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Efficacy of a physiotherapy, yoga and patient education programme for patients with breast cancer and hormone therapy-induced pain: a multicentre randomised study protocol (SKYPE 2)

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ABSTRACT

Introduction Osteoarticular pain is experienced by approximately 50% of patients with breast cancer under hormone therapy and can increase the risk of therapy discontinuation. Among complementary therapies, yoga has shown efficacy regarding reduction of fatigue, anxiety, pain due to hormone therapy and inflammation. Personalised patient education programmes increase engagement and motivation, and induce effective behavioural changes. The SKYPE programme, an integrated intervention combining physiotherapy, yoga and patient education, showed promising efficacy on hormone therapy-induced pain in a previous pilot study. In this study, we hypothesised that using theory-based patient education favour learning and practising 15 min of at-home yoga every day to decrease hormone therapy-induced pain.

Methods and analysis This multicentre randomised study will assess the efficacy of the SKYPE programme on pain reduction compared with standard care in patients with breast cancer reporting osteoarticular pain due to hormone therapy. Main secondary objectives will describe pain evolution and characteristics, patient adhesion to yoga sessions and home practice, forward flexibility, quality of life, fatigue, anxiety and compliance to hormone therapy. Patients in the intervention group will participate in 1 weekly educational yoga session of 90 min for 6 weeks, supervised by physiotherapists (period 1). They will also perform daily at-home 15 min yoga sessions for 12 weeks, the total duration of the intervention (periods 1 and 2). Pain will be evaluated during physiotherapy check-ups at baseline (T0), at 6 weeks (T1) and at 12 weeks (T2).

Ethics and dissemination This study was approved by the ethics committee (CPP Ile de France 8 on 22 June 2020). The results will be disseminated to patients and healthcare professionals, and published in a peer-reviewed journal.

Trial registration number NCT04457895.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The SKYPE 2 study, based on promising results of a pilot study, is a randomised multicentre trial and will include 108 patients.
⇒ The SKYPE protocol proposes an integrated yoga programme, supervised by physiotherapists, with a theory-based patient education approach, to enhance patients' autonomy and induce a sustainable behavioural change in their daily practice.
⇒ The use of digital format to perform the main part of yoga training allows the inclusion of patients living far from healthcare centres.
⇒ Patient's self-reporting of home practice is one of the limitations.
⇒ Blinding is not suitable because of the characteristics of SKYPE 2 programme, that is, physiotherapy, yoga and patient education intervention.

INTRODUCTION

Oestrogen-positive breast cancers account for 65%–75% of all early breast cancer cases and require adjuvant hormone therapy (HT) after initial treatment,[1] administered for a long time period, usually 5 years and up to 10 years for some patients.[2] During treatment, as much as 50% of women report osteoarticular and/or musculoskeletal pain.[3 4] HT-related side effects constitute a major issue with consequences on patients' quality of life (QoL), treatment efficiency, including dose reductions or early treatment discontinuation and patient's survival.[5–11]

Over the last years, complementary therapies, including yoga practice, have brought increasing attention. According to guidelines, 48%–80% of patients with breast cancer use them as integrative therapies and supportive care.[12] Moreover, they were recently endorsed by the American Society of Clinical Oncology.[13]

A review comparing efficacy of various therapies to decrease osteoarticular pain due to HT concluded to the highest efficacy of anti-inflammatory treatments, paracetamol

and yoga.[14] In addition, one randomised and two pilot trials showed promising results on HT-related pain.[15–17] Some studies suggested that yoga practice could modulate inflammation by regulating the level of expression of a wide range of proinflammatory and anti-inflammatory cytokines.[18–20] For example, Kiecolt-Glaser *et al* reported a yoga programme in breast cancer survivors, consisting of one 90 min session twice per week, for 12 weeks, and showed benefits on inflammation and fatigue.[19] However, these studies mainly used supervised yoga programmes, and few of them associate it with at-home practice. Moreover, these programmes are generally delivered during short-term periods or in women undergoing chemotherapy but not HT.[21 22] In addition, none of them includes supervised home practice nor a theory-based educational component. When home practice is performed, it is mainly based on the use of educational support (video, audio guide or booklet), and patients' adherence is not always reported.[21 22] Eventually, yoga sessions were mainly supervised by yoga teachers.

