

A Feasibility Study of the Mistletoe and Breast Cancer (MAB) Trial: A Protocol for a Randomised Double-blind Controlled Trial

Susan Bryant

University of Bristol

Lorna Duncan

University of Bristol

Gene Feder

University of Bristol

Alyson Huntley (✉ alyson.huntley@bristol.ac.uk)

University of Bristol <https://orcid.org/0000-0001-9409-7891>

Study Protocol

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Abstract

Background:

A Cochrane review of mistletoe therapy concludes that there is some evidence that mistletoe extracts may offer benefits on measures of quality of life during chemotherapy for breast cancer, but these results need replication. Our aim was to test the feasibility of a placebo controlled, double blind randomised controlled trial of mistletoe therapy in patients with breast cancer undergoing chemotherapy with or without radiotherapy.

Methods/design:

A placebo controlled, double blind randomised controlled trial of mistletoe therapy in patients with breast cancer. There will be three arms (groups) in the trial: Iscador M, Iscador P, with physiological saline as the placebo. The aim is to recruit 45 adult patients with a new diagnosis of early or locally advanced breast cancer, up to 12 weeks following definitive breast surgery whose standard treatment plan includes chemotherapy with or without radiotherapy. They will be taught to administer the MAB therapies subcutaneously and will titrate up to their optimal dose. MAB therapy will continue throughout their standard chemotherapy and radiotherapy and one month beyond. The main outcome of the MAB study is the feasibility of conducting such a trial within the NHS in order to inform a future fully powered investigative trial. Feasibility will be measured through recruitment, retention and patient experience using clinical research forms, patient diaries, cancer-related questionnaires and qualitative interviews conducted with both patients and oncology staff.

Discussion:

This trial is the first of its kind in the UK. Currently mistletoe therapy is mostly available through private practice in the UK. Completion of this feasibility study will support applications for further funding for a fully powered randomised controlled trial which will measure effectiveness and cost-effectiveness of this herbal therapy.

Background

In Europe, *Viscum album L* (mistletoe) is the most commonly used therapy by patients with cancer and is integrated into conventional oncology treatment programmes in Germany, Switzerland and Holland. Despite this use of mistletoe therapy, it is only relatively recently that it has been the subject of randomised controlled trials (RCTs), although most of these have been poorly designed and reported. Nevertheless, a relatively consistent finding of a Cochrane review of these trials measuring the effects of mistletoe on the adverse effects of chemotherapy and radiotherapy was a reduction of these effects and/or improvement of quality of life (QOL) in breast cancer patients.¹ The magnitude of these effects cannot be reliably estimated from current trials and were not pooled in the Cochrane review.¹

Potential recruitment of cancer patients into placebo controlled RCTs of mistletoe on mainland Europe is limited by the popularity of the therapy. This RCT is the first of its kind in the United Kingdom (UK). Whilst mistletoe can be prescribed in the UK, uncertainty about its effectiveness makes it a contentious therapy, despite its potential to improve the patient experience of cancer care, a major priority of the NHS cancer plan.² The aim of this pilot trial is to test the feasibility of a placebo controlled, double blind RCT of mistletoe therapy in patients with breast cancer undergoing chemotherapy with or without radiotherapy.

Methods

Design

Placebo controlled, double blind RCT of mistletoe therapy in patients with breast cancer undergoing chemotherapy with or without radiotherapy. The feasibility of the trial will be considered in terms of recruitment, retention, attrition, blinding and acceptability to patients and health professionals. There will be three arms (groups) in the trial: Iscador M, Iscador P (mistletoe therapy) with physiological saline as the placebo.

Participants

We aim to recruit 45 adult patients with a new diagnosis of early or locally advanced breast cancer, up to 12 weeks following definitive breast surgery whose standard treatment plan includes chemotherapy with or without radiotherapy. The patients in this feasibility trial will be recruited via one site the Bristol Haematology and Oncology Centre (BHOC) at University Hospitals Bristol NHS Foundation Trust. Patients who are to receive only radiotherapy will be excluded as this treatment is generally well tolerated and of short duration.

