed a significant difference (p = .038) between the two groups.

Note that the means presented in Table 62 above correspond to the means presented in Table 27 on page 211 and in Table 47 on page 284. As these means correspond, we can conclude that the difference in the calculated percentage response rate for the two groups (49.8% for the TA group, 35.9% for the NADA group) is significant. Thus, we can say that the two groups are comparable for hot flush frequency at baseline, and that the reduction at EOT is significantly different, in favour of the TA group.

9.5.1.3 Dealing with "repeat" participants

Three women participated in both studies. Even though they had received a course of treatment in Study 1: TA, they met the entry criteria for Study 2: NADA. They were eligible in terms of numbers of hot flushes at baseline, and over three months had elapsed since the end of their previous acupuncture treatment (refer to the inclusion and exclusion criteria in section 3.10 starting on page 110). Consequently, we did not exclude them from the analyses presented in Chapter 6 and Chapter 8. However, their inclusion in this comparison might be a violation of one of the criteria for a t test, namely independence of the two samples. Consequently, we checked to ensure that these participants were representative of the groups as a whole, and were not at the extremes where they might skew the data.

To do this, I retested the log change data after removing the data for these three participants. Table 63 below presents the results.

Table 63 T test result on the change from log baseline – log EOT ("repeat" participants excluded)

		Group Statistics			Independent Samples Test		
	Study	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Log (baseline) – log (EOT)	TA NADA	45 44	.661 .418	.549 .517	2.151	87	**.034**

Sig. (2-tailed)

The result shows that removing the repeat participants enhances the significance of the result (p = 0.034 as opposed to p = 0.038). We conclude that this very slight difference in the results (0.004) does not warrant adjusting the data sets by removing these participants, and rerunning all the analyses.

9.5.1.4 Summary of the results

The results of the Student's t tests support the hypothesis that the TA would show a greater effect on reducing hot flushes at EOT than the NADA treatment (t = 2.104, df = 93, p = 0.038).

9.5.2 Comparing the short term and longer term results

The primary endpoint was at EOT, and we based our hypothesis on this endpoint. However, we were interested in exploring the changes at the three other measurement points. Consequently, we carried out the same comparison for hot flush frequency at Mid tx, Post tx 4 and Post tx 18.

For each measurement point, we compared the hot flush frequency data at baseline for those participants who had complete sets of data at

baseline and at the respective measurement point. This was to establish whether there was any difference between the groups at baseline. Table 64 below shows the results of these tests, which show there is no significant difference in the hot flush frequency at baseline for any of the measurement points.

Table 64 Comparisons of baseline hot flush frequency for participants having complete baseline and other measurement point data for each measurement point

		Group Statistics			Independent Samples Test		
Log of frequency @ baseline	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Log (Baseline) for all participants with Mid tx data	TA NADA	48 50	2.2 2.3	.58 .45	-1.06	96	.29
Log (Baseline) for all participants with Post tx 4 data	TA NADA	47 45	2.2 2.3	.55 .45	-.87	90	.39
Log (Baseline) for all participants with Post tx 18 data	TA NADA	47 38	2.2 2.3	.58 .46	-.55	83	.58

Sig. (2-tailed)

Having established that there are no significant differences in the baseline hot flush frequency data for both groups, we then compared the log change data at each measurement point. Table 65 below presents the results of these independent groups t tests.

Table 65 Comparing log change data from baseline to each measurement point

		Group Statistics			Independent Samples Test		
	Study	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Log (baseline) – Log (Mid tx)	TA NADA	48 50	.525 .273	.528 .379	2.716	96	**.008**
Log (baseline) – Log (Post tx 4)	TA NADA	47 45	.530 .470	.533 .591	.517	90	.606
Log (baseline) – Log (Post tx 18)	TA NADA	47 38	.513 .465	.583 .545	.388	83	.699

Sig. (2-tailed)

These tests showed there was a significant difference in hot flush frequency between the two groups at Mid tx. At p = .008, this is more significant than the difference in change at EOT (p = 0.038). There were no significant differences between the groups at Post tx 4 or Post tx 18.

9.6 Comparing emotional & physical well-being

9.6.1 Hypothesis

Based on the observations of the change in hot flush frequency, my hypothesis was that at EOT the TA would show a greater effect on improving physical and emotional well-being than the NADA treatment.

9.6.2 WHQ results

As with hot flush frequency, the first step was to compare the baseline results for all participants in both groups to establish whether there was any significant difference in their baseline WHQ scores. Table 66 below displays the results, and there were no significant differences between the groups on any of the WHQ measures at baseline.

Table 66 T test results for comparison of WHQ scores for both groups at baseline

Baseline		Group Statistics			Independent Samples Test		
WHQ domain	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Anxiety/fears	TA	53	.26	.27	.85	102	.40
	NADA	51	.30	.27			
Attractiveness	TA	52	.57	.31	.44	100	.66
	NADA	50	.54	.32			
Depressed mood	TA	53	.21	.25	-.62	102	.54
	NADA	51	.24	.22			
Memory/concentration	TA	52	.59	.35	-.58	102	.57
	NADA	52	.63	.33			
Menstrual symptoms	TA	53	.33	.24	.72	103	.47
	NADA	52	.29	.22			
Sexual behaviour	TA	44	.46	.32	-0.9	79	.93
	NADA	37	.47	.34			
Sleep problems	TA	53	.65	.32	.22	103	.83
	NADA	52	.64	.30			
Somatic symptoms	TA	53	.49	.21	.81	102	.42
	NADA	51	.46	.22			
Vasomotor symptoms	TA	53	.99	.07	.62	102	.54
	NADA	51	.98	.10			

Sig. (2-tailed)

Having established that there were no significant differences between the two groups at baseline, we carried out independent groups t tests on the change in WHQ scores from baseline to EOT, comparing the two groups. Table 67 below presents the results.

Table 67 Results of independent groups t tests for changes in WHQ scores baseline – EOT

Baseline - EOT		Group Statistics			Independent Samples Test		
WHQ domain	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
Anxiety/fears	TA	47	.17	.25	1.25	92	.21
	NADA	47	.10	.24			
Attractiveness	TA	47	.09	.37	.42	90	.68
	NADA	45	.06	.31			
Depressed mood	TA	47	.06	.20	-1.85	92	.07
	NADA	47	.15	.24			
Memory/concentration	TA	47	.24	.35	1.66	92	.10
	NADA	47	.12	.35			
Menstrual symptoms	TA	48	.15	.18	2.38	94	**.02**
	NADA	48	.06	.20			
Sexual behaviour	TA	38	.14	.31	.92	70	.36
	NADA	34	.08	.26			
Sleep problems	TA	47	.25	.37	.39	93	.70
	NADA	48	.22	.32			
Somatic symptoms	TA	48	.15	.22	.67	93	.51
	NADA	47	.12	.23			
Vasomotor symptoms	TA	48	.17	.26	-.95	92	.34
	NADA	46	.23	.36			

Sig. (2-tailed)

The results show no significant differences between the two groups in any of WHQ domains except for Menstrual Symptoms (p = .02).

9.6.3 Problem Rating Score (PRS) results

As in the previous comparison, the first step was to compare the baseline results for all participants in both groups to establish whether there was any significant difference in their baseline PRS scores. Table 68 below displays the results, and there were no significant differences between the groups at baseline.

Table 68 Comparison PRS at baseline

		Group Statistics			Independent Samples Test		
PRS Baseline	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
	TA	52	6.80	1.94	-.05	102	.96
	NADA	52	6.81	1.69			

Sig. (2-tailed)

Having established that there was no significant difference in the PRS scores at baseline, we carried out independent groups t tests on the change in the PRS from baseline to EOT, comparing the two groups. Table 69 below presents the results, which show there was no significant difference in the change between the groups.

Table 69 Comparison of the change in PRS baseline – EOT for the two groups

		Group Statistics			Independent Samples Test		
PRS Baseline – PRS EOT	**Study**	**n =**	**Mean**	**Std Dev**	**t =**	**df**	**Sig**
	TA	48	2.21	2.15	.17	94	.87
	NADA	48	2.15	2.06			

Sig. (2-tailed)

9.6.4 Summary of results for physical & emotional well-being

Overall, there was no significant difference in the change in WHQ scores between the two groups at EOT, except on the domain Menstrual Symptoms ($t = 2.38$, $df = 94$, $p = .02$). Thus, we did not prove the hypothesis that the TA would show a greater effect on improving physical and emotional well-being than the NADA treatment at EOT.

9.7 Data not compared

As physical and emotional well-being was a secondary measure, and as the results at EOT showed no significant difference, we chose not to analyse the data at all other measurement points. We also chose not to compare the data for the Somatic Symptoms sub-analysis.

9.8 Conclusion

In this chapter, I explored the data in an attempt to answer the question "how do these two acupuncture approaches compare?" We used numerical comparison, chi-square tests and Student t tests to compare the two studies. The results suggest that for the primary measure, hot flush frequency at EOT, there was a significant difference between the two groups, in favour of the TA approach. Further exploration indicated that there was a significant difference at mid-tx, but not at Post tx 4 and Post tx 18. The two studies showed no significant difference in the effects on physical and emotional well-being at EOT. In the next chapter, I discuss the implications of these findings.

Chapter 10 Discussion

10.1 Synopsis

In this chapter, I discuss the findings of this research and its implications. I restate the original questions the research set out to answer, and review the results, identifying factors other than the acupuncture that may have influenced these results. I compare these results with those of other studies, and then evaluate the design and methods used in my research, discussing the limitations and strengths of the approach used. Many questions arise from this research, and I discuss some of these, as well as some recommendations for future research. Finally, I conclude by summing up the contribution that this work makes to the evidence base for using acupuncture to manage tamoxifen-related hot flushes in women who have been treated for early breast cancer.

10.2 Introduction

The research in this thesis sprang from a desire to discover whether acupuncture could be a helpful form of complementary medicine for people with cancer. In conducting the two observational studies on using acupuncture to manage hot flushes, my initial impression is that acupuncture may be an acceptable and beneficial tool in the management of cancer-related symptoms, which can be used in conjunction with standard medical treatments. However, further analysis of the strengths and limitations of the studies is required to understand more fully what these studies reveal.

