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Efficacy of a Physiotherapy Yoga and Patient Education program for breast cancer patients with hormone therapy-induced pain: a multicentre randomized study protocol (SKYPE 2)

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Abstract

Introduction

Among complementary therapies, yoga has shown efficacy on reduction of fatigue, anxiety, pain due to hormone therapy and inflammation level in breast cancer patients. Personalized patient education programs increase engagement and motivation, and induce effective behavioral changes in patients. The SKYPE program, a combined intervention of physiotherapy, yoga and patient education, showed promising efficacy on hormone therapy-induced pain in a previous pilot study.

Methods and analysis

This multicenter randomized study will compare efficacy on pain reduction of the SKYPE program to standard care for breast cancer patients reporting osteoarticular pain due to hormone therapy, with a score ≥ 4/10 on the Numeric Pain Rating Scale. 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 6 weekly 90-min educational yoga group sessions supervised by physiotherapists (Period 1). They will also engage in daily at-home 15-minute yoga sessions for the 12 weeks of the program (Periods 1 and 2). Pain will be evaluated at baseline and after each period in a physiotherapy check-up.

Ethics and dissemination

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

Trial registration: ClinicalTrials.gov Identifier: NCT04457895; Protocol V4.0_20220601.

Strengths and limitations

- The SKYPE 2 protocol is a randomized multicenter study, including 108 patients, evaluating an innovating theory-based intervention combining physiotherapy, yoga and patient education.
- The previous pilot study SKYPE validated the feasibility of this combined protocol; its efficacy may allow better compliance to hormone therapy treatment.
- Physiotherapists trained in both yoga and patient education supervise the yoga sessions.
- Participation for patients living far from healthcare centers is made possible by the digital format of the yoga sessions.
- Self-reporting of home practice by the patients is one of the study limitations.

INTRODUCTION

Estrogen-positive breast cancers account for 65 to 75% of all early breast cancer cases, and require adjuvant hormone therapy after initial treatment,[1] usually administered for a long time period, most often 5 years, and up to 10 for some patients.[2] During treatment, as much as 50% of women report osteoarticular and/or musculoskeletal pain.[3,4] Hormone therapy side effects have thus become a real issue because of their consequences on the patients' quality of life (QoL), but also on treatment efficiency and survival when they induce dose reductions or premature treatment arrest.[5–11]

Complementary therapies such as acupuncture, hypnosis or yoga, have become more and more popular these last years. They are eventually chosen by 48 to 80% of breast cancer patients according to the published guidelines for use of integrative therapies and supportive care in patients treated for breast cancer.[12] These complementary treatments were recently endorsed by the American Society of Clinical Oncology (ASCO).[13]

A review comparing efficacy of various therapies to decrease osteoarticular pain due to hormone therapy concluded to the highest efficacy of anti-inflammatory treatments, paracetamol and yoga.[14] The short-term effects of yoga practice on anxiety, stress, fatigue and quality of life have been widely demonstrated.[15–18] Some studies suggest that yoga practice could have a beneficial effect on the inflammation level.[19–21] Specifically, the feasibility of a yoga program (two 90 minute-sessions twice a week for 12 weeks) was reported in 2014 with a beneficial effect on inflammation and fatigue.[20]

However, the mechanisms of hormone therapy-induced pain are not completely described yet, and yoga interventions may influence inflammation through their effects on the level of a wide range of pro- and anti-inflammatory cytokines.[21]

Yoga has also shown in some studies a benefit in terms of pain reduction in patients with breast cancer treated with hormone therapy.[22,23] These studies mostly assessed supervised yoga programs, and only few described programs with additional at-home yoga practice.[16,20,22,24] However, these programs often had light home-practice or short-term follow-up.

Osteoarticular and/or musculoskeletal pains are specifically the secondary effect on which physical therapy may have a real benefit. It thus appeared innovative to propose a yoga program supervised by physiotherapists. In addition, as for such a care program to be effective, long-term behavioral changes are necessary, we added to this combined physiotherapy-yoga program a patient educational project. Indeed, autonomy within the context of the intervention, choice of one's goal and modules, and personalized educational follow-up will allow increase of engagement and motivation and induce effective behavioral changes.[25,26] Physical activity interventions meeting these requirements have been evaluated and were successful in increasing physical activity levels.[27,28]

We recently conducted a monocentric pilot study, SKYPE,[29] using the Medical Research Council framework for developing complex interventions[30,31] and proposed a theory-based multifaceted program to the patients. Patient education was completely integrated in the supervised yoga sessions and patient education techniques were used to guide the patients towards behavioral change in addition to the at-home tools given to the patients. We included 24 algic breast cancer patients treated with hormone therapy, which showed promising results with 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.[29] Our results confirmed such integrative and educational care meets a real need for women with breast cancer treated with hormone therapy. We now propose a multicenter randomized study to compare the efficacy on pain reduction of the SKYPE program, a combined physiotherapy-yoga program with integrated patient education care, to a control group (standard care) for breast cancer patients treated with hormone therapy reporting osteoarticular and/or musculoskeletal pain.

METHODS AND ANALYSIS

Study design and setting

SKYPE 2 is a randomized controlled multicenter trial. Six French hospitals participate in the study: the Montpellier Cancer Institute, the Pays Basque Institute of Oncology (Bayonne), the West-France Cancer Institute (Angers), the Lorraine Cancer Institute (Nancy), the Nîmes University Hospital and the Libourne Hospital. The centers selected for participation in the study are all oncology centers with high experience in hormone therapy treatment for breast cancer patients. To participate in the study, physiotherapists are trained in postural yoga (minimum of 9 days training, with certification) and receive a patient education training before the beginning of the study.

Eligibility criteria

The patients' inclusion criteria are as follows: adult patients (≥ 18 years) operated for an early, non-metastatic, breast cancer, ongoing adjuvant treatment with hormone therapy (either tamoxifen or aromatase inhibitor), with no treatment modification in the 30 days prior inclusion, and with osteoarticular and/or musculoskeletal pain due to hormone therapy ≥ 4 on the Numeric Pain Rating Scale (NPRS).[32] The previous treatment (surgery, adjuvant chemotherapy or radiotherapy) must have ended at least 2 months prior to inclusion; all included patients will be informed and sign an informed consent prior to any study procedure. Non-inclusion criteria are the following: need of specific care for chronic rheumatological pain, regular yoga practice in 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.

Study objectives

The primary objective of the SKYPE 2 study is to compare the efficacy of the combined physical therapy, yoga and patient education intervention *versus* standard care on pain reduction in the treatment of osteoarticular and/or musculoskeletal pain due to hormone therapy in patients with breast cancer.

Secondary objectives are to describe:

1. The evolution of osteoarticular and/or musculoskeletal pain characteristics related to hormone therapy.
2. Patient adhesion to the yoga sessions and self-practice, and the reasons for adhesion or non-adhesion to yoga self-practice.
3. Quality of life, fatigue, anxiety and depression.
4. Hormone therapy treatment and patient's compliance.

And to assess:

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

Study endpoints

The primary endpoint will be the proportion of patients with a 2-point reduction on the Numeric Pain Rating Scale (NPRS) of osteoarticular and/or musculoskeletal pain due to hormone therapy treatment between inclusion and the end of treatment.[32]

Secondary endpoints, related to secondary objectives, will be the following:

1. The Brief Pain Inventory will be used to describe the evolution of osteoarticular and/or musculoskeletal pain characteristics.[33]
2. Logbooks filled by the patients will report patient's adhesion to sessions and home-practice, and reasons for practice or non-practice (cf Supplementary material).
3. Quality of life will be measured by the EORTC QLQ-C30,[34] QLQ-BR23 and SF-36[35] questionnaires ; fatigue, by the fatigue dimension of the EORTC QLQ-C30 questionnaire and the vitality dimension of the SF-36 questionnaire; anxiety and depression by the HADS scale,[36,37]
4. Hormone therapy treatments and compliance will be self-reported during assessments.
5. Forward-flexion flexibility, defined as the distance between the fingertips and the floor, will be measured in centimeters with a ruler.

6. Respiratory capacity will be measured with a spirometer (Forced Expiratory Volume in 1 second (FEV1), liters Forced Vital capacity (FVC), Tiffeneau FEV1/FVC, liters peak expiratory flow (PEF)).
7. Self-competence feeling will be assessed with the GSES questionnaire.[38]
8. Patient's satisfaction will be assessed using a 7-items Likert scale ranging from "extremely unsatisfied" to "extremely satisfied".
9. Blood samples of circulating inflammatory biomarkers to assess the inflammatory biological profile.