We designed an innovative approach, combining supervised yoga sessions and at-home practice, all supervised by physiotherapists, with a theory-based educational programme in the aim to improve long-term patient behavioural changes. We hypothesised that a personalised educational programme, including weekly determination of personal objectives and selection of appropriate yoga postures with the physiotherapist, could increase patient's engagement and motivation, and induce effective behavioural changes regarding yoga practice.[23 24] Physical activity interventions, using this approach, have been evaluated and successfully increased patient physical activity levels.[25 26] We also include a physiotherapy approach which could provide real benefits on osteoarticular and/or musculoskeletal pain after breast cancer.[27]

We recently conducted a monocentric, single-arm pilot study, SKYPE (*Suivi en Kinésithérapie et Yoga Projet Educatif*),[28] using the Medical Research Council framework for developing complex interventions.[29 30] Patient education (PE) was completely integrated into the supervised yoga sessions to guide the patients towards behavioural change, in addition to the at-home tools given to the patients. We included 24 patients with breast cancer treated with HT and presenting treatment-related pain, and showed a 2-point decrease of the numeric pain scale in 58% of patients, an increase in flexibility in the majority of patients, and a 10/10 patient satisfaction for all patients.[28] Our results confirmed such integrative and educational care meets a real need for women with breast cancer treated with HT. To our knowledge, the SKYPE protocol is the first to offer a theory-based PE programme, supervised by physiotherapists, to enhance patients' autonomy and allow a behavioural change in order to include daily yoga practice in their lives. We now propose to evaluate our programme in a multicentre randomised study on patients with breast cancer treated with HT and reporting osteoarticular and/or musculoskeletal pain. We will assess the efficacy of the SKYPE programme[28] on pain reduction and compare it with a control group receiving standard care treatment.

METHODS AND ANALYSIS

Study design and setting

SKYPE 2 is a randomised controlled trial performed in six French oncology healthcare centres with high experience in HT for patients with breast cancer: the Montpellier Cancer Institute, the Pays Basque Institute of Oncology (Bayonne), the West-France Cancer Institute (Angers), the Lorraine Cancer Institute (Nancy) and the Nîmes University Hospital and the Libourne Hospital. Physiotherapists will follow a 9-day training in postural yoga with final certification and will receive a PE training before the beginning of the study. All interventions will be provided in French. This study protocol is written in accordance with the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).

Patient and public involvement

A patient representative with personal experience of breast cancer gave valuable opinions during study conception about patients' participation.

Eligibility criteria

The patients' inclusion criteria are: adult patients (≥18 years) operated for an early, non-metastatic, breast cancer, ongoing adjuvant treatment with HT (either tamoxifen or aromatase inhibitor) for at least 1 month, with no treatment modification in the 30 days prior inclusion, and with osteoarticular and/or musculoskeletal pain due to HT≥4 on the Numeric Pain Rating Scale (NPRS).[31] The previous treatment (surgery, adjuvant chemotherapy or radiotherapy) must have ended at least 2 months prior to inclusion. Indeed, based on medical considerations, after surgery and radiotherapy the wound and the skin need to heal for at least 1 month, and neuropathy can persist for several weeks after chemotherapy. Thus, we chose a 2-month safety margin to take into account these parameters and focus on HT-induced pain. Included patients will sign an informed consent prior to any study procedure. Non-inclusion criteria are the following: need of specific care or medical treatment for chronic rheumatological pain or other chronic pain condition, regular yoga practice over the 3 months prior inclusion, contraindication or clinical state not allowing physical practice, regular follow-up not possible (psychological, family, social or geographical reasons), pregnant or breastfeeding women. If patients experience a recurrence of their cancer during the intervention, they will not be excluded but can choose to withdraw their participation. In such a case, the physiotherapist will record the information.

Study objectives

The primary objective of the SKYPE 2 study is to compare the efficacy of a 12-week programme combining physiotherapy, yoga and PE intervention on reduction of

Table 1 Study assessments and outcome evaluations

	T0	P1						T1 (W6)	P2						T2 (W12)
	Inclusion D–30 to D0	W1	W2	W3	W4	W5	W6	End of period 1 evaluation	W1	W2	W3	W4	W5	W6	End of period 2 evaluation/end of study visit
Inclusion/non-inclusion criteria	X														
Informed signed consent	X														
Patient inclusion	X														
Randomisation	X														
Medical history	X														
Physiotherapy check-ups (including NRPS)	X							X							X
Educational check-ups (experimental group only)	X							X							X
Questionnaires (GSES, EORTC QLQ-C30 and BR23, HADS, SF-36, BPI)	X							X							X
Blood sample	X														X
Reminder email (experimental group only)										X		X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supervised yoga session (experimental group only)		One 90 min supervised yoga session/ week													
At-home yoga practice (experimental group only)		One daily 15 min at-home session							One daily 15 min at-home session						

BPI, Brief Pain Inventory; D, day; EORTC QLQ-C30 and BR23, European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire of Cancer Patients and Breast cancer-specific module; GSES, General Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; NRPS, Numeric Pain Rating Scale; SF-36, 36-Item Short Form Health Survey; W, week.