10.3 Restating the questions

At the outset of this research, my endeavour was to find answers to the following questions:

- Can acupuncture be used to manage the hot flushes and night sweats that are a side effect in women taking tamoxifen as an adjuvant treatment for early breast cancer?
- Does acupuncture affect the overall physical and emotional well-being of the recipient? If so, is it possible to measure this?
- Is acupuncture acceptable to women who have had invasive treatments for breast cancer?

In the studies, I also explored two questions that are of specific interest to an acupuncturist. Study 1: TA provided the opportunity to investigate whether the theories of traditional acupuncture used to treat the symptoms of natural menopause could be applied to manage pharmaceutically-induced menopause symptoms. Study 2: NADA provided the opportunity to explore the effects of a standardised treatment protocol delivered in a group setting. Taken together, the studies offer the opportunity to compare the results of two types of acupuncture.

10.4 Reviewing the results

10.4.1 Hot flush frequency

The primary outcome measure was reduction, over the baseline measurement, in hot flush frequency at the end of eight acupuncture

treatments. According to our methodology and statistical analysis, the results are as follows:

- For Study 1: TA, the data show that the 48 women with complete hot flush diaries for baseline and EOT, and who completed the course of treatment, had a mean reduction in hot flush frequency of 49.8% over baseline (95% CI 40.5 - 56.5), and this reduction was statistically significant ($t = 8.72$, $df = 47$, $p < 0.0001$). (See section 6.4.1.6 starting on page 210 for details.)
- For Study 2: NADA, the data show that the 47 women with complete hot flush diaries for baseline and EOT, and who completed the course of treatment, had a mean reduction in hot flush frequency of 35.9% over baseline (95% CI 25.4 – 45.4), and this reduction was statistically significant ($t = 5.79$, $df = 46$, $p < 0.0001$). (See section 8.4.1.6 starting on page 283 for details.)

10.4.2 Physical and emotional well-being

10.4.2.1 Results of the Women's Health Questionnaire (WHQ)

Acupuncture patients often report changes in symptoms other than the main complaint as they undergo treatment. In these studies, I used the validated Women's Health Questionnaire (WHQ) to monitor these changes. The data suggest that women experienced benefits in physical and emotional well-being, and the results at the primary endpoint, the change at EOT over baseline, are as follows:

- For Study 1: TA, the group showed statistically significant improvements in the WHQ domains Anxiety/Fear, Depressed Mood,

Memory/Concentration, Menstrual Symptoms, Sexual Behaviour, Sleep Problems, Somatic Symptoms, and Vasomotor Symptoms (see section 6.5.1.3 starting on page 213 for details).

- For Study 2: NADA, the group showed statistically significant improvements in the WHQ domains Anxiety/Fear, Depressed Mood, Memory/Concentration, Sleep Problems, Somatic Symptoms, and Vasomotor Symptoms (see section 8.5.1.3 starting on page 286 for details).

10.4.2.2 Results of the Somatic Symptoms sub-analysis

I took the opportunity to analyse the Somatic Symptoms domain of the WHQ following the recommendation of Dr Hunter (the developer of the WHQ), who suggested that this might yield interesting information. This was to identify which, if any, symptoms in that sub-scale appeared to change during treatment. The results are as follows:

- For Study 1: TA, the scores show statistically significant reductions for Dizzy Spells, Frequent Urination, Headache, Nausea, and Tiredness. Of these five symptoms, Tiredness showed the greatest reduction at EOT (see section 6.5.2.2 starting on page 221 for details).
- For Study 2: NADA, the scores show statistically significant reductions for Backache/Pain, Pins and Needles, and Tiredness. Of these three symptoms, Tiredness showed the greatest reduction at EOT (see section 8.5.2.2 starting on page 293 for details).

Fatigue is a major symptom in women with breast cancer (Dow et al. 1996), and the results suggest that the women in both groups experienced reductions in this, as indicated by the reduced levels of

tiredness. This appears to support an assumption about acupuncture, which is that a general effect of acupuncture treatment is improved energy levels (Hicks 2005).

10.4.2.3 Results of the Problem Rating Scale (PRS)

I used the Hot Flushes and Night Sweats Questionnaire (HFNSQ), a validated companion questionnaire to the WHQ, to measure the Problem Rating Scale (PRS). The PRS identifies changes in the participants' perceptions of their hot flushes as a problem in daily life. The results suggest that women see their hot flushes as less of a problem at EOT over baseline, and a summary of the results is as follows:

- For Study 1: TA, the data show that the 48 women with complete questionnaires at baseline and EOT, and who completed the course of treatment, had a mean reduction in PRS of 2.22 points (out of 10) over baseline (95% CI 1.60 – 2.84), and this reduction was statistically significant ($t = 7.16$, $df = 47$, $p < 0.0001$). (See section 6.5.3.2 starting on page 225 for details.)
- For Study 2: NADA, the data show that the 48 women with complete questionnaires at baseline and EOT, and who completed the course of treatment, had a mean reduction in PRS of 2.15 points (out of 10) over baseline (95% CI 1.55 – 2.74), and this reduction was statistically significant ($t = 7.22$, $df = 47$, $p < 0.0001$). (See section 8.5.3.2 starting on page 297 for details.)

10.4.3 Acceptability of acupuncture

The participants in both groups appeared to find acupuncture an acceptable mode of treatment, as evidenced by the low dropout rates. Overall, their written comments confirm that they found the treatment acceptable (as presented in section 6.6 starting on page 228, and in section 8.6 starting on page 300).

In fact, one of the findings of this research is that these women are highly motivated to take action to deal with their hot flushes. Many women were prepared to overcome their fear of needles or of the unknown to find a solution to their problem, and this is confirmed by the findings of the focus groups that were conducted as a separate sub-study (Walker et al. 2004, Walker 2005).

In Study 1: TA, the participants expressed a range of expectations about having acupuncture, including the assumption that it would be painful. However, only one participant commented that she actually found the experience painful, but that this was not off-putting. Many participants found the experience relaxing. Three participants later took part in Study 2, and only two participants said they would not recommend acupuncture to a friend.

The participants in Study 2: NADA also expressed a range of expectations, and overall their written comments suggest that this was a more painful or uncomfortable experience than the body acupuncture

used in Study 1. Overall, the women appreciated being treated in a group. However, comments reveal divided opinions over whether the group should remain silent, or whether talking should be allowed. Several participants stated a preference for silence during the group sessions, as they found that talking was disruptive. Others found the opportunity to share information and to discuss their experiences of hot flushes and their cancer treatment beneficial (see "Case 2: May" in the publication *Serenity, patience, wisdom, courage, acceptance: reflections on the NADA protocol* (de Valois 2006, p 48) in Appendix 31). This interesting range of feedback can inform the set-up of future services, with providers considering it when making decisions about the aims and objectives of the group aspect of an ear acupuncture service[23].

10.4.4 Short-term and longer-term effects

In both studies, I gathered data to gauge the short-term and longer-term effects. Due to the volume of data collected, as well as the number of analyses conducted (as per discussion of the Bonferroni correction in section 6.5.1.4 on page 214), the following results should be viewed cautiously. However, the data suggest interesting trends.

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[23] For example, in setting up the ear acupuncture service at the LJMC (subsequent to this research project) the Complementary Therapies Co-ordinator has opted to encourage silence during sessions. However, she reports that this is challenging to enforce, and she does not ban talking completely. NADA UK maintains strict rules of silence for their detox programmes, whilst quiet talking is allowed at the Lincoln Recovery Centre in the Bronx, where the NADA protocol originated. See *Serenity, patience, wisdom, courage, acceptance: reflections on the NADA protocol* de Valois B (2006) Serenity, patience, wisdom, courage, acceptance: reflections on the NADA protocol. *European Journal of Oriental Medicine,* 5(3): 44-9. in Appendix 31 for further discussion.

I measured the changes at Mid tx (after four treatments) to ascertain whether there would be sufficient improvement to reduce the total number of treatments needed. The data indicate that although in both studies the hot flush frequency and emotional and physical well-being show signs of improvement after four treatments, considerable change takes place over the course of the last four treatments. This suggests that, within the context of this study, a course of at least eight treatments is advisable to obtain an optimum effect. (In section 3.7.3, starting on page 91, I discussed the difficulties of establishing the optimum dose. My examination of the literature (see section 5.7.4, starting on page 174) shows the range of treatment doses and durations used in studies, and highlights the fact that there is, as yet, no consensus about how many treatments are "optimum".)[24]

For longer-term effects, I measured at four weeks after the end of treatment (Post tx 4) and again at 18 weeks after the end of treatment (Post tx 18). The data indicate a trend for hot flushes levels to rise as time from treatment increases, although the frequency does not return to the baseline levels, even after 18 weeks after EOT. Overall, physical and emotional well-being show a similar trend, although there are some

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[24] As an example of the range of pressures and opinions on this subject, the LJMC have proposed to reduce the number of treatments in a course to between four to six. In contrast, I have been advised by an obstetrician and gynaecologist working in Sweden that the optimum number of treatments is in the range of 13 to 16 sessions (Stener-Victorin E, personal communication, 10 July 2003). A longer course of treatment is likely to be more suitable for what is, in effect, a chronic condition. Experience gained in my private clinic suggests that the "optimum" dose is dependent on the individual's circumstances, and may include a range of factors such as age, menopausal status, cancer treatment history, constitution, and lifestyle.

exceptions to this pattern in individual domains of the WHQ. PRS results also show the greatest improvement at EOT, with the scores increasing slightly as time from EOT increases, but they do not return to their baseline levels, even at 18 weeks after EOT.

These trends suggest that there might be a long lasting effect of treatment. However, I cannot say this with certainty, for the reasons discussed in section 10.5 below.

10.4.5 Comparing the studies

10.4.5.1 Hot flush frequency

The exercise of comparing the results of the change in hot flush frequency for both groups at EOT shows that there was a statistically significant difference in favour of the traditional acupuncture group ($t = 2.104$, $df = 93$, $p = .038$). (See section 9.5 starting on page 321 for details for hot flush frequencies.)