Inclusion and exclusion criteria

Potential participants will include adults 18 years or over with histologically verified early or locally advanced invasive breast cancer and with planned adjuvant chemotherapy, with or without radiotherapy and able to be randomised within 12 weeks of surgery. They must be willing to self-administer or have a nominated person administer injections. Their Eastern Cooperative Oncology Group (ECOG) performance status must be 0 or 1 and they should have no active, uncontrolled infection. Female participants of childbearing age must be willing to adopt adequate contraceptive measures and males must follow the chemotherapy guidance of the BHOC with regards to contraception. Patients will be excluded if they are: receiving immunomodulatory therapy; receiving endocrine therapy as a stand-alone treatment; have previously had invasive breast cancer or bilateral breast cancer or have chronic viral infections such as Hepatitis B and C and HIV; known allergy to mistletoe or be using/have had mistletoe within the last 5 years; acute inflammatory or pyrexial conditions; chronic granulomatous disease; active auto-immune diseases or hyperthyroidism with tachycardia. Where appropriate patients who are recommended to receive Trastuzumab and/or endocrine therapy, as well as chemotherapy, are eligible.

Randomization and blinding (Fig. 1).

It was decided to proceed with a three arm trial for two reasons: a) both Iscador® M and Iscador® P are recommended by Iscador AG (<https://www.iscador.com/de/>) for treatment of breast cancer with no evidence for either one being superior to the other b) by having a 1;1;1 randomization regime, the participants involved will get a better chance of receiving mistletoe therapy and therefore it may enhance recruitment.

The patient randomisation list and the medication block randomisation lists will be produced by an in-house statistician at Iscador AG. Randomisation of patients will be conducted by University Hospitals Bristol Pharmacy (UHBP). Allocation of participants to Iscador® M/Iscador® P/control 1:1:1 ratio will be performed by the UHBP. A separate randomisation list will be held by UHBP for individual emergency unblinding. In the case of a serious adverse event and unblinding being required, the pharmacist will be asked by the principal investigator to look at the unblinding randomisation list using the package coding of the prescription without resulting in the unblinding of all the other patients due to the block randomisation. Both participants and healthcare professionals will be blinded to the group assignment. Any unblinding will be logged by the pharmacy. Breaking the blinding (for a single patient) will only be considered when knowledge of the treatment assignment is deemed essential by the investigator for the patient's care.

Intervention group

Participants will receive mistletoe preparations Iscador® M (Maleus) or Iscador® P (Pinus) and these will be available as 1 ml ampoules for sub-cutaneous injection. The quantity of fermented, aqueous extract from *Viscum album* L from apple and pine tree respectively used to produce one ampoule of Iscador® product is expressed in milligrams (mgs) e.g. for one ampoule (1.0 ml of solution) of Iscador® M 1 mg contains the extract of 1 mg fermented apple tree mistletoe. The proposed dose escalating regime is outlined in Table 1. This standard therapy regime was devised from the manufacturer's recommendation in conjunction with the MAB advisory group.

Table 1
Example of typical study therapy & maintenance regime for both Iscador® M (Maleus) and Iscador® P (Pinus)

Induction phase	
Week 1	0.01 mg (1.0 ml) x3 = total of 0.03 mg Iscador M or P
Week 2	0.1 mg (1.0 ml) x3 = total of 0.3 mg of Iscador M or P
Week 3	1 mg (1.0 ml) x3 = total of 3 mg of Iscador M or P
Week 4	10 mg (1.0 ml) x3 = total of 30 mg of Iscador M or P
Week 5	20 mg (1.0 ml) x3 = total of 60 mg of Iscador M or P

Placebo (control group)

The 1 ml placebo ampoules will have identical external packaging and labelling as the mistletoe ampoules. The placebo is physiological saline 0.90% w/v of sodium chloride, 308 mOsm/L or 9.0 g per litre. Physiological saline has been prepared by the manufacturer of the study medication according to Good Manufacturing Process (GMP) criteria.

Treatment & maintenance regime

The study medication will be titrated upwards by the research nurse using the standardized regime until an optimal dose is achieved and then the participant will stay on this dose for the rest of the study (Table 1). An identical procedure will be carried out with both the Iscador and the saline products. However if the participant is randomised to saline, the same dose will be administered throughout (Physiological saline 0.90% w/v of sodium chloride, (1.0 ml)). There is unlikely to be a sustained local reaction with the saline placebo but essentially the same rule applies as for the mistletoe arm: the participant would continue on the same saline preparation in week five and this will be called the maintenance dose.

Outcome Measures

Feasibility will be measured using mixed methods to assess the objectives of:

- Recruitment rate
- Specific obstacles to recruitment
- Adherence to the study therapy schedule
- Acceptability of regular sub-cutaneous injections
- Adverse events from mistletoe and placebo subcutaneous injections
- Completion of outcome measures
- Attrition rate with reasons if possible
- Assessment of blinding of patients, based on simple questions in the final questionnaire about which study therapy they think they received
- Assessment of therapy related symptoms and health related quality of life in the sample population

Participants will receive a diary card pack to record their study therapy and responses.