Sample size

The sample size calculation was based on the comparison of the proportion of patients who will report a reduction of at least 2 units of their osteoarticular and/or musculoskeletal pain due to hormone therapy between baseline (T0) and end of study (T2) in each group, assessed on the Numeric Pain Rating Scale from 0-10. Indeed, a reduction of two units measured on the Numerical Pain Rating Scale is considered as the minimal clinically important difference in chronic musculoskeletal pain intensity.[39] 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 with 10% of potentially non-evaluable patients, 108 patients are to be included in the study, 54 patients per group.

Patient timeline and study flow diagram

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

Randomization

After the patient has given her informed consent for study participation, if all inclusion and non-inclusion criteria are met, the investigator proceeds to patient registration and randomization via an eCRF. The patients are randomized (1:1 ratio) in a web-based digital portal ("CSOnline") to the experimental group participating in the combined intervention of physiotherapy and yoga with patient education or to the control group with standard care without intervention (Figure 1). Randomization is

stratified according to the study centre, painkillers intake by the patient (yes/no) and intensity of hormone therapy-induced pain on a 0 to 10 numerous scale (< or ≥ 6).

The study is an open study; no blinding is possible due to the type of intervention.

Physiotherapy-Yoga-Patient Education intervention

Patients in the intervention group undergo a 90-min educational yoga session per week for 6 weeks, supervised by a physiotherapist trained in postural yoga. As pain is usually felt by the patients in distal joints, yoga postures have been chosen as to avoid putting the body weight on the wrists. As it is often reported in yoga sessions, patients are encouraged to adapt the postures proposed to their limits and physical capabilities. The day after the first supervised yoga session, they start a daily 15-min at-home yoga session using the "My Yoga Guide" leaflet and a yoga audio guide. The intervention is carried out over 12 weeks, separated into 2 periods, P1 (6 weeks): supervised yoga sessions and at-home yoga practice, and P2 (6 weeks): at-home yoga practice only (Figure 1).

Supervised sessions (P1): patients benefit from one 90-minute yoga session per week supervised by a trained physiotherapist, in groups of 2 to 5 patients. The first session takes place at the participating center or at the physiotherapist's institute, followed by 5 digital yoga sessions as required by the French ethics committee in the context of the Covid pandemics. Each patient receives a learning kit with the "*My yoga guide*" booklet describing 10 illustrated postures, and a 15-minute audio yoga session guide sent by email or copied on a USB stick. A logbook is also provided to report daily on the regularity and duration of at-home yoga practice, and reasons for practice or non-practice. As patient education is essential in the program, each patient will set-up with the physiotherapist, at each session, personal objectives for the week to come. A patient education follow-up is performed at each session. The supervised sessions are detailed in "*The Physiotherapist's Guide book*" to ensure the homogeneity and reproducibility of the intervention. The first two sessions are dedicated to learning the at-home yoga practice based on "*My yoga guide*" then 2 to 3 new postures are introduced each week. The different steps of the sessions are detailed in Table 1.

At-home yoga practice (P1 and P2): patients are invited to practice 15 minutes of yoga at home from the day after their first supervised session and during all P1 and P2 periods, using "*My Yoga Guide*" and/or the audio guide as preferred. Postures can be practiced from 1 to 10 (morning practice) or from

10 to 1 (evening practice) (Table 1). Patients receive motivational collective e-mails from the physiotherapist at week 2 and 4 during P2. On patient's request, personal support may be provided by phone or mail.

Compliance to the program and yoga sessions are favoured and motivated using the patient education techniques (personalized check-up, self-choice of personalized objectives, adapted integrative care…) based on the Intention Implementation Model and the concept of perceived personal control [40–42] and with logbooks, e-mails and follow-up.

Control group

The control group patients receive standard care with no yoga program. They are invited to participate in yoga sessions after the end of their participation in the study (3 months).

Discontinuation or modification of allocated interventions

No modification regarding the allocated intervention is planned. The intervention will be early discontinued in case of participant request (withdrawal of consent) or by the 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 concurrent treatments are allowed. Analgesic treatments intake during the study are reported on the pages of the electronic case report form (eCRF) provided for this purpose. Modifications of the hormone therapy regimen and molecules are not allowed 30 days prior inclusion. Then, during the study, modifications of hormone therapy are allowed and must be collected in the eCRF. For patients of the control group, no yoga sessions are allowed during the 12-week study period.

Data collection

At inclusion, for all patients, pain and respiratory capacity are evaluated, a first physiotherapy check-up is performed, as well as a blood sample, and questionnaires are given to the patients. At the end of periods 1 and 2, pain and respiratory capacity are evaluated, physiotherapy checks 2 and 3 are performed

and questionnaires are completed; a second blood sample is performed after period 2 only. At each supervised session the physiotherapist reports adhesion to the session. Self-reported adhesion to at home-yoga practice is collected at the end of period 1 and 2 from the patients' logbooks. Data is also collected from the shared educational check-up at inclusion and after periods 1 and 2 for patients in the intervention group. All data are collected using an e-CRF by authorized 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. At declaration, it must be specified that the patient is participating in the SKYPE 2 trial (title and IRB number). In case patient safety should be impacted in the context of the trial, the investigator will inform the study sponsor without delay.

Data management, quality and monitoring

The sponsor will be responsible for managing the database, and the data will be stored at the Data processing center, Biometrics Unit of the Montpellier Cancer Institute. To design case report forms and manage clinical data, the Ennov Clinical® software will be used. Access to data and trial documents will be made possible upon 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 anonymization, special precautions will be taken throughout the study.

Data monitoring will be performed in all participating centers, 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 the database is closed for final analysis (no intermediary statistical analysis is planned). All analyses will be conducted on the intention-to-treat population, and the efficacy analysis will also be conducted on the per-protocol population. Intergroup comparisons will be carried out for all baseline characteristics.

The primary endpoint, efficacy of the intervention, will be analyzed using a chi-square test (or the Fisher's exact test if the expected frequencies are less than 5) to compare the rate of patients with pain reduction in the two groups. In case of missing data no imputation method will be used. The statistical analysis will be conducted using the Stata 16 software (StataCorp LP, College Station, TX).

Responsibilities

The study sponsor, ICM, is responsible for the study design and management, for obtaining all study authorizations (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 presented here is a follow-up of the previously published feasibility study, SKYPE.[29] Hormone therapy side-effects have a real impact on patients' treatment efficacy and patients' quality of life, and osteoarticular pain[3,9] during aromatase inhibitor treatment was shown to be associated with premature discontinuation of treatment.[7] Yoga was shown in many studies to decrease this pain[22,23,43–46] and effect on stress-related symptoms, fatigue have also been published.[15,24,46,47] Moreover, decrease of stress and anxiety is known to impact inflammation, and recent studies have shown an effect of yoga on inflammation.[19,20] However, these studies evaluating the effect of yoga on osteoarticular and/or musculoskeletal pain have mostly assessed programs with only supervised yoga sessions,[23,48] programs with limited yoga home practice (twice a week), with short periods (4 or 6 weeks),[22,24] or in women undergoing chemotherapy. The yoga programs proposed in these studies were yoga sessions supervised by yoga teachers. In our study, we chose to combine physiotherapy and yoga sessions and the group yoga sessions will be supervised by physiotherapists trained in yoga. In the same way, 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. This allows yoga sessions and postures to be taught and adapted to the physical limitations of the patients, as supervised by healthcare professionals with experience in these patients undergoing hormone therapy.

Concerning home practice, previous published programs, as for our interventions, used tools given to the patients (DVD, audio guide, booklet)[16,24] but patients' adhesion is not always reported.[16] Another major addition to our program, compared to published interventions, is the addition of the patient education project to the combined physiotherapy and yoga intervention. Indeed, our theory-based multifaceted intervention foresees, anticipates and optimizes at-home yoga practice. Individual educational check-ups at inclusion and at the end of periods 1 and 2 are be performed. At each supervised session, personal follow-up of at-home practice is shared. At the end of the sessions, personal experience about the session are expressed and personal educational objectives are set-up for the week to come, and to adapt at-home practice if needed.

The SKYPE pilot study highlighted the special care required for assessment of the study primary endpoint, decrease of pain due to hormone therapy treatment.[29] 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 hormone therapy". It was important that the evaluator would insist on the link to hormone therapy, and was careful to the answer given, which sometimes needed correction, especially in patients with arthrosis for example. Special attention on this point will be insisted on during participating centres set-up visits in this SKYPE 2 multicentre study. Furthermore, we have added the Brief Pain Inventory questionnaire to better qualify and assess pain in all patients.

Due to 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 program on its impact on fatigue and pain in patients treated with hormone therapy.[49] 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 6 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 program. This first in-person session is, in our view, essential for bonds to be created between the physiotherapist and the patients before the following digital sessions. The patient satisfaction questionnaire includes open questions and the patients will give their feeling towards such digital yoga sessions; analysis of these answers will be of interest. Last, six French centres participate in the present study, with both 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, as it is rare in France for them to participate. It will also increase awareness and training of physiotherapists to 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 is collected according to the law "Informatique et Libertés" n°78-17 (January 6, 1978), modified by the law relating to the protection of personal data in accordance with the General Data Protection Regulation (GDPR) (UE regulation 2016/679, May 25, 2018).