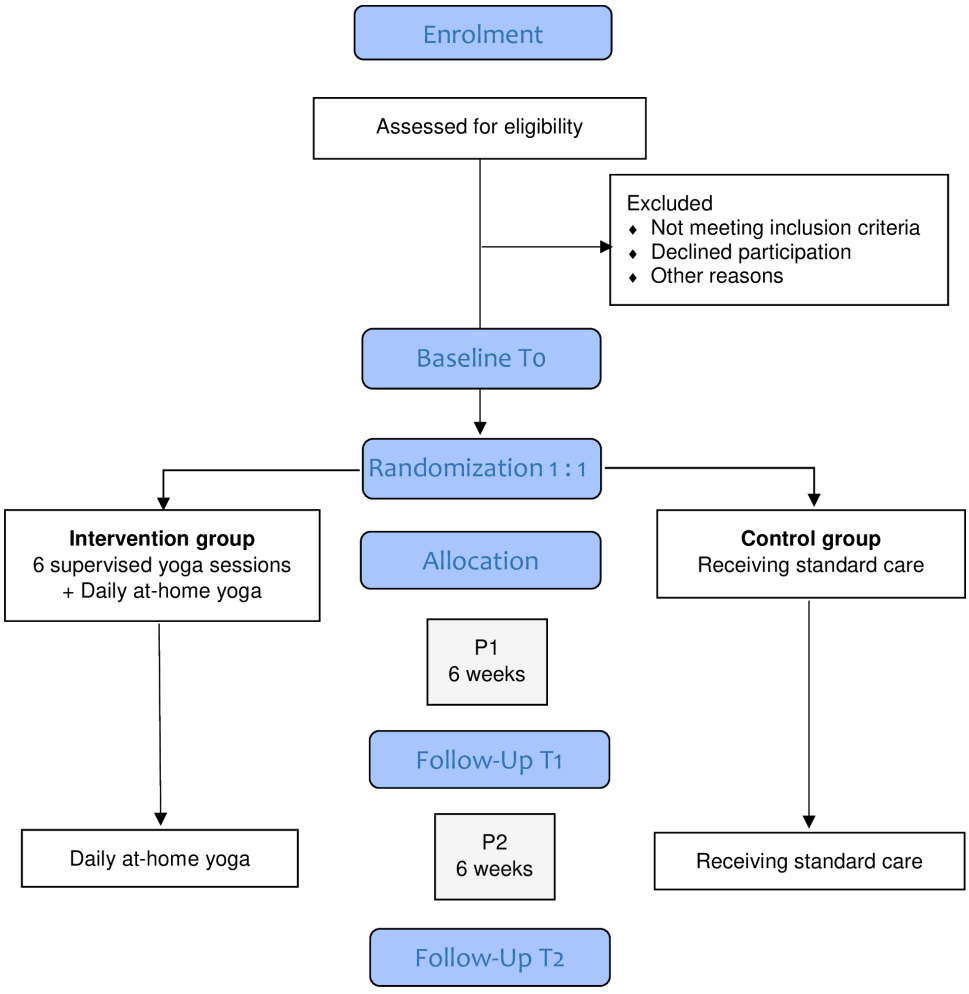

Figure 1 Study flow diagram.

osteoarticular and/or musculoskeletal pain due to HT in patients with breast cancer between inclusion (T0) and the end of the intervention, at 12 weeks (T2).

Secondary objectives are to describe:

1. The evolution of osteoarticular and/or musculoskeletal pain characteristics related to HT.
2. Patient adherence to yoga sessions and self-practice, and the reasons for adherence or non-adherence to at-home yoga practice.
3. QoL, fatigue, anxiety and depression.
4. HT and patient's compliance.

And to assess:

5. Forward flexibility.
6. Patient's respiratory capacity.
7. Induced self-competence feeling.
8. Patient's satisfaction towards the intervention.
9. Inflammatory biological profile.

Study endpoints

Study endpoints will be assessed at inclusion (T0), and at 6 weeks (T1) and at 12 weeks (T2). Time frame of study assessments and outcomes are summarised in table 1.

