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Connected device and therapeutic patient education to promote physical activity among women with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised controlled trial

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ABSTRACT

Introduction: Despite safety and benefits of physical activity during treatment of localized breast cancer, successful exercise strategies remain to be determined. Primary objective of the DISCO trial is to evaluate the efficacy of two 6-month exercise interventions concomitant to adjuvant treatments, either alone or combined, on the physical activity level of breast cancer patients, compared to usual care: an exercise program using a connected device (activity tracker, smartphone application, website) and a therapeutic patient education intervention. Secondary objectives are to evaluate adherence to interventions, their impact at 6 and 12 months, representations and acceptability of interventions, and to assess the cost-effectiveness of the interventions using quality-adjusted life year.

Methods and analysis: This is a 2x2 factorial, multicentre, phase III randomised controlled trial. The study population (with written informed consent) will consist of 432 women diagnosed with primary localized invasive breast carcinoma and eligible for adjuvant chemotherapy, hormonotherapy and/or radiotherapy. They will be randomly allocated between one of four arms: (i) web-based connected device (evolving target number of daily steps and individualized, semi-supervised, adaptive program of two walking and one muscle strengthening sessions per week in autonomy), (ii) therapeutic patient education (one educational diagnosis, two collective educational sessions, one evaluation), (iii) combination of both interventions and (iv) control. All participants will benefit from the international physical activity recommendations. Assessments (baseline, 6 and 12 months) will include physical fitness tests, anthropometrics measures, body composition (CT-scan, impedancemetry), self-administered questionnaires [physical activity profile (RPAQ), quality of life (EORTC QLQ-C30, EQ-5D-5L), fatigue (PFS-12), social deprivation (EPICES), lifestyle, physical activity barriers, occupational status] and biological parameters (blood draw).

Ethics and dissemination: This study was reviewed and approved by the French Ethics Committee. The findings will be disseminated to the scientific and medical community via publications in peer-reviewed journals and conference presentations.

Registration: ClinicalTrials.gov NCT03529383; 05/17/2018.

Keywords: Breast cancer, Physical activity, Sitting time, Activity tracker, Connected device, Web-based, eHealth, Therapeutic patient education, Randomised controlled trial

Word count: 8445

Strengths and limitations of this study

- This study findings will provide novel data on the efficacy of two innovative interventions promoting physical activity during breast cancer adjuvant treatment (a web-based connected device and therapeutic patient education, either alone or combined) developing autonomy of patients in their practice of physical activity.
- The cost-effectiveness evaluation planned in the DISCO trial will provide valuable information for decision makers given limited evidence for cost-effectiveness of physical activity in the treatment of cancers.
- While the connected device intervention is semi-supervised, the exercise program has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy. It provides organisational flexibility to patients that may facilitate adherence, as well as to overcome barriers due to distance of facilities.
- Despite the potential benefits of connected devices in cancer care, their use may face important issues, such as ethical challenges related to the security of sensitive data storage, technical challenges related to technological robustness and reliability, exacerbating access disparities, and self-assessment of the participant's fatigue or health condition.
- The primary outcome measure is based on a declarative evaluation of physical activity that confers methodological limits to the study; but the validated questionnaire was chosen according for its easy implementation for cancer patients compared to accelerometer

monitoring and its relevance for the primary outcome, although the performance and reliability of activity trackers are increasingly validated.

INTRODUCTION

Breast cancer is the leading cause of cancer in women worldwide with 1.6 million new cases diagnosed each year,[1] representing more than a third of all new cancer cases in women. In France, breast cancer also represents the leading cause of cancer incidence and mortality among women, with approximately 58,000 new cases and 12,000 breast cancer deaths estimated in 2018.[2] Despite very good prognosis worldwide with an overall survival of 85% at 5 years (87% in France) and 71% at 10 years (78% in France) for all stages combined,[3–5] a large number of patients with breast cancer experience adverse effects of cancer and its treatments such as fatigue, impaired quality of life, anxiety or weight gain.[6–8]

In women with breast cancer, deterioration of physical activity level and decline in cardiorespiratory fitness are frequent.[9,10] Lack of physical activity, obesity and weight gain have been shown to increase the risk of cancer-related comorbidities and treatments adverse effects, to worsen long-term health and to cause poor prognosis.[11–13] The benefits of physical activity are well recognized in primary cancer prevention[14] and numerous studies have shown the safety[15] and benefits of physical activity performed concomitant to breast cancer treatments. These benefits include reduced fatigue[16–18] and comorbidities[19], improved quality of life[20,21] and physical functioning,[10,16,18,21] as well as possibly reduced risk of recurrence[22] and improved overall and specific survival with a positive dose-response relationship.[13,22,23] Despite these benefits and international evidence-based guidelines of physical activity prescription for clinicians and their patients, accessibility to exercise programs and implementing the guidelines in the cancer care process remain a challenge for patients and health care providers.[24–26] While a growing number of facilities offer physical activity programs to cancer patients, distance from home constitutes a barrier to regular exercise during cancer treatments.[25] Successful exercise strategies during and beyond cancer treatment remain to be determined in clinical trials.[27]

The recent development of connected devices such as activity trackers offers a real opportunity in oncology to promote and monitor patients' physical activity.[28] While adherence to lifestyle interventions is a major challenge, connected activity trackers and smartphone applications enable

structured monitoring of health parameters and provide feedback to patients. A systematic review of randomised controlled trials of physical activity interventions using new technologies such as activity trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly increased their number of steps per day in the majority of the studies.[29] Recent reviews of intervention studies conducted among breast cancer patients have also shown that patients increased their physical activity when they used activity trackers.[30,31] Overall, connected activity trackers receive increasing interest for being systematically integrated into clinical oncology practice.[32,33] But more research is needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the preferences of breast cancer patients.[34–36]

Therapeutic patient education has emerged in the 1990s in response to the recognition of the need to support patients in the self-management of their chronic diseases, such as diabetes and asthma.[37,38] According to the WHO, therapeutic patient education aims to "help patients acquire or maintain the skills they need to best manage their lives with a chronic disease".[39] In the cancer field, several cancer-specific programs of therapeutic patient education have been set up to manage pain, fatigue, side effects of treatment (chemotherapy, surgery) or compliance to treatment.[40–43] By enhancing knowledge and skills level, therapeutic patient education may greatly contribute to increase patients' autonomy in their disease management. Despite the performance in modifying long-term individual behaviours and adherence to oral cancer treatments,[43] the benefits of therapeutic patient education on physical activity levels in cancer patients early after diagnosis has been poorly investigated.[44,45]

Several biological mechanisms have been proposed to explain the effects of physical activity on breast cancer risk and outcome. These mechanisms suggest an influence of physical activity on several signalling pathways involved in tumour development and progression, including the insulin signalling pathway, chronic inflammation (involving inflammatory cytokines) and endocrine hormone regulation.[46–48] Based on the data in the literature, it is not possible to conclude for a causal relationship between the metabolic effects of physical activity and the impact on survival, and biological effects of physical activity remain to be elucidated.[48]

In this context, given the accumulating evidence for the benefits and safety of regular exercise during treatments of localized breast cancer, it is necessary to systematically encourage patients to remain or become physically active from the time of diagnosis and to implement and assess the most appropriate strategies of physical activity in clinical practice. The aim of the DISCO trial is to propose exercise during breast cancer treatment through two innovative types of interventions, a web-based connected device and therapeutic patient education, which aim to develop patients' autonomy in their practice of physical activity. The primary objective of the DISCO trial is to evaluate the efficacy of two interventions concomitant to adjuvant treatments, either alone or combined, on the physical activity level of breast cancer patients at the end of the 6-month interventions, compared to usual care: one is an exercise program using a connected device (comprising an activity tracker linked to a smartphone application and a website and providing an individualized, semi-supervised, technology-based exercise program) and the other is a therapeutic patient education intervention. The research hypothesis is that patients participating in the 6-month connected device or therapeutic education intervention will be more likely to achieve the international physical activity recommendations, compared to women receiving physical activity recommendations only (usual care). The international recommendations of the World Health Organization (WHO) for health are to do at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity or an equivalent combination each week, and muscle-strengthening activities at least two days a week.[49] Secondary objectives are: (i) to evaluate the adherence to the interventions; the impact of the interventions on physical fitness, physical activity profile, anthropometrics, quality of life, fatigue, biological parameters, occupational status and lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12 months; the representations and acceptability of activity tracker and of therapeutic patient education; and ii) to assess the cost-effectiveness of the interventions. If one of the interventions is individually effective, the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.

METHODS AND DESIGN

Trial design

The DISCO (acronym for "dispositif connecté", i.e., connected device in English) trial is a 2x2 prospective, multicentre, factorial, randomised, controlled and open-label study (phase III), conducted by the Léon Bérard comprehensive cancer centre (Lyon, France) among women receiving treatment for localized breast cancer. The clinical protocol was designed and written according to the SPIRIT guidelines (see Supplementary file 1). The flowchart of the study is presented in Figure 1. Patients will be randomly assigned to one of the four arms of the study according to the 2×2 factorial design (1:1:1:1 ratio). They will all receive international recommendations on physical activity,[49] and: (i) women allocated to the "connected device" arm will benefit from a 6-month individualized, semi-supervised exercise program carried out autonomously, consisting of an evolving goal of daily number of steps using an activity tracker and of two sessions of brisk walking and one session of muscle strengthening per week, using dedicated smartphone application and website; (ii) women allocated to the "therapeutic patient education" arm will benefit from four therapeutic education sessions on exercise; (iii) women allocated to the "combined" arm will benefit from both interventions in parallel; (iv) women allocated to the "control" arm will receive usual care.

Eligibility criteria for participants

Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and requiring adjuvant treatment (chemotherapy, hormonotherapy, radiotherapy) that will be realised in one of the investigating centres; providing a medical certificate of no contraindication to exercise; being available and willing to participate in the study for the duration of the interventions and follow-up; using a personal smartphone compatible with the application (iOS operating system from version 9.3, Android operating system from version 5.0, no Microsoft operating system) and having a computer with Internet access; being able to understand, read and write French; and being affiliated with a social security scheme.

Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal history or co-existence of other primary cancer (except of in situ cancer regardless of the site, basal cell skin cancer and non-mammary cancer in complete remission for more than 5 years); presenting a contraindication to exercise according to the investigator (such as cardiorespiratory or bone pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe malnutrition according to the criteria of the French National Health Authority (i.e., for women ≤70 years: weight loss ≥15% in 6 months or ≥10% in 1 month; for women >70 years: weight loss ≥15% in 6 months or ≥10% in 1 month, and body mass index <18 kg/m²);[50] being unable to be followed for medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or breastfeeding or of childbearing age without effective contraception for the duration of the study.

Recruitment

Recruitment started on May 2018. Participants will be recruited at several national comprehensive cancer centres, clinics or hospitals located in France (see ClinicalTrials.gov NCT03529383), which will ensure adequate participant enrolment to reach the target sample size in a timely manner. Inclusion of patients will be carried out after surgery and confirmation of the indication of adjuvant treatment. The study will be proposed to patients at the postoperative, pre-chemotherapy or pre-radiotherapy consultation (by the surgeon, oncologist or radiotherapist investigator, respectively) depending on the patient's treatment plan. At this visit, the investigator will check all eligibility criteria and propose to the eligible patients to participate in the study, explain the objectives and study process and give them an information notice. After sufficient time for reflection, eligible patients who agree to participate will date and sign an informed consent and will be included prior to the onset of adjuvant therapy (or within one month thereafter). The number of eligible patients refusing to participate in the study and reason for non-participation will be recorded.

Randomisation

Prior to randomisation, participants will be asked to complete the Recent Physical Activity Questionnaire (RPAQ) to assess their level of physical activity.[51] Their weight, size and prescribed adjuvant treatments will be collected from the patient's medical record.

Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris, France) into one of the four arms of the trial, by using the following minimization criteria:[52,53] body mass index (BMI) (<25 kg/m², ≥25 and <30 kg/m², ≥30 kg/m²), baseline physical activity level from RPAQ (<150 min/week, ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant treatments at inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ± radiotherapy, chemotherapy ± radiotherapy, radiotherapy only).

INTERVENTIONS

At baseline, all participants will benefit from the international recommendations in terms of physical activity for promoting health in the general population[49] delivered by a certified exercise instructor.

Intervention with connected device

Participants randomised to the "connected device" arm will benefit from a 6-month exercise program. The connected device consists of an activity tracker (connected wristband, LS417-F model, CARE Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application and a dedicated website proposing an individualized, semi-supervised exercise program adapted to cancer patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based exercise program will aim to support participants to enhance physical activity in two ways: doing structured physical activity sessions and increasing daily physical activity (number of steps). Physical activity sessions will be automated generated by an algorithm based on the patient profile (described below). The participants will receive notifications informing them of a new structured physical activity session available on the website or mobile application, or alerting them when a session was not carried out

and inviting them to execute it when possible. Participants will receive a free 6-month subscription to the program.

—*Setting up the connected device:* At the end of the baseline assessment, the certified exercise instructor will introduce the participants to the customized exercise program and will give them the activity tracker and a user guide for the connected device. Then, the certified exercise instructor will explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated website, as well as assist the participants to install the application on their smartphone. The participants will be registered in the customized exercise program by the certified exercise instructor. The registration will consist of completing a web-based questionnaire about personal and health data to determine the participant profile (age, weight, height, level of aerobic and muscular strength, treatment, symptoms, availabilities for exercise sessions and sport materials).

—*Baseline level of aerobic and muscular strength for the individualisation of the exercise program:* The physical fitness tests performed at baseline will be used to classify the participants at the start of the exercise program according to their aerobic level (for the walking sessions) and their muscular strength level (for the strengthening sessions). The aerobic level categories will be determined by the distance performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level will be determined by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test: muscular strength group 1 (≤10 repetitions), muscular strength group 2 (11 to 14 repetitions) and muscular strength group 3 (≥15 repetitions). Thresholds were based on average values reached by women on treatment for breast cancer for the 6MWT (pooled mean value, 523 m) and the Sit-to-stand test (pooled mean value, 13 repetitions);[54] these values were checked for consistency with percentile scores obtained at the 6MWT and Sit-to-stand test in community-dwelling older women,[55] then the percentiles were used to determine the thresholds for the three groups.

—*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise instructor through an individual follow-up of participants (see 'Participant follow-up' part and

'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using the smartphone application and the website. The program is based on three structured unsupervised sessions per week alternating two types of exercise: two walking sessions (by following oral instructions given via the smartphone application) and one muscle strengthening session (by using videos accessible on the website). The levels of the first walking and muscle strengthening sessions will be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent sessions will be programmed according to the participant's availability days and strengthening exercises will be adapted according to sport materials available to the participants at home (e.g., Swiss ball, sports mat, stick, weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a body session of 10 to 35 minutes of strengthening exercises developing, or 10 to 50 minutes of walking sessions (mixing continuous and/or intermittent effort); 3) a 5-minute recovery period, consisting of stretching and relaxation during strength training sessions, or a cool down during walking sessions. Sessions will be of moderate-to-high intensity (≥ 3 and ≤ 9 METs).

The three structured unsupervised exercise sessions per week are configured by a unique algorithm hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to plan the exercise sessions and determine the exercise level in an adapted and progressive manner. At the beginning of each session, the duration and intensity of the session will be determined according to the perceived difficulties (evaluated by a Borg scale) and participant's emotional state (recorded by an emoji) in the previous session, and will be modified or postponed according to the level of fatigue (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg scale), the presence or absence of unusual muscle pain and the presence or absence of unusual nausea/diarrhea. In case of a severe adverse event related to disease or treatment (i.e., joint disability, osteoarthritis, cachexia, hand-foot syndrome, aplasia, diuretic, axillary node dissection, pace-maker, chemotherapy, targeted therapy, hormone therapy, radiotherapy, COPD, diabetes) or temporary contraindication to exercise, declared by the participant on her device, the program and sessions will be adapted or suspended until the participant's health improves.

In addition, participants will have the opportunity to perform additional exercise sessions according to their preferences and lifestyle, outside the program. Participants will be asked to record these sessions through the smartphone application or the website: type of activity (e.g., walking, hiking, cycling) from a list adapted from the Ainsworth's Compendium,[56] duration and intensity.

—*Number of daily steps:* Participants will be advised to wear the activity tracker daily and regularly (preferably daily) launch the application, which will automatically synchronize with the activity tracker via Bluetooth connection and will collect the number of steps. The target number of steps will be 3,000 steps per day at the program onset, and then will be set on the basis of the daily average steps during the first week after inclusion. The target number of daily steps will evolve automatically every three weeks based on the average number of daily steps achieved during the previous three weeks, and will be updated automatically in the application. Consistent with principles of exercise training and progression,[57,58] after each 3-week cycle, if the objective of steps per day is reached by the participant, the target objective will increase by 15% during the following 3-week-cycle, within a maximum target of 10,000 daily steps. If the average number of daily steps does not meet the objective, the target will remain unchanged in the next cycle.

—*Participant follow-up*: A telephone follow-up will be carried out by the certified exercise instructor at 10 days, 2 months and 4 months after randomisation to ensure the proper functioning of the connected device, review the use of the connected device, review the conduct of the sessions and answer the participants' questions. Participants will be orally encouraged to remain physically active on a daily basis (reminder of the benefits and recommendations of physical activity, success and satisfaction during the exercise sessions). During the 6-month intervention, the participants will have the opportunity to contact the certified exercise instructor or the clinical research assistant at any time, by e-mail (directly through the website) or by telephone for any question or assistance with the connected device.

—*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device by the participants and their progress in the program through a dedicated professional website that

provides real-time access to the participants' data. On this website, an automatically generated daily event table will inform the certified exercise instructor of the occurrence of disabilities reported by the participants that may lead to modify their program (e.g., severe fatigue, dyspnea, unusual muscle pain) or if participants have not performed their planned sessions or used their activity tracker for seven consecutive days. Upon these alerts, the certified exercise instructor will contact the participants to precisely analyse the reported disabilities, advice participants, identify the causes of non-use of the connected device, solve possible technical problems or reinforce participant's motivation if necessary.

End of the intervention: At the end of the 6-month program, participants will keep their activity tracker to be encouraged to continue regularly exercising in autonomy. Upon their request, continued subscription to the dedicated application and website will be offered for six other months, with no individual follow-up anymore.

Intervention of therapeutic patient education

Participants randomised to the therapeutic patient education arm will benefit from a therapeutic patient education intervention, in addition to the international recommendations in terms of physical activity. The intervention is part of the therapeutic patient education program set up at the Léon Bérard cancer centre and validated by the Regional Health Agency ("Agence Régionale de Santé Rhône-Alpes") and will be disseminated in the investigating centres according to the criteria of the Regional Health Agency. The therapeutic patient education intervention consists in four sessions that will be scheduled according to participants' availability during their follow-up visits as part of their usual clinical management over a 6-month period.

First, participants will be invited to an initial 1-hour individual session of educational diagnosis with a health professional trained in therapeutic patient education. This session will assess their needs and establish a contract of objectives to reach. Then, participants will be invited to participate in two collective educational sessions of 1h30 each (group of 10 patients maximum). These sessions will be composed of theoretical and practical workshops to help them understand their physical activity in

their daily life and implement the necessary means to practice regular exercise in autonomy. Finally, an educational evaluation will be conducted during a 1-hour individual session, during which the participants will identify whether they have achieved their individual objectives set at the time of the educational diagnosis.

Combined interventions

Participants randomised to the 'combined intervention' arm will benefit from a combination of the connected device intervention and the therapeutic patient education intervention in parallel for 6 months.