The study was approved by the Ethics Committee (CPP Ile de France 8 on June 22, 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. Upon 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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Author contributions

KF, AS, WJ are responsible for conception and design of the work and the writing of the protocol. MT participated in the discussion about pain assessment. MD participated in the conception and design of the work as patient representative and moreover she identified how the biological analysis will be proceeded. MJ is responsible for methodological and statistical design and defined the planned analyses. LM is responsible for legal, ethics and administrative aspects. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

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

Availability of data and materials

The datasets used and analyzed during the current study will be available from the corresponding author upon reasonable request.

Consent for publication

Not applicable

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TABLES

Table 1 Study assessments and outcome evaluations

	T0	P1						T1	P2						T2
	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 treatment visit
Inclusion / non-inclusion criteria	X														
Informed signed consent	X														
Patient inclusion	X														
Randomization	X														
Medical history	X														
Physiotherapy check-ups	X							X							X
Educational check-ups (experimental group only)	X							X							X
Questionnaires (GSES, QLQC30, BR23, HADS, SF36, BPI)	X							X							X
Blood sample	X														X
Reminder e-mail (experimental group only)										X		X			
Adverse events	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
Supervised yoga session (experimental group only)		90-min supervised yoga session													
At-home yoga practice (experimental group only)		One daily 15-min at-home session							One daily 15-min at-home session						

D: Day – W: Week

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
Number of sessions	6 group sessions First session in-person, five digital sessions	78 at-home yoga sessions
Duration of session	1 h 30 min	≥ 15 min
Total duration	9 h	9 h (P1) and 10 h 30 (P2) = 19h30
Content	Welcome and handing-in of the previous week logbooks (5') Introduction (5') Sharing/exchanging of experiences (10') Philosophical perspective (10') [1] Postural yoga (Asanas) + relaxation (30') (no 1-2 learning of "My Yoga guide", no 3-6 introduction to other postures) [2] • **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.[2] 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)

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

Figures and tables study protocol SKYPE 2

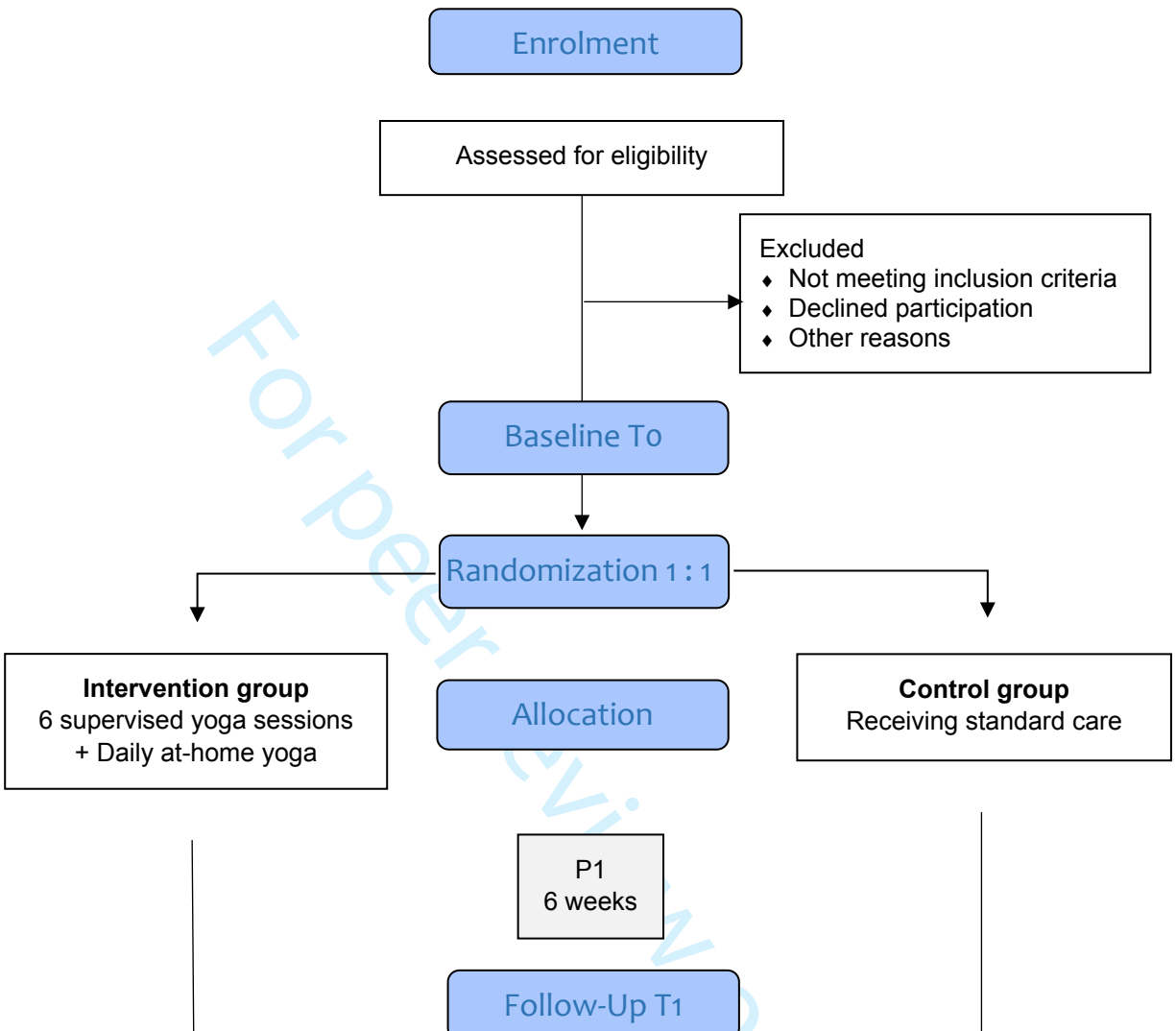

Figure 1 Study flow diagram

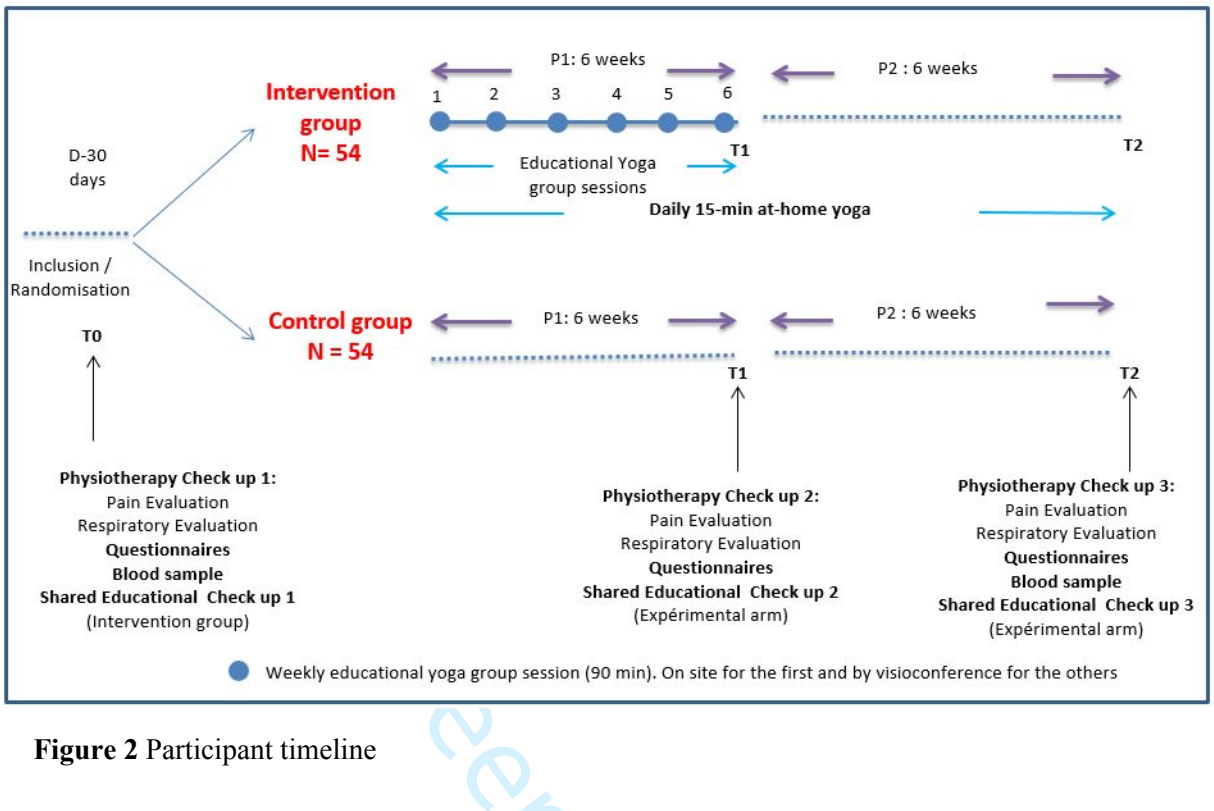

Figure 2 Participant timeline

Patient's logbook

SEANCES QUOTIDIENNES DE YOGA A DOMICILE PERIODE 1 SEMAINE N°1 du __/__/20__ au __/__/20__		
	Séances réalisées	Prises d'antalgiques
J1 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J2 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J3 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J4 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J5 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J6 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J7 (jj/mm/aaaa) __/__/20__	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)