The primary endpoint will be the proportion of patients with a 2-point reduction on the NPRS of osteoarticular and/or musculoskeletal pain due to HT between T0 and T2.[31]

Secondary endpoints will be the following:

1. The Brief Pain Inventory (BPI) will be used to describe the evolution of osteoarticular and/or musculoskeletal pain characteristics.[32]
2. Physiotherapists will register adherence to supervised yoga sessions and patients will record home adherence, at-home yoga practice and reasons for practising or not in logbooks (online supplemental material).
3. QoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire of Cancer Patients (QLQ-C30),[33] Quality of Life Questionnaire Brest cancer-specific module (QLQ-BR23) and the 36-Item Short Form Health Survey questionnaire (SF-36)[34]; and fatigue both with EORTC QLQ-C30 (fatigue dimension) and SF-36 (vitality dimension) questionnaires; anxiety and depression by the Hospital Anxiety and Depression Scale (HADS).[35 36]
4. HT treatments will be collected from medical journals and compliance will be self-reported during assessments.

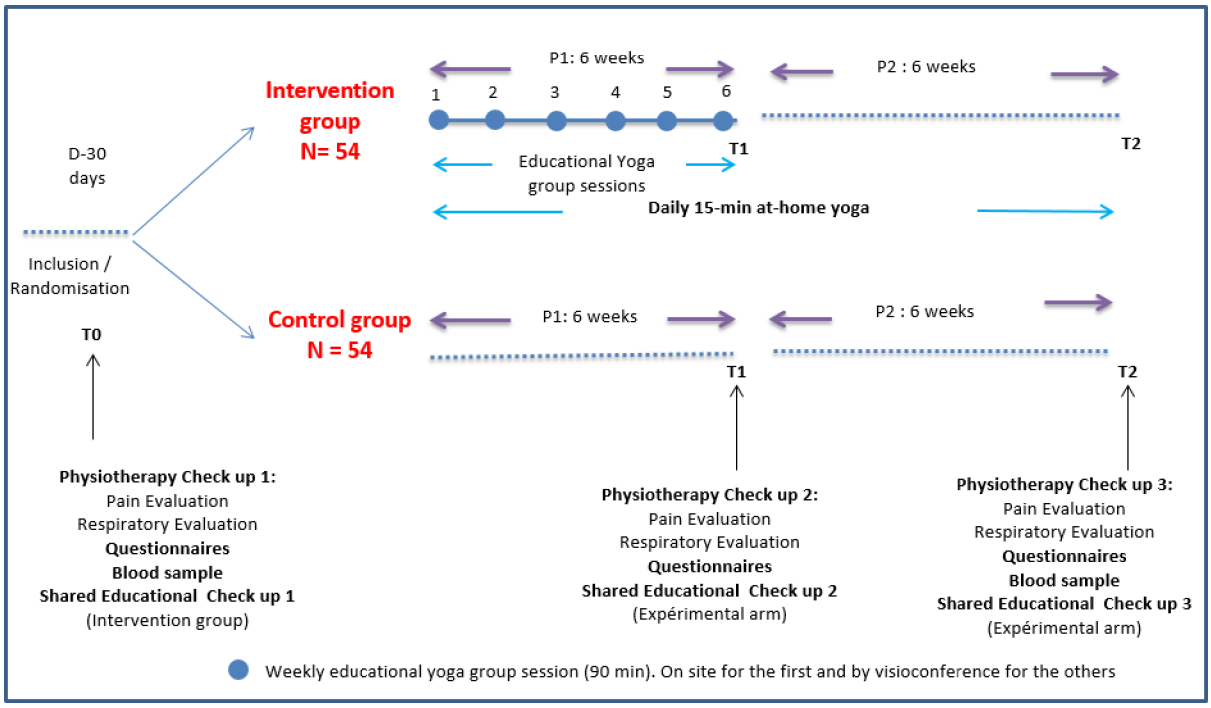

Figure 2 Participant timeline.