STUDY OUTCOMES

The primary endpoint will be the proportion of women who achieve at 6 months the internationally recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical activity, i.e., intensity ≥3 METs) assessed according to the RPAQ self-administered questionnaire.

Secondary endpoints will be:

1. Assessment of the efficacy of the programs at 12 months (i.e., proportion of women who achieve the internationally recommended level of physical activity);

2. Assessment of the adherence to the interventions at 6 months (proportion of participants who are compliant to the program, participation rate in planned sessions);

3. Assessment of the impact between baseline and 6 months and between 6–12 months of the interventions on physical activity profile (change in time spent in different intensities of physical activity and time spent in sedentary activities), physical fitness (change in results to the 6-minute walk test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test), anthropometrics (change in weight, waist and hip circumferences, BMI, fat mass, lean body mass, muscle mass, dry lean mass and body water), quality of life (change in scores obtained from the EORTC QLQ-C30 questionnaire and its BR-23 module), fatigue condition (change in scores obtained from the

PFS-12 questionnaire), health-related quality of life (change in scores obtained from the EQ-5D-5L questionnaire), social deprivation (change in scores obtained from the EPICES self-administered questionnaire), occupational status (proportion of participants who changed their employment status, with return to work and who perceived difficulty at work obtained from a self-administered questionnaire) and lifestyle factors (proportion of participants who change their tobacco use and alcohol intake obtained from a self-administered questionnaire).

4. Assessment of the impact of the interventions on biological parameters between baseline and 6 months (change in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], change in plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines: adiponectin and leptin], proportion of participants with a modification on vitamin D status).

5. Assessment of the representations and acceptability of activity tracker and of therapeutic patient education, at baseline, 6 and 12 months (proportion of participants who accept the connected device and who accept the therapeutic program, according to scores obtained from a self-administered qualitative questionnaire used in social psychology science).

6. Assessment of refusal rate among eligible patients (proportion of patients who refuse to participate).

7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital costs (national data) and benefit in physical activity level.

EVALUATIONS

The initial assessment (T0) will be performed prior to randomisation for minimization purposes. Three evaluations will then be conducted at baseline (T1), 6 months (T2) and 12 months (T3). All study participants will then be followed at 6 months ±1 month post-randomisation (corresponding to the end of participation in the interventions for women in the connected device, therapeutic patient education and combined arms) and at 12 months ±1 month post-randomisation (corresponding to a follow-up period of 6 months post-interventions). Assessments will be carried out by a clinical research

assistant and a certified exercise instructor. The clinical research assistant will contact participants by phone to invite them to follow-up visits and to promote participant retention and complete follow-up. Participants will have no compensation for participation and all study visits will be scheduled on days of medical or health-related appointments.

All evaluations (baseline, 6 and 12 months) will include physical fitness tests, anthropometrics measures, self-administered questionnaires and a non-fasting blood draw (baseline and 6 months only). Data will be recorded using an electronic case report form (eCRF).

DATA COLLECTION

The study outcome measures and their schedule are summarised in Table 1.

Socio-demographic and clinical data

Demographic and clinical data, including month/year of birth, age at diagnosis, family status, level of education, hormonal status, tumour histology and personal history of breast cancer will be collected at baseline. Family status, potential cancer progression and all treatments received for cancer will be collected at 6 and 12 months. All data will be extracted from patients' electronic medical records, except family status and level of education that will be self-reported in a questionnaire.

Occupational status will be assessed using a self-administered questionnaire asking employment status, occupation, size of the company, perceived intensity of the physical effort at work, evolution of employment status at return to work.[59]

Anthropometrics and body composition

The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be measured using standardized procedures and BMI will be calculated as the body weight in kilograms divided by the square of the height in meters (kg/m²). The waist circumference will be measured midway between the last floating rib and the iliac crest. The hip circumference will be measured at the tip of the pubis. Body composition will be measured by bioelectronic impedancemetry (Biody XPert

ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid (in L).

Physical fitness

Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance covered in metres) with perceived difficulty using Borg scale.[60] During this test, participants will be asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes.

The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as many times as possible during 30 seconds.[61]

Hand prehensile strength will be measured using hand dynamometry (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the isometric strength of the hand and forearm muscles.[62] During this hand-grip test, participants will be asked to squeeze the handgrip as strongly as possible to obtain the maximal force (in kg). Two measures will be performed on each hand and the best performance registered.

Flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe Baseline flexibility test, 3B Scientific, Bartenheim, France).[63] In this test, participants will be seated on the floor on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering the level of the feet as recording zero, any measure that does not reach the toes is negative and any measure beyond the toes is positive).

The balance will be measured using the bilateral unipodal equilibrium test.[64] The participants will stand and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).

Physical activity level, sitting time and achievement of physical activity recommendations

The validated self-administered questionnaire RPAQ will be used to measure the self-reported physical activity.[51,65] RPAQ was designed to assess usual physical activity in the last four weeks and covers three activity domains: domestic physical activity, including sitting time that is a good proxy of sedentary behaviour; occupational physical activity, including transportation to and from work; and recreational physical activity. RPAQ gives specific scores in the metabolic equivalent of task (MET) unit for activities of very low intensity (<1.5 METs, i.e., sedentary activities), low intensity (1.5 to <3 METs), moderate intensity (3 to <6 METs) and high intensity (≥6 METs, i.e., vigorous activities) within each domain during the past four weeks. Questions will be coded and converted in MET-minute per four weeks according to the Compendium of Physical Activities[56] by multiplying the number of METs by the duration and frequency of each activity. Then, the global score of physical activity will be obtained by adding the number of MET-minutes per four weeks in each intensity and each domain. The physical activity profile will be defined as the time spent in physical activities of low, moderate and high intensities. The physical activity level will be defined by the overall weekly physical activity (average expressed in MET-hour/week).

Achievement of international physical activity guidelines will be computed for each individual by dividing the time spent in moderate-to-vigorous physical activity (i.e., ≥3 METs) into two categories:[49] <150 min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines); ≥150 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).

Patient-reported outcomes

The quality of life will be measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality-Of-Life Questionnaire (QLQ-C30) and its specific module for breast cancer (BR-23).[66] The QLQ-C30 is a 30-item validated self-administered questionnaire that evaluates five functioning domains (i.e., physical, role, emotional, cognitive and social), a global quality-of-life domain, three symptom domains (i.e., pain, fatigue and nausea) and six single items (i.e., dyspnea,

insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds to a better functioning level. For scales related to symptoms, a lower score corresponds to a better functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.

The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.[67] This standardized self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight, moderate, severe and extreme problems) and comprises a 0-100 visual analogue scale recording the self-rated health (where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine').

Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of fatigue):[68] the higher the score, the worse the fatigue. All items together will produce a total score for fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3), moderate fatigue (score 4-6) and severe fatigue (score 7-10).

Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centres) score.[69] The score will be computed by adding each question coefficient to the intercept whenever the answer is "yes." The score ranges from 0 to 100 (i.e., the higher the score, the greater the deprivation level) with the threshold for deprivation at 30.

Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e., never, former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol intake over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer, cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses). The amount of alcohol will be computed by multiplying the frequency of consumption by the amount

of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.

Determinants of Physical activity

The 21-item self-administered questionnaire "Barriers to Being Active Quiz" will qualitatively assess barriers to regular practice of physical activity.[70]

Uses, representations and motivation towards physical activity will be assessed within the study population using a self-administered questionnaire available online. Acceptability of connected devices and acceptability of therapeutic patient education will be assessed among participants randomised to the corresponding arms using a paper-based self-administered questionnaire. These questionnaires will be built in accordance with the Unified Theory of Acceptance and Use of Technology (UTAUT),[71] which is a specification of the Theory of Planned Behaviour[72] designed to explain and predict the probability of behaviour change among individuals faced with new technologies. The Theory of Planned Behaviour has been massively used during the last two decades to promote health behaviours such as physical activity. Besides, items wording will be based on the results of individual and collective interviews conducted for that purpose and designed to identify social representations[73] of health protection and physical activity incentive devices.

Biological assessments

A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at baseline and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant treatments, otherwise the two blood samples will not be collected. The following biological factors will be assessed in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol), circulating plasma levels of inflammatory cytokines (IL-6, TNFα, CRP) and circulating plasma levels of adipokines (adiponectin, leptin).

STATISTICAL ANALYSIS

Sample size determination

The efficacy rate assumptions are μ=40 %, μ+μA=55 % and μ+μB=65 % for the "control", "therapeutic patient education" and "connected device" arm modalities, respectively. The expected benefit in the "therapeutic patient education" arm compared to the "control" arm is 15% (40% efficacy in the "control" arm versus 55% efficacy in the "therapeutic patient education" arm). The expected benefit in the "connected device" arm compared to the "control" arm is 25% (40% efficacy in the "control" arm versus 65% efficacy in the "connected device" arm).[22]

The sample size is calculated to allow the two comparisons of interest to be tested bilaterally at the 0.025 threshold. Assuming that the "therapeutic patient education" intervention and the "connected device" intervention act independently (additive model), the sample size required to compare therapeutic patient education (i.e., participants assigned to the "therapeutic patient education" and "combined" arms) versus no therapeutic patient education (i.e., participants assigned to the "control" and "connected device" arms) is given by the following formula:

[μ + (μ+μB)] / 2, versus [(μ+μA) + (μ + μA + μB)/2]

that is, (40 % + 65 %) / 2 = 52,5 %, versus (55 % + 80 %) / 2 = 67,5 %

With a first species risk α=0.025 and a power of 80% in bilateral situation, the number of patients to include per treatment arm to demonstrate the efficacy of the therapeutic patient education will be 108 (or 432 for the four treatment arms) (nQuery V6.0, Chi-two test with continuity correction). This number of patients will also allow a power greater than 95% to evaluate the effectiveness of the "connected device" intervention, always with a risk α =0.025 in bilateral situation.

Data analysis plan

The following populations will be defined for statistical analyses: i) the intent-to-treat (ITT) population, which includes all randomised participants in the study; ii) the per-protocol population, which consists of a subgroup of participants from the ITT population who had no major protocol violations and who

followed the procedure for the duration of the study. Analyses in the ITT population will be performed for all the study endpoints; analysis in the per-protocol population will be performed for exploratory purposes. The randomisation date will be considered as the reference date in all delay calculations, unless otherwise specified.

Baseline data will be described in the ITT population and presented by randomisation arm. For the primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who received the connective device vs. participants who did not; (ii) participants who benefited from the therapeutic patient education intervention vs. participants who did not. Results will be presented with their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the efficacy of the intervention with a connected device (compared to the absence of a connected device); the efficacy of the therapeutic patient education intervention (compared to no therapeutic patient education); and the interest of combining the two intervention modalities (i.e., connected device and therapeutic patient education) compared to the intervention with the connected device only or the intervention with therapeutic patient education only. The analysis strategy will therefore be as follows:[74] 1) searching first for an interaction by a specific interaction test, performed at the significance level of 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the absence of interaction, testing each of the two bilateral interest comparisons at the 0.025 threshold, namely the efficacy of the intervention with connected device and the efficacy of the therapeutic patient education intervention; 3) in case of efficacy of either one of the intervention modalities, evaluating the interest of the combination of the two interventions compared to the intervention with connected device only or the intervention with therapeutic patient education only.

For secondary outcome variables, the efficacy of the program at 12 months, as well as according to stratification criteria, will be analysed similarly to the primary outcome. The adherence to the interventions will be studied by the proportion of compliant participants and participation rate in planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life, fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative

variations of each of these endpoints; these variations will be compared between an intervention and the absence of this intervention, for each intervention, and between their combination and either intervention, using a parametric test. Occupational status and lifestyle factors will be analysed by comparing proportion of participants between interventions or their combination. Representations and acceptability of activity tracker and of therapeutic patient education will be analysed by comparing proportion of participants between randomisation and follow-up assessments. A method for imputing missing data will be considered if necessary.

Statistical analyses will be performed using SAS® software version 9.4 or later.

Medico-economic analysis

The cost-effectiveness analysis will be conducted alongside the trial using the French national health insurance perspective. The time horizon will be 12 months. Hence, neither costs nor effectiveness will be discounted. Mean costs and effectiveness will be derived for all four strategies under consideration: connected device, therapeutic patient education, combined and control arms. Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per quality-adjusted life year (QALY) gained using EQ-5D-5L to estimate utility, cost per life year gained, cost per BMI unit lost and cost per centimetre of waist-to-hip circumference lost. One-way sensitivity analyses will be conducted by varying resource consumption and unit cost parameters and graphically illustrated in a Tornado diagram. The uncertainty surrounding the ICERs will be also captured by a probabilistic analysis using non-parametric bootstrap methods as recommended by the French National Authority for Health.[75]

ADVERSE EVENTS

All participants will continuously report the occurrence of adverse events regarding neuropathies and joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped with the connected device will also report potential adverse events before and after each session of their

exercise program (see *Connected device*). Due to the low risks associated with the interventions,[15] data monitoring will not be conducted for other adverse events.

DATA MANAGEMENT

The database for clinical data and randomisation will be created using EnnovClinical® software. Its access will be secured (personal identification and password protection) for maintaining confidentiality at all times. Individual participants will not be identified in any reports of this trial. All data from the connected device will be merge to the clinical database at the end of the study. Investigators and data analysts will have access to the final dataset.

Data monitoring will be provided by the trial steering committee, including overall project supervision, progress monitoring, advice on scientific credibility, and ensuring the integrity and appropriate running of the project. The clinical research assistant will verify all consent forms, compliance with established protocol and procedures, and data quality in the eCRF. The research team will make biannual reports to the trial steering committee.

PATIENT AND PUBLIC INVOLVEMENT

An association of breast cancer patients' representatives (Europa Donna France, http://www.europadonna.fr/) was involved in preparing the conduct of interventions and evaluations, in particular by considering patients' expectations, experience and desire for global care. The association will be involved in plans to disseminate the study results to breast cancer patients, study participants and wider patient communities concerned.

ETHICS AND DISSEMINATION

The study protocol was approved by the French ethics committee (Comité de Protection des Personnes Est I, ID RCB 2017-A03360-53, 1st February 2018) and its database was reported to the French National Commission for Data Protection and Liberties (CNIL, ref. MR-001 no. 2016177, 13th December 2016).

Substantial protocol modifications will be submitted to the ethics committee for approval and protocol amendment. The trial is prospectively registered on http://www.ClinicalTrials.gov (NCT number: NCT03529383, 17th May 2018).

The study findings will be widely disseminated through the clinical community by publications in international, peer-reviewed journals and by presentations at national and international conferences. They will also be communicated to patients through associations of patients' representatives and science-based information websites. They will be useful for improving clinical care of cancer patients and provide health professionals, institutions and public authorities with useful information for implementing exercise programs for cancer patients. The study sponsors will disseminate the study findings to their stakeholders.

DISCUSSION

This article presents the protocol for the DISCO trial, which aims to evaluate the efficacy of a web-based connected device intervention and of a therapeutic patient education intervention, either alone or combined, on the physical activity levels of breast cancer patients undergoing adjuvant treatment, as well as to assess the cost-effectiveness of the interventions. In the short term, the expected results are to develop autonomy of breast cancer patients in their practice of physical activity, as well as to identify the best strategies of physical activity during breast cancer adjuvant treatments to increase and sustain physical activity levels in patients, overall or in specific subgroups according to BMI, baseline physical activity level and type of adjuvant treatment. In the medium term, the goal of the DISCO trial is to disseminate innovative programs in supportive cancer care, based on evidence-based practice, to systematically integrate exercise in breast cancer cares.

While an increasing number of studies have demonstrated the benefits of exercise in breast cancer patients, the routine implementation in the cancer care process lacks behind evidence and practice guidelines.[76–78] While the prescription of physical activity in supervised programs have been shown superior compared to non-supervised programs,[21,79] semi-supervised interventions seem to yield

comparable or superior benefits than supervised programs.[80] Therefore, the semi-supervised exercise program of the DISCO trial through continuous follow-up has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy.[35,81] Connected devices are tools developed over the last 10 years that are very promising for promoting physical activity in the general population and in chronic diseases such as cancer[82,83] and for developing distance-based physical activity interventions.[84]

The semi-supervised home-based physical activity program of the DISCO trial using the connected device provides flexibility to patients that may facilitate adherence, as well as to overcome barriers due to distance of facilities from women's home and spatial inequalities of access.[26] Connected devices allow proposing a tailored physical activity program to patients regardless of their place of residence, and enable patients to practice physical activities of their choice, at a time that suits them. Therefore, they may reduce geographical and organisational barriers in the access of patients to exercise, a key issue to improve their engagement in regular and sustained physical activity.[26] To overcome motivational barriers to physical activity in oncology, the use of mobile devices has reported benefits such as patient's engagement, as they can help patients staying physically active over the medium and long term.[85,86] Moreover, while some studies have shown that breast cancer patients achieve higher fitness levels during supervised training compared to unsupervised training, low and medium levels of supervision have been shown to be effective and may represent less resource-intensive options for effective and longer term behaviour change strategies based on exercise in cancer patients and survivors.[80,87]

Activity trackers have become increasingly popular in recent years. They have been reported to be pleasant to wear, with positive patients' experience, easy to use and to have a strongly motivational role through real-time display of the number of steps.[88] Also, walking is an inexpensive activity that can be performed anywhere and does not require specific skills. A study that assessed preferences for technology-supported interventions in breast cancer survivors has reported that 63% would like to use

a physical activity mobile application and 90% would find a physical activity tracker useful to monitor and increase physical activity.[34]

Despite the potential benefits of connected devices in cancer care, their use may face important issues. First, their use raises important ethical challenges, related to the sensitivity of data and the security of data storage.[89] To ensure that data transfer and storage guarantee informational privacy and patient safety,[90] an activity tracker made in France (i.e., allowing storing health data in France) and an accredited national health data host were chosen for the DISCO trial. Particularly, insuring medical data security is a reassuring choice for patients to participate in this new kind of medical research. Second, connected devices may raise technical challenges, related to technological robustness, reliability of data collection and processing, and ease of use. Therefore, an activity tracker with step display on the screen, user-friendly interface, good reliability and good price-performance ratio was chosen in the DISCO trial. Third, connected devices may create or exacerbate access disparities related to technological literacy and economic means, as well as reliable access to internet in rural or isolated areas.[89] Fourth, medical reasons are usually not easy to control in patients' adherence to exercise programs. Reliance upon self-assessment of the participant's fatigue, evaluation of the participant before and after each session on the remote monitoring, up as the source of information about the participant's health, can result in the ignorance of aspects of the participant's health that cannot easily be monitored.[89]

Therapeutic patient education has been suggested to increase physical activity in patients with chronic diseases[45] and to improve multiple health outcomes, including behavioural interventions combined with physical activity.[91] Therapeutic patient education interventions might be promising for promoting a physically active lifestyle in cancer patients as it helps patients establish changes in lifestyle and reinforce self-management.[91] Therapeutic patient education differs from patient education in its intrinsic structure. Patient education is directed towards informing and teaching patients how to manage their condition or disease. In contrast, by its structure, therapeutic patient education differs from patient education in the self-management conferred on the patient.[39] Therefore, therapeutic

patient education is more broadly directed towards how the patient accepts his/her condition and manages his/her problems on a daily basis and the impact of the disease on personal, family, professional and social life. Yet, in oncology, few therapeutic patient education studies targeting pain, fatigue, toxicities or treatment adherence are ongoing, and evaluations are rarely published.[40] To our knowledge, only one program of therapeutic patient education specific to physical activity have been evaluated in cancer patients.[44] However, a recent qualitative study has shown the value of promoting therapeutic patient education to better understand the attitudes towards physical activity of women with breast cancer to promote regular exercise, which is a guarantee of a better quality of life.[92]

As the DISCO trial was designed to evaluate the efficacy of two interventions, the primary outcome was based on the physical activity level of the participants comparatively to international recommendations. The primary outcome measure was chosen according to the RPAQ questionnaire for its easy implementation. The authors acknowledge that this declarative evaluation confers methodological limits to the study. But the RPAQ questionnaire has been validated against objective methods (i.e., combined accelerometry and heart rate monitoring)[65] to evaluate moderate-to-vigorous physical activities, which is relevant for the primary outcome. No objective measures of physical activity were planned because of organisational and logistic difficulties to equip and follow participants for one week (i.e., the usual duration of monitoring with an accelerometer such as Actigraph™).[93] Such a test would even be particularly overwhelming for cancer patients during the demanding period of adjuvant treatment onset. Additionally, the number of daily steps reported by the activity tracker was not chosen as primary outcome because the activity tracker used in the study was not validated for monitoring physical activity in research or for medical purposes when the study was designed, although its reliability was checked against other devices (data not shown). However, the performance and reliability of smart devices tends to be increasingly validated.[94]

To understand results of the DISCO clinical study, it is essential to study beliefs about connected devices and their appropriation by the patients, in order to understand why behaviours tend to fade over time. In therapeutic education, beliefs and representations are essential to the success of the

intervention. Moreover, with connected devices, only technical dimensions are not sufficient to understand and highlight why individuals adopt or misuses connected devices.[71,72]

There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of interventions promoting physical activity among women with breast cancer from studies conducted in France, the Netherland and Australia.[95–100] In various chronic conditions other than cancer, there is now clear evidence in favour of exercise-based programs for the treatment of various chronic conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.[101] As more research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers, particularly breast cancer, the economic evaluation planned in the DISCO trial will add useful information.