Si une ou plusieurs séances ont été réalisées merci de cocher la ou les raisons :

- ☐ J'en retire un bénéfice personnel
- ☐ Je pense ou je constate qu'elles sont utiles
- ☐ Je pense que cela fait partie de mon traitement
- ☐ Je fais confiance à l'équipe soignante
- ☐ Pour faire avancer la recherche
- ☐ Pour avoir un suivi régulier
- ☐ Je n'ai pas osé refuser
- ☐ Mon entourage m'a convaincu de les faire
- ☐ Autres, préciser.....

Si une ou plusieurs séances n'ont pas été réalisées merci de cocher la ou les raisons :

- ☐ J'ai oublié
- ☐ J'ai été trop fatiguée
- ☐ Je manque de temps
- ☐ J'ai eu trop de douleurs
- ☐ Je n'ai pas eu envie
- ☐ J'ai peur de mal faire
- ☐ Je n'en vois pas l'intérêt
- ☐ Je manque d'information sur quand et comment le faire
- ☐ Autres, préciser.....

Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)	Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)
J1			J5		
J2			J6		
J3			J7		
J4					

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p.2
	2b	All items from the World Health Organization Trial Registration Data Set	Protocol More information can be provided if wished by the editor
Protocol version	3	Date and version identifier	Abstract p.2
Funding	4	Sources and types of financial, material, and other support	Funding p.14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page p.1 and Authors' contribution p.14
	5b	Name and contact information for the trial sponsor	p. 1 and Responsibilities p. 11

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Responsibilities p.11 and Funding p. 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Responsibilities p.11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction p.3-4
	6b	Explanation for choice of comparators	Introduction p.3-4
Objectives	7	Specific objectives or hypotheses	Introduction p.3-4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction p.3-4 and Study design p.4 and Randomization p.7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Study design and setting p.5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Eligibility criteria p. 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Intervention p. 8 data collection p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Concomitant care section p.9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Objectives and endpoints, p.5-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2 and Table 1 and text p.7-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample size section p.7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Sample size p7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Randomization section p.7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Randomization section p.7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Patient timeline p7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA p. 7

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, no blinding possible
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Endpoints p. 6-7 Data collection p. 9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8-9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Data collection p.9 Data Management p.10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Statistical methods p.10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA, no subgroup analyses are planned
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Statistical methods p.10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Data management and monitoring p.10

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA, no interim analyses scheduled
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Safety section p.10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA, no auditing scheduled
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics approval and dissemination p. 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics approval and dissemination p. 13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Patient timeline p.7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA, no ancillary study
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Data collection p 9 Ethics and Dissemination p13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Funding p.14 Competing interest p.15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics p.13 Responsibilities p.11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and Dissemination p.13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol More information can be provided if wished by the editor
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA, no such plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material More information can be provided if wished by the editor
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of a Physiotherapy Yoga and Patient Education program for breast cancer patients with hormone therapy-induced pain: a multicentre randomised study protocol (SKYPE 2)

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Efficacy of a Physiotherapy Yoga and Patient Education program for breast cancer patients with hormone therapy-induced pain: a multicentre randomised study protocol (SKYPE 2)

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Key words: breast tumours, rehabilitation medicine, complementary therapy, physical therapy, pain management, health education, yoga.

Word count: 4324 words

Tables: 2

Figures: 2

Abstract

Introduction

Osteoarticular pain is experienced by approximately 50% of breast cancer patients under hormonal 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. Personalized patient education programs increase engagement and motivation, and induce effective behavioural changes. The SKYPE program, 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 hypothesized that using theory-based patient education favour learning and practicing 15 minutes 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 program on pain reduction compare to standard care in breast cancer patients 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 one weekly educational yoga session of 90 minutes for six weeks, supervised by physiotherapists (Period 1). They will also perform daily at-home 15-minute 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 June 22, 2020). The results will be disseminated to patients and healthcare professionals, and published in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov Identifier: NCT04457895; Protocol V4.0_20220601.

Strengths and limitations

- The SKYPE 2 study, based on promising results of a pilot study, is a randomised multicentre trial and will include 108 patients.
- To our knowledge, the SKYPE protocol is the first to propose an integrated yoga program, supervised by physiotherapists, with a theory-based patient education approach, in the aim to enhance patients' autonomy and induce a sustainable behaviour 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 program, *i.e.* physiotherapy, yoga, and patient education intervention.

INTRODUCTION

Estrogen-positive breast cancers account for 65 to 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 to 80% of breast cancer patients (BCP) use them as integrative therapies and supportive care.[12] Moreover, they were recently endorsed by the American Society of Clinical Oncology (ASCO).[13]

A review comparing efficacy of various therapies to decrease osteoarticular pain due to hormone therapy 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 pro- and anti-inflammatory cytokines.[18–20] For example, Kiecolt-Glaser *et al*. reported a yoga program in breast cancer survivors, consisting of one 90 minute-session twice per week, for 12 weeks, and showed benefits on inflammation and fatigue.[19] However, these studies mainly used supervised yoga programs, and few of them associate it with at-home practice. Moreover, these program 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 (DVD, 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 program in the aim to improve long-term patient behavioural changes. We hypothesised that a personalized educational program, 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,[28] using the Medical Research Council framework for developing complex interventions.[29,30] Patient education (PE) was completely integrated in 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 BCP 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 patient.[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 program, supervised by physiotherapists, to enhance patients' autonomy and allow a behaviour change in order to include daily yoga practice in their lives. We now propose to evaluate our program in a multicentre randomised study on BCP treated with HT and reporting osteoarticular and/or musculoskeletal pain. We will assess the efficacy of the SKYPE program[28] on pain reduction , and compare it to 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 BCP : the Montpellier Cancer Institute, the Pays Basque Institute of Oncology (Bayonne), the West-France Cancer Institute (Angers), the Lorraine Cancer Institute (Nancy), the Nîmes University Hospital and the Libourne Hospital. Physiotherapists will follow a 9-days 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.

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 one 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; all 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 weeks program combining physical therapy, yoga and PE intervention on reduction of osteoarticular and/or musculoskeletal pain due to HT in BCP 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). Timeframe 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 Numeric Pain Rating Scale (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 practicing or not in logbooks (Supplemental material).
3. QoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30,[33] QLQ-BR23 and SF-36[34] questionnaires ; 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.
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) indicates 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 second (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 (PEF) 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 7-items Likert scale at T1 and T2. The items are: extremely satisfied, very satisfied, little satisfied, not satisfied/not unsatisfied, little unsatisfied, very unsatisfied, 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, 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 2 units of their osteoarticular and/or musculoskeletal pain due to HT between T0 and T2 in each group, assessed on the NPRS from 0-10. 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 Figure 1 and Figure 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 painkiller intake (yes/no) and the intensity of HT-induced pain on a 0 to 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-Patient Education 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 patient education, 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 six-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 practicing 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 program and a 15-minutes audio yoga session guide sent by email or copied on a USB stick. In addition, the physiotherapist will provide a logbook to document at-home daily practices, their duration, and the reasons for practicing or not. A specific section is also dedicated to monitor painkiller intake (drug, dose and duration).

Supervised sessions (P1)

During six weeks, patients will follow a training yoga program and attend one weekly 90-minute yoga session under the supervision of a physiotherapist expert in postural yoga, in groups of 2 to 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 to 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 others sessions will be conducted using digital format, in accordance with the French ethics committee recommendations in the context of the COVID pandemics. During each session, the physiotherapist follows up on the patient's yoga at-home practice and sets personal goals for the week ahead.

At-home yoga practice (P1 and P2)

Patients will be invited to practice 15 minutes 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 practiced from 1 to 10 (morning practice) or from 10 to 1 (evening practice) (Table 2). Patients will receive collective motivational e-mails from the physiotherapist at week 2 and 4 during P2. On patient's request, personal support may be provided by phone or mail.