It is interesting to note that the greatest difference between the two groups occurs at Mid tx. Once again, there is a significant difference in favour of the traditional acupuncture group ($t = 2.716$, $df = 96$, $p = .008$). This greater difference between the groups at Mid tx supports my clinical observation of treating these participants: the women in the TA group appeared to report changes in their hot flushes at an earlier stage in the treatment sequence than did the ear acupuncture group.

10.4.5.2 Comparing emotional and physical well-being

Comparing the two groups for changes in emotional and physical well-being showed that, of the domains of the WHQ, only Menstrual Symptoms showed a significant difference, in favour of the traditional acupuncture group (as presented in section 9.6 starting on page 326). There was no significant difference between the PRS scores for the two groups at EOT. These results suggest that, within the context of this research, there is little difference between the two approaches with regard to changes in overall physical and emotional well-being.

10.4.5.3 Commentary on the comparison

The result of this comparison must be interpreted as being indicative only. The comparison is between two studies conducted at different times. As far as I can establish, there were no significant differences between the two groups of women at baseline, either in terms of baseline medical or sociodemographic characteristics. Although during Study 2: NADA there were changes in prescribing brands of tamoxifen, and Arimidex was introduced, I do not think this would have had a significant effect on the women in these studies. It is also unlikely that there was a difference between women who would consent to have body acupuncture and those who would consent to have ear acupuncture. Thus, for the variables I was able to measure, I cannot identify major differences between the groups that would affect the difference at EOT.

However, other factors may affect the two studies. Two of these relate to my experience and approach as an acupuncturist. At the outset of Study

1: TA, I was a relatively new acupuncturist with just over two years of clinical experience, and no specific expertise in treating menopausal or tamoxifen-related hot flushes. I learned a great deal during the course of Study 1, and this may have a bearing on the results reported here. In addition, I was far more confident when I commenced Study 2. I had more experience of working with these women, and I had the benefit of knowing the results of Study 1. Thus, I was more confident of the benefits of acupuncture, and may have conveyed this to the participants in Study 2 (see section 10.4.5.3 on page 340).

Introducing a minimum time of 10 weeks to complete the course of treatment in Study 2: NADA may also have influenced results. Several of the women in Study 1: TA completed the course of eight treatments over many weeks, and it is possible that infrequent, irregular treatment reduces the effect of acupuncture treatment.

These are examples of variables that are unmeasured and that changed over the course of the two studies. There may be other unidentified confounders; it is only through assessing the two treatments simultaneously in a randomised control trial that the likelihood that the two groups differ on some unknown, but possibly influential, variable(s) may be reduced.

10.5 Possible influences on the results

The results of these studies look promising; however, the single arm observational design means that all results must be interpreted as being indicative only. I discuss some of the aspects to consider below.

10.5.1 Single-arm observational study design

In section 3.6 (starting on page 84), I discussed the limitations of observational studies, as well as their appropriateness over RCT designs when there is little information available about an intervention. The debate about appropriate designs for research into complementary medicine is vibrant (Lewith et al. 2002, Broom et al. 2004, Verhoef et al. 2005, Hyland 2003, Walker and Anderson 1999, Nahin and Straus 2001) and there is increasing discussion about the inappropriateness of RCTs for early phase studies into complementary medicines (Aickin 2005). As discussed in section 3.6, the Medical Research Council advises thorough investigation into complex interventions before attempting to design a definitive RCT (2000). The NHS Research and Development Health Technology Assessment has also recognised that there are situations where RCT design is not possible, for reasons such as ethical considerations or cost. In these circumstances, it maintains that well designed non-randomised studies are acceptable, and are often preferable to poorly designed RCTs (Britten et al. 1998).

This is not an argument for a relaxed or sloppy approach to research design; instead, it is a plea for appropriateness of research design, and

for adequate groundwork to be carried out before launching into the challenges and expense of good RCT investigations.

In this research, I have endeavoured to work systematically and with rigour within the context of a single-arm observational study, with the intention of gathering data to inform subsequent studies, including the possibility of an RCT. The observational design is appropriate for this area of healthcare, in which I have established there was little existing data to inform good RCT design. The methodology used in this study, and its results, can make a valuable contribution to informing future studies.

10.5.2 Natural decline of symptoms over time

Evidence suggests that hot flushes, whether related to natural menopause or tamoxifen, decline over time. McKinlay et al (1992) monitored 2570 American women for five years, and showed a tendency for the symptoms of natural menopause to decline, with hot flushes reported in 50% of participants at the final menstrual period, declining to 40% two years later, to 20% after four years.

Love and Feyzi (1993) studied 140 breast cancer patients randomised to tamoxifen or placebo. In their study, hot flush severity peaked after 6 months of taking tamoxifen, and decreased linearly over the subsequent 18 months (compared with the placebo group, which remained relatively constant over the two-year observation period). Canney and Hatton's (1994) study of 108 women treated for breast cancer (of whom 74% (78)

were taking tamoxifen) also reports a decline in symptoms measured from the time of primary surgery. This reduced from 70% (33/47) of women experiencing symptoms at less than 12 months, to 63% (22/35) at 12 – 36 months, and 36% (8/22) at over 36 months, with a median duration of symptoms for 17 months (range 0 – 136 months).

However, even though symptoms may show a tendency to decline, the women in the cancer-related studies were still experiencing hot flushes well into their course of taking tamoxifen. In the Love and Feyzi study, the tamoxifen group continued to report hot flushes after two years, recording higher severity than the placebo group (Love et al. 1991, Love and Feyzi 1993). Canney and Hatton's data show the decrease from the 12-month measurement period to the 12 to 36 month period is only 7%.

Hunter's (2004) study of 113 tamoxifen users reports that 80% (90) of the women were experiencing hot flushes (average frequency 20.3 per week, range 0 - 140), 72% (81) were having night sweats (average frequency 9.6 per week, range 0 – 42), and the mean interval since starting tamoxifen was 2.8 years (SD = 1.6). In Study 1: TA, participants (n = 52) experienced an average of 10.4 hot flushes and night sweats per day, range 0 – 40, and the mean interval since starting tamoxifen was 1.7 years (SD = 0.85). In Study 2: NADA participants (n = 51), experienced an average of 10.5 incidents per day, range 0 – 28, and the mean interval of time taking tamoxifen was 1.7 years (SD = 1.2).

These studies support the argument that even though hot flushes may decline over time, they are still a significant symptom in many tamoxifen users for long periods. However, without a comparison group, there is no way to evaluate whether the women in my studies would have improved as a natural course of events, and this possibility cannot be ruled out as a contributing factor to the reductions in hot flush frequency. However, it is unlikely that the decrease is due merely to spontaneous reduction (Thompson and Reilly 2003), especially as there is such a sizeable decrease (49.8% for the TA group, and 35.9% for the NADA group) after eight weekly treatments (Nedstrand et al. 2005). Furthermore, the levels start to rise again as time from EOT increases, which again may support the argument that some aspect of the acupuncture treatment had an effect on the hot flushes.

10.5.3 Placebo effect

In evaluating the results of any study, a frequently asked question is "how much of the improvement is due to the placebo effect?" This is particularly the case with modes of complementary medicine, which are often dismissed by the scientific community as being merely placebo in their effects (Collins and Pinch 2005, Ernst 2001). Again, the design of the observational studies that are the subject of this thesis did not accommodate placebo evaluation, and therefore I cannot say for sure.

One way to approach this question is to compare the results with those of other placebo-controlled studies. Researchers at the Mayo Clinic in New York have conducted a suite of placebo-controlled studies on various

pharmacological and over-the-counter interventions to manage hot flushes (Quella et al. 2000, Loprinzi et al. 1994, Goldberg et al. 1994, Barton et al. 1998, Loprinzi et al. 2000). They state that they have observed a substantial placebo effect in hot flush studies, and claim that "hot flash frequencies and hot flash scores diminish by approximately 20% to 30% with four weeks of placebo", although a minority of patients receiving a placebo report greater decreases in hot flush activity (Sloan et al. 2001). In their suite of studies, they cite an average reduction in patients who receive a placebo of 1.5 hot flushes per day (or 24%) from baseline to the end of four weeks of treatment (median hot flushes at baseline = 7.3, n = 375).

Direct comparison with the results of Study 1: TA and Study 2: NADA is difficult, given the baseline number of flushes is higher in my studies, and treatment continues for longer than the Mayo Clinic studies. A rough comparison suggests that my studies might have an effect beyond placebo, given the 48.9% and 35.9% reductions in hot flush frequency at EOT. However, to make a meaningful comparison, it is necessary to make statistical adjustments to ensure that the groups are comparable.

10.5.4 Therapeutic relationship

Critics of complementary medicine often attribute improvements to the time and attention the patient receives during the therapeutic encounter. This is often classified as a non-specific, "placebo" effect, and there is pressure to separate it from healthcare evaluations. In a drug trial, this may be easier to do than in the administration of a complementary

medicine, where often the focus is on patient-practitioner interactivity (verbally and often physically). For example, amongst professional acupuncturists in the UK, importance is placed on interacting with the patient through the processes of taking a case history, making a diagnosis (often using pulse taking and tongue examination), and establishing and maintaining rapport (see section 1.10.2 starting on page 32 for my discussion of the characteristics of integrated acupuncture). Many acupuncturists regard these as essential features of treatment, and each aspect may be as valuable as the needling itself is (Paterson and Britten 2004). The therapeutic relationship is also present in orthodox medical encounters. Historically, it was fashionable to downplay this, but its importance in all encounters is gradually being acknowledged (Reilly 2001, Dixon and Sweeney 2000, Benson and Friedman 1996).

In Study 1: TA, I spent nine treatment hours with each participant. This labour intensive approach appeared to shock orthodox medical practitioners, especially doctors, who had little patience even for the 20-minutes the TA protocol demanded. (I would like to emphasise that TA need not be so time-intensive, and many professional practitioners schedule shorter treatment sessions, or treat several patients simultaneously. I designed the study to have hour-long sessions for two reasons. The first was to conform to the usual treatment time for complementary therapies at the LJMC; the second was to use the time to gather as much information about the participants and their experience of hot flushes as possible.) Sensitive to the very real constraints on

healthcare professionals in the NHS, and to the potential criticism of attention per patient in terms of research, I sought to adapt this in Study 2. In the NADA study, I deliberately reduced the time I spent with the participants, attempting to limit this to a maximum of seven minutes at the beginning of each treatment. In general, removal of the needles was rapid, and apart from checking that the participant was fine after treatment, there was usually little interaction. (However, I was not rigid about this time-keeping, and when participants needed more time, I gave it.)