5. Forward flexibility, defined as the distance between the fingertips and the floor, will be measured while the patient is bending forward, keeping knees straight and feet together and placed on a step. Values will be expressed as median and range (cm). Negative values (under the floor level) indicate more flexibility.
6. Respiratory capacity will be measured with a spirometer at the end of the physiotherapy check-up, in a resting condition. Four values will be collected: (1) the forced expiratory volume in 1 s (FEV1) in litres, (2) the forced vital capacity (FVC) in litres, (3) the Tiffeneau proportion FEV1/FVC in percentage and (4) the peak expiratory flow in litres/min.
7. Self-competence feeling will be assessed with the General Self-Efficacy Scale (GSES) questionnaire.[37]
8. Patient's satisfaction will be evaluated using a seven-item Likert scale at T1 and T2. The items are extremely satisfied, very satisfied, little satisfied, not satisfied/not unsatisfied, little unsatisfied, very unsatisfied and extremely unsatisfied.
9. To assess inflammation, the level of expression of a panel of 20 proteins (GM-CSF, IFNα, IFNγ, IL-1α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-17A,TNFα, IP-10, MCP-1, MIP-1α, MIP-1β, ICAM-1, CD62E and CD62P) implicated in the inflammatory response will be quantified at T0 and T2. Patients are not requested to be fasting; however, the blood samples are collected at the same time during the day to reduce the impact of metabolism factors.

Sample size

The sample size calculation is based on the comparison of the proportion of patients who will report a reduction of at least two units of their osteoarticular and/or musculoskeletal pain due to HT between T0 and T2 in each group, assessed on the NPRS from 0 to 10. Indeed, a reduction of two units measured on the NPRS is considered as the minimal clinically important difference in chronic musculoskeletal pain intensity.[38] To detect a difference of 25% between the control and the experimental groups (15% vs 40%) and based on a bilateral alpha risk of 5%, with a power of 80%, 98 patients, 49 per group, would be required. Accounting for 10% of potentially non-evaluable patients, 108 patients are to be included in the study, with 54 patients per group.

Patient timeline and study flow diagram

The study flow diagram and patient participation are detailed in figures 1 and 2. Patients are recruited in the oncology and radiotherapy departments, during their HT follow-up visits. The oncologist or the physiotherapist will inform the patient of the study and will collect the patient's informed consent.

Randomisation

After signature of the informed consent form, and if patients meet eligibility criteria, the investigator will proceed to patient registration and randomisation via an electronic case report form (eCRF). The patients will be randomised (1:1 ratio) in a web-based digital portal ('CSOnline') either to the experimental group (SKYPE 2) or to the control group (figure 1). Randomisation will be stratified according to the study centre, patient's pain-killer intake (yes/no) and the intensity of HT-induced pain on a 0–10 numerous scale (< or ≥6).

The study is an open study; no blinding is possible due to the type of intervention. Thus, neither the statistician,

the patient nor the physiotherapist trained in yoga are blinded.

Physiotherapy-yoga-PE intervention

The study proposes an integrated intervention combining physiotherapy, yoga and PE. These three components are closely interwoven during the entire intervention (figure 2).

Physiotherapy

The intervention is designed and supervised by physiotherapists trained in postural yoga and PE, ensuring safety and adaptability for each patient. During physiotherapy check-ups, any limitations requiring adjustments will be recorded, such as mobility restriction, scar tightness and oedema. During yoga sessions, the physiotherapists will adapt the postures for each patient according to the assessed limitations.

Yoga

The yoga intervention will last for 12 weeks and be divided into two 6-week periods, P1 and P2. During P1, patients will follow a combination of supervised yoga sessions and at-home yoga practice, in the aim to become independent in their practice. During P2, patients will be invited to keep practising at-home yoga sessions (figure 2). Each patient will receive a learning kit consisting of the '*My yoga guide*' booklet, which describes the ten illustrated postures used during the programme and a 15 min audio yoga session guide sent by email or copied on a memory stick. In addition, the physiotherapist will provide a logbook to document at-home daily practices, their duration and the reasons for practising or not. A specific section is also dedicated to monitor painkiller intake (drug, dose and duration).

Supervised sessions (P1)

During 6 weeks, patients will follow a training yoga programme and attend 1 weekly 90 min yoga session under the supervision of a physiotherapist expert in postural yoga, in groups of 2–5 patients. Supervised sessions are detailed in '*The Physiotherapist's Guide book*' to ensure the homogeneity and reproducibility of the intervention. The initial two sessions are intended to learning the at-home yoga practice based on '*My yoga guide*', then 2–3 new postures will be introduced each week. Table 2 provides details regarding the different steps of the sessions. Patients will be taught specific yoga postures to avoid placing their body weight on their wrists, and prevent pain in their distal joints. Patients will be encouraged to adapt their yoga practice according to their limits and physical capabilities. The first session will take place at the participant's healthcare centre or at the physiotherapist's institute. The other sessions will be conducted using digital format, in accordance with the French ethics committee recommendations in the context of the COVID-19 pandemics. During each session, the physiotherapist follows up on the patient's at-home yoga practice and sets personal goals for the week ahead.