Patient Education

Compliance to the program and yoga sessions will be favoured and motivated using PE techniques (preparing the behaviour change before the intervention start at personalized check-ups, self-choice of personalized objectives, adapted integrative care…). It is based on the intention implementation model and the concept of perceived personal control [39–41], using logbooks, e-mails and educational follow-up. Moreover, the protocol follows the French national guidelines defined by 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, *i.e.* 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 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 a eCRF by authorized 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 upon 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 anonymization, 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, *i.e.* the proportion of patients who have experienced a reduction of at least 2 points on the NPRS at 12 weeks, will be compared between the two groups using a chi-square 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 to baseline will be calculated.

Quantitative outcomes, including the scores from different questionnaires, will be described using the mean, standard deviation (SD), the 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 Chi-square 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 16 software (StataCorp LP, College Station, TX).

Responsibilities

The study sponsor, ICM, is responsible for the study design and management, for obtaining all authorizations (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 an effect of yoga on inflammation.[18–20]

The originality of our program is the introduction of the PE approach. Indeed, our theory-based multifaceted intervention foresees, anticipates and optimizes 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 pro- 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 minutes of yoga practice.[20] Our study offers a total of 1710 minutes 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 program 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 6 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 program. 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 is collected according to the law "Informatique et Libertés" n°78-17 (January 6, 1978), modified by the law relating to the protection of personal data in accordance with the General Data Protection Regulation (GDPR) (UE regulation 2016/679, May 25, 2018).

The study was approved by the Ethics Committee (CPP Ile de France 8 on June 22, 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. Upon 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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Author contributions

KF, AS, WJ are responsible for conception and design of the work and the writing of the protocol. MT participated in the discussion about pain assessment. MD participated in the conception and design of the work as patient representative and moreover she identified how the biological analysis will be proceeded. MJ is responsible for methodological and statistical design and defined the planned analyses. LM is responsible for legal, ethics and administrative aspects. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

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

Availability of data and materials

The datasets used and analysed during the current study will be available from the corresponding author upon reasonable request.

Consent for publication

Not applicable

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TABLES

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 treatment visit
Inclusion / non-inclusion criteria	X														
Informed signed consent	X														
Patient inclusion	X														
Randomization	X														
Medical history	X														
Physiotherapy check-ups (including NRPS)	X							X							X
Educational check-ups (experimental group only)	X							X							X
Questionnaires (GSES, QLQC30, BR23, HADS, SF36, BPI)	X							X							X
Blood sample	X														X
Reminder e-mail (experimental group only)										X		X			
Adverse events	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
Supervised yoga session (experimental group only)		90-min supervised yoga session													
At-home yoga practice (experimental group only)		One daily 15-min at-home session							One daily 15-min at-home session						

D: Day – W: Week

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
Number of sessions	6 group sessions First session in-person, five digital sessions	78 at-home yoga sessions
Duration of session	1 h 30 min	≥ 15 min
Total duration	9 h	9 h (P1) and 10 h 30 (P2) = 19h30
Content	Welcome and handing-in of the previous week logbooks (5') Introduction (5') Sharing/exchanging of experiences (10') Philosophical perspective (10') [1] Postural yoga (Asanas) + relaxation (30') (no 1-2 learning of "My Yoga guide", no 3-6 introduction to other postures) [2] • **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.[2] 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)

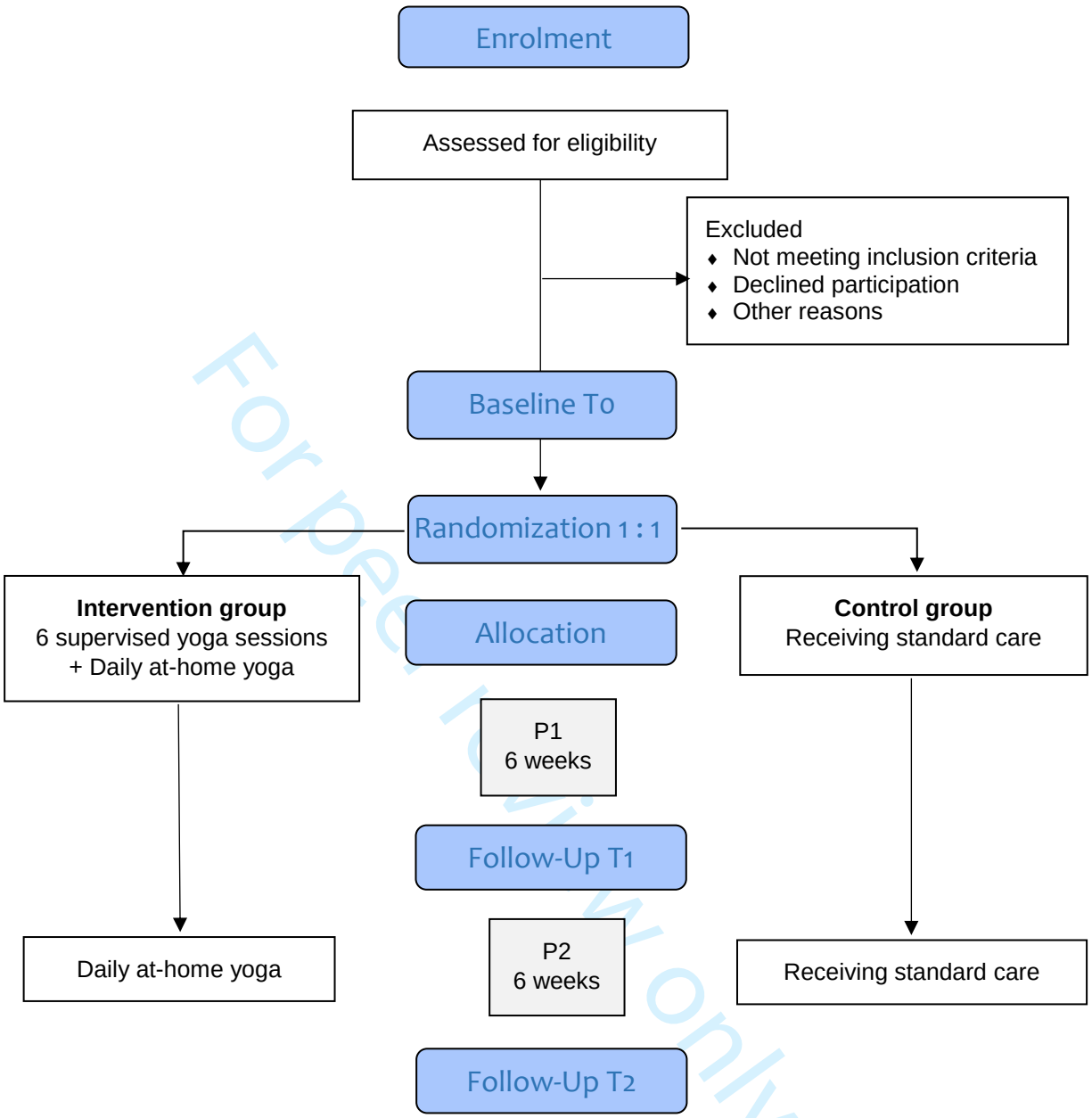

Figure 1 Study flow diagram

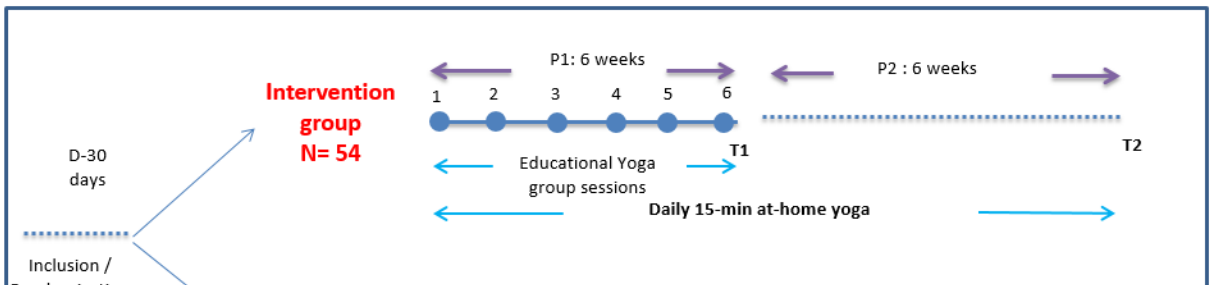

Figure 2 Participant timeline

Formulaire de consentement de participation de la patiente

ETUDE RANDOMISEE EVALUANT L'EFFICACITE D'UNE INTERVENTION COMBINEE DE KINESITHERAPIE INTEGRANT UN PROJET EDUCATIF CHEZ DES PATIENTES AVEC DES DOULEURS AVEREES LIES A L'HORMONOTHERAPIE APRES UN CANCER DU SEIN SKYPE 2

Promoteur: Institut du Cancer de Montpellier ICM, Parc Euromédecine, 208 rue des Apothicaires, 34298 Montpellier Cedex 5

Coordonnateur de l'étude:

Madame Kerstin FARAVEL
Kinésithérapeute, professeur de yoga
Service de Kinésithérapie
Institut régional du Cancer de Montpellier
208 rue des Apothicaires
34298 Montpellier Cedex 05

Je soussignée :

Nom :…… **Prénom** :……

Date de naissance: I__I__I I__I__I I__I__I__I__I

ACCEPTE DE PARTICIPER A CETTE RECHERCHE SELON LES CONDITIONS DEFINIES DANS LE DOCUMENT D'INFORMATION.