Any effects of this reduction in practitioner-participant interaction in Study 2 may be offset by the group effect, the effect of the women spending time with each other, and thus getting attention from each other. NADA places great store by the power of the group effect as a contributor to the treatment effect (Peckham 2005). In my studies, it is impossible to separate out and measure the effect of the therapeutic relationship, or the importance of the group effect.

10.5.5 Summary of possible influences on the results

A number of factors may be contributing to the effects, other than (or in addition to) the acupuncture. To separate out these effects would be complex, and may be impossible. Whilst some factors might be measured with elaborate but well constructed randomised controlled trial design, such options are not often within the reach of research budgets for CAM studies. Other influences, such as the therapeutic relationship, should be seen as an integral part of the treatment (Paterson and Dieppe

2005, Mason et al. 2002). Research should seek to include this as part of a complex intervention, as is consistent with the emerging concept of "whole systems research" which seeks to assess the whole therapy rather than separate out its constituent parts (Verhoef et al. 2005).

10.6 Comparison with other studies

10.6.1 Comparison with other acupuncture related studies

In this section, I discuss my studies in relation to the other published studies of using acupuncture to manage cancer-treatment-related hot flushes (Tukmachi 2000a, Tukmachi 2000b, Towlerton et al. 1999, Filshie et al. 2005, Porzio et al. 2002, Cumins and Brunt 2000, Johnstone 2003, Davies 2001).

Like these, my studies do not have a comparison with a control group. Only Davies' (2001) study was randomised, and none of the studies appears to use blinding. My research uses a considerably larger sample compared with the other studies, with 50 women completing treatment in each study. Other sample sizes range from 13 to 26 subjects. Filshie and Bolton's (2005) study uses 159 patients, but this is a retrospective audit of patient records, whereas all the other studies are prospective.

My studies focus very specifically on women with early breast cancer, who are taking tamoxifen, and who completed active treatment at least six months prior to joining the studies. Their active cancer treatment could have comprised any combination of surgery, chemotherapy or

radiotherapy. Other studies differ. They may include men undergoing treatment for prostate cancer (Johnstone 2003), or focus on women who all received the same cancer treatment regime. For example, the participants in the sample used by Porzio et al (2002) all had specific forms of surgery, radiotherapy, and six specific chemotherapy treatments.

Furthermore, the studies used different approaches to acupuncture. Johnstone used electro-acupuncture, Tukmachi combined acupuncture with a strict dietary regime, and Filshie used self-needling and/or use of semi-permanent indwelling needles.

My studies use a consistent number of treatments (eight), and as far as practically possible, consistent treatment frequency (weekly). Other studies are not clear on the frequency and duration of treatment (Johnstone), use variable frequencies and durations (Tukmachi treated twice weekly, but for three to eight weeks) or provide treatment for longer (Porzio's study treated weekly for 3 months, followed by monthly maintenance treatments). As is often the case with publications of acupuncture research, many of the studies are vague about the acupuncture rationale, methodology, and procedures used (Smith J. et al. 2005, Walji and Boon 2006, MacPherson et al. 2001).

Such differences make it difficult to make confident comparisons across the range of studies (Smith J. et al. 2005). Bearing this in mind, all the studies except Cumins' indicate that acupuncture helped flushes to

reduce; of these, only Tukmachi and Porzio cite statistical significance, which for both studies is $p < .0001$. Porzio is the only researcher to detail the statistical methodology used to analyse the results, while Tukmachi's evaluation category "effectively cured" is an inappropriate assessment (Smith J. et al. 2005). Cumins' non-significant result may be due to the small number of treatments, which is four. As discussed above (in section 10.4.4, on page 337) the trends from my studies suggest that participants may benefit from more than four treatments.

Porzio and Davies measured aspects other than frequency and severity, and they use validated tools for this. Porzio used the Green Menopause Index, while Davies used the FACT-ES (Functional Assessment of Cancer Therapy -plus Endocrine Subscale) for quality of life. The FACT-ES appears to be the only symptom scale used in these studies that is validated for use with breast cancer patients (Fallowfield et al. 1999).

The follow-up period in my study is longer than that in most other studies. Only Porzio follows up for 6 months, which is longer than the 18 weeks (just over four months) used in my studies. Tukmachi's follows up for five weeks; other studies do not report follow-up periods.

Most of these studies do not provide details of ethics approval, handling of missing values, consent, statistical methodology, losses to follow-up, or co-interventions, or the acupuncture rationale and methodology (Smith J. et al. 2005). The exceptions are Porzio et al, and Filshie and Bolton's

recently published audit results. Filshie and Bolton (2005) are the only other authors who appear to report their study according to STRICTA guidelines (see Appendix 21). In this thesis, I have endeavoured to supply this detail, and to be clear about the methods used. In addition, this work provides the first potential opportunity to compare modes of acupuncture from different theoretical frameworks, delivered using similar strategies.

10.6.2 Comparison with Hunter's WHQ studies

Hunter has used the WHQ to measure emotional and physical well-being in different groups of women, and these studies provide useful comparisons with the participants in my research. In particular, her development of the 'norms' (healthy women going through the menopause transition)(1992), and her research with women with breast cancer (BCG) (2004) provide useful comparison data (see section 6.5.1.6 starting on page 217 and section 8.5.1.6 starting on page 290).

In Study 1 and Study 2, Vasomotor Symptoms are higher than Hunter's norms and BCG, and this is probably because the women in my studies were recruited specifically for hot flushes. While my acupuncture groups show reductions in their Vasomotor Symptom scores, they remain higher than Hunter's comparison groups at EOT and during the follow-up period.

With other WHQ domains, my acupuncture groups register higher symptom scores at baseline than Hunter's comparison groups, but some of these reduce at EOT and Post tx 18 to levels similar to the norms and

BCG. In Study 1, this is the case for Memory/Concentration, Sleep Problems, and Somatic Symptoms, and in Study 2, for Memory/Concentration and Sleep Problems.

These comparisons support Hunter's findings about the high prevalence and frequency of menopausal symptoms in women taking tamoxifen (Hunter et al. 2004). They also suggest that women with early breast cancer suffer more emotional and physical discomfort than do healthy women going through natural menopause. It is interesting that the women in my studies register higher symptom scores at baseline that Hunter's breast cancer group. One possible reason for this is that there may be a difference between the women selected from a hospital database to complete questionnaires and take part in an interview (as in Hunter's study) and those motivated to take part in a course of acupuncture treatment (as in my studies). The women in Hunter's study expressed a preference for non-intrusive interventions such as vitamins, herbal remedies, cognitive behaviour treatment, relaxation, self-help booklets, and complementary therapy (acupuncture is not specified). The women in my study were prepared to try a relatively intrusive therapy, using needles (of which many were apprehensive). This may mean that the women in my studies were experiencing such high levels of discomfort that they were motivated to try anything that might offer relief, and this would be reflected in their high symptom scores.

In any case, the results suggest that the process of acupuncture treatment reduced the emotional and physical discomfort at EOT to comparable levels with Hunter's norms and her breast cancer group study.

10.7 Evaluating the outcome measurement tools

10.7.1 Measuring hot flushes

I discussed the complexity of measuring hot flushes (in section 3.9.1.2, starting on page 100) and would like to highlight one important finding of my work with using paper-based diaries used on an ambulatory monitoring basis. While women reported that completing the paper diaries was a nuisance and hard work, for some they became useful tools for learning about, and managing, their hot flushes (Walker et al. 2004, Walker et al. 2005). Keeping the diaries helped women to understand patterns of flushing or to identify triggers, which could be specific foods, drinks, environmental temperatures, or specific stressors. This process facilitated a means of taking control of some aspects of the flushing, and women could make choices about their actions and the resulting effect on flushing. For example, certain women reported that drinking alcohol triggered their flushes, but at the same time, said that eliminating alcohol from their lifestyle was unacceptable. However, awareness of the link between drinking and having hot flushes empowered them to make choices (either "I will not drink as it causes flushes", or "I will have a drink and realise that I will probably have a flush"). While this may not reduce the flushes, it reduces the sense of helplessness that many women

experience when they have hot flushes. Paper diaries were also a useful visual aid for monitoring fluctuations, changes, and improvements in hot flush frequencies.

The use of paper diaries may also have minimised recall bias, as their design facilitated completion at the time of the hot flush incidents (known as "ecological momentary assessments" (National Institutes for Health 2004, p 27)). However, recall bias cannot be ruled out entirely. Women found it difficult to fill in their diaries in real-time; some devised intricate recording methods such as noting the flushes that occurred during their working day on slips of paper, and transferring them to the diary at the end of the day (Walker et al. 2005). Others reported that they missed recording flushes because they were otherwise engaged at the time of the flush, and filling in the diary would have been inconvenient or embarrassing. Recording night sweats was also a problem. Many women do not wake up fully with a night sweat, and these women may not have recorded incidents. Other women complained that the requirement to record a night sweat as it happened further disrupted their sleep, further contributing to their sleep problems. Thus, many of the counts for night sweats may be inaccurate.

These considerations suggest that as ambulatory self-reporting measures, electronic diaries might provide a more accurate record of flushing incidents (as discussed in section 3.9.1.2 starting on page 100). However, it is important to realise that in using electronic diaries, the

benefits of identifying hot flush triggers and patterns would be lost, and the diary's value as a tool to learn how to manage hot flushes would be sacrificed. Thus, it is important to match the tool to the purpose: if this is to ensure the most accurate measurement possible, then electronic diaries may be appropriate; if the purpose is to facilitate women taking more control of their hot flushes, then paper diaries may be more beneficial.

There are limitations and problems with using paper diaries. However, their usefulness as a tool for helping to manage hot flushes should be acknowledged in the debate about how to measure hot flushes.