At-home yoga practice (P1 and P2)

Patients will be invited to practice 15 min of yoga at home from the day after their first supervised session and during the entire intervention, using '*My yoga guide*' and/or the audio guide as preferred. Postures can be practised from 1 to 10 (morning practice) or from 10 to 1 (evening practice) (table 2). Patients will receive collective motivational emails from the physiotherapist at weeks 2 and 4 during P2. On patient's request, personal support may be provided by phone or mail.

Patient education

Compliance to the programme and yoga sessions will be favoured and motivated using PE techniques (preparing the behaviour change before the intervention start at personalised check-ups, self-choice of personalised objectives and adapted integrative care…). The protocol is based on the implementation intentions model and the concept of perceived personal control,[39–41] using logbooks, emails and educational follow-ups. Moreover, the educational protocol follows the French national guidelines defined by the National Authority for Health (HAS).[42]

Control group

Participants in the control group will receive standard care, including all cancer-related treatments, but will be requested not to practice yoga during the study, that is, 12 weeks. At the end of the protocol (12 weeks), we will offer them the possibility to join a yoga group.

Discontinuation or modification of allocated interventions

No modification regarding the allocated intervention is planned. The intervention will be early discontinued on participant's request (withdrawal of consent) or by decision of the investigator or the physiotherapist or in case of major deviation from the protocol.

Regarding patients lost to follow-up, the investigator will do everything possible to contact the patient in order to identify the reason for not attending the visit and to determine their medical condition, including at least their vital status. Attempts to contact these patients will be documented in the patient's clinical record.

Concomitant care

All concomitant treatments will be allowed. Analgesic treatments intake during the study will be reported on the eCRF. Modifications of the HT regimen and molecules are not allowed 30 days prior to inclusion. Modifications of HT will be allowed during the course of the study and must be recorded in the eCRF.

Data collection

At inclusion, all patients will receive a first physiotherapy check-up where pain, forward flexibility and respiratory capacity will be evaluated. Different types of limitations requiring adjustments, such as mobility restriction, scar tightness, oedema, will be recorded. Blood sample collection will be performed and patients complete

Table 2 Detailed description of the supervised and at-home yoga sessions

Yoga sessions		
	Supervised by physiotherapist	Home practice
Period	Only during P1	During P1 and P2
No of sessions	Six group sessions First session in-person, five digital sessions	78 at-home yoga sessions
Duration of session	1 hour 30 min	≥15 min
Total duration	9 hours	9 hours (P1) and 10 hours 30 (P2)=19h30
Content	Welcome and handing-in of the previous week logbooks (5') Introduction (5') Sharing/exchanging of experiences (10') Philosophical perspective (10')* Postural yoga (asanas)+relaxation (30') (no 1–2 learning of '*My yoga guide*', no 3–6 introduction to other postures)† ► Ardha uttanasana (standing half forward bend) ► Parsva uttanasana (standing forward bend one leg forward) ► Utkatasana (squatting pose) ► Urdhva prasrta padasana (lying raised legs) ► Paschimatanasana (seated forward bend) ► Virabhadrasana 2 (warrior pose) ► Prasarita pada uttanasana (standing forward bend legs apart) ► Upavista konasana (seated forward bend legs apart) Breathing exercises: Pranayama (10') ► Ujjayi (throat breathing) ► Nadi sodhana (alternate nostril breathing) Sharing personal experience about session (10') Definition of personal educational goals (5') Conclusion (5')	10 postures in 'My Yoga Guide' 6 lying down and 4 standing up, with movements of flexion, extension, rotation and balance. No pressure on wrists. 1. Savasana (relaxation pose) and body scan 2. Savasana and hand rotation 3. Half side stretch 4. Jathara parivritti knees bent (lying twist) 5. Dvipada pitham (table pose) 6. Apanasana (lying knees to chest) 7. Utthita trikonasana 2 (rotation triangle pose) 8. Uttanasana (standing forward bend) 9. Utthita trikonasana 1 (lateral bend triangle pose) 10. Tadasana (standing straight) Option 1: Recommended as an aid for waking-up: sequence of postures from 1 to 10 (lying down first, then standing postures). Option 2: Recommended for evening relaxation: sequence of postures from 10 to 1 (standing first, then lying down postures)

* Mazet F. Yoga-Sutras de Patanjali. Albin Michel. 1991
† Mohan AG. Yoga for Body, Breath and Mind. Shambala Publications Inc. Massachusetts. 1993

questionnaires. At T1 and T2, physiotherapy check-ups will be performed and questionnaires completed. A second blood sample will be collected at T2. During each supervised session, the physiotherapist will report adherence to the session. Self-reported adherence to at home-yoga practice will be collected at T1 and T2 from the patients' logbooks. Data will also be collected from the shared educational check-up at T0, T1 and T2 for patients in the intervention group. All data will be collected using an eCRF by authorised personnel submitted to confidentiality of the patient's data.