J'atteste être affiliée ou bénéficiaire d'un régime français d'assurance maladie (sécurité sociale), condition obligatoire pour pouvoir être incluse dans la recherche.

J'ai bien compris que ma participation à la recherche était libre et volontaire, et que je pouvais refuser d'être incorporée dans celle-ci sans avoir à me justifier, tout en continuant à bénéficier des meilleurs soins disponibles.

J'ai bien noté que mon consentement ne dégageait pas les investigateurs et le promoteur de leurs responsabilités, et que je conservais tous les droits qui me sont garantis par la loi.

Les conditions de ma participation, notamment la durée de celle-ci, ainsi que les bénéfices et les risques éventuels de l'étude en question, m'ont été expliqués clairement par le Dr/Pr/Mme/Mr……

Formulaire de consentement de participation de la patiente

J'ai bien pris connaissance de l'objectif de l'étude, des conditions de sa réalisation et des contraintes en découlant. J'ai eu la possibilité de lire, de comprendre et de conserver une lettre d'information (en date du 01/06/2022 version 4.0) qui m'a été remise.

J'ai compris également que je pouvais retirer à tout moment mon consentement à la poursuite de mon inclusion dans l'étude, sans avoir à me justifier, sans encourir aucune responsabilité ni aucun préjudice de ce fait, sans être pénalisé, et en continuant à recevoir les meilleurs soins disponibles.
Toutefois, dans ce cas, je m'engage à prévenir le médecin responsable de l'étude, afin qu'il mette en œuvre les mesures propres à assurer ma sécurité.

J'accepte le traitement informatisé des données nominatives en conformité avec la loi n°2018-493 du 20 juin 2018 relative à la protection des données personnelles et modifiant les loi n°2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et n°78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés.

J'ai bien compris que je pouvais à tout moment exercer le droit d'accès, de rectification et d'opposition qui m'est garanti par les articles 39 et 40 de la loi n°2018-493 du 20 juin 2018 relative à la protection des données personnelles et modifiant la loi n°2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel, et relative au traitement informatisé des données nominatives me concernant et le Règlement européen 2016/679 relatif à la protection des personnes physiques à l'égard du traitement des données à caractère personnel et à la libre circulation de ces données dit « RGPD » (règlement général sur la protection des données).

Je reconnais avoir pu poser toutes les questions souhaitées et avoir reçu des réponses satisfaisantes sur toutes les informations désirées, ainsi que la possibilité qui m'est offerte de disposer à tout moment des informations complémentaires que je pourrais souhaiter.

Je reconnais avoir disposé d'un temps de réflexion suffisant entre ces informations et le présent consentement et avoir eu si je le souhaitais l'opportunité d'en discuter avec mon médecin ou mes proches. Je reconnais en particulier que le droit à me faire assister par une personne de mon choix m'a été communiqué.

Je reconnais avoir été informée que l'étude pouvait être interrompue à tout moment sur décision du promoteur ou des autorités de santé, et que toutes les mesures seraient prises dans ce cas pour assurer ma sécurité et, le cas échéant, la poursuite de mon traitement, et que ma participation personnelle à l'étude pouvait être suspendue si je ne respectais pas le protocole.

Formulaire de consentement de participation de la patiente

Je reconnais avoir été informée que le promoteur de l'étude, l'Institut régional du Cancer Montpellier (ICM, 208 Rue des Apothicaires 34298 Montpellier cedex 5) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société SHAM (contrat n° 140474).

J'ai bien compris que tout fait nouveau susceptible de remettre en cause mon consentement à ma participation à l'étude me serait communiqué.

Je m'engage à observer les contraintes expliquées et spécifiées dans le document d'information, à la fois pour minimiser les risques et pour la bonne fin du protocole.

Le cas échéant, j'autorise dans la mesure où elles sont indispensables à la bonne fin de la recherche, l'enregistrement de données personnelles me concernant. Je sais que le promoteur s'engage à ce que ces données soient rendues confidentielles par un codage sans mention du nom et du prénom.

J'ai bien noté que j'ai le droit d'être informé des résultats globaux de cette recherche selon les modalités qui ont été précisées dans le document d'information.

□	J'accepte que mes prélèvements sanguins, soient utilisés pour l'étude comme décrit dans la lettre d'information

Nom de la patiente :
Date :

Signature :

Nom de l'investigateur :
Date :

Signature :

Je reconnais qu'un des deux exemplaires de ce formulaire attestant mon consentement m'a été remis.

IDENTIFICATION DE LA PATIENTE	SKYPE 2
|____|____| |____|____|____| |____|-|____| Centre N° Patiente N° Initiales (code lettre)	SEANCES PHASE 1/2

SEANCES QUOTIDIENNES DE YOGA A DOMICILE
PERIODE 1/2
SEMAINE N°XX du |__|__|-|__|__|-20|__|__| **au** |__|__|-|__|__|-20|__|__|

Séances réalisées		Prises d'antalgiques
J1 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J2 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J3 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J4 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J5 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J6 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J7 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)

Si une ou plusieurs séances ont été réalisées merci de cocher la ou les raisons :

- ☐ J'en retire un bénéfice personnel
- ☐ Je pense ou je constate qu'elles sont utiles
- ☐ Je pense que cela fait partie de mon traitement
- ☐ Je fais confiance à l'équipe soignante
- ☐ Pour faire avancer la recherche
- ☐ Pour avoir un suivi régulier
- ☐ Je n'ai pas osé refuser
- ☐ Mon entourage m'a convaincu de les faire
- ☐ Autres, préciser……

Si une ou plusieurs séances n'ont pas été réalisées merci de cocher la ou les raisons :

- ☐ J'ai oublié
- ☐ J'ai été trop fatiguée
- ☐ Je manque de temps
- ☐ J'ai eu trop de douleurs
- ☐ Je n'ai pas eu envie
- ☐ J'ai peur de mal faire
- ☐ Je n'en vois pas l'intérêt
- ☐ Je manque d'information sur quand et comment le faire
- ☐ Autres, préciser……...

Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)	Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)
J1			J5		
J2			J6		
J3			J7		
J4					

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p.2
	2b	All items from the World Health Organization Trial Registration Data Set	Protocol More information can be provided if wished by the editor
Protocol version	3	Date and version identifier	Abstract p.2
Funding	4	Sources and types of financial, material, and other support	Funding p.14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page p.1 and Authors' contribution p.14
	5b	Name and contact information for the trial sponsor	p. 1 and Responsibilities p. 11

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Responsibilities p.11 and Funding p. 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Responsibilities p.11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction p.3-4
	6b	Explanation for choice of comparators	Introduction p.3-4
Objectives	7	Specific objectives or hypotheses	Introduction p.3-4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction p.3-4 and Study design p.4 and Randomization p.7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Study design and setting p.5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Eligibility criteria p. 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Intervention p. 8 data collection p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Concomitant care section p.9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Objectives and endpoints, p.5-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2 and Table 1 and text p.7-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample size section p.7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Sample size p7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Randomization section p.7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Randomization section p.7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Patient timeline p7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA p. 7

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, no blinding possible
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Endpoints p. 6-7 Data collection p. 9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8-9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Data collection p.9 Data Management p.10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Statistical methods p.10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA, no subgroup analyses are planned
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Statistical methods p.10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Data management and monitoring p.10

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA, no interim analyses scheduled
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Safety section p.10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA, no auditing scheduled
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics approval and dissemination p. 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics approval and dissemination p. 13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Patient timeline p.7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA, no ancillary study
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Data collection p 9 Ethics and Dissemination p13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Funding p.14 Competing interest p.15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics p.13 Responsibilities p.11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and Dissemination p.13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol More information can be provided if wished by the editor
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA, no such plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material More information can be provided if wished by the editor
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of a Physiotherapy Yoga and Patient Education program for patients with breast cancer and hormone therapy-induced pain: a multicentre randomised study protocol (SKYPE 2)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075378.R2
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Efficacy of a Physiotherapy Yoga and Patient Education program 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 hormonal 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. Personalized patient education programs increase engagement and motivation, and induce effective behavioural changes. The SKYPE program, 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 hypothesized that using theory-based patient education favour learning and practicing 15 minutes 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 program on pain reduction compare to 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 one weekly educational yoga session of 90 minutes for six weeks, supervised by physiotherapists (Period 1). They will also perform daily at-home 15-minute 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 June 22, 2020). The results will be disseminated to patients and healthcare professionals, and published in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov Identifier: NCT04457895; Protocol V4.0_20220601.