10.7.2 Measuring emotional and physical well-being

I chose the Women's Health Questionnaire because I wanted to measure changes that an acupuncturist might expect to observe in a patient undergoing treatment for menopausal symptoms. From my acupuncturist's point of view, the WHQ served this purpose well. It provided important information about other symptoms that might improve because of the acupuncture approaches used in these studies.

I have summarised the statistically significant changes in the WHQ results (see section 10.4.2.1, page 333). Hunter suggests that a meaningful clinically significant change on the subscales is a difference of 0.10 to 0.20 points (Hunter 2003). Using this criterion, the data indicate that there were clinically significant improvements in all domains except Depressed Mood for the women in Study 1: TA, and Menstrual

Symptoms and Sexual Behaviour for the women in Study 2: NADA. Most significant for the participants in both studies was the improvement in quality of sleep, as Sleep Problems registered a reduction of over 0.20 points at EOT in both studies. The sub-analysis of the Somatic Symptoms indicates that women felt less tired. These results confirm the changes that participants reported verbally during the course of their treatment, and some women experienced these even if they did not report changes in their hot flushes.

Outcome measures used in hot flush studies for people with cancer are often criticised as they are not validated for use with cancer patients (Smith J. et al. 2005). This criticism applies to the WHQ, although Hunter used it for her breast cancer study, and does not cite this as a short-coming (2004). Two possible drawbacks to the questionnaire are more general. The domain Vasomotor Symptoms might be critiqued for being quite crude. It is based on two questions only:

- I have hot flushes
- I suffer from night sweats.

This, plus the method of reducing domain scores to binary options (1 for "yes", 2 for "no") gives a measure of vasomotor symptoms that can be described as "minimal" (Newton 2004, p 24). This may not be as sensitive to change as is desirable, and it does not give very much information about the hot flushes themselves, a criticism that has been applied to menopausal questionnaires in general (National Institutes for Health 2004).

Anxiety/fears is the second domain on which I would comment. My results show that the women in both studies reported lower scores at baseline for this domain than did Hunter's norms or BCG group. This surprised me, as my clinical observation of the participants was that they were highly anxious, with fears particularly about the possibility of recurrence of cancer. This often manifested at the time of follow-up consultations with their oncologists, or at the onset of any unexplained new symptom, however slight. These observations are congruent with studies of the concerns of breast cancer survivors (Mast 1998, Fredette 1995). I discussed this disparity in scores with Dr Hunter, who confirmed that this was "the first study in which the anxiety levels are particularly low" (Hunter M, personal communication by e-mail, 11 July 2005). As the other scores fell in line with expectations set from her other studies, she suggested that there must be reason for these low scores, perhaps that the women were being reassured because they were going to have treatment. This is an area where questionnaires validated for use with people with cancer might be advantageous, to register anxieties related to cancer rather than menopause-related issues.

However, as stated at the beginning of this section, the WHQ provided the data I required of it when designing the study. The identification of symptoms that showed improvement during the course of acupuncture treatment is valuable, and can be used to inform future studies. Specifically designed questionnaires could be deployed to provide more

detailed data on particular symptoms, depending on the aims and objectives of those future studies.

10.8 Evaluating the statistical methodology

To ensure rigour in the handling of statistical methodology, I referred to standards for good, basic statistical reporting (Greenhalgh 2001), which provide a useful check for the procedures I used. Within each study, I conducted paired t tests on paired data. In comparing the two studies, I ascertained as far as is possible that the two groups were comparable and applied unpaired Student's t tests, as appropriate. In the comparison, I also applied two-tailed tests, which is recommended practice for testing hypotheses (Altman et al. 2000, Greenhalgh 2001). I have calculated p values and confidence intervals, and believe I have interpreted these appropriately. I did not correct the data for outliers, and the statistical consultant advised that this was not necessary (Atkins R, personal communication by letter, 23 January 2005). I took all strategic statistical decisions in consultation with the statistical consultant, and the research co-ordinator double-checked all the analytical procedures and results to ensure that I carried them out correctly. Thus, the statistical procedures are robust and reliable, within the context of the resources available for this research.

The use of log transformations is appropriate to the hot flush frequency data collected, which showed distributions that were not normal. Although the data for some WHQ domains were not normal, log

transformations were not appropriate. To remain consistent with Hunter's work (1992), I followed her example, and carried out tests to confirm that there were no significant differences when applying parametric and non-parametric tests to this data (as presented in Appendix 19). Thus, I can confidently compare WHQ data with other studies using this questionnaire, provided they have analysed the data according to the instructions in the *WHQ User Manual* (Girod et al. 2004).

The data gathered will help us to determine an adequate sample size for future projects, and enables power calculations for a potential RCT design. Based on the Mayo Clinic experience, my studies exceeded the recommended size of 20 participants for a pilot study (Sloan et al. 2001); however, I was keen to collect as much data as possible – especially to identify recruitment issues, and other practical considerations of administering treatment and conducting a study. I was also keen to collect as much clinical information about treating them, and to obtain as much clinical experience of treating these women.

10.9 Design, execution, and reporting of the study

10.9.1 The design

In this research, I followed as closely as possible the recommendations for designing research studies, which are reiterated by Birch for acupuncture studies (2004). The design team set clear questions, and articulated clear hypotheses to be answered by the research. The study design was developed within the constraints set by the Local Research

Ethics Committee at the outset of this research, and the observational design was constructed to answer the questions that we wanted to investigate. This design was appropriate for investigating a treatment for which there was very little available information.

The design included before and after measurements, and I used validated tools to measure emotional and physical well-being. The hot flush diaries are not validated, but their use has precedents in other hot flush studies, and I have discussed their advantages and shortcomings.

10.9.2 Methodology

I obtained informed consent, using a standard NHS format, and issued Patient Information Sheets according the Department of Health guidelines current at the times of designing the studies. I clearly articulated inclusion and exclusion criteria, and applied them as rigorously as possible.

These studies draw on a sample that may be limited as it reflects patients of the Cancer Treatment Centre at Mount Vernon Hospital, and thus is predominately white, English speaking, and middle-class. However, within that population, I have sought to include women who are "real-life" patients; they were not excluded if they had illnesses in addition to cancer. Thus, the sample includes women with a variety of illnesses, some of which are complex, chronic conditions such as diabetes, cardiovascular disease, post-viral syndrome, chronic fatigue syndrome, Hashimoto's disease, and clinical depression. In this, they reflect typical

cancer patients, who often have other health issues. Furthermore, women were not excluded if they smoked or drank, had a history of taking HRT, or took other medications, including medications for their hot flushes (see inclusion and exclusion criteria in section 3.10 starting on page 110).

I believe that duration of follow-up was appropriate for this study, and that longer follow-up may pose problems. Hot flushes are implicated in women discontinuing tamoxifen use (Demissie et al. 2001), and my records indicate that three participants on Study 1 and two on Study 2 ceased taking tamoxifen before the end of their five-year treatment period. Furthermore, it may be unreasonable to ask women to avoid taking action to relieve their hot flushes for a long period. Thus, the data at longer term follow-up points risks becoming confounded, either because women have stopped taking adjuvant treatment, have switched from tamoxifen to Arimidex (in the belief that this will reduce hot flushing), or have introduced other medications or therapies to help to manage their symptoms. It is also an unfortunate fact of cancer care that women may experience recurrence, and this possibility may complicate long-term follow-up of issues like hot flushes.

There may be recruitment bias, as many participants were self-referred, and may have had a particular interest in having acupuncture. However, healthcare professionals referred many of the participants, and many

participants had to overcome fears about having acupuncture in order to participate in the study.

Systematic bias becomes a consideration in the comparison of the two studies. I attempted to minimise this by ensuring participants had a similar number of contacts with me in both studies, and I was rigorous in applying the same assessment tools and measurements to both groups. However, there may have been differences in the explanations I gave to both groups. In Study 1, I had very little information about the effect of acupuncture on hot flushes, and reflected this in my discussions with participants. By Study 2, I had information about the results of Study 1, and was open about this in my discussions with participants. Thus, the women may have had different expectations in Study 2, as they may have been more inclined to believe that acupuncture worked than those participants in Study 1, who did not have the benefit of this evidence.

Bias might also be present in that I carried out the data entry for Study 1, but not for Study 2. However, we obtained statistical advice from statisticians who were external to the LJMC, and who were not directly involved in the research.

As discussed in section 3.6.1 on page 86, there was insufficient quality data in the literature on which to base calculations for an RCT. These observational studies have provided valuable data, both in terms of determining numbers of hot flushes at baseline, and the levels of

reduction that might be possible. These data can usefully inform calculations for subsequent research.

One improvement that is required for future studies is in data collection and management, particularly in the area of other health care issues, previous experience of acupuncture, and monitoring of medications. In particular, the Baseline Medical Questionnaire, as well as semi-structured EOT and follow-up questionnaires, need improvement. Classification of other health issues needs to be more extensive and accurate, as does monitoring of medications and changes in those. Furthermore, it would be helpful to find a better way to record activities of daily living, such as weather, holidays, stressors, unusual events, and to understand how to incorporate them into analysis, to determine whether, and how much, they affect hot flush patterns. Although I collected this information, I did not have a method of factoring it into the analyses, nor did I generate any study hypotheses for these factors.

10.9.3 Generalisability of the results

The generalisability of the results is open to debate. The study was designed for the specific environment of the LJMC, and the participants reflect the women who might typically access LJMC services. The research focuses on Caucasian, English-speaking, primarily middle-class women, and thus the results cannot be generalised to the wider population of women with early breast cancer. Further investigation is needed to determine how this approach would affect a wider population with more diverse ethnic and socioeconomic characteristics.

Furthermore, the TA approach I applied reflects a specific school of acupuncture, the "integrated" style, which combines techniques from Five Element and eight-principles theoretical frameworks. As my experience in this study has shown, it is difficult to convey the underpinning philosophy and the complexity of the TA techniques to practitioners of Western medical acupuncture. Thus, the NADA protocol, characterised by its standardised, formulaic approach that requires no diagnostic skills, may be more suitable for non-traditional acupuncturists. Traditional acupuncturists, on the other hand, might regard the NADA approach as reductionist and unsuitable to meet the wider objectives of patient care.