In conclusion, the study findings will provide valuable information on the efficacy of exercise interventions during breast cancer treatments, overcoming current barriers of access to facilities. They will further guide the development of evidence-based innovative interventions, to systematically include physical activity in the breast cancer care process. Finally, the economic evaluation planned in the DISCO trial will provide useful information for decision makers.

Supplementary file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.

Abbreviations

BMI: body mass index;

eCRF: electronic case report form;

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-Of-Life Questionnaire;

EPICES: Evaluation of Deprivation and Inequalities in Health Examination Centres (questionnaire);

ITT: intent-to-treat;

MET: metabolic equivalent of task;

PFS-12: Piper Fatigue Scale-12;

RPAQ: Recent Physical Activity Questionnaire;

WHO: World Health Organization;

6MWT: six-minute walk test.

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Authors' contributions

BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise training. LP, MT, OP, AM and EB designed the medico-economic study and eCRF. MP, TL, MT, OP and AM designed the part on uses and representations. J-BF, MT and OP designed the part on occupational status. All authors were involved in in planning the methods and measurement and a priori analysis planning. MT and BFo wrote initial draft of the manuscript. All authors reviewed and provided comprehensive contribution to the manuscript, and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

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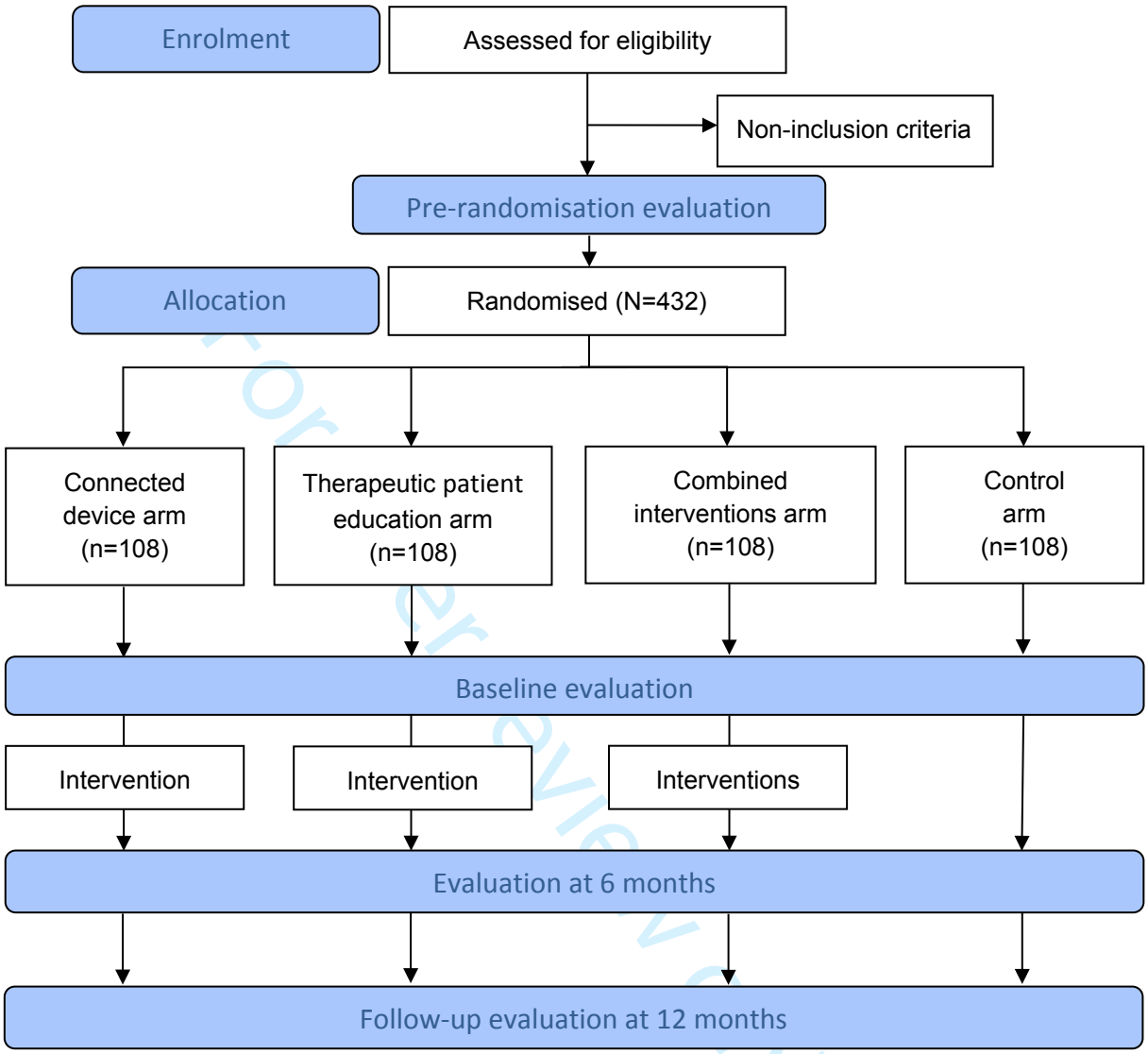
1098 **Table 1** Summary of outcome measures and data collection schedule for the DISCO trial

Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
Demographic and clinical data	Patient's medical record			
- Month/year of birth		X		
- Age at diagnosis		X		
- Employment status		X	X	X
- Personal history of breast cancer		X		
- Current treatment		X	X	X
- Hormonal receptor status		X		
- Tumour histology		X		
- Disease progression			X	X
Anthropometrics				
- Height	Gauge	X		
- Weight	Scale	X	X	X
- Waist-to-hip circumference	Measuring tape	X	X	X
- Body composition: fat mass, lean mass, dry lean mass, body water	Bioelectronic impedancemetry	X	X	X
Physical fitness		X	X	X
- Walking endurance with perceived difficulty	6MWT and Borg scale			
- Lower limb muscle strength	Sit-to-stand test			
- Hand prehensile strength	Hand-grip test			
- Flexibility of lower limbs	Sit-and-reach flexibility test			
- Balance	Bilateral unipodal equilibrium test			
Physical activity level, sitting time and achievement of physical activity recommendations	RPAQ Questionnaire	X	X	X
Patient-reported outcomes				
- Quality of life	EORTC QLQ-C30 questionnaire and BR-23 module	X	X	X
- Health-related quality of life	EQ-5D-5L Questionnaire	X	X	X
- Fatigue	PFS-12 questionnaire	X	X	X
- Social vulnerability	EPICES questionnaire	X		X
Determinants of physical activity				
- Barriers to regular physical activity, lifestyle	Self-administered questionnaire	X	X	X
- Uses, representations and motivation towards physical activity, acceptability of activity trackers (only for patients in the "connected device" and "combined" arms), acceptability of therapeutic patient education (only for patients in the "therapeutic patient education" and "combined" arms)	Online self-administered questionnaire	X	X	X
Biological data	Blood sample	X	X	
- Serum endocrine factors (IGF-1, insulin, estradiol)				

Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
- Plasmatic inflammatory cytokines (IL-6, TNFα, CRP) - Plasmatic adipokines (adiponectin, leptin) - Vitamin D status				
Compliance with each intervention (only for patients in the “connected device”, “therapeutic patient education” and "combined" arms)	Connected device and/or patient’s record		X	
Adverse events (neuropathies, joint pain)	Patient’s diary		X	X

Notes. 6MWT: six-minute walk test

Figure 1 Flow chart of participants through the DISCO trial.



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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 26
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	8, ethics copy
Funding	4	Sources and types of financial, material, and other support	30, funding copy
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 31-32
	5b	Name and contact information for the trial sponsor	1
	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	31
	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)	31

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	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
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)	8
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	8
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)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-15
	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)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	17, Table 1
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)	9, 16-17, Figure1, Table1

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	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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	17-21
	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	17

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	17, 24
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	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24
	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)	23-24
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	25
	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	N/A
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	14, 24-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32
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)	26

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32
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	25
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	N/A
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	25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	31
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9
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	21

*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.

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Connected device and therapeutic patient education to promote physical activity among women with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised controlled trial

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Connected device and therapeutic patient education to promote physical activity among women with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised controlled trial

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ABSTRACT

Introduction: Despite safety and benefits of physical activity during treatment of localized breast cancer, successful exercise strategies remain to be determined. The primary objective of the DISCO trial is to evaluate the efficacy of two 6-month exercise interventions, either single or combined, concomitant to adjuvant treatments, on the physical activity level of breast cancer patients, compared to usual care: an exercise program using a connected device (activity tracker, smartphone application, website) and a therapeutic patient education intervention. Secondary objectives are to evaluate adherence to interventions, their impact at 6 and 12 months, representations and acceptability of interventions, and to assess the cost-effectiveness of the interventions using quality-adjusted life years.

Methods and analysis: This is a 2x2 factorial, multicentre, phase III randomised controlled trial. The study population (with written informed consent) will consist of 432 women diagnosed with primary localized invasive breast carcinoma and eligible for adjuvant chemotherapy, hormonotherapy and/or radiotherapy. They will be randomly allocated between one of four arms: (i) web-based connected device (evolving target number of daily steps and an individualized, semi-supervised, adaptive program of two walking and one muscle strengthening sessions per week in autonomy), (ii) therapeutic patient education (one educational diagnosis, two collective educational sessions, one evaluation), (iii) combination of both interventions, (iv) control. All participants will receive the international physical activity recommendations. Assessments (baseline, 6 and 12 months) will include physical fitness tests, anthropometrics measures, body composition (CT-scan, bioelectrical impedance), self-administered questionnaires [physical activity profile (RPAQ), quality of life (EORTC QLQ-C30, EQ-5D-5L), fatigue (PFS-12), social deprivation (EPICES), lifestyle, physical activity barriers, occupational status] and biological parameters (blood draw).

Ethics and dissemination: This study was reviewed and approved by the French Ethics Committee. The findings will be disseminated to the scientific and medical community via publications in peer-reviewed journals and conference presentations.

Registration: ClinicalTrials.gov NCT03529383; 05/17/2018.

Keywords: Breast cancer, Physical activity, Sitting time, Activity tracker, Connected device, Web-based, eHealth, Therapeutic patient education, Randomised controlled trial

Word count: 8445

Strengths and limitations of this study

- This randomized clinical trial with four arms has the advantage to evaluate the efficacy of two interventions, either single or their combination, using a 2x2 factorial design, ensuring a higher statistical power than a classic trial with three arms, for a similar sample size.
- While the connected device intervention is semi-supervised, the exercise program has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy and to provide organisational flexibility to patients to facilitate adherence.
- Despite the potential benefits of connected devices in cancer care, their use may face important issues, such as ethical challenges related to the security of sensitive data storage, technical challenges related to technological robustness and reliability, exacerbating access disparities, and self-assessment of the participant's fatigue or health condition.
- The primary outcome measure is based on a declarative evaluation of physical activity that confers methodological limits to the study, but the validated questionnaire was chosen according for its easy implementation for cancer patients compared to accelerometer monitoring and its relevance for the primary outcome.

INTRODUCTION

Breast cancer is the leading cause of cancer in women worldwide with 1.6 million new cases diagnosed each year,[1] representing more than a third of all new cancer cases in women. In France, breast cancer also represents the leading cause of cancer incidence and mortality among women, with approximately 58,000 new cases and 12,000 breast cancer deaths estimated in 2018.[2] Despite a very good prognosis worldwide with overall survival of 85% at 5 years (87% in France) and 71% at 10 years (78% in France) for all stages combined,[3–5] a large number of patients with breast cancer experience adverse effects of cancer and its treatments such as fatigue, impaired quality of life, anxiety or weight gain.[6–8]

In women with breast cancer, deteriorations of physical activity level and cardiorespiratory fitness are frequent.[9,10] Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, including any daily life activity of household, occupation, recreation (e.g., sports) or transportation. Exercise is a subset of physical activity that is planned, structured and repetitive, in the purpose of improving or maintaining physical fitness.[11] After a breast cancer diagnosis, lack of physical activity, obesity and weight gain have been shown to increase the risk of cancer-related comorbidities and treatment adverse effects, to worsen long-term health and to cause poor prognosis.[12–14] The benefits of physical activity have been well recognized in primary cancer prevention.[15] Numerous studies have shown the safety[16] and benefits of physical activity performed concomitantly with breast cancer treatments. These benefits include reduced fatigue[17–19] and comorbidities[20], improved quality of life[21,22] and physical functioning,[10,17,19,22] as well as possibly reduced risk of recurrence[23] and improved overall and specific survival with a positive dose-response relationship.[14,23,24] Despite these benefits and international evidence-based guidelines of physical activity prescription for clinicians and their patients, accessibility to exercise programs and implementing the guidelines in the cancer care process remain a challenge for patients and health care providers.[25–27] While a growing number of facilities offer exercise programs to cancer patients, distance

from home constitutes a barrier to regular exercise during cancer treatments.[26] Successful exercise strategies during and beyond cancer treatment remain to be determined in clinical trials.[28]

The recent development of connected devices such as activity trackers offers a real opportunity in oncology to promote and monitor patients' physical activity.[29] While adherence to lifestyle interventions is a major challenge, connected activity trackers and smartphone applications enable structured monitoring of health parameters and provide feedback to patients. A systematic review of randomised controlled trials of physical activity interventions using new technologies such as activity trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly increased their number of steps per day in the majority of the studies.[30] Recent reviews of intervention studies conducted among breast cancer patients have also shown that patients increased their physical activity when they used activity trackers.[31,32] Overall, connected activity trackers receive increasing interest for being systematically integrated into clinical oncology practice.[33,34] Yet, more research is needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the preferences of breast cancer patients.[35–37]

Therapeutic patient education has emerged in the 1990s in response to the recognition of the need to support patients in the self-management of their chronic diseases, such as diabetes and asthma.[38,39] According to the World Health Organization (WHO), therapeutic patient education aims to "help patients acquire or maintain the skills they need to best manage their lives with a chronic disease".[40] In the cancer field, several cancer-specific programs of therapeutic patient education have been set up to manage pain, fatigue, side effects of treatment (chemotherapy, surgery) or compliance to treatment.[41–44] By enhancing relevant knowledge and skills, therapeutic patient education may greatly contribute to increasing patients' autonomy in their disease management. Despite the performance in modifying long-term individual behaviours and adherence to cancer treatments,[44] the benefits of therapeutic patient education on physical activity levels in cancer patients early after diagnosis has been poorly investigated.[45,46] The research on therapeutic patient education in the breast cancer and exercise context is limited to date and warrants further research.

Several biological mechanisms have been proposed to explain the effects of physical activity on breast cancer risk and outcome. Preclinical and human studies have shown the influence of physical activity on several signalling pathways involved in tumour development, growth and progression, including the insulin signalling pathway (IGF-1, insulin), chronic inflammation (involving inflammatory cytokines such as IL-6, TNFα, CRP) and endocrine hormone regulation (estrogens, adipokines).[47–49] By affecting the endogenous systemic milieu, physical activity is believed to influence cellular processes and tumour growth, and therefore reduce the risk of recurrence, increase treatment efficacy and improve survival.[50] Also, because vitamin D alters mechanisms implicated in cellular growth and proliferation, accumulating evidence suggests that normal-to-high ranges of serum vitamin D levels improve breast cancer prognosis and outcome.[51] Based on the data in the literature, it is not possible to conclude a causal relationship between the metabolic effects of physical activity and the impact on breast cancer risk and survival. Biological effects of physical activity on these biomarkers of endogenous mechanisms interfering in cancer suppression or proliferation remain to be elucidated in order to better understand the benefit of physical activity during adjuvant treatment.[49]

In this context, given the accumulating evidence for the benefits and safety of regular exercise during treatments of localized breast cancer, it is necessary to systematically encourage patients to remain or become physically active from the time of diagnosis and to implement and assess the most appropriate strategies of physical activity in clinical practice. The aim of the DISCO trial is to encourage engagement in exercise during breast cancer treatment through two innovative types of interventions, that is to say a web-based connected device and therapeutic patient education, which aim to develop patients' autonomy in their practice of physical activity. The primary objective of the DISCO trial is to evaluate the efficacy of two interventions, either single or combined, concomitant to adjuvant treatments, on the physical activity level of breast cancer patients at the end of the 6-month interventions, compared to usual care: one is an exercise program using a connected device (comprising an activity tracker linked to a smartphone application and a website and providing an individualized, semi-supervised, technology-based exercise program) and the other is a therapeutic

patient education intervention. The research hypothesis is that patients participating in the 6-month exercise program using the connected device or therapeutic education intervention are more likely to achieve the international physical activity recommendations, compared to women receiving physical activity recommendations only (usual care). The WHO recommendations to maintain or improve health, which applied when the study protocol was developed, are to do at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity or an equivalent combination each week, and muscle-strengthening activities at least two days a week.[11] Secondary objectives are: (i) to evaluate the adherence to the interventions; the impact of the interventions on physical fitness, physical activity profile, anthropometrics, quality of life, fatigue, biological parameters, occupational status and lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12 months; the representations and acceptability of activity tracker and therapeutic patient education; and ii) to assess the cost-effectiveness of the interventions. If one of the interventions is individually effective, the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.

METHODS AND DESIGN

Trial design

The DISCO (an acronym for “dispositif connecté”, i.e., connected device in English) trial is a 2x2 prospective, multicentre, factorial, randomised, controlled and open-label study (phase III), conducted by the Léon Bérard comprehensive cancer centre (Lyon, France) among women receiving treatment for localized breast cancer. The clinical protocol was designed and written according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Supplementary file 1). The flowchart of the study is presented in Figure 1. Patients will be randomly assigned to one of the four arms of the study according to the 2×2 factorial design (1:1:1:1 ratio). They will all receive international recommendations on physical activity,[11] and: (i) women allocated to the “connected device” arm will benefit from a 6-month individualized, semi-supervised exercise program carried out autonomously. The program consists of an evolving goal of daily numbers of steps using an activity

tracker and two sessions of brisk walking and one session of muscle strengthening per week, using dedicated smartphone application and website; (ii) women allocated to the "therapeutic patient education" arm will benefit from four therapeutic education sessions on exercise; (iii) women allocated to the "combined" arm will benefit from both interventions in parallel; (iv) women allocated to the "control" arm will receive usual care.