Strengths and limitations

- 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 propose an integrated yoga program, supervised by physiotherapists, with a theory-based patient education approach, to enhance patients' autonomy and induce a sustainable behaviour 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 program, *i.e.* physiotherapy, yoga, and patient education intervention.

INTRODUCTION

Estrogen-positive breast cancers account for 65 to 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 to 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 (ASCO).[13]

A review comparing efficacy of various therapies to decrease osteoarticular pain due to hormone therapy 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 pro- and anti-inflammatory cytokines.[18–20] For example, Kiecolt-Glaser *et al*. reported a yoga program in breast cancer survivors, consisting of one 90 minute-session twice per week, for 12 weeks, and showed benefits on inflammation and fatigue.[19] However, these studies mainly used supervised yoga programs, and few of them associate it with at-home practice. Moreover, these program 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 (DVD, 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 program in the aim to improve long-term patient behavioural changes. We hypothesised that a personalized educational program, 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,[28] using the Medical Research Council framework for developing complex interventions.[29,30] Patient education (PE) was completely integrated in 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 patient.[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 program, supervised by physiotherapists, to enhance patients' autonomy and allow a behaviour change in order to include daily yoga practice in their lives. We now propose to evaluate our program 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 program[28] on pain reduction , and compare it to 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), the Nîmes University Hospital and the Libourne Hospital. Physiotherapists will

follow a 9-days 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.

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 one 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 one month, and neuropathy can persist for several weeks after chemotherapy. Thus, we chose a two-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 weeks program combining physical therapy, yoga and PE intervention on reduction of 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). Timeframe 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 Numeric Pain Rating Scale (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 practicing or not in logbooks (Supplemental material).
3. QoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30,[33] QLQ-BR23 and SF-36[34] questionnaires ; 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.
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) indicates 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 second (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 (PEF) 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 7-items Likert scale at T1 and T2. The items are: extremely satisfied, very satisfied, little satisfied, not satisfied/not unsatisfied, little unsatisfied, very unsatisfied, 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, 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 2 units of their osteoarticular and/or musculoskeletal pain due to HT between T0 and T2 in each group, assessed on the NPRS from 0-10. 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 Figure 1 and Figure 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 painkiller intake (yes/no) and the intensity of HT-induced pain on a 0 to 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-Patient Education 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 patient education, 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 six-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 practicing 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 program and a 15-minutes audio yoga session guide sent by email or copied on a USB stick. In addition, the physiotherapist will provide a logbook to document at-home daily practices, their duration, and the reasons for practicing or not. A specific section is also dedicated to monitor painkiller intake (drug, dose and duration).

Supervised sessions (P1)

During six weeks, patients will follow a training yoga program and attend one weekly 90-minute yoga session under the supervision of a physiotherapist expert in postural yoga, in groups of 2 to 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 to 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 others sessions will be conducted using digital format, in accordance with the French ethics committee recommendations in the context of the COVID pandemics. During each session, the physiotherapist follows up on the patient's yoga at-home practice and sets personal goals for the week ahead.

At-home yoga practice (P1 and P2)

Patients will be invited to practice 15 minutes 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 practiced from 1 to 10 (morning practice) or from 10 to 1 (evening practice) (Table 2). Patients will receive collective motivational e-mails from the physiotherapist at week 2 and 4 during P2. On patient's request, personal support may be provided by phone or mail.

Patient Education

Compliance to the program and yoga sessions will be favoured and motivated using PE techniques (preparing the behaviour change before the intervention start at personalized check-ups, self-choice of personalized objectives, adapted integrative care…). It is based on the intention implementation model and the concept of perceived personal control [39–41], using logbooks, e-mails and educational follow-up. Moreover, the protocol follows the French national guidelines defined by 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, *i.e.* 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 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 a eCRF by authorized 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 upon 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 anonymization, 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, *i.e.* the proportion of patients who have experienced a reduction of at least 2 points on the NPRS at 12 weeks, will be compared between the two groups using a chi-square 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 to baseline will be calculated.

Quantitative outcomes, including the scores from different questionnaires, will be described using the mean, standard deviation (SD), the 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 Chi-square 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 16 software (StataCorp LP, College Station, TX).

Responsibilities

The study sponsor, ICM, is responsible for the study design and management, for obtaining all authorizations (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 an effect of yoga on inflammation.[18–20]

The originality of our program is the introduction of the PE approach. Indeed, our theory-based multifaceted intervention foresees, anticipates and optimizes 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 pro- 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 minutes of yoga practice.[20] Our study offers a total of 1710 minutes 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 program 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 6 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 program. 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 is collected according to the law "Informatique et Libertés" n°78-17 (January 6, 1978), modified by the law relating to the protection of personal data in accordance with the General Data Protection Regulation (GDPR) (UE regulation 2016/679, May 25, 2018).

The study was approved by the Ethics Committee (CPP Ile de France 8 on June 22, 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. Upon 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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Author contributions

KF, AS, WJ are responsible for conception and design of the work and the writing of the protocol. MT participated in the discussion about pain assessment. MD participated in the conception and design of the work as patient representative and moreover she identified how the biological analysis will be proceeded. MJ is responsible for methodological and statistical design and defined the planned analyses. LM is responsible for legal, ethics and administrative aspects. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

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

Availability of data and materials

The datasets used and analysed during the current study will be available from the corresponding author upon reasonable request.

Consent for publication

Not applicable

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TABLES

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 treatment visit
Inclusion / non-inclusion criteria	X														
Informed signed consent	X														
Patient inclusion	X														
Randomization	X														
Medical history	X														
Physiotherapy check-ups (including NRPS)	X							X							X
Educational check-ups (experimental group only)	X							X							X
Questionnaires (GSES, QLQC30, BR23, HADS, SF36, BPI)	X							X							X
Blood sample	X														X
Reminder e-mail (experimental group only)										X		X			
Adverse events	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
Supervised yoga session (experimental group only)		90-min supervised yoga session													
At-home yoga practice (experimental group only)		One daily 15-min at-home session							One daily 15-min at-home session						

D: Day – W: Week

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
Number of sessions	6 group sessions First session in-person, five digital sessions	78 at-home yoga sessions
Duration of session	1 h 30 min	≥ 15 min
Total duration	9 h	9 h (P1) and 10 h 30 (P2) = 19h30
Content	Welcome and handing-in of the previous week logbooks (5') Introduction (5') Sharing/exchanging of experiences (10') Philosophical perspective (10') [1] Postural yoga (Asanas) + relaxation (30') (no 1-2 learning of "My Yoga guide", no 3-6 introduction to other postures) [2] • **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.[2] 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)