Safety

All adverse events will be declared according to the current regulation of declaration of adverse events depending on the treatment to which they will be imputed. If patient safety is impacted during the trial, the investigator will inform the study sponsor immediately.

Data management, quality and monitoring

The sponsor will be responsible for managing the database. Data will be stored at the Biometrics Unit of the Montpellier Cancer Institute. The Ennov Clinical software will be used to design the eCRF and manage clinical data. Access to data and trial documents will be possible on reasonable request, after signing a data access agreement.

In compliance with the General Data Protection Regulation (GDPR), each patient will be identified with a registration number and the corresponding table will be encrypted and securely stored. To ensure data anonymisation, special precautions will be taken throughout the study.

Data monitoring will be performed in all participating centres, according to the monitoring plan decided by the sponsor. Data to be monitored will be decided accordingly, at least all signed informed consents will be verified. Data will be stored according to the current regulation.

Statistical methods

The planned analysis will be described in a statistical analysis plan before closing the database for final analysis (no intermediate analysis is planned). All analyses will be conducted on the intention-to-treat population, and the efficacy analysis will be conducted on the per-protocol population. Intergroup comparisons will be carried out for all baseline characteristics.

The primary endpoint, that is, the proportion of patients who have experienced a reduction of at least two points on the NPRS at 12 weeks, will be compared between the two groups using a χ^2 test (or the Fisher's exact test if the expected frequencies are less than 5).

A mixed-linear model will be used to evaluate the pain raw scores (a quantitative variable) over time. The variables included in the fixed part of the model will be the number of weeks and the intervention group, and their interaction will be also evaluated. The model will also be adjusted for analgesic medication. Random intercepts and random slopes will also be considered to take into account the time effect. The model coefficients will be estimated through maximum likelihood.

Secondary endpoints: In the intervention arm, we will describe the number of supervised and at-home yoga sessions per week and per period, along with the duration of at-home yoga sessions (minutes) for each patient. Descriptive statistics will include those mentioned below for quantitative variables.

QoL questionnaires EORTC QLQ-C30 and QLQ-BR23 will be analysed according to the EORTC guidelines; the SF-36 according to the SF-36 user manual and score interpretation guide. The HADS questionnaire will be described using the overall score and anxiety and depression scores. The individual's perceived self-efficacy (measured using GSES questionnaire) will be described by the overall score, and categories will be established based on the median score and/or tertiles.

The analysis of blood markers of inflammation will include a description of markers at baseline as well as a comparison of the evolution of these markers between the two arms. For each marker, the relative difference in the assay at 12 weeks compared with baseline will be calculated.

Quantitative outcomes, including the scores from different questionnaires, will be described using the mean, SD, median and range. Two group comparisons will be performed at T2, using the Student's t-test (comparison of means between two samples following a normal distribution) or the Wilcoxon rank-sum test (comparison of distributions). Moreover, the evolution of variables of interest over time will be analysed using a mixed-linear model.

Qualitative outcomes will be described by frequency and percentages for each modality. The χ^2 test will be used for the comparison of proportions (or Fisher's exact test if the expected frequencies are less than 5).

In case of missing data, no imputation method will be used. The statistical analysis will be conducted using the Stata V.16 software (StataCorp).

Responsibilities

The study sponsor, Montpellier Cancer Institute (ICM), is responsible for the study design and management, for obtaining all authorisations (Persons Protection Committee, National Agency for Medical Security), study insurance and conformity to ethics. It will also declare to these authorities the inclusion period beginning and end, produce the final study report, inform the competent authorities of the trial results, and store all study-related documents for at least 15 years after the study. ICM is also responsible for the quality of data, their analysis, confidentiality and storage.

The study investigators are responsible for study participation according to the Good Clinical Practices and respect of the study protocol, collect the patient's signed informed consent after proper patient information and collection of data.