In terms of attention, I designed Study 1: TA to reflect the attention received by patients attending the LJMC for complementary therapy treatments, and to reflect the common practice of private professional acupuncturists in the UK, where treatment times of up to an hour are the norm. I designed Study 2: NADA to reflect the limited practitioner-patient time that is more common in the NHS.

10.9.4 Acupuncture reporting and procedures

In terms of reporting the acupuncture procedures, I have attempted to apply systematic and rigorous methods in the study, and have reported these studies adhering to STRICTA guidelines (see Appendix 21).

In these studies, I made an initial foray into investigating the adequacy of the test treatments. My studies have provided thorough data about

weekly treatment over eight weeks, but more work needs to be done, especially with regard to frequency and duration of treatment. For both styles of acupuncture, would longer-term treatment yield better or longer lasting results? Would more frequent treatments give quicker or superior results? After all, recommended treatment frequency with the NADA protocol in substance detoxification is daily. However, would such an approach be appropriate, or even practical, for women with early breast cancer, who usually have busy work, family, and social lives. Would it even be possible to deliver treatments this often in an NHS environment? Establishing the optimum frequency and duration is a challenge for acupuncture studies (Birch 2004), and this is an area that would benefit from further investigation.

10.9.5 Summary

This new research adds to the literature in that Study 1 and Study 2 are larger than any of the other uncontrolled studies in this area. The studies measure before and after results, and follow-up for longer than any existing studies with the exception of the six-month follow-up used by Porzio et al (2002).

Although this research was not an RCT, the baseline hot flush measurements and the results at EOT provide useful data to compare with other studies. The WHQ results can be compared as appropriate with the many other studies using this questionnaire.

Hot flushes are not life threatening, and their importance is often underplayed in comparison to the life threatening nature of breast cancer itself. Yet, this study indicates that women suffer high levels of discomfort and embarrassment. As the discussion in Chapter 2 shows, hot flushes are a frequent side effect of adjuvant treatment for breast cancer, and as the incidence of breast cancer is currently high and is on the increase, this is a widespread problem that deserves attention. These side effects have been implicated in women discontinuing tamoxifen use (as discussed in section 10.9.2 above); it may be that by reducing the discomfort of adjuvant treatment side effects, women may be inclined to continue taking the treatments, thereby optimising their overall survival rates.

The aim of this research was to conduct research in the normal working context of the LJMC; therefore, I hope that the research results can be imitated in normal clinical practice. A project emerging from this research is an evaluation of a NADA ear acupuncture service for managing hot flushes offered by the LJMC, which opened in November 2005. Thus, I hope that the findings from this study can be used to guide practice in relation to wider patient groups.

10.10 Some questions arising from this research

There are a number of questions raised by this research, and I discuss some of these below.

10.10.1 Who got better, who got worse?

The data shows that some participants benefited, and some got worse during the course of acupuncture (see Table 25 on page 209 and Table 45 on page 282). It would be interesting to examine the data to identify any factors or patterns that might contribute to this variable response.

10.10.2 What factors affect the hot flush experience?

There may be factors that exacerbate the hot flush experience. Some of these may include:

Menopausal status

What effect does menopausal status have on the cancer-treatment-related hot flush experience? Do women whose natural menopause coincides with their cancer treatment have more, or worse, hot flushes than those who are pre- or post-menopausal?

Measuring this accurately may pose challenges. Women rarely remember the date of their last period, and women do not routinely have tests to confirm their hormone status (Soules et al. 2001). In fact, my observation from these studies is that the only women who accurately remembered the date of their last period were those who stopped menstruating during their chemotherapy or radiotherapy treatment. It was particularly difficult to obtain even an estimate of the last date for women who had started taking HRT before ceasing menstruation, and who had regular bleeding as a result of the HRT.

Previous use of HRT

Women are advised to stop taking HRT almost immediately they receive a breast cancer diagnosis (see section 2.6.2.1, starting on page 64). How much does this sudden withdrawal contribute to the hot flush experience?

Cancer treatment regime

Does the cancer treatment regime have any effect on the levels of hot flushing? Do women who have had chemotherapy in addition to surgery and radiotherapy experience more severe symptoms than those who have had radiotherapy and surgery, or surgery alone?

Complex health issues

As discussed in section 10.9.2 on page 361, the participants in these studies had complex health conditions in addition to breast cancer. Do such women experience more severe symptoms, or do these health problems impact the rate at which women experience the benefits of acupuncture treatment?

10.10.3 What factors affect acupuncture response?

The conditions discussed in the previous section may also affect an individual's response to acupuncture treatment, and this would be an interesting area to explore.

In addition, there is the concept of "responders" and "non-responders" in the literature. Tukmachi (2000a) classified patients who do not show response in a set time as "non-responders", but is that an appropriate

classification? My experience with clearing blocks to energy suggests that some "non-responders" can become "responders". However, this is merely an observation and certainly requires further investigation before it can be asserted with confidence.

10.10.4 Severity

What role does severity play in the total experience of having hot flushes? The CAMEOL systematic review recommends that research should include hot flush severity (Smith J. et al. 2005), and as discussed in section 4.8.4 starting on page 142, I collected data on this, which is being analysed as a separate sub-project. It may also be necessary to investigate the relationship between frequency and severity, and to understand this impact on the overall well-being of the individual. Does a woman who experiences three severe night sweats per day suffer more, or less, than a woman who experiences twelve mild to moderate flushes per day? Can this be evaluated?

10.11 Acupuncture as a package of care

As previously mentioned, there is a great degree of pressure on researchers to attempt to separate out the elements of acupuncture interventions, in order to identify the active components. A response to this is recognition that acupuncture is a complex intervention, and that the elements such as patient-practitioner interaction and co-interventions such as lifestyle advice are integral parts of the process (Paterson and Britten 2004). As such, the intervention as a whole should be evaluated (Ritenbaugh et al. 2003).

It was not the purpose of my studies to identify any single active components of the treatment, although I did attempt to reduce practitioner-participant interaction in Study 2. However, any effects of this reduction may be counteracted by the group effect in the group clinics.

I believe it is appropriate to regard the interventions studied in this research as packages of care. Thus, I have made no attempt to separate out the effect of the needling from the non-specific effects. Both interventions in this research include a range of important elements, including acknowledging the patient's concerns, focusing on general well-being as well the main complaint, encouraging appropriate changes in lifestyle, and developing a relationship with the participant, as well as carrying out acupuncture needling and its associated processes. Such packages of care seem appropriate in the context of supportive care for people with life-threatening illness. They integrate the key principles of supportive care, including good symptom control, focus on quality of life, a focus on the person as a whole, a respect for patient autonomy and choice, and open and sensitive communication (Regnard and Kindlen 2002).

10.12 Dissemination

During the course of this research, I have been active in disseminating the results to the medical, research, and acupuncture communities. This has largely been in the form of conference presentations and formal talks,

and I include a list of these activities from 2001 through 2005 in Appendix 32.

I have also endeavoured to initiate a publications strategy. Publications to date are included in Appendix 31, and I have further plans to publicise the results and findings of these studies on completion of this thesis.

These studies have also received some attention from the media, and the resulting articles are included in Appendix 33.

10.13 Progressing this research

These studies provide a basis for further research in this area. As discussed in section 10.9.4 on page 365, there is still considerable investigation required into establishing the optimum treatment frequency and duration, for both traditional acupuncture and the NADA protocol. It may be that this groundwork is required before further, more complex study design takes place.

However, there is always pressure to conduct randomised controlled trials, and it may now be feasible to consider this. Conducting these two studies has given my colleagues at the LJMC and me experience in conducting acupuncture studies, and a greater understanding of working with women with early breast cancer. This experience may be a valuable platform for developing and implementing more complex studies.

Further investigation into the experience of having hot flushes may be a fruitful area for research. In this regard, there is considerable scope for qualitative research, to develop deeper insight into the experience of the individuals (Saks 2005). In particular, the use of patient narratives could enrich the understanding of how women with breast cancer perceive their hot flushes, and may reveal further options for diagnosis and treatment of this condition (Greenhalgh and Hurwitz 1999). A study of clinicians' attitudes to hot flushes may also be useful, and might identify areas where patient care can be improved.

Furthermore, there is now an opportunity to assess the use of the NADA ear acupuncture protocol as a service, rather than a research project. It would be interesting to compare the data for women attending a service with that for the study participants, to evaluate whether there is any difference in the results.

Finally, there is much scope for further investigative studies into the use of acupuncture for people with cancer. Managing hot flushes in patients undergoing active treatment, rather than hormonal adjuvant treatments, for (breast) cancer might require a different approach and yield different results. There is also scope for working with women with advanced breast cancer.

Acupuncture for hot flushes in men undergoing treatment for prostate cancer is also an area identified for further research (Smith J. et al. 2005).

This raises some interesting questions. Would the traditional acupuncture protocol used in Study 1 be appropriate or effective for this group, or would the treatment principles be different for men than for women. Would men prefer ear acupuncture or body acupuncture? Would they find it more comfortable to be treated by male practitioners?

In addition, a study into the use of acupuncture to help survivors recover from the experience of cancer and its treatments may be an interesting new area to investigate. The focus of research and supportive care tends to be on cancer patients undergoing active treatment or palliative care, and there is limited research on the issues associated with disease-free survival after cancer treatment (Mast 1998, Fredette 1995). That which does exist indicates there are long-term emotional and physical problems that persist long after treatment ends (Holzner et al. 2001, Ganz et al. 2002, Dow et al. 1996). I hypothesise that acupuncture treatment could be of considerable value to these patients in assisting them to overcome the long-term damage of cancer and its treatments, and helping them to return their health, and their lives, to "normal".

In designing future studies, I believe there are a number of considerations to take into account, and I discuss these in the next section.

10.13.1 Considerations regarding using breast cancer patients in research

Having conducted these studies on women with early breast cancer, I believe it is important to take into account their concerns and anxieties when designing research projects. My observation is that the priority for these women is to return to normal life as soon as possible. This is, after all, a strong motivating force for reducing their hot flushes. I suggest that the following elements are considered when designing research projects with breast cancer patients. (These considerations may also apply to cancer patients in general.)