Eligibility criteria for participants

Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and requiring adjuvant treatment (chemotherapy, hormonotherapy and/or radiotherapy) that present at one of the investigating centres; providing a medical certificate of no contraindication to exercise; being available and willing to participate in the study for the duration of the interventions and follow-up; using a personal smartphone compatible with an application used for the intervention (iOS operating system from version 9.3, Android operating system from version 5.0, no Microsoft operating system) and having a computer with Internet access; being able to understand, read and write French; and being affiliated with a social security scheme.

Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal history or co-existence of other primary cancer (except for in situ cancer regardless of the site, basal cell skin cancer and non-mammary cancer in complete remission for more than 5 years); presenting a contraindication to exercise according to the investigator (such as cardiorespiratory or bone pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe malnutrition according to the criteria of the French National Health Authority (i.e., for women ≤70 years: weight loss ≥15% in 6 months or ≥10% in 1 month; for women >70 years: weight loss ≥15% in 6 months or ≥10% in 1 month, and body mass index (BMI) <18 kg/m²);[52] being unable to be followed for medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or breastfeeding or of childbearing age without effective contraception for the duration of the study.

Recruitment

Recruitment started in May 2018. Participants will be recruited at several national comprehensive cancer centres, clinics or hospitals located in France (see ClinicalTrials.gov NCT03529383), which will ensure adequate participant enrolment to reach the target sample size in a timely manner. Inclusion of patients will be carried out after surgery and confirmation of the indication of adjuvant treatment. The study will be proposed to patients at the postoperative, pre-chemotherapy or pre-radiotherapy consultation (by the surgeon, oncologist or radiotherapist investigator, respectively) depending on the patient's treatment plan. At this visit, the investigator will check all eligibility criteria and propose to the eligible patients to participate in the study, explain the objectives and study process and give them an information notice. After sufficient time for reflection, eligible patients who agree to participate will date and sign an informed consent (see Supplementary file 2) and will be included prior to the onset of adjuvant therapy (or within one month thereafter). The number of eligible patients refusing to participate in the study and the reason for non-participation will be recorded.

Randomisation

Prior to randomisation, participants will be asked to complete the Recent Physical Activity Questionnaire (RPAQ) to assess their level of physical activity.[53] Their weight, body size and prescribed adjuvant treatments will be collected from the patient's medical record.

Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris, France) into one of the four arms of the trial, by using the following minimization criteria:[54,55] BMI (<25 kg/m², ≥25 and <30 kg/m², ≥30 kg/m²), baseline physical activity level from RPAQ (<150 min/week, ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant treatments at inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ± radiotherapy, chemotherapy ± radiotherapy, radiotherapy only).

INTERVENTIONS

At baseline, all participants will receive the international recommendations in terms of physical activity for promoting health in the general population[11], which will be delivered orally by a certified exercise instructor with the help of a leaflet.

Intervention with a connected device

Participants randomised to the "connected device" arm will benefit from a 6-month exercise program. The connected device consists of an activity tracker (connected wristband, LS417-F model, CARE Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application and a dedicated website proposing an individualized, semi-supervised exercise program adapted to cancer patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based exercise program will aim to support participants to enhance physical activity in two ways: doing structured exercise sessions and increasing daily physical activity (number of steps). Exercise sessions will be automatically generated by an algorithm based on the patient profile (described below). The participants will receive notifications informing them of a new structured exercise session available on the website or mobile application, or alerting them when a session was not carried out, and inviting them to execute it when possible. Participants will receive a free 6-month subscription to the program.

—*Setting up the connected device:* At the end of the baseline assessment, the certified exercise instructor will introduce the customized exercise program to the participants and will give them the activity tracker and a user guide for the connected device. Then, the certified exercise instructor will explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated website, as well as assist the participants to install the application on their smartphone. The participants will be registered in the customized exercise program by the certified exercise instructor. The registration will consist of completing a web-based questionnaire about personal and health data to determine the participant profile (age, weight, height, level of aerobic and muscular strength, treatment, symptoms, availabilities for exercise sessions and sports materials).

—*Baseline level of aerobic and muscular strength for the individualised exercise program:* The physical fitness tests performed at baseline will be used to classify the participants at the start of the exercise program according to their aerobic level (for the walking sessions) and their muscular strength level (for the strengthening sessions). The aerobic level categories will be determined by the distance performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level categories will be determined by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test: muscular strength group 1 (≤10 repetitions), muscular strength group 2 (11 to 14 repetitions) and muscular strength group 3 (≥15 repetitions). Thresholds were based on average values reached by women receiving breast cancer treatments for the 6MWT (pooled mean value, 523 m) and the Sit-to-stand test (pooled mean value, 13 repetitions) from a previous study;[56] these values were checked for consistency with percentile scores obtained at the 6MWT and Sit-to-stand test in community-dwelling older women,[57] then the interquartile range was used to determine the thresholds for the three groups of this study. The level categories assigned will be entered by the exercise instructor in the baseline patient profile and will be used by the automated algorithm to set up the level of the first walking and muscle strengthening sessions.

—*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise instructor through an individual follow-up of participants (see 'Participant follow-up' part and 'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using the smartphone application and the website. The program is based on three structured unsupervised sessions per week alternating two types of exercise: two walking sessions (by following oral instructions given via the smartphone application) and one muscle strengthening session (by using videos accessible on the website). The levels of the first walking and muscle strengthening sessions will be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent sessions will be planned according to the available days of the participant. Strengthening exercises will be adapted according to sports materials available at their home (e.g., Swiss ball, sports mat, stick,

weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a body session of 10 to 35 minutes of strengthening exercises, or 10 to 50 minutes of walking (mixing continuous and/or intermittent effort); 3) a 5-minute recovery period, consisting of stretching and relaxation during strengthening sessions or a cool down during walking sessions. Sessions will be of moderate-to-high intensity (≥ 3 and ≤ 9 METs).

The three structured unsupervised exercise sessions per week are configured by a unique algorithm hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to plan the exercise sessions and determine the exercise level in an adapted and progressive manner by increasing the duration and then intensity in accordance with principles of exercise training and progression.[58,59] At the beginning of each session, the duration and intensity of the session will be determined according to the perceived difficulties (evaluated by a Borg scale) and emotional state (recorded by an emoji) of the participant in the previous session, and will be modified or postponed according to the level of fatigue (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg scale), the presence or absence of unusual muscle pain and the presence or absence of unusual nausea/diarrhea. In case of a severe adverse event related to disease or treatment (i.e., joint disability, osteoarthritis, cachexia, hand-foot syndrome, aplasia, diuretic, axillary node dissection, pace-maker, chemotherapy, targeted therapy, hormone therapy, radiotherapy, COPD, diabetes) or temporary contraindication to exercise, declared by the participant on her device, the program and sessions will be adapted or suspended until the participant's health improves.

In addition, participants will have the opportunity to perform additional exercise sessions according to their preferences and lifestyle, outside the program. Participants will be asked to record these sessions through the smartphone application or the website: type of activity (e.g., walking, hiking, cycling) from a list adapted from Ainsworth's Compendium,[60] and its duration and intensity.

—*Number of daily steps:* Participants will be advised to wear the activity tracker daily and to launch the application regularly (preferably daily), which will automatically synchronize with the activity tracker via Bluetooth connection and will collect the number of steps. The target number of steps will

be 3,000 steps per day at the program onset, and then will be re-set based on the average number of daily steps during the first week after inclusion. The target number of daily steps will evolve automatically every three weeks based on the average number of daily steps achieved during the previous three weeks, and will be updated automatically in the application. Consistent with principles of exercise training and progression,[58,59] after each 3-week cycle, if the goal of steps per day is reached by the participant, the target goal will increase by 15% during the following 3-week-cycle, within a maximum target of 10,000 daily steps. If the average number of daily steps does not meet the goal, the target will remain unchanged in the next cycle.

—*Participant follow-up*: Telephone follow-ups will be carried out by the certified exercise instructor at 10 days, 2 months and 4 months after the intervention onset to ensure the proper functioning of the connected device, review the use of the connected device, review the conduct of the sessions and answer the participants' questions if they may have. Participants will be orally encouraged to remain physically active on a daily basis (reminder of the benefits and recommendations of physical activity, success and satisfaction during the exercise sessions). During the 6-month intervention, the participants will have the opportunity to contact the certified exercise instructor or the clinical research assistant at any time, by e-mail (directly through the website) or by telephone for any question or assistance with the connected device.

—*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device by the participants and their progress in the program through a dedicated professional website that provides real-time access to the participants' data. On this website, an automatically generated daily event table will inform the certified exercise instructor of the occurrence of disabilities reported by the participants that may lead to modifying their program (e.g., severe fatigue, dyspnea, unusual muscle pain) or if participants have not performed their planned sessions or used their activity tracker for seven consecutive days. Upon these alerts, the certified exercise instructor will contact the participants to precisely analyse the reported disabilities, advise participants, identify the causes of non-use of the connected device, solve possible technical problems or reinforce participant's motivation if necessary.

—*End of the intervention*: At the end of the 6-month program, participants will keep their activity tracker to be encouraged to continue regularly exercising in autonomy. Upon their request, continued subscription to the dedicated application and website will be offered for another six months, with no individual follow-up anymore.

Intervention of therapeutic patient education

Participants randomised to the therapeutic patient education arm will benefit from a therapeutic patient education intervention, in addition to receiving the international physical activity recommendations. The intervention is part of the therapeutic patient education program set up at the Léon Bérard cancer centre and validated by the Regional Health Agency ("Agence Régionale de Santé Rhône-Alpes"). It will be disseminated in the investigating centres according to the criteria of the Regional Health Agency. The therapeutic patient education intervention consists of four sessions that will be scheduled according to participants' availability during their follow-up visits as part of their usual clinical management over a 6-month period.

First, participants will be invited to an initial 1-hour individual face-to-face session of educational diagnosis with a health professional trained in therapeutic patient education. This session will assess their needs and establish a contract of objectives to reach. Then, participants will be invited to participate in two collective educational sessions (1h30 each with a group of 10 patients maximum per session). These sessions will be composed of theoretical and practical workshops to help them understand their physical activity in their daily life and implement the necessary means to practice regular exercise in autonomy. Finally, participants will be invited to another 1-hour individual session, where an educational evaluation will be conducted to identify whether they achieve their individual objectives set at the time of the educational diagnosis.

Combined interventions

Participants randomised to the 'combined intervention' arm will benefit from a combination of the connected device intervention and the therapeutic patient education intervention in parallel for 6 months.

EVALUATIONS

The initial assessment (T0) will be performed prior to randomisation for minimization purposes. The other three evaluations will then be conducted at baseline (T1), 6 months (T2) and 12 months (T3). All study participants will then be followed at 6 months ±1 month post-randomisation (corresponding to the end of participation in the interventions for women in the connected device, therapeutic patient education and combined arms) and at 12 months ±1 month post-randomisation (corresponding to a follow-up period of 6 months post-interventions). Assessments will be carried out by a clinical research assistant and a certified exercise instructor. The clinical research assistant will contact participants by phone to invite them to follow-up visits and to promote participant retention and complete follow-up. Participants will have no compensation for participation and all study visits will be scheduled on days of their medical or health-related appointments.

All evaluations (baseline, 6 and 12 months) will include physical fitness tests, anthropometric measures, self-administered questionnaires and a non-fasting blood draw (baseline and 6 months only). Data will be recorded using an electronic case report form (eCRF).

DATA COLLECTION

The study outcome measures and their schedule are summarised in Table 1.

Socio-demographic and clinical data

Socio-demographic and clinical data, including month/year of birth, age at diagnosis of breast cancer, family status, level of education, hormonal status, tumour histology and personal history of

breast cancer will be collected at baseline. Family status, potential cancer progression and all treatments received for cancer will be collected at 6 and 12 months. All data will be extracted from patients' electronic medical records, except family status and level of education that will be self-reported in a questionnaire.

The occupational status will be assessed using a self-administered questionnaire asking employment status, occupation, size of the company, the perceived intensity of the physical effort at work, the evolution of employment status at return to work in case of sick leave.[61]

Anthropometrics and body composition

The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be measured using standardized procedures and BMI will be calculated as the body weight in kilograms divided by the square of the height in meters (kg/m²). The waist circumference will be measured midway between the last floating rib and the iliac crest. The hip circumference will be measured at the tip of the pubis. Body composition will be measured by a bioelectrical impedance meter (Biody XPert ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid (in L).

Physical fitness

Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance covered in metres) with perceived difficulty using the Borg scale.[62] During this test, participants will be asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes. The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as many times as possible during 30 seconds.[63]

Hand prehensile strength will be measured by the handgrip test using hand dynamometry (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the isometric strength of the hand and forearm muscles.[64] During this hand-grip test, participants will be asked to squeeze the handgrip as strongly as possible to obtain the maximal force (in kg). Two measures will be performed on each hand and the best performance will be registered.

The flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe Baseline flexibility test, 3B Scientific, Bartenheim, France).[65] In this test, participants will sit on the floor on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering the level of the feet as recording zero, any measure that does not reach the toes is negative and any measure beyond the toes is positive).

The balance will be measured using the bilateral single-leg stance test.[66] The participants will stand and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).

Physical activity level, sitting time and achievement of physical activity recommendations

The validated self-administered questionnaire RPAQ will be used to measure the self-reported physical activity.[53,67] The RPAQ was designed to assess usual physical activity in the last four weeks, covering three activity domains: domestic physical activity, including sitting time that is a good proxy of sedentary behaviour; occupational physical activity, including transportation to and from work; and recreational physical activity. The RPAQ gives specific scores in the metabolic equivalent of task (MET) unit for activities of very low intensity (<1.5 METs, i.e., sedentary activities), low intensity (1.5 to <3 METs), moderate intensity (3 to <6 METs) and high intensity (≥6 METs, i.e., vigorous activities) within each domain during the past four weeks. Questions will be coded and converted in MET-minute per four weeks according to the Compendium of Physical Activities[60] by multiplying the number of METs by the duration and frequency of each activity. Then, the global score of physical activity will be

obtained by adding the number of MET-minutes per four weeks in each intensity and each domain. The physical activity profile will be defined as the time spent in physical activities of low, moderate and high intensities. The physical activity level will be defined by the overall weekly physical activity (average expressed in MET-hour/week).

Achievement of international physical activity guidelines will be computed for each individual by dividing the time spent in moderate-to-vigorous physical activity (i.e., ≥3 METs) into two categories:[11] <150 min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines); ≥150 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).

Patient-reported outcomes

The quality of life will be measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality-Of-Life Questionnaire (QLQ-C30) and its specific module for breast cancer (BR-23).[68] The QLQ-C30 is a 30-item validated self-administered questionnaire that evaluates five functioning domains (i.e., physical, role, emotional, cognitive and social), a global quality-of-life domain, three symptom domains (i.e., pain, fatigue and nausea) and six single items (i.e., dyspnea, insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds to a better functioning level. For scales related to symptoms, a lower score corresponds to a better functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.

The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.[69] This standardized self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight, moderate, severe and extreme problems), and comprises a 0-100 visual analogue scale recording the self-rated health (where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine').

Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of fatigue):[70] the higher the score, the worse the fatigue. All items together will produce a total score for fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3), moderate fatigue (score 4-6) and severe fatigue (score 7-10).

Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centres) score.[71] The score will be computed by adding each question coefficient to the intercept whenever the answer is "yes." The score ranges from 0 to 100 (i.e., the higher the score, the greater the deprivation level) with the threshold for deprivation at 30.

Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e., never, former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol intake over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer, cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses). The amount of alcohol will be computed by multiplying the frequency of consumption by the number of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.

Determinants of Physical activity

The 21-item self-administered questionnaire "Barriers to Being Active Quiz" will be used to qualitatively assess barriers to the regular practice of physical activity.[72]

Uses, representations and motivation towards physical activity will be assessed within the study population using a self-administered questionnaire available online. Acceptability of connected devices and acceptability of therapeutic patient education will be assessed among participants randomised to the corresponding arms using a paper-based self-administered questionnaire. These questionnaires will be developed following the Unified Theory of Acceptance and Use of Technology

(UTAUT),[73] which is a specification of the Theory of Planned Behaviour[74] designed to explain and predict the probability of behaviour change among individuals faced with new technologies. The Theory of Planned Behaviour has been massively used during the last two decades to promote health behaviours such as physical activity. Besides, item wording will be based on the results of individual and collective interviews conducted for that purpose and designed to identify social representations[75] of health protection and physical activity incentive devices.

Compliance with interventions

Compliance with each intervention will be assessed at the 6-month evaluation only for patients randomized to the “connected device”, “therapeutic patient education” and "combined" arms. Compliance will be assessed by the number of days of use of the activity tracker, the participation rate in scheduled exercise sessions, the participation rate in scheduled therapeutic education sessions and the proportion of compliant patients, depending on the intervention allocated, following the recommendations of the protocol. Patients’ compliance and reasons for non-compliance during the intervention period (6 months) will be described for each arm.

Biological assessments

A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at baseline and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant treatments, otherwise no blood samples will be collected. The following biological factors will be assessed in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol), circulating plasma levels of inflammatory cytokines (IL-6, TNFα, CRP), circulating plasma levels of adipokines (adiponectin, leptin) and vitamin D status.

STUDY OUTCOMES

The primary endpoint will be the proportion of women who achieve at 6 months the internationally recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical activity, i.e., intensity ≥3 METs) assessed by the RPAQ self-administered questionnaire.

Secondary endpoints will be:

1. Assessment of the efficacy of the programs at 12 months (i.e., the proportion of women who achieve the internationally recommended level of physical activity);

2. Assessment of the adherence to the interventions at 6 months (the proportion of participants who are compliant to the program, participation rate in planned sessions);

3. Assessment of the impact between baseline and 6 months and between 6–12 months of the interventions on physical activity profile (changes in time spent in different intensities of physical activity and time spent in sedentary activities), physical fitness (changes in results to the 6-minute walk test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test), anthropometrics (changes in weight, waist and hip circumferences, BMI, fat mass, lean body mass, muscle mass, dry lean mass and body water), quality of life (changes in scores obtained from the EORTC QLQ-C30 questionnaire and its BR-23 module), fatigue condition (changes in scores obtained from the PFS-12 questionnaire), health-related quality of life (changes in scores obtained from the EQ-5D-5L questionnaire), social deprivation (changes in scores obtained from the EPICES self-administered questionnaire), occupational status (the proportion of participants who changed their employment status, with return to work and who perceived difficulty at work obtained from a self-administered questionnaire) and lifestyle factors (the proportion of participants who change their tobacco use and alcohol intake obtained from a self-administered questionnaire).

4. Assessment of the impact of the interventions on biological parameters between baseline and 6 months (changes in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], changes in plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines: adiponectin and leptin], the proportion of participants with a modification on vitamin D status).

5. Assessment of the representations and acceptability of activity tracker and therapeutic patient education, at baseline, 6 and 12 months (proportions of participants who accept the connected device and who accept the therapeutic program, according to scores obtained from a self-administered qualitative questionnaire used in social psychology science).

6. Assessment of refusal rate among eligible patients (the proportion of patients who refuse to participate).

7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital costs (national data) and benefit in physical activity level.