DISCUSSION

The SKYPE 2 study is a follow-up of the previously published feasibility study, SKYPE.[28] HT side effects have a real impact on patients' QoL and treatment efficacy.[7] Various studies showed that yoga can decrease pain[15 16 43–46] and can act on stress-related symptoms, but also fatigue.[21 46–48] Moreover, stress and anxiety are known to impact inflammation, and recent studies have shown the effect of yoga on inflammation.[18–20]

The originality of our programme is the introduction of the PE approach. Indeed, our theory-based multifaceted intervention foresees, anticipates and optimises at-home yoga practice. Individual educational check-ups at T0, at T1 and T2 are performed. At each supervised session, a personal follow-up of at-home practice is realised. At the end of each session, patients share personal experience and set personal educational objectives for the week ahead. The physiotherapist adapt at-home practice if needed. In addition, physiotherapists trained in yoga will supervise sessions. The sponsor physiotherapist produced all tools given to the patients to guide their at-home yoga practice, and physiotherapy check-ups will be performed at the end of each period. Yoga sessions and postures are taught and adapted to the physical limitations of the patients because supervised by healthcare professionals with experience in these patients undergoing HT.

The SKYPE pilot study highlighted the special care required for assessment of the study primary endpoint, decrease of pain due to HT.[28] One given question was systematically asked to all patients 'Please grade your maximum pain in the past week, taking into account only the pain due to HT'. It was important that the evaluator would insist on the link to HT and was careful to the answer given, which sometimes needed correction, especially in patients with arthrosis for example. A special

attention will be addressed to this point during follow-up visits during the SKYPE 2 study. Furthermore, we added the BPI questionnaire to better qualify and assess pain. We will also assess the inflammatory response and try to correlate it with patients' pain evaluation and questionnaires. The overall effect of an inflammatory response is dictated by the balance between proinflammatory and anti-inflammatory mediators and will be analysed patient per patient and globally. Djalilova *et al* reported a significant effect of yoga on inflammation in five studies, offering a total of 1000–2000 min of yoga practice.[20] Our study offers a total of 1710 min of supervised and at-home yoga practice. Furthermore, we wish to evaluate the effect of respiratory exercises (pranayama) on respiratory capacity.[49]

Because of the COVID-19 pandemic context, the ethics committee required for the SKYPE 2 study that the supervised physiotherapy-yoga sessions, except for the first session, were held in digital format and not in person as we had first planned. An ongoing study assesses a digital yoga programme on its impact on fatigue and pain in patients treated with HT.[50] The digitally distributed yoga sessions are probably differently accepted by the patients as regards to facility and at-home well-being. From our point of view, it will probably make inclusions easier than for the previous SKYPE study during which we faced refusals of participation because of the distance from home to study centre or patients' non-availability. In addition, group formation will likely be facilitated by the digital format, as it was not easy to find six patients included in the study at the same period and available at the same time to start a new yoga group. Only the first session is performed in person, and we advised against a complete digital programme. In our opinion, this first in-person session is crucial to create mutual trust between the physiotherapist and the patients before digital sessions. Patient's satisfaction questionnaire includes open questions and the patients will give their feeling towards such digital yoga sessions. Eventually, six French centres participate in the study, including physiotherapists of the cancer institutes and private practitioners. This study is a very good opportunity to tighten the hospital-city bonds and include private physiotherapists in clinical research. This will also increase awareness and training of physiotherapists regarding patient educative approaches and techniques, which seem to give promising results.

Ethics approval and dissemination

A patient representative with personal experience of breast cancer gave valuable opinions during study conception about patients' participation. The study was designed in accordance with the current regulation. The study is conducted according to the Good Clinical Practices. All patients are informed of the study procedures, benefits and risks, and her informed consent is signed before the beginning of the study, at the inclusion visit by the oncologist or physiotherapist. Participants are free to withdraw from the study at any time during the trial.

Data are collected according to the law 'Informatique et Libertés' no 78-17 (6 January 1978), modified by the law relating to the protection of personal data in accordance with the GDPR (UE regulation 2016/679, 25 May 2018).

The study was approved by the Ethics Committee (CPP Ile de France 8 on 22 June 2020) and received the ID-RCB 2020-A00783-36 number. It was declared on ClinicalTrials.gov, NCT number NCT04457895.

In the event of substantial modification, the request will be sent by the sponsor to the ethics committee for an opinion. On receipt of the favourable opinion, the sponsor will send the amended version of the protocol to all investigators.

The results of this study will be disseminated to participants and to healthcare professionals. Presentations will be given in national and international conferences and the results published in peer-reviewed journals.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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