Treatment environment

For many women, returning to the site where they received treatment for cancer is an unpleasant experience. In Study 2, this may have been an important factor for one participant leaving the study, as she experienced great distress in returning to the Mount Vernon Hospital site. In Study 1, renovation of the LJMC meant that I had to use treatment rooms in the hospital wards and the chemotherapy suite for several weeks, and participants expressed discomfort about returning to these locations. Thus, from research and treatment perspectives, consideration should be given to the clinic locations, bearing in mind the sensitivity of these women to the medical environment.

Intrusive medical tests and interventions

Most women will have experienced many medical tests and interventions during the course of their treatment for cancer. In designing research into

the management of hot flushes, any use of further medical tests for outcome measures should be carefully considered in the light of the distress that these may cause the participants.

Intrusive research assessment measurements

As these women are striving to be as "normal" as possible, I strongly recommend avoiding using measurement tools that draw attention to their predicament. For example, wearing devices to monitor hot flushes might provide objective measurements of hot flush frequency (as well as perhaps severity), but may cause the participants undue stress, as such devices may draw attention to the "un-normalness" of their condition.

Placebo and no-treatment arms

Whilst placebo and no-treatment arms are deemed essential to good research design, careful consideration should be given to whether these are necessary or appropriate for participants with sensitive issues, such as these. Studies indicate that unwillingness to take placebo (as well as to aversion to random allocation) may affect recruitment (Ross et al. 1999) and compliance (Hart 2001). Users involved in the design of the UK HRT study expressed an aversion to placebo medication, thereby influencing the study design so that it comprised two arms only: standard treatment vs. HRT. There was no placebo control arm. This may set an important precedent for research design for studies for women with breast cancer.

User Involvement in study design

NHS practice for good research and design is to ensure user participation in the design of studies (INVOLVE 2004). I implemented this by involving users in the set up of Study 2. Users should be involved at an early stage of design development, to help to ensure that the research design and methodology are relevant to their experience and needs.

Summary

It is important to understand that cancer patients are living with a chronic disease that is potentially terminal. For survivors of cancer and its treatments, there is a real and ever-present fear that the disease may recur. I strongly believe that researchers should be sensitive to this aspect of their participants' lives, and construct research designs that remain sensitive to the issues that surround these fears.

10.14 Conclusion

The management of tamoxifen-related hot flushes is a complex issue, comprising a number of other complex issues. Menopause itself is complex and not well understood (Soules et al. 2001); hot flushes are complex and not well understood (National Institutes for Health 2005, National Institutes for Health 2004); breast cancer and its treatments are also complex issues. In addition, acupuncture is a complex intervention.

This research has attempted to begin to find a way to manage these side effects in spite of the many layers of complexity associated with this

condition. I have discussed the limitations of this research, and will conclude with a review of its achievements.

This research is original in that it uses a consistent, fully articulated traditional acupuncture approach to attempt to manage tamoxifen-related hot flushes. It is the first study to apply the NADA protocol to the management of hot flushes, and the first study to systematically collect data on the effect of the NADA protocol on hot flush frequency, and to measure the effects of the NADA protocol on emotional and physical well-being. It is amongst the first to report the details according to STRICTA guidelines, which are deemed important for the reporting of acupuncture studies. Finally, it is the first study to have the potential to compare two forms of acupuncture, administered in the same setting and adhering to the same project design and methodology.

Although this work does not provide definitive evidence that acupuncture "works", the data collected confirm the potential of acupuncture to manage cancer-treatment-related hot flushes, as indicated by the majority of the other studies in this area.

This research has also provided a sound basis for further research, and demonstrated that further research in this area is warranted. Through this work, I have tested many aspects of research, including recruitment processes, the identification and application of relevant outcome measures, and data management and statistical procedures. In addition,

I have tested two types of acupuncture, derived from different theoretical frameworks, as well as two different modes of delivery. This testing was necessary to determine whether conducting studies in this area was feasible, and I am pleased that my experience confirms that such research is feasible.

Most importantly, this research suggests that acupuncture is a treatment that is acceptable to women receiving adjuvant treatment for early breast cancer. This study also indicates that it was acceptable to the medical professionals associated with Mount Vernon Hospital Cancer Treatment Centre, who were responsible for the healthcare of these women[25]. It is satisfying to know that this research has already influenced practice in the NHS: the LJMC have opened an ear acupuncture service for managing hot flushes, and several other NHS trusts have been influenced by this research to develop their services, largely using the NADA ear acupuncture protocol.

This study indicates that women with tamoxifen-related hot flushes are highly motivated to take action to reduce their discomfort. It is rewarding, therefore, to know that for some women acupuncture has helped, as this comment from a participant on Study 2 confirms:

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[25] As supported by the financial support for this study, the encouragement for the research, and their referral of their patients into the study.

"I would recommend acupuncture as my quality of life was much improved as a result."

Abbreviations

AE	Aggressive Energy
AI	Aromatase Inhibitor
BAAB	British Acupuncture Accreditation Board
BAcC	British Acupuncture Council
BMQ	Baseline Medical Questionnaire
CAM	Complementary and Alternative Medicine
CAMEOL	Complementary and Alternative Medicine Evidence OnLine
CCHIM	Centre for Complementary Healthcare & Integrated Medicine
CF	Constitutional Factor
CI	Confidence Interval
CICM	College of Integrated Chinese Medicine
CM	Chinese Medicine
CSE	Certificate of Secondary Education
CSEO	Colour, sound, emotion, odour
CTC	Cancer Treatment Centre
df	Degrees of freedom
DGH	District General Hospital(s)
EC	Ethics Committee
EOT	End of Treatment
EQ	Exit Questionnaire
ER-	Oestrogen Receptor Negative
ER+	Oestrogen Receptor Positive
FECA	Five Element Constitutional Acupuncture
FQ1	Follow-up Questionnaire 1
FFQ	Final Follow-up Questionnaire
FMP	Final Menstrual Period
HABITS	HRT after breast cancer – is it safe?
HFNSQ	Hot Flush and Night Sweats Questionnaire
HRT	Hormone Replacement Therapy
GCSE	General Certificate of Secondary Education
Lic. Ac.	Licensed Acupuncturist
LJMC	Lynda Jackson Macmillan Centre
ln	Natural logarithm (to the base of e)
LREC	Local Research Ethics Committee

mg	milligram
MVH	Mount Vernon Hospital
NADA	National Acupuncture Detoxification Association
NAMS	North American Menopause Society
NASBP-14	National Surgical Adjuvant Breast and Bowel Project
NCCAM	National Centre for Complementary & Alternative Medicine
NHS	National Health Service
NIH	National Institutes for Health
NMSC	Non-Melanoma Skin Cancer
OTC	Over-the-counter
p	significance
PIS	Patient Information Sheet
PR-	Progesterone Receptor Negative
PR+	Progesterone Receptor Positive
PRS	Problem Rating Scale
RCT	Randomised Controlled Trial
SAE	Stamped Addressed Envelope
SD	Standard Deviation
SDQ	Sociodemographic Questionnaire
SERM	Selective Oestrogen Receptor Modulator
SF36	Short Form 36
SORT	Supportive Oncology Research Team
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitors
std dev	Standard Deviation
STRAW	STages of Reproductive Aging Workshop
TA	Traditional Acupuncture
TCM	Traditional Chinese Medicine
TD	Traditional Diagnosis
TNM	Tumour, Node, Metastases
TVU	Thames Valley University
tx	Treatment
USD	Untransformed Summary Data
WHQ	Women's Health Questionnaire

Glossary

[3]	**Adjuvant treatment**	The use of one treatment, e.g. radiotherapy, in addition (as an 'adjunct') to another treatment (e.g. surgery).
	Advanced breast cancer	Breast cancer that has spread to other parts of the body, that is, it has metastasised. Also called late stage breast cancer.
[1]	**Aggressive Energy (AE)**	A form of 'polluted' qi that can occur in the yin organs.
[1]	**Back shu points**	The back shu points lie on the bladder channel next to the spine. There is one point for each of the organs and they have a powerful effect by making direct contact with the organ.
[1]	**Blood**	In Chinese medicine, a form of qi that moistens and nourishes the body and houses the shen.
[2]	**Bonferroni**	A method that allows for the problems associated with making multiple comparisons.
[3]	**Cancer**	A collection of cancer cells that have uncontrolled growth and the ability to invade other tissues.
[3]	**Cancer cell**	A cell that differs from normal cells in two ways: • It duplicates itself without restriction, causing uncontrolled growth • It has the potential to invade nearby tissues as well as travel to and grow in distant metastases.
[3]	**Carcinoma**	This is a cancer that has developed from a surface tissue, e.g. skin carcinoma.
[3]	**Cell**	The building block of all tissues that contains our genes and makes each tissue function correctly. Cells are normally under tight control so that they produce tissues that are the right size and function.
[1]	**Channels**	The pathways or meridians of qi. There are 12 main channels that are linked to each organ as well as the ren and du channels, which traverse the back and front of the body. Other channels include the eight extraordinary channels.
[3]	**Chemotherapy**	Usually means treatment of cancer with drugs that have the capability of killing cancer cells.
[2]	**Confidence Interval (CI)**	A range of values within which we are fairly confident the true population value lies. For example, a 95% CI means that we can be 95% confident that the population value lies within those limits.
[1]	**Constitutional Factor (CF)**	A person's constitutionally weakest element. The main focus of treatment in Five Element Constitutional Acupuncture.