STATISTICAL ANALYSIS

Sample size determination

The efficacy rate assumptions are μ=40 %, $\mu+\mu A$=55 % and $\mu+\mu B$=65 % for the “control”, “therapeutic patient education” and “connected device” arm modalities, respectively. The expected benefit in the “therapeutic patient education” arm compared to the “control” arm is 15% (40% efficacy in the “control” arm versus 55% efficacy in the “therapeutic patient education” arm). The expected benefit in the “connected device” arm compared to the “control” arm is 25% (40% efficacy in the “control” arm versus 65% efficacy in the “connected device” arm).[23]

The sample size is calculated to allow the two comparisons of interest to be tested bilaterally at the threshold of 0.025. Assuming that the "therapeutic patient education" intervention and the "connected device" intervention act independently (additive model), the sample size required to compare therapeutic patient education (i.e., participants assigned to the "therapeutic patient education" and "combined" arms) versus no therapeutic patient education (i.e., participants assigned to the "control" and "connected device" arms) is given by the following formula:

$[\mu + (\mu+\mu B)] / 2$, versus $[(\mu+\mu A) + (\mu + \mu A + \mu B)/2]$

that is, (40 % + 65 %) / 2 = 52,5 %, versus (55 % + 80 %) / 2 = 67,5 %

With a first species risk α=0.025 and a power of 80% in the bilateral situation, the number of patients to include per treatment arm to demonstrate the efficacy of the therapeutic patient education will be 108 (or 432 for the four treatment arms) (nQuery V6.0, Chi-two test with continuity correction). This number of patients will also allow a power greater than 95% to evaluate the efficacy of the "connected device" intervention, always with a risk α = 0.025 in the bilateral situation.

Data analysis plan

The following populations will be defined for statistical analyses: i) the intent-to-treat (ITT) population, which includes all randomised participants in the study; ii) the per-protocol population, which consists of a subgroup of participants from the ITT population, who has no major protocol violations and who follows the procedure for the duration of the study. Analyses in the ITT population will be performed for all the study endpoints; analyses in the per-protocol population will be performed for exploratory purposes. The randomisation date will be considered as the reference date in all delay calculations, unless any other way is specified.

Baseline data will be described in the ITT population and presented by randomised arms. For the primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who received the connected device vs. participants who did not; (ii) participants who benefited from the therapeutic patient education intervention vs. participants who did not. Results will be presented with their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the efficacy of the intervention with a connected device (compared to without a connected device); the efficacy of the therapeutic patient education intervention (compared to no therapeutic patient education); and the interest of two combined intervention modalities (i.e., connected device and therapeutic patient education) compared to the single intervention with the connected device only or with therapeutic patient education only. The analysis strategy will therefore be as follows:[76] 1) searching first for an interaction by a specific interaction test, performed at the significance level of 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the absence of interaction,

testing each of the two bilateral interest comparisons at the threshold of 0.025, namely the efficacy of the intervention with the connected device and the efficacy of the therapeutic patient education intervention; 3) in case of the efficacy of either one of the intervention modalities, evaluating the interest of the combination of the two interventions compared to the single intervention with the connected device only or with therapeutic patient education only.

For secondary outcome variables, the efficacy of the program at 12 months, as well as according to stratification criteria, will be analysed similarly to the primary outcome. The adherence to the interventions will be evaluated by the proportion of compliant participants and participation rate in planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life, fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative variations in each of these endpoints; these variations will be compared between with and without each intervention, for each intervention, and between combined interventions and the single one, using a parametric test. Occupational status and lifestyle factors will be analysed by comparing the proportion of participants between interventions or their combination. Representations and acceptability of activity tracker and therapeutic patient education will be analysed by comparing the proportion of participants between randomisation and follow-up assessments. A method for imputing missing data will be considered if necessary.

Statistical analyses will be performed using SAS® software version 9.4 or later.

Medico-economic analysis

The cost-effectiveness analysis will be conducted alongside the trial using the French national health insurance perspective. Quantities of resources used [external consultations, hospital stays including Diagnosis-related groups, drugs with extra payments and other healthcare-related costs] will be collected on the eCRF and multiplied by the respective unit costs. The intervention with therapeutic patient education and the intervention with connected device will be evaluated using a bottom-up micro-costing approach.[77,78] Using the Diagnosis-related group, hospital stays will be evaluated based

on the French National hospital costs study database. External consultations and wider examinations, community care (general practitioner visits, nurse visits, etc.) will be valued on the basis of the General Nomenclature of Professional Treatments (NGAP, "Nomenclature Générale des Actes Professionnels"). The cost of biological treatments will be estimated using the Nomenclature of Biological Medical Treatments (NABM, "Nomenclature des Actes de Biologie Médicale"). The cost of technical treatments (e.g., imaging) will be estimated using the Common Classification of Medical Treatments (CCAM, "Classification Commune des Actes Médicaux"). Acquisition costs for the most expansive drugs will be based on the list of common units of dispensation for supplementary medicines ("liste des unités communes de dispensation prise en charge en sus"). Finally, costs of medical transport will be derived from the French Court of Audit's report on medical transport expenses covered by the French National Health insurance. The time horizon will be 12 months. Hence, neither costs nor effectiveness will be discounted. Mean costs and effectiveness will be derived for all four strategies under consideration: connected device, therapeutic patient education, combined and control arms. Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per quality-adjusted life year (QALY) gained using EQ-5D-5L to estimate utility, cost per life year gained, cost per BMI unit lost and cost per centimetre of waist-to-hip circumference lost. One-way sensitivity analyses will be conducted by varying resource consumption and unit cost parameters and graphically illustrated in a Tornado diagram. The uncertainty surrounding the ICERs will be also captured by a probabilistic analysis using non-parametric bootstrap methods as recommended by the French National Authority for Health.[79]

ADVERSE EVENTS

All participants will continuously report the occurrence of adverse events regarding neuropathies and joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped with the connected device will also report potential adverse events before and after each session of their exercise program (see *Connected device*). Due to the low risks associated with the interventions,[16]

this study is part of the so-called “intervention research with minimal risks and constraints” in the French legislation and therefore only these adverse events arising within the framework of the study will be reported.

In the occurrence of an adverse event regarding neuropathies and joint pain, the principal investigator will report it to the health authorities responsible for vigilance without delay. The promotor will also report the adverse events, as well as any safety measures to be proposed, to the French Ethics Committee and the investigators without delay.

DATA MANAGEMENT

The database for clinical data and randomisation will be created using EnnovClinical® software. Its access will be secured (personal identification and password protection) for maintaining confidentiality at all times. Individual participants will not be identified in any reports of this trial. All data from the connected device will be merged to the clinical database at the end of the study. Investigators and data analysts will have access to the final dataset.

Data monitoring will be provided by the trial steering committee, including overall project supervision, progress monitoring, advice on scientific credibility, and ensuring the integrity and appropriate running of the project. The clinical research assistant will verify all consent forms, compliance with established protocol and procedures, and data quality in the eCRF. The research team will make biannual reports to the trial steering committee.

PATIENT AND PUBLIC INVOLVEMENT

An association of breast cancer patients’ representatives (Europa Donna France, http://www.europadonna.fr/) was involved in preparing the conduct of interventions and evaluations, in particular by considering patients' expectations, experience and desire for global care. The association will be involved in plans to disseminate the study results to breast cancer patients, study participants and wider patient communities concerned.

ETHICS AND DISSEMINATION

The study protocol was approved by the French ethics committee (Comité de Protection des Personnes Est I, ID RCB 2017-A03360-53, 1st February 2018) and its database was reported to the French National Commission for Data Protection and Liberties (CNIL, ref. MR-001 no. 2016177, 13th December 2016). Substantial protocol modifications will be submitted to the ethics committee for approval and protocol amendment. The trial has been prospectively registered on http://www.ClinicalTrials.gov (NCT number: NCT03529383, 17th May 2018).

The study findings will be widely disseminated through the clinical community by publications in international, peer-reviewed journals and by presentations at national and international conferences. They will also be communicated to patients through associations of patients' representatives and science-based information websites. They will be useful for improving the clinical care of cancer patients and providing useful information for implementing exercise programs for cancer patients to health professionals, institutions and public authorities. The study sponsors will disseminate the study findings to their stakeholders.

DISCUSSION

This article presents the protocol for the DISCO trial, which aims to evaluate the efficacy of a web- and mobile-based connected device intervention and of a therapeutic patient education intervention, either single or combined, on the physical activity levels of breast cancer patients undergoing adjuvant treatment, as well as to assess the cost-effectiveness of the interventions. This multicentre study opened in May 2018 and recruitment is expected to end in Summer 2021. In the short term, the expected results are to develop the autonomy of breast cancer patients in their practice of physical activity, as well as to identify the best strategies of physical activity during breast cancer adjuvant treatments to increase and sustain physical activity levels in patients, overall or in specific subgroups according to BMI, baseline physical activity level and type of adjuvant treatment. In the medium term,

the goal of the DISCO trial is to disseminate innovative programs in supportive cancer care, based on scientific evidence, to systematically integrate exercise in breast cancer cares.

While an increasing number of studies have demonstrated the benefits of exercise in breast cancer patients, the routine implementation in the cancer care process lacks behind evidence and practice guidelines.[80–82] While the prescription of physical activity in supervised programs has been shown superior compared to non-supervised programs,[22,83] semi-supervised interventions seem to yield comparable or superior benefits to supervised programs.[84] Therefore, the semi-supervised exercise program of the DISCO trial through continuous follow-up has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy.[36,85] Connected devices are tools developed over the last 10 years that are very promising for promoting physical activity in the general population and in patients with chronic diseases such as cancer[86,87] and for developing distance-based physical activity interventions.[88]

The semi-supervised home-based physical activity program of the DISCO trial using the connected device provides flexibility to patients that may facilitate adherence and to overcome barriers due to distance of facilities from women's home and spatial inequalities of access.[27] Connected devices allow proposing a tailored physical activity program to patients regardless of their place of residence, and enable patients to practice physical activities of their choice, at any time that suits them. Therefore, they may reduce geographical and organisational barriers in the access of patients to exercise, a key issue to improve their engagement in regular and sustained physical activity.[27] Previous studies in oncology have reported that the use of mobile devices has benefits to overcome motivational barriers to physical activity, which can help patients staying physically active over the medium and long term.[89,90] Moreover, some studies have shown that breast cancer patients achieved higher fitness levels during supervised training compared to unsupervised training, even low and medium levels of supervision have been effective, as less resource-intensive options for effective and longer-term behaviour change strategies based on exercises in cancer patients and survivors.[84,91]

Activity trackers have become increasingly popular in recent years. Patients have reported positive feedback on using activity trackers such as pleasant to wear, easy to use and a strong motivational role through the real-time display of daily number of steps.[92] Also, walking is an inexpensive activity that can be performed anywhere and does not require specific skills. A study on preferences for technology-supported interventions in breast cancer survivors has reported that 63% would like to use a physical activity mobile application and 90% would find a physical activity tracker useful to monitor and increase physical activity.[35]

Despite the potential benefits of connected devices in cancer care, their use may face several important issues. First, ethical challenges related to the security of sensitive data storage have been raised.[93] To ensure that data transfer and storage guarantee informational privacy and patient safety,[94] an activity tracker made in France (i.e., allowing storing health data only in France) and an accredited national health data host were chosen for the DISCO trial. Particularly, ensuring medical data security is a reassuring choice for patients to participate in this new kind of medical research. Second, technical challenges have been raised, related to technological robustness, reliability of data collection and processing, and ease of use. Therefore, an activity tracker with a step display on the screen, a user-friendly interface, good reliability and a good price-performance ratio was chosen in the DISCO trial. Third, connected devices may create or exacerbate access disparities related to technological literacy and economic means, as well as reliable access to the internet in rural or isolated areas.[93] Fourth, medical reasons are usually not easy to control in patients' adherence to exercise programs. Reliance upon self-assessment of the participant's fatigue, evaluation of the participant before and after each session on the remote monitoring, up as the source of information about the participant's health, can result in the ignorance of aspects of the participant's health that cannot easily be monitored.[93]

Therapeutic patient education has been suggested to increase physical activity level in patients with chronic diseases[46] and to improve multiple health outcomes, together with behavioural interventions including physical activity.[95] Therapeutic patient education interventions might be promising for promoting a physically active lifestyle in cancer patients as it helps patients establish lifestyle changes

and reinforce self-management.[95] Therapeutic patient education differs from traditional patient education in its intrinsic structure. Traditional patient education is directed towards informing and teaching patients how to manage their condition or disease. In contrast, therapeutic patient education differs from traditional patient education in the self-management conferred on the patient.[40] Therefore, therapeutic patient education is more broadly directed towards how the patient accepts his/her condition and manages his/her problems on a daily basis and the impact of the disease on personal, family, professional and social life. Yet, in oncology, few therapeutic patient education studies targeting pain, fatigue, toxicities or treatment adherence are ongoing, and evaluations are rarely conducted.[41] To our knowledge, only one program of therapeutic patient education specific to physical activity has been evaluated in cancer patients.[45] However, a recent qualitative study has shown the value of therapeutic patient education on the attitudes towards the physical activity of women with breast cancer to promote regular exercise, which is a guarantee of a better quality of life.[96]

In order to evaluate the efficacy of two interventions in the DISCO trial, the primary outcome measure will be based on the physical activity level of the participants with or without interventions compared to international recommendations. The RPAQ questionnaire will be used for the primary outcome measure on account of its easy implementation. The authors acknowledge that this declarative evaluation confers methodological limits to the study. But the RPAQ questionnaire has been validated against objective methods (i.e., combined accelerometry and heart rate monitoring)[67] to evaluate moderate-to-vigorous physical activities, which is relevant for the primary outcome. No objective measures of physical activity have been planned because of organisational and logistic difficulties to equip and follow participants for one week (i.e., the usual duration of monitoring with an accelerometer such as Actigraph™).[97] Such a test would even be particularly overwhelming for cancer patients during the demanding period of adjuvant treatment onset. Additionally, the number of daily steps reported by the activity tracker was not chosen as the primary outcome because the activity tracker used in the study was not validated for monitoring physical activity in research or for

medical purposes when the study was designed, although its reliability was evaluated against other devices (data not shown). However, recently the performance and reliability of smart devices tend to be increasingly validated.[98]

To understand the results of the DISCO clinical study, it is essential to study beliefs about connected devices and their appropriation by the patients, particularly to understand why behaviours of the patients tend to fade over time. In therapeutic education, beliefs and representations are essential to the success of the intervention. Moreover, with the connected devices, only technical dimensions are not sufficient to understand and highlight why individuals adopt or misuse the connected devices.[73,74]

There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of interventions promoting physical activity among women with breast cancer from studies conducted in France, the Netherland and Australia.[99–104] In various chronic conditions other than cancer, there is now clear evidence in favour of exercise-based programs for the treatment of various chronic conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.[105] As more research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers, particularly breast cancer, the economic evaluation planned in the DISCO trial will fill in the gap by adding useful information.

In conclusion, the study findings will provide valuable information on the efficacy of exercise interventions during breast cancer treatments, overcoming current barriers of access to facilities. They will further guide the development of evidence-based innovative interventions, to systematically include physical activity in the breast cancer care process. Finally, the economic evaluation planned in the DISCO trial will provide useful information for decision-makers.

Supplementary file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.

Supplementary file 2: English language example of the patient consent

Abbreviations

BMI: body mass index;

eCRF: electronic case report form;

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-Of-Life Questionnaire;

EPICES: Evaluation of Deprivation and Inequalities in Health Examination Centres (questionnaire);

ITT: intent-to-treat;

MET: metabolic equivalent of task;

PFS-12: Piper Fatigue Scale-12;

RPAQ: Recent Physical Activity Questionnaire;

WHO: World Health Organization;

6MWT: six-minute walk test.

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Authors' contributions

BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise

training. LP, MT, OP, AM and EB designed the medico-economic study and eCRF. MP, TL, MT, OP and AM designed the part on uses and representations. J-BF, MT and OP designed the part on occupational status. All authors were involved in in planning the methods and measurement and a priori analysis planning. MT and BFo wrote the initial draft of the manuscript. All authors reviewed and provided comprehensive contribution to the manuscript, and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethics approval was provided by the French Ethics Committee (Comité de Protection des Personnes Est I).

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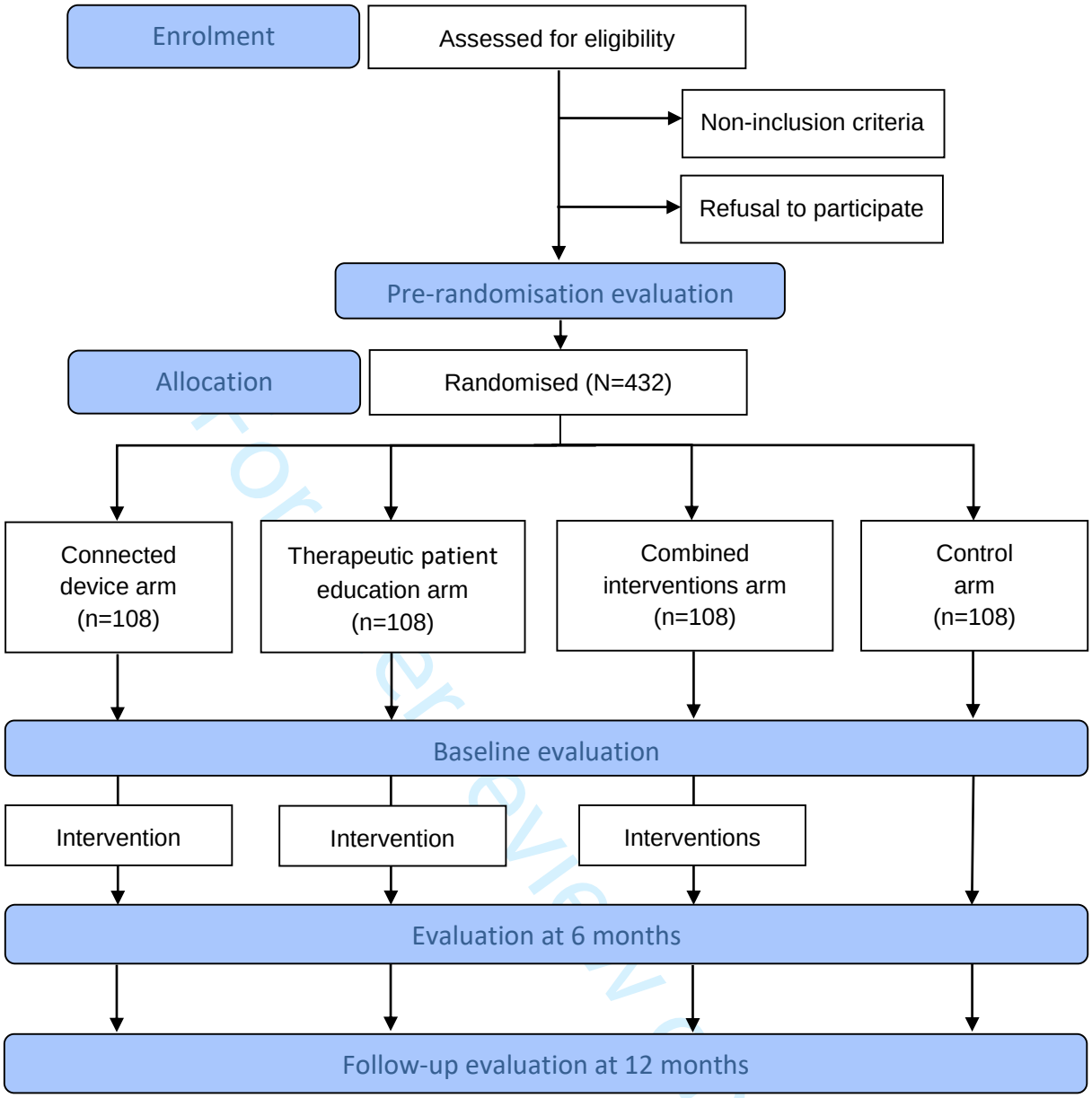
Table 1 Summary of outcome measures and data collection schedule for the DISCO trial

Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
Demographic and clinical data	Patient's medical record			
- Month/year of birth		X		
- Age at diagnosis		X		
- Employment status		X	X	X
- Personal history of breast cancer		X		
- Current treatment		X	X	X
- Hormonal receptor status		X		
- Tumour histology		X		
- Disease progression			X	X
Anthropometrics				
- Height	Gauge	X		
- Weight	Scale	X	X	X
- Waist-to-hip circumference	Measuring tape	X	X	X
- Body composition: fat mass, lean mass, dry lean mass, body water	Bioelectrical impedance analysis	X	X	X
Physical fitness		X	X	X
- Walking endurance with perceived difficulty	6MWT and Borg scale			
- Lower limb muscle strength	Sit-to-stand test			
- Hand prehensile strength	Hand-grip test			
- Flexibility of lower limbs	Sit-and-reach flexibility test			
- Balance	Single-leg stance test			
Physical activity level, sitting time and achievement of physical activity recommendations	RPAQ Questionnaire	X	X	X
Patient-reported outcomes				
- Quality of life	EORTC QLQ-C30 questionnaire and BR-23 module	X	X	X
- Health-related quality of life	EQ-5D-5L Questionnaire	X	X	X
- Fatigue	PFS-12 questionnaire	X	X	X
- Social vulnerability	EPICES questionnaire	X		X
Determinants of physical activity				
- Barriers to regular physical activity; lifestyle	Self-administered questionnaire	X	X	X
- Uses, representations and motivation of physical activity; acceptability of activity trackers (only for patients in the "connected device" and "combined" arms); acceptability of therapeutic patient education (only for patients in the "therapeutic patient education" and "combined" arms)	Online self-administered questionnaire	X	X	X
Biological data	Blood sample	X	X	
- Serum endocrine factors (IGF-1, insulin, estradiol)				

Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
- Plasmatic inflammatory cytokines (IL-6, TNFα, CRP) - Plasmatic adipokines (adiponectin, leptin) - Vitamin D status				
Compliance with each intervention (only for patients in the "connected device", "therapeutic patient education" and "combined" arms)	Connected device and/or patient's record		X	
Adverse events (neuropathies, joint pain)	Patient's diary		X	X

Notes. 6MWT: six-minute walk test

1161 **Figure 1**: Flow chart of participants through the DISCO trial.