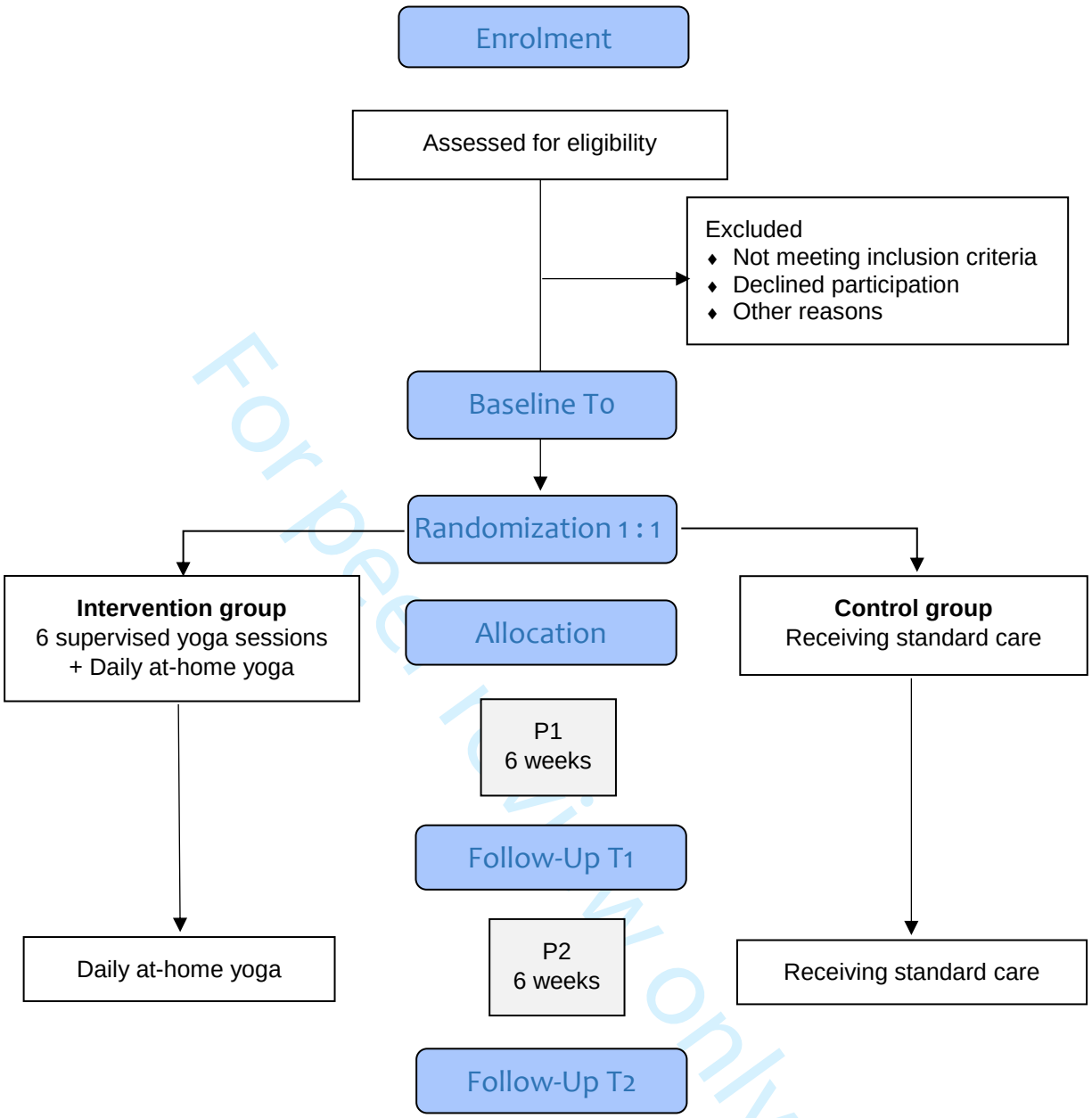

Figure 1 Study flow diagram

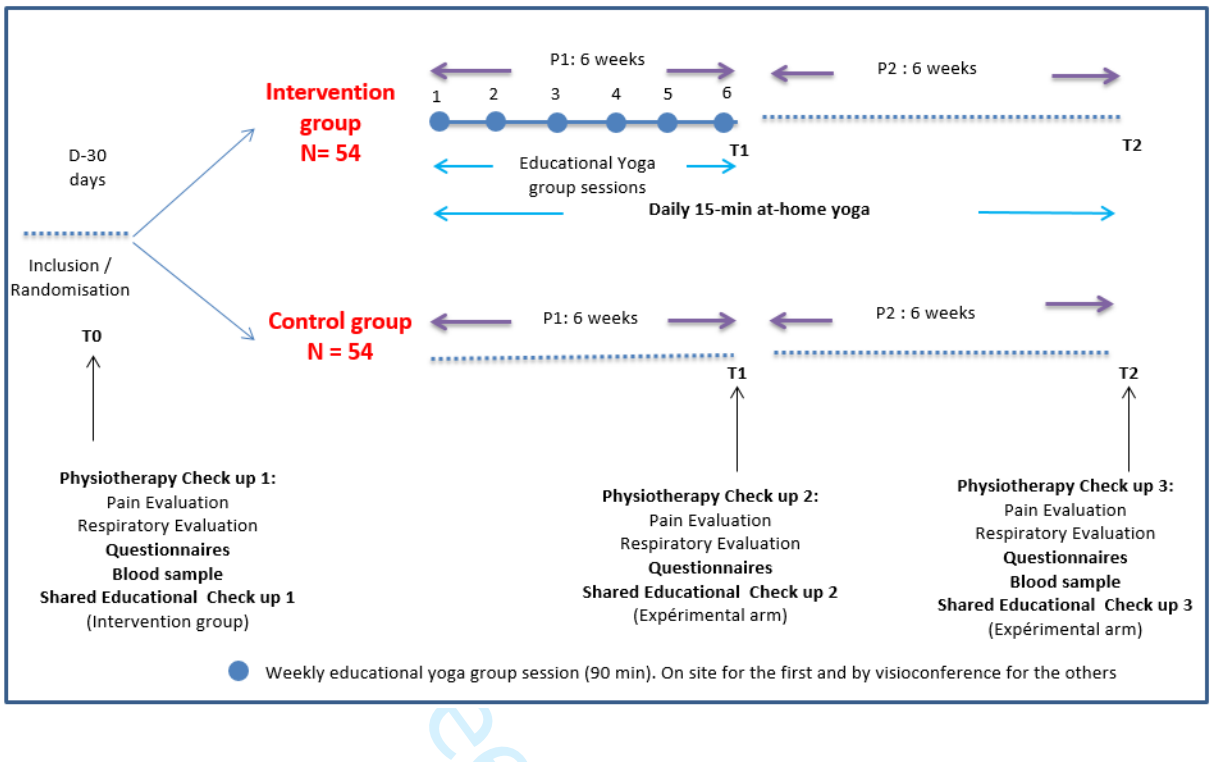

Figure 2 Participant timeline

IDENTIFICATION DE LA PATIENTE	SKYPE 2
|____|____| |____|____|____| |____|-|____| Centre N° Patiente N° Initiales (code lettre)	SEANCES PHASE 1/2

SEANCES QUOTIDIENNES DE YOGA A DOMICILE
PERIODE 1/2
SEMAINE N°XX du |__|__|-|__|__|-20|__|__| **au** |__|__|-|__|__|-20|__|__|

Séances réalisées		Prises d'antalgiques
J1 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J2 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J3 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J4 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J5 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J6 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)
J7 (jj/mm/aaaa) |__|__|-|__|__|-20|__|__|	☐ OUI ☐ NON si oui durée : I_____I min	☐ NON ☐ OUI (merci de préciser en bas)

Si une ou plusieurs séances ont été réalisées merci de cocher la ou les raisons :

- ☐ J'en retire un bénéfice personnel
- ☐ Je pense ou je constate qu'elles sont utiles
- ☐ Je pense que cela fait partie de mon traitement
- ☐ Je fais confiance à l'équipe soignante
- ☐ Pour faire avancer la recherche
- ☐ Pour avoir un suivi régulier
- ☐ Je n'ai pas osé refuser
- ☐ Mon entourage m'a convaincu de les faire
- ☐ Autres, préciser……

Si une ou plusieurs séances n'ont pas été réalisées merci de cocher la ou les raisons :

- ☐ J'ai oublié
- ☐ J'ai été trop fatiguée
- ☐ Je manque de temps
- ☐ J'ai eu trop de douleurs
- ☐ Je n'ai pas eu envie
- ☐ J'ai peur de mal faire
- ☐ Je n'en vois pas l'intérêt
- ☐ Je manque d'information sur quand et comment le faire
- ☐ Autres, préciser……...

Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)	Jour	Traitement (ex : Doliprane)	Dose/fréquence (ex : 1g, 3/j)
J1			J5		
J2			J6		
J3			J7		
J4					

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p.2
	2b	All items from the World Health Organization Trial Registration Data Set	Protocol More information can be provided if wished by the editor
Protocol version	3	Date and version identifier	Abstract p.2
Funding	4	Sources and types of financial, material, and other support	Funding p.14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page p.1 and Authors' contribution p.14
	5b	Name and contact information for the trial sponsor	p. 1 and Responsibilities p. 11

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Responsibilities p.11 and Funding p. 14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Responsibilities p.11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction p.3-4
	6b	Explanation for choice of comparators	Introduction p.3-4
Objectives	7	Specific objectives or hypotheses	Introduction p.3-4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Introduction p.3-4 and Study design p.4 and Randomization p.7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Study design and setting p.5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Eligibility criteria p. 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Intervention p. 8 data collection p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Concomitant care section p.9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Objectives and endpoints, p.5-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2 and Table 1 and text p.7-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample size section p.7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Sample size p7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Randomization section p.7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Randomization section p.7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Patient timeline p7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA p. 7

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, no blinding possible
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Endpoints p. 6-7 Data collection p. 9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8-9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Data collection p.9 Data Management p.10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Statistical methods p.10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA, no subgroup analyses are planned
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Statistical methods p.10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Data management and monitoring p.10

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA, no interim analyses scheduled
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Safety section p.10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA, no auditing scheduled
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics approval and dissemination p. 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics approval and dissemination p. 13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Patient timeline p.7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA, no ancillary study
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Data collection p 9 Ethics and Dissemination p13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Funding p.14 Competing interest p.15

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics p.13 Responsibilities p.11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and Dissemination p.13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol More information can be provided if wished by the editor
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA, no such plans
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material More information can be provided if wished by the editor
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.