Questionnaire pack

This comprises six questionnaires and will be administered at three time points during the trial: *Time point 0 or baseline* following randomisation and before start of chemotherapy regime; *Time point one* following the 3rd cycle of chemotherapy; *Time point two* four weeks after last standard treatment (chemotherapy with or without radiotherapy), on the day of the last study treatment. The questionnaires included are:

1) European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (quality of life -cancer 30 items) questionnaire and 2) EORTC QLQ-BR23 (quality of life -breast cancer 23 items) questionnaire,^{3,4} 3) Functional Assessment of Cancer Therapy-Neutropenia (FACT-N) scale,⁵ 4) Cancer Fatigue Scale,⁶ 5) Autonomic regulation scale,⁷ and 6) the CompleMentary and Alternative Beliefs Inventory (CAMBI).⁸

Participant and staff interviews

Semi-structured interviews will be conducted with MAB study participants and BHOC staff to explore acceptability of the MAB therapy, therapy-related symptoms, and administration of/ participation in the trial. Interviewees will be selected via purposive sampling where enough exist; otherwise all participants who have indicated their consent to interview will be approached for interview, as well as relevant staff. These data will help plan the delivery and processes of the study therapy for the full trial and establish appropriate training needs. Pro-formas will be utilised in interviews, to include the following topics (as appropriate to participants and staff):

Interview 1 (to be completed as soon as possible after recruitment to the study in the case of participants, and throughout the trial in the case of staff):

Understanding and expectations of MAB therapy

Awareness, interest in and use of complementary and/ or alternative therapies

Study processes including recruitment; administration of the MAB therapy; administration and completion of diaries and questionnaires

Local availability and perspectives on the role of CAM in cancer treatments in the NHS (staff only)

Interview 2 (to be completed with participants as soon as possible on completion of study participation and, if possible, towards/ at the end of the trial in the case of staff):

Further exploration of the topics in interview 1 to identify any changes/ clarification, and overall views on the trial. Participants' understanding of the placebo effect will be investigated and their ideas on the MAB therapy treatment which they think they may have received.

Procedures

Participation in the study will be approximately ten months. Patient informed consent will be taken in BHOC either by the consultant or delegated by the consultant to an appropriately trained and qualified member of the research team. The patients will be given at least 24 hours to consider whether they want to participate or not. If a patient decides to take part, they will be randomised into either one of the two mistletoe therapies or a placebo therapy. The first study therapy will be given within a week of randomisation to the study and, ideally, prior to the start of chemotherapy.

The participants treatment regime will be three subcutaneous injections per week. It is advised that the injections will be given every other day, followed by a two-day break. There will be no breaks in the study therapy regime unless the participants request one, or a clinician advises one. In the case of a participant stopping their standard treatment they will be encouraged to continue their MAB therapy during this period, but the dose will not be escalated.

Injections will be initiated by research nurses in the clinic with the aim of teaching the participant to self-administer, or a nominated person (e.g. relative) to administer to the participant and continue the study therapy at home. The injections will be administered in the abdomen or thigh.

The participants will be given a booklet which contains information on self-administration of the study treatments, the expected responses and potential undesired responses and contraindications of the study therapy, as well as a diary to record their study therapy and responses. The strength of reaction at 24 hours after the injection is the indicator for either increasing or maintaining the dose. We estimate that most participants will be able to self-administer their optimal dose within one month (~ 12 visits) and some of these visits will coincide with other treatment or appointments.

Data monitoring

The Trial Steering Committee (TSC) will also incorporate the Data Monitoring and Ethics Committee (DMEC). This group has established Terms of Reference and will incorporate members who are independent of the sponsor and have no competing interest.

Sample size calculation and power

Studies suggest there is no formal way of determining numbers for a feasibility trial.^{9, 10} The aim of recruiting 45 patients was decided following discussion both with the MAB study team, its steering and advisory groups as well as the BHOC staff. This number was chosen to allow fair assessment of the aims of recruitment, retention, and completion of outcomes and an assessment of the viability of blinding.

Analysis plan

The recruitment rate will be expressed using descriptive statistics. Retention will be summarised by recording the number of participants in each study group at the pre-specified worst toxicity time point (after 3rd chemotherapy cycle, T1) and 4 weeks post standard treatment (at end of study treatment, T2). The patient related outcome data will be summarised per each individual questionnaire (T0, T1& T2). Completion will be noted if the form can be used. For example, the EORTC QLQ-C30 can be used if at least half the questions from the factors of interest are complete. Blinding will be assessed by asking the patient in their final questionnaire at T2. This will be analysed using Bang's blinding index. Blinding will potentially be discussed in their qualitative interview if appropriate.