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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 26
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	8, ethics copy
Funding	4	Sources and types of financial, material, and other support	30, funding copy
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 31-32
	5b	Name and contact information for the trial sponsor	1
	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	31
	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)	31

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	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
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)	8
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	8
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)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-15
	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)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	17, Table 1
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)	9, 16-17, Figure1, Table1

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	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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	17-21
	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	17

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	17, 24
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	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24
	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)	23-24
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	25
	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	N/A
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	14, 24-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32
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)	26

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32
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	25
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	N/A
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	25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	31
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9, Suppl file 2
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	21

*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

Connected device and therapeutic patient education to promote physical activity among women with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised controlled trial

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Secondary Subject Heading:	Sports and exercise medicine, Nutrition and metabolism, Health economics, Sociology

Keywords:	Breast tumours < ONCOLOGY, SPORTS MEDICINE, MEDICAL EDUCATION & TRAINING

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Connected device and therapeutic patient education to promote physical activity among women with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised controlled trial

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ABSTRACT

Introduction: Despite safety and benefits of physical activity during treatment of localized breast cancer, successful exercise strategies remain to be determined. The primary objective of the DISCO trial is to evaluate the efficacy of two 6-month exercise interventions, either single or combined, concomitant to adjuvant treatments, on the physical activity level of breast cancer patients, compared to usual care: an exercise program using a connected device (activity tracker, smartphone application, website) and a therapeutic patient education intervention. Secondary objectives are to evaluate adherence to interventions, their impact at 6 and 12 months, representations and acceptability of interventions, and to assess the cost-effectiveness of the interventions using quality-adjusted life years.

Methods and analysis: This is a 2x2 factorial, multicentre, phase III randomised controlled trial. The study population (with written informed consent) will consist of 432 women diagnosed with primary localized invasive breast carcinoma and eligible for adjuvant chemotherapy, hormonotherapy and/or radiotherapy. They will be randomly allocated between one of four arms: (i) web-based connected device (evolving target number of daily steps and an individualized, semi-supervised, adaptive program of two walking and one muscle strengthening sessions per week in autonomy), (ii) therapeutic patient education (one educational diagnosis, two collective educational sessions, one evaluation), (iii) combination of both interventions, (iv) control. All participants will receive the international physical activity recommendations. Assessments (baseline, 6 and 12 months) will include physical fitness tests, anthropometrics measures, body composition (CT-scan, bioelectrical impedance), self-administered questionnaires [physical activity profile (RPAQ), quality of life (EORTC QLQ-C30, EQ-5D-5L), fatigue (PFS-12), social deprivation (EPICES), lifestyle, physical activity barriers, occupational status] and biological parameters (blood draw).

Ethics and dissemination: This study was reviewed and approved by the French Ethics Committee. The findings will be disseminated to the scientific and medical community via publications in peer-reviewed journals and conference presentations.

Registration: ClinicalTrials.gov NCT03529383; 05/17/2018.

Keywords: Breast cancer, Physical activity, Sitting time, Activity tracker, Connected device, Web-based, eHealth, Therapeutic patient education, Randomised controlled trial

Word count: 8445

Strengths and limitations of this study

- This randomized clinical trial with four arms has the advantage to evaluate the efficacy of two interventions, either single or their combination, using a 2x2 factorial design, ensuring a higher statistical power than a classic trial with three arms, for a similar sample size.
- While the connected device intervention is semi-supervised, the exercise program has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy and to provide organisational flexibility to patients to facilitate adherence.
- Despite the potential benefits of connected devices in cancer care, their use may face important issues, such as ethical challenges related to the security of sensitive data storage, technical challenges related to technological robustness and reliability, exacerbating access disparities, and self-assessment of the participant's fatigue or health condition.
- The primary outcome measure is based on a declarative evaluation of physical activity that confers methodological limits to the study, but the validated questionnaire was chosen according for its easy implementation for cancer patients compared to accelerometer monitoring and its relevance for the primary outcome.

INTRODUCTION

Breast cancer is the leading cause of cancer in women worldwide with 1.6 million new cases diagnosed each year,[1] representing more than a third of all new cancer cases in women. In France, breast cancer also represents the leading cause of cancer incidence and mortality among women, with approximately 58,000 new cases and 12,000 breast cancer deaths estimated in 2018.[2] Despite a very good prognosis worldwide with overall survival of 85% at 5 years (87% in France) and 71% at 10 years (78% in France) for all stages combined,[3–5] a large number of patients with breast cancer experience adverse effects of cancer and its treatments such as fatigue, impaired quality of life, anxiety or weight gain.[6–8]

In women with breast cancer, deteriorations of physical activity level and cardiorespiratory fitness are frequent.[9,10] Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, including any daily life activity of household, occupation, recreation (e.g., sports) or transportation. Exercise is a subset of physical activity that is planned, structured and repetitive, in the purpose of improving or maintaining physical fitness.[11] After a breast cancer diagnosis, lack of physical activity, obesity and weight gain have been shown to increase the risk of cancer-related comorbidities and treatment adverse effects, to worsen long-term health and to cause poor prognosis.[12–14] The benefits of physical activity have been well recognized in primary cancer prevention.[15] Numerous studies have shown the safety[16] and benefits of physical activity performed concomitantly with breast cancer treatments. These benefits include reduced fatigue[17–19] and comorbidities[20], improved quality of life[21,22] and physical functioning,[10,17,19,22] as well as possibly reduced risk of recurrence[23] and improved overall and specific survival with a positive dose-response relationship.[14,23,24] Despite these benefits and international evidence-based guidelines of physical activity prescription for clinicians and their patients, accessibility to exercise programs and implementing the guidelines in the cancer care process remain a challenge for patients and health care providers.[25–27] While a growing number of facilities offer exercise programs to cancer patients, distance

from home constitutes a barrier to regular exercise during cancer treatments.[26] Successful exercise strategies during and beyond cancer treatment remain to be determined in clinical trials.[28]

The recent development of connected devices such as activity trackers offers a real opportunity in oncology to promote and monitor patients' physical activity.[29] While adherence to lifestyle interventions is a major challenge, connected activity trackers and smartphone applications enable structured monitoring of health parameters and provide feedback to patients. A systematic review of randomised controlled trials of physical activity interventions using new technologies such as activity trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly increased their number of steps per day in the majority of the studies.[30] Recent reviews of intervention studies conducted among breast cancer patients have also shown that patients increased their physical activity when they used activity trackers.[31,32] Overall, connected activity trackers receive increasing interest for being systematically integrated into clinical oncology practice.[33,34] Yet, more research is needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the preferences of breast cancer patients.[35–37]

Therapeutic patient education has emerged in the 1990s in response to the recognition of the need to support patients in the self-management of their chronic diseases, such as diabetes and asthma.[38,39] According to the World Health Organization (WHO), therapeutic patient education aims to "help patients acquire or maintain the skills they need to best manage their lives with a chronic disease".[40] In the cancer field, several cancer-specific programs of therapeutic patient education have been set up to manage pain, fatigue, side effects of treatment (chemotherapy, surgery) or compliance to treatment.[41–44] By enhancing relevant knowledge and skills, therapeutic patient education may greatly contribute to increasing patients' autonomy in their disease management. Despite the performance in modifying long-term individual behaviours and adherence to cancer treatments,[44] the benefits of therapeutic patient education on physical activity levels in cancer patients early after diagnosis has been poorly investigated.[45,46] The research on therapeutic patient education in the breast cancer and exercise context is limited to date and warrants further research.

Several biological mechanisms have been proposed to explain the effects of physical activity on breast cancer risk and outcome. Preclinical and human studies have shown the influence of physical activity on several signalling pathways involved in tumour development, growth and progression, including the insulin signalling pathway (IGF-1, insulin), chronic inflammation (involving inflammatory cytokines such as IL-6, TNFα, CRP) and endocrine hormone regulation (estrogens, adipokines).[47–49] By affecting the endogenous systemic milieu, physical activity is believed to influence cellular processes and tumour growth, and therefore reduce the risk of recurrence, increase treatment efficacy and improve survival.[50] Also, because vitamin D alters mechanisms implicated in cellular growth and proliferation, accumulating evidence suggests that normal-to-high ranges of serum vitamin D levels improve breast cancer prognosis and outcome.[51] Based on the data in the literature, it is not possible to conclude a causal relationship between the metabolic effects of physical activity and the impact on breast cancer risk and survival. Biological effects of physical activity on these biomarkers of endogenous mechanisms interfering in cancer suppression or proliferation remain to be elucidated in order to better understand the benefit of physical activity during adjuvant treatment.[49]

In this context, given the accumulating evidence for the benefits and safety of regular exercise during treatments of localized breast cancer, it is necessary to systematically encourage patients to remain or become physically active from the time of diagnosis and to implement and assess the most appropriate strategies of physical activity in clinical practice. The aim of the DISCO trial is to encourage engagement in exercise during breast cancer treatment through two innovative types of interventions, that is to say a web-based connected device and therapeutic patient education, which aim to develop patients' autonomy in their practice of physical activity. The primary objective of the DISCO trial is to evaluate the efficacy of two interventions, either single or combined, concomitant to adjuvant treatments, on the physical activity level of breast cancer patients at the end of the 6-month interventions, compared to usual care: one is an exercise program using a connected device (comprising an activity tracker linked to a smartphone application and a website and providing an individualized, semi-supervised, technology-based exercise program) and the other is a therapeutic

patient education intervention. The research hypothesis is that patients participating in the 6-month exercise program using the connected device or therapeutic education intervention are more likely to achieve the international physical activity recommendations, compared to women receiving physical activity recommendations only (usual care). The WHO recommendations to maintain or improve health, which applied when the study protocol was developed, are to do at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity or an equivalent combination each week, and muscle-strengthening activities at least two days a week.[11] Secondary objectives are: (i) to evaluate the adherence to the interventions; the impact of the interventions on physical fitness, physical activity profile, anthropometrics, quality of life, fatigue, biological parameters, occupational status and lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12 months; the representations and acceptability of activity tracker and therapeutic patient education; and ii) to assess the cost-effectiveness of the interventions. If one of the interventions is individually effective, the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.

METHODS AND DESIGN

Trial design

The DISCO (an acronym for “dispositif connecté”, i.e., connected device in English) trial is a 2x2 prospective, multicentre, factorial, randomised, controlled and open-label study (phase III), conducted by the Léon Bérard comprehensive cancer centre (Lyon, France) among women receiving treatment for localized breast cancer. The clinical protocol was designed and written according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Supplementary file 1). The flowchart of the study is presented in Figure 1. Patients will be randomly assigned to one of the four arms of the study according to the 2×2 factorial design (1:1:1:1 ratio). They will all receive international recommendations on physical activity,[11] and: (i) women allocated to the “connected device” arm will benefit from a 6-month individualized, semi-supervised exercise program carried out autonomously. The program consists of an evolving goal of daily numbers of steps using an activity

tracker and two sessions of brisk walking and one session of muscle strengthening per week, using dedicated smartphone application and website; (ii) women allocated to the "therapeutic patient education" arm will benefit from four therapeutic education sessions on exercise; (iii) women allocated to the "combined" arm will benefit from both interventions in parallel; (iv) women allocated to the "control" arm will receive usual care.

Eligibility criteria for participants

Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and requiring adjuvant treatment (chemotherapy, hormonotherapy and/or radiotherapy) that present at one of the investigating centres; providing a medical certificate of no contraindication to exercise; being available and willing to participate in the study for the duration of the interventions and follow-up; using a personal smartphone compatible with an application used for the intervention (iOS operating system from version 9.3, Android operating system from version 5.0, no Microsoft operating system) and having a computer with Internet access; being able to understand, read and write French; and being affiliated with a social security scheme.

Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal history or co-existence of other primary cancer (except for in situ cancer regardless of the site, basal cell skin cancer and non-mammary cancer in complete remission for more than 5 years); presenting a contraindication to exercise according to the investigator (such as cardiorespiratory or bone pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe malnutrition according to the criteria of the French National Health Authority (i.e., for women ≤70 years: weight loss ≥15% in 6 months or ≥10% in 1 month; for women >70 years: weight loss ≥15% in 6 months or ≥10% in 1 month, and body mass index (BMI) <18 kg/m²);[52] being unable to be followed for medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or breastfeeding or of childbearing age without effective contraception for the duration of the study.

Recruitment

Recruitment started in May 2018. Participants will be recruited at several national comprehensive cancer centres, clinics or hospitals located in France (see ClinicalTrials.gov NCT03529383), which will ensure adequate participant enrolment to reach the target sample size in a timely manner. Inclusion of patients will be carried out after surgery and confirmation of the indication of adjuvant treatment. The study will be proposed to patients at the postoperative, pre-chemotherapy or pre-radiotherapy consultation (by the surgeon, oncologist or radiotherapist investigator, respectively) depending on the patient's treatment plan. At this visit, the investigator will check all eligibility criteria and propose to the eligible patients to participate in the study, explain the objectives and study process and give them an information notice. After sufficient time for reflection, eligible patients who agree to participate will date and sign an informed consent (see Supplementary file 2) and will be included prior to the onset of adjuvant therapy (or within one month thereafter). The number of eligible patients refusing to participate in the study and the reason for non-participation will be recorded.

Randomisation

Prior to randomisation, participants will be asked to complete the Recent Physical Activity Questionnaire (RPAQ) to assess their level of physical activity.[53] Their weight, body size and prescribed adjuvant treatments will be collected from the patient's medical record.

Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris, France) into one of the four arms of the trial, by using the following minimization criteria:[54,55] BMI (<25 kg/m², ≥25 and <30 kg/m², ≥30 kg/m²), baseline physical activity level from RPAQ (<150 min/week, ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant treatments at inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ± radiotherapy, chemotherapy ± radiotherapy, radiotherapy only).

INTERVENTIONS

At baseline, all participants will receive the international recommendations in terms of physical activity for promoting health in the general population[11], which will be delivered orally by a certified exercise instructor with the help of a leaflet.

Intervention with a connected device

Participants randomised to the "connected device" arm will benefit from a 6-month exercise program. The connected device consists of an activity tracker (connected wristband, LS417-F model, CARE Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application and a dedicated website proposing an individualized, semi-supervised exercise program adapted to cancer patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based exercise program will aim to support participants to enhance physical activity in two ways: doing structured exercise sessions and increasing daily physical activity (number of steps). Exercise sessions will be automatically generated by an algorithm based on the patient profile (described below). The participants will receive notifications informing them of a new structured exercise session available on the website or mobile application, or alerting them when a session was not carried out, and inviting them to execute it when possible. Participants will receive a free 6-month subscription to the program.

—*Setting up the connected device:* At the end of the baseline assessment, the certified exercise instructor will introduce the customized exercise program to the participants and will give them the activity tracker and a user guide for the connected device. Then, the certified exercise instructor will explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated website, as well as assist the participants to install the application on their smartphone. The participants will be registered in the customized exercise program by the certified exercise instructor. The registration will consist of completing a web-based questionnaire about personal and health data to determine the participant profile (age, weight, height, level of aerobic and muscular strength, treatment, symptoms, availabilities for exercise sessions and sports materials).

—*Baseline level of aerobic and muscular strength for the individualised exercise program:* The physical fitness tests performed at baseline will be used to classify the participants at the start of the exercise program according to their aerobic level (for the walking sessions) and their muscular strength level (for the strengthening sessions). The aerobic level categories will be determined by the distance performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level categories will be determined by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test: muscular strength group 1 (≤10 repetitions), muscular strength group 2 (11 to 14 repetitions) and muscular strength group 3 (≥15 repetitions). Thresholds were based on average values reached by women receiving breast cancer treatments for the 6MWT (pooled mean value, 523 m) and the Sit-to-stand test (pooled mean value, 13 repetitions) from a previous study;[56] these values were checked for consistency with percentile scores obtained at the 6MWT and Sit-to-stand test in community-dwelling older women,[57] then the interquartile range was used to determine the thresholds for the three groups of this study. The level categories assigned will be entered by the exercise instructor in the baseline patient profile and will be used by the automated algorithm to set up the level of the first walking and muscle strengthening sessions.

—*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise instructor through an individual follow-up of participants (see 'Participant follow-up' part and 'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using the smartphone application and the website. The program is based on three structured unsupervised sessions per week alternating two types of exercise: two walking sessions (by following oral instructions given via the smartphone application) and one muscle strengthening session (by using videos accessible on the website). The levels of the first walking and muscle strengthening sessions will be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent sessions will be planned according to the available days of the participant. Strengthening exercises will be adapted according to sports materials available at their home (e.g., Swiss ball, sports mat, stick,

weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a body session of 10 to 35 minutes of strengthening exercises, or 10 to 50 minutes of walking (mixing continuous and/or intermittent effort); 3) a 5-minute recovery period, consisting of stretching and relaxation during strengthening sessions or a cool down during walking sessions. Sessions will be of moderate-to-high intensity (≥ 3 and ≤ 9 METs).