2	**Continuous variable**	A variable that can take any value within a given range, for instance Blood Pressure. Compare this with discrete variable.
1	**Correspondences**	The 'associations' or 'resonances' between the Five Elements' seasons, emotions, odour, climates, etc.
2	**Database**	A collection of records that is organised for ease and speed of retrieval.
2	**Degrees of freedom (df)**	The number of degrees of freedom, often abbreviated to df, is the number of independent pieces of information available for the statistician to make the calculations.
	Deqi	The needling sensations felt by the patient, and also those sensations experienced by the practitioner.
2	**Descriptive statistics**	Descriptive statistics are those that describe the data in a sample. They include means, medians, standard deviations, quartiles and histograms. They are designed to give the reader an understanding of the data.
3	**Differentiated cancer cells**	Normal cells are designed for a specific place and purpose, e.g. a heart cell. Although differentiated cancer cells grow in an uncontrolled way, most still look and function like normal cells.
2	**Discrete variable**	A variable where the data can only be certain values, usually whole numbers, for example the number of children within families. Compare this with continuous variable.
3	**Distress**	The outer sign of a person's physical or psychological discomfort.
2	**Distribution**	A distinct pattern of data may be considered as following a distribution. Many patterns have been described, the most useful of which is the normal distribution.
1	**Dragons**	The combination of points used to treat 'possession'.
4	**Early (stage) breast cancer**	Breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers.
1	**Eight Extraordinary Vessels**	The eight vessels that act as reservoirs of qi for the channels. Each vessel has its own functions. See ren channel.
3	**Epithelial tissues**	These are tissues whose cells are on the surface (e.g. skin) or form the linings of hollow organs such as the bowel.
1	**Essence**	In Chinese medicine, one of the 'three treasures' of humanity. Stored in the kidneys, it is our genetic inheritance. Also known as 'jing'.

[1]	**Five Elements or Phases**	The five different qualities of qi, which are fire, earth, metal, and water, wood. These are best exemplified by the cyclical succession of the seasons.
[4]	**Grading**	A system for classifying cancer cells in terms of how abnormal they appear when examined under a microscope. The objective of a grading system is to provide information about the probable growth rate of the tumour and its tendency to spread. The systems used to grade tumours vary with each type of cancer. Grading plays a role in treatment decisions.
[2]	**Histogram**	A graph of continuous data with the data categorised into a number of classes.
[3]	**Hormone therapy**	Some cancers are dependent on the presence of natural hormones to grow, e.g. breast cancer, prostate cancer. Hormone therapy uses drugs that suppress these natural hormones and so stop or reduce cancer growth.
[3]	**Hormones**	These are proteins that influence many of the ways in which the body grows and functions. Oestrogen is an example. The growth of some cancers is influenced by hormones, e.g. breast cancer can be affected by oestrogen.
[4]	**Hot Flush**	A sudden, temporary onset of body warmth, flushing, and sweating (often associated with menopause).
[2]	**Hypothesis**	A statement that can be tested that predicts the relationship between variables.
[2]	**Incidence**	The rate or proportion of a group developing a condition within a certain period.
	Integrated acupuncture	A style of acupuncture that integrates the theories and practices of two styles of acupuncture: Five Elements Constitutional Acupuncture and Eight Principles acupuncture. The integration of these two styles allows the practitioner to have a wider range of approaches to treatment to ensure the well being of the patient.
	Likert scale	A scale in which respondents indicate their level of agreement with statements that express a favourable or unfavourable attitude toward a concept being measured.
	Logarithms	The power to which a base, such as 10, must be raised to produce a given number. If $n^x = a$, the logarithm of a, with n as the base, is x; symbolically, $\log_n a = x$. For example, $10^3 = 1{,}000$; therefore $\log_{10} 1{,}000 = 3$. The kinds most often used are the common logarithm (base 10), the natural logarithm (base e), and the binary logarithm (base 2). Using logarithms is a way of simplifying very complicated calculations.

3	**Lymph channels**	Part of the lymphatic system. They carry fluid called lymph, draining it through the lymph nodes and eventually returning the fluid back to the blood.
3	**Lymph nodes**	One type of lymphatic tissue. Lymph nodes act as junctions for lymphatic channels, as well as a place where special cells that fight infection live.
3	**Lymphatic tissues**	Tissues that are part of the immune system, whose functions include fighting infection and draining lymph from the tissues through the lymphatics and lymph glands.
3	**Lymphoedema**	Blockage or damage to lymphatic tissues causes an accumulation of fluid, e.g. if the lymph nodes of the armpit are damaged or removed, a swollen arm may result.
3	**Malignant tumour**	A collection of cells with uncontrolled growth and the ability to invade nearby tissues as well as travel to and grow in distant tissues. Its effects are often widespread.
3	**Mastectomy**	Surgical removal of the breast to remove a cancer.
2	**Mean**	The sum of the observed values divided by the number of observations. Compare this with median.
2	**Median**	The middle observation when the observed values are ranked from smallest to largest. Compare this with mean.
4	**Menopause**	The time of life when a woman's menstrual periods stop. A woman is in menopause when she has not had a period for 12 consecutive months. Also called "change of life."
3	**Metastases**	Sites where cancer cells have grown, having travelled from the original cancer (often through the blood or lymph channels). Also known as secondary cancer.
	Moxibustion (moxa)	Used in acupuncture, this is the use of a burning herb *Artemesia vulgaris latiflora* (commonly called "mugwort") to warm and stimulate qi.
	Night sweats	Copious perspiration occurring in bed at night and occurring during the menopause, as well as in conditions such as tuberculosis and lymphomas. Also referred to as nocturnal hot flushes.
2	**Non-parametric test**	A test that is not dependent on the distribution (shape) of the data.
2	**Normal distribution**	This refers to the distribution of data that is symmetrical. In a graph it forms a characteristic bell shape.
2	**Null hypothesis**	A hypothesis postulating that there is no difference between the groups being tested. The result of the test either supports or rejects the hypothesis.

3	**Oestrogen**	A protein which is a hormone. Some female cancers (e.g. breast cancer) are dependent for their growth on oestrogen.
1	**Organ**	In Chinese medicine, a complex system that focuses upon a wide range of functions rather than just the anatomical structure.
2	***p* value**	Usually used to test a null hypothesis, the *p* value gives the probability of any observed differences happening by chance.
2	**Parametric test**	Any test that has an assumption that the data needs to follow a certain distribution can be considered to be a parametric test. The most common distribution that the data need to follow is the normal distribution.
1	**Pathogenic factors**	The 'external' causes of disease, i.e. climatic factors, which can 'invade' a person's qi.
2	**Percentage**	The number of items in a category, divided by the total number in the group, and then multiplied by 100.
3	**Platelets**	Small structures in the blood that ensure the blood clots properly to prevent bleeding.
1	**Points**	The places on the channels of the body where the qi can be most easily influenced.
1	**Possession**	A term used to describe when a person is no longer fully in control of their mind or spirit.
2	**Prevalence**	The proportion of a group with a condition at a single point in time.
3	**Primary cancer**	The original site of the cancer.
1	**Pulse diagnosis**	A traditional method of feeling the pulse in different positions on the wrist to diagnose the condition of the organs, qi and blood.
1	**Qi**	Usually translated as 'energy', although the Chinese concept also includes 'matter'. It is present in all phenomena.
3	**Radiotherapy**	The use of radiation to kill actively growing cancer cells. It can be given by external beam therapy, radioactive sealed sources, or by injected radioisotopes.
2	**Range**	The difference between the maximum and minimum score in a set of figures.
1	**Rapport**	The bond of trust and intimacy that exists between people.
2	**Rate**	The number of times that an event happens in a fixed period of time.
3	**Receptors**	Chemical structures that act as 'locks' for a chemical 'key', e.g. oestrogens are a chemical key that lock onto oestrogen receptors. Once the key and lock fit together, the receptor's function is activated.

3	**Recurrence**	Cancer cells that were not killed by treatment which then grow and restart cancer.
1	**Ren channel**	The channel of the ren mai (one of the extraordinary vessels). It runs up the front of the body.
3	**Secondary cancer**	Sites where cancer cells have grown, having travelled from the original cancer (often through the blood or lymph channels). These sites are known as 'metastases'.
1	**Shen**	In some contexts, the 'spirit' of the heart, in others the person's spirit in its entirety.
3	**Side effects**	Unwanted actions of medical or surgical treatments, e.g. a dry mouth from a drug to treat hay fever.
2	**Significance**	The probability of getting results by chance if the null hypothesis is true.
2	**Skewed data**	A lack of symmetry in the distribution of data.
4	**Staging**	Performing examinations and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.
2	**Standard Deviation (SD or Std Dev)**	A measure of the spread of scores away from the mean.
2	**Student's t test**	See t test.
4	**Supportive care**	Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of the disease, side effects caused by treatment of the disease, and psychological, social, and spiritual problems related to the disease or its treatment. Also called palliative care, comfort care, and symptom management.
1	**Syndrome**	A pattern of disharmony in an organ that is defined by pathology of yin/yang, substances and pathogenic factors.
2	**t test (often referred to as Student's t test)**	The t test is a parametric test used to compare the means of two groups.
3	**Tissues**	A collection of cells that has a specific function in the body, e.g. heart tissue, liver tissue.
4	**TNM Staging**	A system for describing the extent of cancer in a patient's body. T describes the size of the tumour and whether it has invaded nearby tissue, N describes any lymph nodes that are involved, and M describes metastasis (spread of cancer from one body part to another).

[1]	**Tongue diagnosis**	A traditional method of observing the signs on the tongue to assess disharmonies of yin/yang, the functions of the organs, the substances, and pathogenic factors.
[2]	**Transformation**	A transformation is where a mathematical formula is used to change the data. This will often be done to try to make the data follow a normal distribution so that a parametric test can be used.
[3]	**Tumour**	A collection of cells with uncontrolled growth. While a benign tumour does not spread to other tissues, a malignant tumour has the ability to invade nearby and distant tissues.
[2]	**Two-tailed test**	A test where the null hypothesis can be rejected whether the new treatment is better, or worse, than the current treatment.
[3]	**Undifferentiated cancer cells**	Normal cells are designed for a specific place and purpose, e.g. a heart cell. Undifferentiated cancer cells do not look and function like normal cells.
	Vasomotor symptoms	Hot flushes, night sweats and palpitations associated with menopause. In this thesis, the term applies to hot flushes and night sweats.
	Yin/Yang	In Chinese philosophy, Yin and Yang represent the two fundamental forces of the universe, and are used to explain how things function in relation to each other and the universe. The concept of Yin/Yang is regarded as the most important underlying theory of Chinese medicine.

Main sources for definitions used in this glossary:

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