For the qualitative work, data from the interviews, as well as qualitative data from participant diaries and questionnaires will be analysed thematically.

Interviews will be transcribed and coded in NVivo using themes broadly linked to those used in the interview pro-formas (recruitment; understanding/ expectations of MAB therapy; views and use of complementary and/ or alternative therapies, and the availability/ role of these in the NHS/ privately; trial recruitment/ retention; MAB therapy administration/ completion of diaries and questionnaires; understanding of the placebo effect; blinding; and possible improvements to the trial). Initial coding and development of themes will be performed by two members of the MAB study team (LD and AH), with remaining coding and synthesis performed by LD. Narrative synthesis of the themes from the perspectives of participants and staff will be reported using the interview data as well as relevant items from participant diaries and questionnaires.

Discussion

Mistletoe therapy provision through the NHS is minimal with most provision occurring through private practice in the UK. This limits patient's awareness of it and access to it. This RCT is the first of its kind in the UK and completion of this feasibility study will increase awareness of mistletoe therapy for oncology patients in the UK and will support applications for further funding for a fully powered RCT which will measure effectiveness and cost-effectiveness.

The MAB study takes a mixed methods approach, not only assessing the feasibility of the trial design in a UK context, but also qualitatively exploring the experience of both health professional and patient participants. The qualitative interviews will inform the design of the main trial, but also expand the relatively small literature on the experience of patients receiving mistletoe therapy.

Trial Status

The current Protocol is version 7.1 dated 01/05/2019; participant recruitment began on 01/08/2019 and was due to end on 31/03/2020 but was curtailed at 19/03/20 due to COVID pandemic.

Abbreviations

BHOC, Bristol Haematology and Oncology Centre, UH Bristol; CRF, Case Report form; RCT, Randomised Control Trial

Declarations

Ethics approval and consent to participate (see additional documents)

All necessary research governance approvals were sought and approved including:

REC reference: 18/SW/0045 / date of favourable opinion 12/04/2018

EudraCT number: 2018-000279-34

Date of registration on EudraCT 05/04/18

URL: <https://www.clinicaltrialsregister.eu/ctr-search/search?query=+2018-000279-34++>

Consent for publication

Not applicable -- no individual person's data in the paper

Availability of data and materials

Not applicable – paper is a protocol

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Authors' contributions:

Susan Bryant¹ -Senior research fellow (trial manager) was involved in the preparation of the manuscript and approved the final version. Susan.bryant@bristol.ac.uk

Lorna Duncan¹ senior research fellow (qualitative researcher) prepared the qualitative methods and analysis section and approved the final version. Lorna.duncan@bristol.ac.uk

Gene Feder¹ Professor of primary health care (co-principal investigator) contributed to the manuscript and approved the final version. Gene.feder@bristol.ac.uk

Alyson L Huntley Senior Research Fellow (Co-principal investigator) prepared the initial manuscript and was involved throughout the whole process. Alyson.huntley@bristol.ac.uk

Centre for Academic Primary Care, Population Health Sciences, Bristol Medical School

University of Bristol, Canynge Hall room BS8 2PS

Competing interests: The authors declare they have no competing interests

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References

1. Horneber MAFAU, Bueschel GF, Huber RF, Linde KF, Rostock M. Mistletoe therapy in oncology. *Cochrane Database Syst Rev* [16], CD003297. 2008.
2. The NHS Cancer Plan: A plan for investment, a plan for reform. September 2000.
3. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365–76.
4. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, Franzini L, Williams A, de Haes HC, Hopwood P, Cull A, Aaronson NK. European Organization for Research & Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a 3-country field study. *J Clin Oncol.* 1996 Oct;14(10):2756–68.
5. Wagner LI, Beaumont JL, Ding B, Malin J, Peterman A, Calhoun E, et al. Measuring health-related quality of life and neutropenia-specific concerns among older adults undergoing chemotherapy: validation of the Functional Assessment of Cancer Therapy-Neutropenia (FACT-N). *Support Care Cancer.* 2008;16(1):47–56.

6. Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J Pain Symptom Manage*. 2000;19(1):5–14.
7. Kröz M, Feder G, von Laue H, Zerm R, Reif M, Girke M, et al. Validation of a questionnaire measuring the regulation of autonomic function. *BMC Complement Altern Med* 2008; **8:26**.
8. Bishop FL, Yardley L, Lewith G. Developing a measure of treatment beliefs: the complementary and alternative beliefs inventory. *Comp Ther Med*. 2005;13(2):144–9.
9. Eldridge SM, Costelloe CE, Kahan BC, Lancaster GA, Kerry SM. How big should the pilot study for my cluster randomised trial be? *Stat Methods Med Res*. 2016;25(3):1039–56.
10. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, Bond CM. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS ONE*; 11(3) 1–11.

Figures

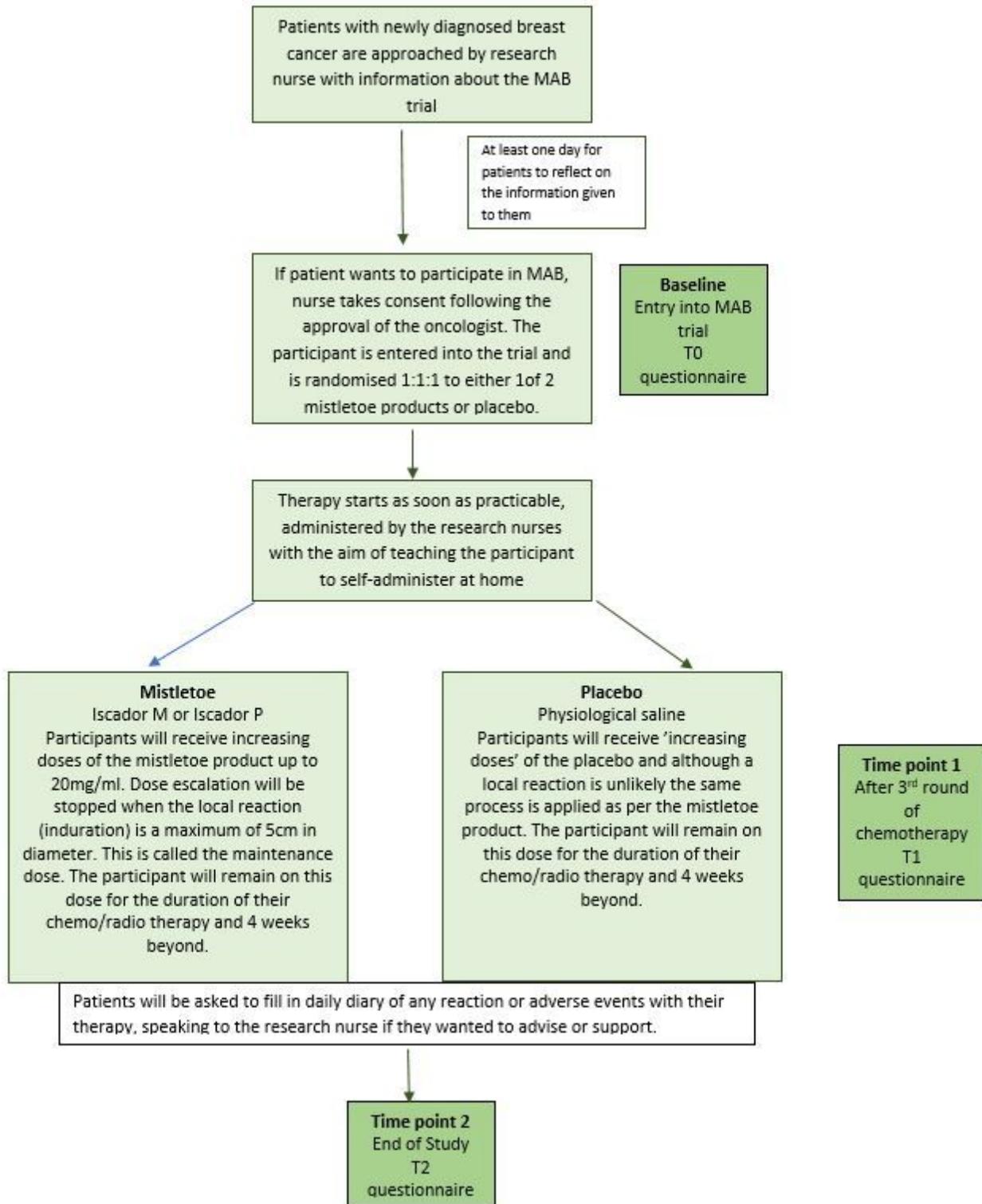


Figure 1

Flow chart of MAB protocol