The three structured unsupervised exercise sessions per week are configured by a unique algorithm hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to plan the exercise sessions and determine the exercise level in an adapted and progressive manner by increasing the duration and then intensity in accordance with principles of exercise training and progression.[58,59] At the beginning of each session, the duration and intensity of the session will be determined according to the perceived difficulties (evaluated by a Borg scale) and emotional state (recorded by an emoji) of the participant in the previous session, and will be modified or postponed according to the level of fatigue (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg scale), the presence or absence of unusual muscle pain and the presence or absence of unusual nausea/diarrhea. In case of a severe adverse event related to disease or treatment (i.e., joint disability, osteoarthritis, cachexia, hand-foot syndrome, aplasia, diuretic, axillary node dissection, pace-maker, chemotherapy, targeted therapy, hormone therapy, radiotherapy, COPD, diabetes) or temporary contraindication to exercise, declared by the participant on her device, the program and sessions will be adapted or suspended until the participant's health improves.

In addition, participants will have the opportunity to perform additional exercise sessions according to their preferences and lifestyle, outside the program. Participants will be asked to record these sessions through the smartphone application or the website: type of activity (e.g., walking, hiking, cycling) from a list adapted from Ainsworth's Compendium,[60] and its duration and intensity.

—*Number of daily steps:* Participants will be advised to wear the activity tracker daily and to launch the application regularly (preferably daily), which will automatically synchronize with the activity tracker via Bluetooth connection and will collect the number of steps. The target number of steps will

be 3,000 steps per day at the program onset, and then will be re-set based on the average number of daily steps during the first week after inclusion. The target number of daily steps will evolve automatically every three weeks based on the average number of daily steps achieved during the previous three weeks, and will be updated automatically in the application. Consistent with principles of exercise training and progression,[58,59] after each 3-week cycle, if the goal of steps per day is reached by the participant, the target goal will increase by 15% during the following 3-week-cycle, within a maximum target of 10,000 daily steps. If the average number of daily steps does not meet the goal, the target will remain unchanged in the next cycle.

—*Participant follow-up*: Telephone follow-ups will be carried out by the certified exercise instructor at 10 days, 2 months and 4 months after the intervention onset to ensure the proper functioning of the connected device, review the use of the connected device, review the conduct of the sessions and answer the participants' questions if they may have. Participants will be orally encouraged to remain physically active on a daily basis (reminder of the benefits and recommendations of physical activity, success and satisfaction during the exercise sessions). During the 6-month intervention, the participants will have the opportunity to contact the certified exercise instructor or the clinical research assistant at any time, by e-mail (directly through the website) or by telephone for any question or assistance with the connected device.

—*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device by the participants and their progress in the program through a dedicated professional website that provides real-time access to the participants' data. On this website, an automatically generated daily event table will inform the certified exercise instructor of the occurrence of disabilities reported by the participants that may lead to modifying their program (e.g., severe fatigue, dyspnea, unusual muscle pain) or if participants have not performed their planned sessions or used their activity tracker for seven consecutive days. Upon these alerts, the certified exercise instructor will contact the participants to precisely analyse the reported disabilities, advise participants, identify the causes of non-use of the connected device, solve possible technical problems or reinforce participant's motivation if necessary.

—*End of the intervention*: At the end of the 6-month program, participants will keep their activity tracker to be encouraged to continue regularly exercising in autonomy. Upon their request, continued subscription to the dedicated application and website will be offered for another six months, with no individual follow-up anymore.

Intervention of therapeutic patient education

Participants randomised to the therapeutic patient education arm will benefit from a therapeutic patient education intervention, in addition to receiving the international physical activity recommendations. The intervention is part of the therapeutic patient education program set up at the Léon Bérard cancer centre and validated by the Regional Health Agency ("Agence Régionale de Santé Rhône-Alpes"). It will be disseminated in the investigating centres according to the criteria of the Regional Health Agency. The therapeutic patient education intervention consists of four sessions that will be scheduled according to participants' availability during their follow-up visits as part of their usual clinical management over a 6-month period.

First, participants will be invited to an initial 1-hour individual face-to-face session of educational diagnosis with a health professional trained in therapeutic patient education. This session will assess their needs and establish a contract of objectives to reach. Then, participants will be invited to participate in two collective educational sessions (1h30 each with a group of 10 patients maximum per session). These sessions will be composed of theoretical and practical workshops to help them understand their physical activity in their daily life and implement the necessary means to practice regular exercise in autonomy. Finally, participants will be invited to another 1-hour individual session, where an educational evaluation will be conducted to identify whether they achieve their individual objectives set at the time of the educational diagnosis.

Combined interventions

Participants randomised to the 'combined intervention' arm will benefit from a combination of the connected device intervention and the therapeutic patient education intervention in parallel for 6 months.

EVALUATIONS

The initial assessment (T0) will be performed prior to randomisation for minimization purposes. The other three evaluations will then be conducted at baseline (T1), 6 months (T2) and 12 months (T3). All study participants will then be followed at 6 months ±1 month post-randomisation (corresponding to the end of participation in the interventions for women in the connected device, therapeutic patient education and combined arms) and at 12 months ±1 month post-randomisation (corresponding to a follow-up period of 6 months post-interventions). Assessments will be carried out by a clinical research assistant and a certified exercise instructor. The clinical research assistant will contact participants by phone to invite them to follow-up visits and to promote participant retention and complete follow-up. Participants will have no compensation for participation and all study visits will be scheduled on days of their medical or health-related appointments.

All evaluations (baseline, 6 and 12 months) will include physical fitness tests, anthropometric measures, self-administered questionnaires and a non-fasting blood draw (baseline and 6 months only). Data will be recorded using an electronic case report form (eCRF).

DATA COLLECTION

The study outcome measures and their schedule are summarised in Table 1.

Socio-demographic and clinical data

Socio-demographic and clinical data, including month/year of birth, age at diagnosis of breast cancer, family status, level of education, hormonal status, tumour histology and personal history of

breast cancer will be collected at baseline. Family status, potential cancer progression and all treatments received for cancer will be collected at 6 and 12 months. All data will be extracted from patients' electronic medical records, except family status and level of education that will be self-reported in a questionnaire.

The occupational status will be assessed using a self-administered questionnaire asking employment status, occupation, size of the company, the perceived intensity of the physical effort at work, the evolution of employment status at return to work in case of sick leave.[61]

Anthropometrics and body composition

The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be measured using standardized procedures and BMI will be calculated as the body weight in kilograms divided by the square of the height in meters (kg/m²). The waist circumference will be measured midway between the last floating rib and the iliac crest. The hip circumference will be measured at the tip of the pubis. Body composition will be measured by a bioelectrical impedance meter (Biody XPert ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid (in L).

Physical fitness

Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance covered in metres) with perceived difficulty using the Borg scale.[62] During this test, participants will be asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes. The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as many times as possible during 30 seconds.[63]

Hand prehensile strength will be measured by the handgrip test using hand dynamometry (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the isometric strength of the hand and forearm muscles.[64] During this hand-grip test, participants will be asked to squeeze the handgrip as strongly as possible to obtain the maximal force (in kg). Two measures will be performed on each hand and the best performance will be registered.

The flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe Baseline flexibility test, 3B Scientific, Bartenheim, France).[65] In this test, participants will sit on the floor on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering the level of the feet as recording zero, any measure that does not reach the toes is negative and any measure beyond the toes is positive).

The balance will be measured using the bilateral single-leg stance test.[66] The participants will stand and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).

Physical activity level, sitting time and achievement of physical activity recommendations

The validated self-administered questionnaire RPAQ will be used to measure the self-reported physical activity.[53,67] The RPAQ was designed to assess usual physical activity in the last four weeks, covering three activity domains: domestic physical activity, including sitting time that is a good proxy of sedentary behaviour; occupational physical activity, including transportation to and from work; and recreational physical activity. The RPAQ gives specific scores in the metabolic equivalent of task (MET) unit for activities of very low intensity (<1.5 METs, i.e., sedentary activities), low intensity (1.5 to <3 METs), moderate intensity (3 to <6 METs) and high intensity (≥6 METs, i.e., vigorous activities) within each domain during the past four weeks. Questions will be coded and converted in MET-minute per four weeks according to the Compendium of Physical Activities[60] by multiplying the number of METs by the duration and frequency of each activity. Then, the global score of physical activity will be

obtained by adding the number of MET-minutes per four weeks in each intensity and each domain. The physical activity profile will be defined as the time spent in physical activities of low, moderate and high intensities. The physical activity level will be defined by the overall weekly physical activity (average expressed in MET-hour/week).

Achievement of international physical activity guidelines will be computed for each individual by dividing the time spent in moderate-to-vigorous physical activity (i.e., ≥3 METs) into two categories:[11] <150 min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines); ≥150 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).

Patient-reported outcomes

The quality of life will be measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality-Of-Life Questionnaire (QLQ-C30) and its specific module for breast cancer (BR-23).[68] The QLQ-C30 is a 30-item validated self-administered questionnaire that evaluates five functioning domains (i.e., physical, role, emotional, cognitive and social), a global quality-of-life domain, three symptom domains (i.e., pain, fatigue and nausea) and six single items (i.e., dyspnea, insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds to a better functioning level. For scales related to symptoms, a lower score corresponds to a better functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.

The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.[69] This standardized self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight, moderate, severe and extreme problems), and comprises a 0-100 visual analogue scale recording the self-rated health (where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine').

Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of fatigue):[70] the higher the score, the worse the fatigue. All items together will produce a total score for fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3), moderate fatigue (score 4-6) and severe fatigue (score 7-10).

Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in Health Examination Centres) score.[71] The score will be computed by adding each question coefficient to the intercept whenever the answer is "yes." The score ranges from 0 to 100 (i.e., the higher the score, the greater the deprivation level) with the threshold for deprivation at 30.

Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e., never, former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol intake over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer, cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses). The amount of alcohol will be computed by multiplying the frequency of consumption by the number of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.

Determinants of Physical activity

The 21-item self-administered questionnaire "Barriers to Being Active Quiz" will be used to qualitatively assess barriers to the regular practice of physical activity.[72]

Uses, representations and motivation towards physical activity will be assessed within the study population using a self-administered questionnaire available online. Acceptability of connected devices and acceptability of therapeutic patient education will be assessed among participants randomised to the corresponding arms using a paper-based self-administered questionnaire. These questionnaires will be developed following the Unified Theory of Acceptance and Use of Technology

(UTAUT),[73] which is a specification of the Theory of Planned Behaviour[74] designed to explain and predict the probability of behaviour change among individuals faced with new technologies. The Theory of Planned Behaviour has been massively used during the last two decades to promote health behaviours such as physical activity. Besides, item wording will be based on the results of individual and collective interviews conducted for that purpose and designed to identify social representations[75] of health protection and physical activity incentive devices.

Compliance with interventions

Compliance with each intervention will be assessed at the 6-month evaluation only for patients randomized to the “connected device”, “therapeutic patient education” and "combined" arms. Compliance will be assessed by the number of days of use of the activity tracker, the participation rate in scheduled exercise sessions, the participation rate in scheduled therapeutic education sessions and the proportion of compliant patients, depending on the intervention allocated, following the recommendations of the protocol. Patients’ compliance and reasons for non-compliance during the intervention period (6 months) will be described for each arm.

Biological assessments

A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at baseline and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant treatments, otherwise no blood samples will be collected. The following biological factors will be assessed in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol), circulating plasma levels of inflammatory cytokines (IL-6, TNFα, CRP), circulating plasma levels of adipokines (adiponectin, leptin) and vitamin D status.

STUDY OUTCOMES

The primary endpoint will be the proportion of women who achieve at 6 months the internationally recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical activity, i.e., intensity ≥3 METs) assessed by the RPAQ self-administered questionnaire.

Secondary endpoints will be:

1. Assessment of the efficacy of the programs at 12 months (i.e., the proportion of women who achieve the internationally recommended level of physical activity);

2. Assessment of the adherence to the interventions at 6 months (the proportion of participants who are compliant to the program, participation rate in planned sessions);

3. Assessment of the impact between baseline and 6 months and between 6–12 months of the interventions on physical activity profile (changes in time spent in different intensities of physical activity and time spent in sedentary activities), physical fitness (changes in results to the 6-minute walk test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test), anthropometrics (changes in weight, waist and hip circumferences, BMI, fat mass, lean body mass, muscle mass, dry lean mass and body water), quality of life (changes in scores obtained from the EORTC QLQ-C30 questionnaire and its BR-23 module), fatigue condition (changes in scores obtained from the PFS-12 questionnaire), health-related quality of life (changes in scores obtained from the EQ-5D-5L questionnaire), social deprivation (changes in scores obtained from the EPICES self-administered questionnaire), occupational status (the proportion of participants who changed their employment status, with return to work and who perceived difficulty at work obtained from a self-administered questionnaire) and lifestyle factors (the proportion of participants who change their tobacco use and alcohol intake obtained from a self-administered questionnaire).

4. Assessment of the impact of the interventions on biological parameters between baseline and 6 months (changes in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], changes in plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines: adiponectin and leptin], the proportion of participants with a modification on vitamin D status).

5. Assessment of the representations and acceptability of activity tracker and therapeutic patient education, at baseline, 6 and 12 months (proportions of participants who accept the connected device and who accept the therapeutic program, according to scores obtained from a self-administered qualitative questionnaire used in social psychology science).

6. Assessment of refusal rate among eligible patients (the proportion of patients who refuse to participate).

7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital costs (national data) and benefit in physical activity level.

STATISTICAL ANALYSIS

Sample size determination

The efficacy rate assumptions are μ=40 %, $\mu+\mu A$=55 % and $\mu+\mu B$=65 % for the “control”, “therapeutic patient education” and “connected device” arm modalities, respectively. The expected benefit in the “therapeutic patient education” arm compared to the “control” arm is 15% (40% efficacy in the “control” arm versus 55% efficacy in the “therapeutic patient education” arm). The expected benefit in the “connected device” arm compared to the “control” arm is 25% (40% efficacy in the “control” arm versus 65% efficacy in the “connected device” arm).[23]

The sample size is calculated to allow the two comparisons of interest to be tested bilaterally at the threshold of 0.025. Assuming that the "therapeutic patient education" intervention and the "connected device" intervention act independently (additive model), the sample size required to compare therapeutic patient education (i.e., participants assigned to the "therapeutic patient education" and "combined" arms) versus no therapeutic patient education (i.e., participants assigned to the "control" and "connected device" arms) is given by the following formula:

$[\mu + (\mu+\mu B)] / 2$, versus $[(\mu+\mu A) + (\mu + \mu A + \mu B)/2]$

that is, (40 % + 65 %) / 2 = 52,5 %, versus (55 % + 80 %) / 2 = 67,5 %

With a first species risk α=0.025 and a power of 80% in the bilateral situation, the number of patients to include per treatment arm to demonstrate the efficacy of the therapeutic patient education will be 108 (or 432 for the four treatment arms) (nQuery V6.0, Chi-two test with continuity correction). This number of patients will also allow a power greater than 95% to evaluate the efficacy of the "connected device" intervention, always with a risk α = 0.025 in the bilateral situation.

Data analysis plan

The following populations will be defined for statistical analyses: i) the intent-to-treat (ITT) population, which includes all randomised participants in the study; ii) the per-protocol population, which consists of a subgroup of participants from the ITT population, who has no major protocol violations and who follows the procedure for the duration of the study. Analyses in the ITT population will be performed for all the study endpoints; analyses in the per-protocol population will be performed for exploratory purposes. The randomisation date will be considered as the reference date in all delay calculations, unless any other way is specified.

Baseline data will be described in the ITT population and presented by randomised arms. For the primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who received the connected device vs. participants who did not; (ii) participants who benefited from the therapeutic patient education intervention vs. participants who did not. Results will be presented with their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the efficacy of the intervention with a connected device (compared to without a connected device); the efficacy of the therapeutic patient education intervention (compared to no therapeutic patient education); and the interest of two combined intervention modalities (i.e., connected device and therapeutic patient education) compared to the single intervention with the connected device only or with therapeutic patient education only. The analysis strategy will therefore be as follows:[76] 1) searching first for an interaction by a specific interaction test, performed at the significance level of 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the absence of interaction,

testing each of the two bilateral interest comparisons at the threshold of 0.025, namely the efficacy of the intervention with the connected device and the efficacy of the therapeutic patient education intervention; 3) in case of the efficacy of either one of the intervention modalities, evaluating the interest of the combination of the two interventions compared to the single intervention with the connected device only or with therapeutic patient education only.

For secondary outcome variables, the efficacy of the program at 12 months, as well as according to stratification criteria, will be analysed similarly to the primary outcome. The adherence to the interventions will be evaluated by the proportion of compliant participants and participation rate in planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life, fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative variations in each of these endpoints; these variations will be compared between with and without each intervention, for each intervention, and between combined interventions and the single one, using a parametric test. Occupational status and lifestyle factors will be analysed by comparing the proportion of participants between interventions or their combination. Representations and acceptability of activity tracker and therapeutic patient education will be analysed by comparing the proportion of participants between randomisation and follow-up assessments. A method for imputing missing data will be considered if necessary.

Statistical analyses will be performed using SAS® software version 9.4 or later.

Medico-economic analysis

The cost-effectiveness analysis will be conducted alongside the trial using the French national health insurance perspective. Quantities of resources used [external consultations, hospital stays including Diagnosis-related groups, drugs with extra payments and other healthcare-related costs] will be collected on the eCRF and multiplied by the respective unit costs. The intervention with therapeutic patient education and the intervention with connected device will be evaluated using a bottom-up micro-costing approach.[77,78] Using the Diagnosis-related group, hospital stays will be evaluated based

on the French National hospital costs study database. External consultations and wider examinations, community care (general practitioner visits, nurse visits, etc.) will be valued on the basis of the General Nomenclature of Professional Treatments (NGAP, "Nomenclature Générale des Actes Professionnels"). The cost of biological treatments will be estimated using the Nomenclature of Biological Medical Treatments (NABM, "Nomenclature des Actes de Biologie Médicale"). The cost of technical treatments (e.g., imaging) will be estimated using the Common Classification of Medical Treatments (CCAM, "Classification Commune des Actes Médicaux"). Acquisition costs for the most expansive drugs will be based on the list of common units of dispensation for supplementary medicines ("liste des unités communes de dispensation prise en charge en sus"). Finally, costs of medical transport will be derived from the French Court of Audit's report on medical transport expenses covered by the French National Health insurance. The time horizon will be 12 months. Hence, neither costs nor effectiveness will be discounted. Mean costs and effectiveness will be derived for all four strategies under consideration: connected device, therapeutic patient education, combined and control arms. Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per quality-adjusted life year (QALY) gained using EQ-5D-5L to estimate utility, cost per life year gained, cost per BMI unit lost and cost per centimetre of waist-to-hip circumference lost. One-way sensitivity analyses will be conducted by varying resource consumption and unit cost parameters and graphically illustrated in a Tornado diagram. The uncertainty surrounding the ICERs will be also captured by a probabilistic analysis using non-parametric bootstrap methods as recommended by the French National Authority for Health.[79]

ADVERSE EVENTS

All participants will continuously report the occurrence of adverse events regarding neuropathies and joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped with the connected device will also report potential adverse events before and after each session of their exercise program (see *Connected device*). The reported adverse events will then be graduated

according the CTCAE v5. Due to the low risks associated with the interventions,[16] this study is part of the so-called "intervention research with minimal risks and constraints" in the French legislation and therefore only these adverse events arising within the framework of the study will be reported.

In the occurrence of an adverse event regarding neuropathies and joint pain, the principal investigator will report it to the health authorities responsible for vigilance without delay. The promotor will also report the adverse events, as well as any safety measures to be proposed, to the French Ethics Committee and the investigators without delay.

DATA MANAGEMENT

The database for clinical data and randomisation will be created using EnnovClinical® software. Its access will be secured (personal identification and password protection) for maintaining confidentiality at all times. Individual participants will not be identified in any reports of this trial. All data from the connected device will be merged to the clinical database at the end of the study. Investigators and data analysts will have access to the final dataset.

Data monitoring will be provided by the trial steering committee, including overall project supervision, progress monitoring, advice on scientific credibility, and ensuring the integrity and appropriate running of the project. The clinical research assistant will verify all consent forms, compliance with established protocol and procedures, and data quality in the eCRF. The research team will make biannual reports to the trial steering committee.

PATIENT AND PUBLIC INVOLVEMENT

An association of breast cancer patients' representatives (Europa Donna France, http://www.europadonna.fr/) was involved in preparing the conduct of interventions and evaluations, in particular by considering patients' expectations, experience and desire for global care. The association will be involved in plans to disseminate the study results to breast cancer patients, study participants and wider patient communities concerned.

ETHICS AND DISSEMINATION

The study protocol was approved by the French ethics committee (Comité de Protection des Personnes Est I, ID RCB 2017-A03360-53, 1st February 2018) and its database was reported to the French National Commission for Data Protection and Liberties (CNIL, ref. MR-001 no. 2016177, 13th December 2016). Substantial protocol modifications will be submitted to the ethics committee for approval and protocol amendment. The trial has been prospectively registered on http://www.ClinicalTrials.gov (NCT number: NCT03529383, 17th May 2018).

The study findings will be widely disseminated through the clinical community by publications in international, peer-reviewed journals and by presentations at national and international conferences. They will also be communicated to patients through associations of patients' representatives and science-based information websites. They will be useful for improving the clinical care of cancer patients and providing useful information for implementing exercise programs for cancer patients to health professionals, institutions and public authorities. The study sponsors will disseminate the study findings to their stakeholders.

DISCUSSION

This article presents the protocol for the DISCO trial, which aims to evaluate the efficacy of a web- and mobile-based connected device intervention and of a therapeutic patient education intervention, either single or combined, on the physical activity levels of breast cancer patients undergoing adjuvant treatment, as well as to assess the cost-effectiveness of the interventions. This multicentre study opened in May 2018 and recruitment is expected to end in Summer 2021. In the short term, the expected results are to develop the autonomy of breast cancer patients in their practice of physical activity, as well as to identify the best strategies of physical activity during breast cancer adjuvant treatments to increase and sustain physical activity levels in patients, overall or in specific subgroups according to BMI, baseline physical activity level and type of adjuvant treatment. In the medium term,

the goal of the DISCO trial is to disseminate innovative programs in supportive cancer care, based on scientific evidence, to systematically integrate exercise in breast cancer cares.

While an increasing number of studies have demonstrated the benefits of exercise in breast cancer patients, the routine implementation in the cancer care process lacks behind evidence and practice guidelines.[80–82] While the prescription of physical activity in supervised programs has been shown superior compared to non-supervised programs,[22,83] semi-supervised interventions seem to yield comparable or superior benefits to supervised programs.[84] Therefore, the semi-supervised exercise program of the DISCO trial through continuous follow-up has been designed according to the preferences of women with breast cancer so as not to leave patients in total autonomy.[36,85] Connected devices are tools developed over the last 10 years that are very promising for promoting physical activity in the general population and in patients with chronic diseases such as cancer[86,87] and for developing distance-based physical activity interventions.[88]

The semi-supervised home-based physical activity program of the DISCO trial using the connected device provides flexibility to patients that may facilitate adherence and to overcome barriers due to distance of facilities from women's home and spatial inequalities of access.[27] Connected devices allow proposing a tailored physical activity program to patients regardless of their place of residence, and enable patients to practice physical activities of their choice, at any time that suits them. Therefore, they may reduce geographical and organisational barriers in the access of patients to exercise, a key issue to improve their engagement in regular and sustained physical activity.[27] Previous studies in oncology have reported that the use of mobile devices has benefits to overcome motivational barriers to physical activity, which can help patients staying physically active over the medium and long term.[89,90] Moreover, some studies have shown that breast cancer patients achieved higher fitness levels during supervised training compared to unsupervised training, even low and medium levels of supervision have been effective, as less resource-intensive options for effective and longer-term behaviour change strategies based on exercises in cancer patients and survivors.[84,91]

Activity trackers have become increasingly popular in recent years. Patients have reported positive feedback on using activity trackers such as pleasant to wear, easy to use and a strong motivational role through the real-time display of daily number of steps.[92] Also, walking is an inexpensive activity that can be performed anywhere and does not require specific skills. A study on preferences for technology-supported interventions in breast cancer survivors has reported that 63% would like to use a physical activity mobile application and 90% would find a physical activity tracker useful to monitor and increase physical activity.[35]

Despite the potential benefits of connected devices in cancer care, their use may face several important issues. First, ethical challenges related to the security of sensitive data storage have been raised.[93] To ensure that data transfer and storage guarantee informational privacy and patient safety,[94] an activity tracker made in France (i.e., allowing storing health data only in France) and an accredited national health data host were chosen for the DISCO trial. Particularly, ensuring medical data security is a reassuring choice for patients to participate in this new kind of medical research. Second, technical challenges have been raised, related to technological robustness, reliability of data collection and processing, and ease of use. Therefore, an activity tracker with a step display on the screen, a user-friendly interface, good reliability and a good price-performance ratio was chosen in the DISCO trial. Third, connected devices may create or exacerbate access disparities related to technological literacy and economic means, as well as reliable access to the internet in rural or isolated areas.[93] Fourth, medical reasons are usually not easy to control in patients' adherence to exercise programs. Reliance upon self-assessment of the participant's fatigue, evaluation of the participant before and after each session on the remote monitoring, up as the source of information about the participant's health, can result in the ignorance of aspects of the participant's health that cannot easily be monitored.[93]

Therapeutic patient education has been suggested to increase physical activity level in patients with chronic diseases[46] and to improve multiple health outcomes, together with behavioural interventions including physical activity.[95] Therapeutic patient education interventions might be promising for promoting a physically active lifestyle in cancer patients as it helps patients establish lifestyle changes

and reinforce self-management.[95] Therapeutic patient education differs from traditional patient education in its intrinsic structure. Traditional patient education is directed towards informing and teaching patients how to manage their condition or disease. In contrast, therapeutic patient education differs from traditional patient education in the self-management conferred on the patient.[40] Therefore, therapeutic patient education is more broadly directed towards how the patient accepts his/her condition and manages his/her problems on a daily basis and the impact of the disease on personal, family, professional and social life. Yet, in oncology, few therapeutic patient education studies targeting pain, fatigue, toxicities or treatment adherence are ongoing, and evaluations are rarely conducted.[41] To our knowledge, only one program of therapeutic patient education specific to physical activity has been evaluated in cancer patients.[45] However, a recent qualitative study has shown the value of therapeutic patient education on the attitudes towards the physical activity of women with breast cancer to promote regular exercise, which is a guarantee of a better quality of life.[96]

In order to evaluate the efficacy of two interventions in the DISCO trial, the primary outcome measure will be based on the physical activity level of the participants with or without interventions compared to international recommendations. The RPAQ questionnaire will be used for the primary outcome measure on account of its easy implementation. The authors acknowledge that this declarative evaluation confers methodological limits to the study. But the RPAQ questionnaire has been validated against objective methods (i.e., combined accelerometry and heart rate monitoring)[67] to evaluate moderate-to-vigorous physical activities, which is relevant for the primary outcome. No objective measures of physical activity have been planned because of organisational and logistic difficulties to equip and follow participants for one week (i.e., the usual duration of monitoring with an accelerometer such as Actigraph™).[97] Such a test would even be particularly overwhelming for cancer patients during the demanding period of adjuvant treatment onset. Additionally, the number of daily steps reported by the activity tracker was not chosen as the primary outcome because the activity tracker used in the study was not validated for monitoring physical activity in research or for

medical purposes when the study was designed, although its reliability was evaluated against other devices (data not shown). However, recently the performance and reliability of smart devices tend to be increasingly validated.[98]

To understand the results of the DISCO clinical study, it is essential to study beliefs about connected devices and their appropriation by the patients, particularly to understand why behaviours of the patients tend to fade over time. In therapeutic education, beliefs and representations are essential to the success of the intervention. Moreover, with the connected devices, only technical dimensions are not sufficient to understand and highlight why individuals adopt or misuse the connected devices.[73,74]

There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of interventions promoting physical activity among women with breast cancer from studies conducted in France, the Netherland and Australia.[99–104] In various chronic conditions other than cancer, there is now clear evidence in favour of exercise-based programs for the treatment of various chronic conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.[105] As more research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers, particularly breast cancer, the economic evaluation planned in the DISCO trial will fill in the gap by adding useful information.

In conclusion, the study findings will provide valuable information on the efficacy of exercise interventions during breast cancer treatments, overcoming current barriers of access to facilities. They will further guide the development of evidence-based innovative interventions, to systematically include physical activity in the breast cancer care process. Finally, the economic evaluation planned in the DISCO trial will provide useful information for decision-makers.

Supplementary file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.

Supplementary file 2: English language example of the patient consent

Abbreviations

BMI: body mass index;

eCRF: electronic case report form;

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-Of-Life Questionnaire;

EPICES: Evaluation of Deprivation and Inequalities in Health Examination Centres (questionnaire);

ITT: intent-to-treat;

MET: metabolic equivalent of task;

PFS-12: Piper Fatigue Scale-12;

RPAQ: Recent Physical Activity Questionnaire;

WHO: World Health Organization;

6MWT: six-minute walk test.

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Authors' contributions

BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise

training. LP, MT, OP, AM and EB designed the medico-economic study and eCRF. MP, TL, MT, OP and AM designed the part on uses and representations. J-BF, MT and OP designed the part on occupational status. All authors were involved in in planning the methods and measurement and a priori analysis planning. MT and BFo wrote the initial draft of the manuscript. All authors reviewed and provided comprehensive contribution to the manuscript, and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethics approval was provided by the French Ethics Committee (Comité de Protection des Personnes Est I).

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1158 **Table 1** Summary of outcome measures and data collection schedule for the DISCO trial

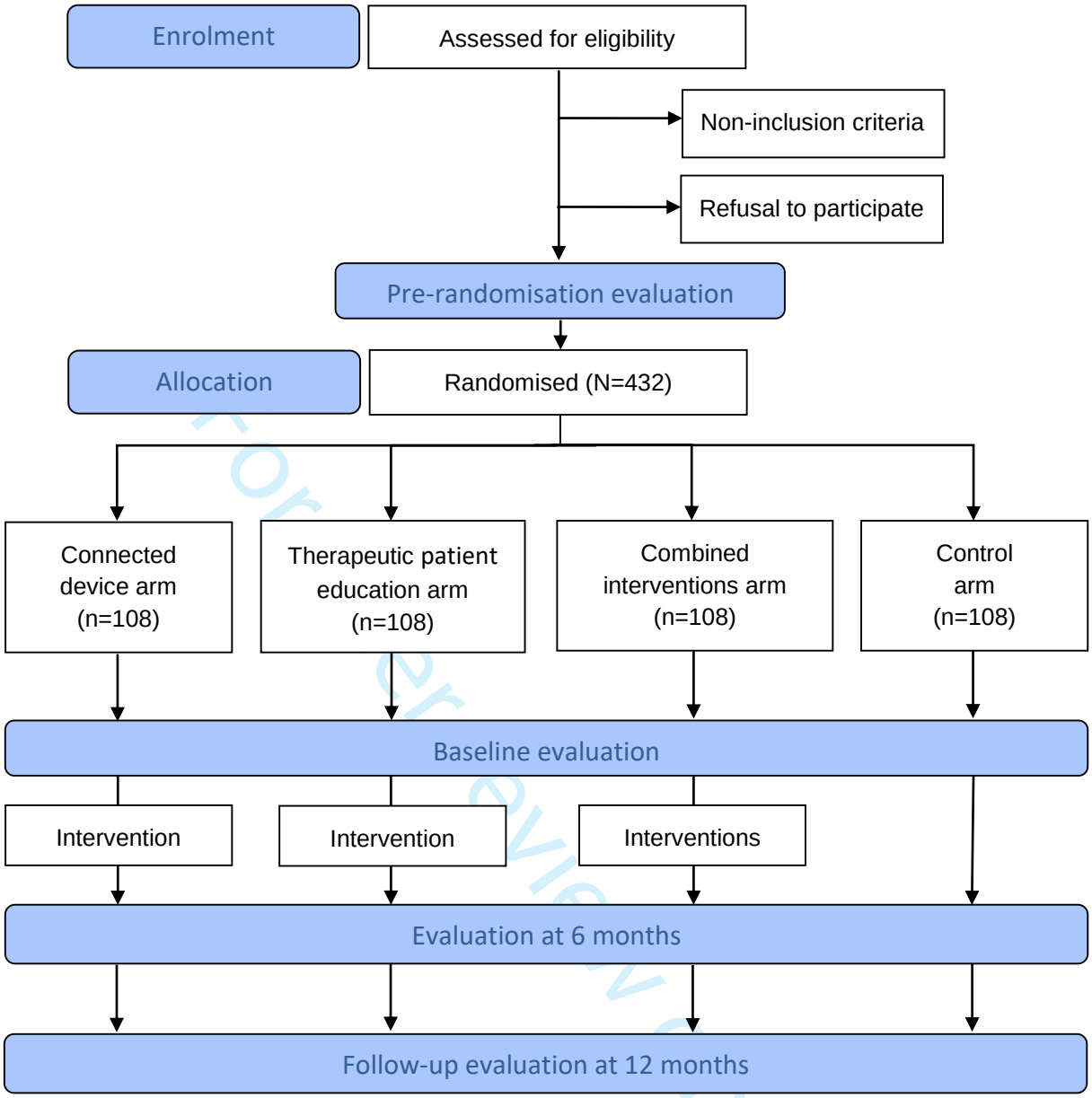
Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
Demographic and clinical data	Patient's medical record			
- Month/year of birth		X		
- Age at diagnosis		X		
- Employment status		X	X	X
- Personal history of breast cancer		X		
- Current treatment		X	X	X
- Hormonal receptor status		X		
- Tumour histology		X		
- Disease progression			X	X
Anthropometrics				
- Height	Gauge	X		
- Weight	Scale	X	X	X
- Waist-to-hip circumference	Measuring tape	X	X	X
- Body composition: fat mass, lean mass, dry lean mass, body water	Bioelectrical impedance analysis	X	X	X
Physical fitness		X	X	X
- Walking endurance with perceived difficulty	6MWT and Borg scale			
- Lower limb muscle strength	Sit-to-stand test			
- Hand prehensile strength	Hand-grip test			
- Flexibility of lower limbs	Sit-and-reach flexibility test			
- Balance	Single-leg stance test			
Physical activity level, sitting time and achievement of physical activity recommendations	RPAQ Questionnaire	X	X	X
Patient-reported outcomes				
- Quality of life	EORTC QLQ-C30 questionnaire and BR-23 module	X	X	X
- Health-related quality of life	EQ-5D-5L Questionnaire	X	X	X
- Fatigue	PFS-12 questionnaire	X	X	X
- Social vulnerability	EPICES questionnaire	X		X
Determinants of physical activity				
- Barriers to regular physical activity; lifestyle	Self-administered questionnaire	X	X	X
- Uses, representations and motivation of physical activity; acceptability of activity trackers (only for patients in the "connected device" and "combined" arms); acceptability of therapeutic patient education (only for patients in the "therapeutic patient education" and "combined" arms)	Online self-administered questionnaire	X	X	X
Biological data	Blood sample	X	X	
- Serum endocrine factors (IGF-1, insulin, estradiol)				

Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
- Plasmatic inflammatory cytokines (IL-6, TNFα, CRP) - Plasmatic adipokines (adiponectin, leptin) - Vitamin D status				
Compliance with each intervention (only for patients in the "connected device", "therapeutic patient education" and "combined" arms)	Connected device and/or patient's record		X	
Adverse events (neuropathies, joint pain)	Patient's diary, CTCAE v5		X	X

Notes. 6MWT: six-minute walk test

1161 **Figure 1** Flow chart of participants through the DISCO trial.

1162



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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 26
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	8, ethics copy
Funding	4	Sources and types of financial, material, and other support	30, funding copy
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 31-32
	5b	Name and contact information for the trial sponsor	1
	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	31
	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)	31

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	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
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)	8
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	8
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)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-15
	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)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	17, Table 1
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)	9, 16-17, Figure1, Table1

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	22_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8_____
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	10_____
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	10_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_____
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	17-21_____
	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	17_____

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	17, 24
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	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24
	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)	23-24
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	25
	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	N/A
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	14, 24-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32
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)	26

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32
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	25
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	N/A
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	25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	31
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9, Suppl file 2
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	21

*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.

Consent to participate in the DISCO trial

Version 4.0 of 28 Oct 2020

I, the undersigned, Surname: .....First name: .....

Address:.....

Phone number: .....

E-mail address:.....

acknowledge having been informed by the Doctor: .....

of the object and modalities of the DISCO study.

I was given an information note. The objective of the study, its constraints, its potential benefits and risks, and its duration were clearly explained to me. I was able to ask all the questions I wanted and I received clear and precise answers. I was given sufficient reflection time between the information and this consent.

I have noted that I am free to accept or refuse to participate in this research and that I will be free at any time to stop my participation without having to specify the reasons and without this changing the quality of the care I will receive nor my relationship with the healthcare team. In the event that I withdraw my consent, the medical and personal data and biological elements concerning me, collected before that date, may be used for the study.

I have noted that all data and information concerning me will be collected and recorded in a strictly confidential and non-identifying manner and will only be consulted by the organizers of this study and representatives of the health authorities. I accept that they may be processed electronically by the promoter (Centre Léon Bérard) or on its behalf. I have noted that I have the right to access, oppose and rectify any personal information concerning me (in accordance with EU regulation n°2016/679 on the protection of personal data (GDPR)) and that I can exercise this right at any time with the doctor in charge of the research, who alone knows my identity. I know that my identity will not appear in any report or publication. I also accept that these data (strictly confidential and treated without mentioning my first and last name) may be used in subsequent research for scientific purposes. I can withdraw my consent to this further use or exercise my right to object at any time.

I have also been informed that I can contact the doctor who follows me or the Data Protection Officer (DPO) of the Centre Léon Bérard (dpd@lyon.unicancer.fr) to obtain information concerning the protection of my data. If, despite the commitment of the Centre Léon Bérard to respect my rights and protecting my data, I remain unsatisfied, I may lodge a complaint with the supervisory authority: the National Commission for Data Protection and Liberties (https://www.cnil.fr/fr/notifier-une-violation-de-donnees-personnelles).

I certify that I am affiliated with or beneficiary of a social security scheme.

I have also been informed of the existence of insurance to cover any damage attributable to the procedures of the study.

My consent does not relieve the organizers of the research of their moral and legal responsibilities. I retain all my rights as guaranteed by law.

I can at any time request any further information from the doctor in charge of the research, Prof. Béatrice Fervers, on 04 69 16 66 44 or 04 69 85 62 18.

In view of the information provided to me, I freely and voluntarily agree to participate in this medical research.

The patient	**The Investigator**
Surname, first name: _____	**Surname, first name:** _____
Done in: _____	**Done in:** _____
Date: _____	**Date:** _____
Patient's signature:	**Physician's signature:**