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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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3 1 **Connected device and therapeutic patient education to promote physical activity among women**  
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5 2 **with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised**  
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7 3 **controlled trial**  
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## 24 **ABSTRACT**

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

33 **Methods and analysis:** This is a 2x2 factorial, multicentre, phase III randomised controlled trial. The  
34 study population (with written informed consent) will consist of 432 women diagnosed with primary  
35 localized invasive breast carcinoma and eligible for adjuvant chemotherapy, hormone therapy and/or  
36 radiotherapy. They will be randomly allocated between one of four arms: (i) web-based connected  
37 device (evolving target number of daily steps and individualized, semi-supervised, adaptive program  
38 of two walking and one muscle strengthening sessions per week in autonomy), (ii) therapeutic patient  
39 education (one educational diagnosis, two collective educational sessions, one evaluation), (iii)  
40 combination of both interventions and (iv) control. All participants will benefit from the international  
41 physical activity recommendations. Assessments (baseline, 6 and 12 months) will include physical  
42 fitness tests, anthropometrics measures, body composition (CT-scan, impedancemetry), self-  
43 administered questionnaires [physical activity profile (RPAQ), quality of life (EORTC QLQ-C30, EQ-5D-  
44 5L), fatigue (PFS-12), social deprivation (EPICES), lifestyle, physical activity barriers, occupational  
45 status] and biological parameters (blood draw).

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

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

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

53

54 **Word count:** 8445

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### 56 **Strengths and limitations of this study**

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

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3 75 monitoring and its relevance for the primary outcome, although the performance and  
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5 76 reliability of activity trackers are increasingly validated.  
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## 78 INTRODUCTION

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

87 In women with breast cancer, deterioration of physical activity level and decline in cardiorespiratory  
88 fitness are frequent.<sup>9,10</sup> Lack of physical activity, obesity and weight gain have been shown to increase  
89 the risk of cancer-related comorbidities and treatments adverse effects, to worsen long-term health  
90 and to cause poor prognosis.<sup>11-13</sup> The benefits of physical activity are well recognized in primary cancer  
91 prevention<sup>14</sup> and numerous studies have shown the safety<sup>15</sup> and benefits of physical activity performed  
92 concomitant to breast cancer treatments. These benefits include reduced fatigue<sup>16-18</sup> and  
93 comorbidities<sup>19</sup>, improved quality of life<sup>20,21</sup> and physical functioning,<sup>10,16,18,21</sup> as well as possibly  
94 reduced risk of recurrence<sup>22</sup> and improved overall and specific survival with a positive dose-response  
95 relationship.<sup>13,22,23</sup> Despite these benefits and international evidence-based guidelines of physical  
96 activity prescription for clinicians and their patients, accessibility to exercise programs and  
97 implementing the guidelines in the cancer care process remain a challenge for patients and health care  
98 providers.<sup>24-26</sup> While a growing number of facilities offer physical activity programs to cancer patients,  
99 distance from home constitutes a barrier to regular exercise during cancer treatments.<sup>25</sup> Successful  
100 exercise strategies during and beyond cancer treatment remain to be determined in clinical trials.<sup>27</sup>  
101 The recent development of connected devices such as activity trackers offers a real opportunity in  
102 oncology to promote and monitor patients' physical activity.<sup>28</sup> While adherence to lifestyle  
103 interventions is a major challenge, connected activity trackers and smartphone applications enable

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3 104 structured monitoring of health parameters and provide feedback to patients. A systematic review of  
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5 105 randomised controlled trials of physical activity interventions using new technologies such as activity  
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7 106 trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly  
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10 107 increased their number of steps per day in the majority of the studies.<sup>29</sup> Recent reviews of intervention  
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12 108 studies conducted among breast cancer patients have also shown that patients increased their physical  
13  
14 109 activity when they used activity trackers.<sup>30,31</sup> Overall, connected activity trackers receive increasing  
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16 110 interest for being systematically integrated into clinical oncology practice.<sup>32,33</sup> But more research is  
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18 111 needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the  
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21 112 preferences of breast cancer patients.<sup>34-36</sup>

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23 113 Therapeutic patient education has emerged in the 1990s in response to the recognition of the need to  
24  
25 114 support patients in the self-management of their chronic diseases, such as diabetes and asthma.<sup>37,38</sup>  
26  
27 115 According to the WHO, therapeutic patient education aims to "help patients acquire or maintain the  
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29 116 skills they need to best manage their lives with a chronic disease".<sup>39</sup> In the cancer field, several cancer-  
30  
31 117 specific programs of therapeutic patient education have been set up to manage pain, fatigue, side  
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33 118 effects of treatment (chemotherapy, surgery) or compliance to treatment.<sup>40-43</sup> By enhancing  
34  
35 119 knowledge and skills level, therapeutic patient education may greatly contribute to increase patients'  
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37 120 autonomy in their disease management. Despite the performance in modifying long-term individual  
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39 121 behaviours and adherence to oral cancer treatments,<sup>43</sup> the benefits of therapeutic patient education  
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41 122 on physical activity levels in cancer patients early after diagnosis has been poorly investigated.<sup>44,45</sup>  
42  
43 123 Several biological mechanisms have been proposed to explain the effects of physical activity on breast  
44  
45 124 cancer risk and outcome. These mechanisms suggest an influence of physical activity on several  
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47 125 signalling pathways involved in tumour development and progression, including the insulin signalling  
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49 126 pathway, chronic inflammation (involving inflammatory cytokines) and endocrine hormone  
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51 127 regulation.<sup>46-48</sup> Based on the data in the literature, it is not possible to conclude for a causal relationship  
52  
53 128 between the metabolic effects of physical activity and the impact on survival, and biological effects of  
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55 129 physical activity remain to be elucidated.<sup>48</sup>  
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3 130 In this context, given the accumulating evidence for the benefits and safety of regular exercise during  
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5 131 treatments of localized breast cancer, it is necessary to systematically encourage patients to remain or  
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7 132 become physically active from the time of diagnosis and to implement and assess the most appropriate  
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9 133 strategies of physical activity in clinical practice. The aim of the DISCO trial is to propose exercise during  
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11 134 breast cancer treatment through two innovative types of interventions, a web-based connected device  
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13 135 and therapeutic patient education, which aim to develop patients' autonomy in their practice of  
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15 136 physical activity. The primary objective of the DISCO trial is to evaluate the efficacy of two interventions  
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17 137 concomitant to adjuvant treatments, either alone or combined, on the physical activity level of breast  
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19 138 cancer patients at the end of the 6-month interventions, compared to usual care: one is an exercise  
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21 139 program using a connected device (comprising an activity tracker linked to a smartphone application  
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23 140 and a website and providing an individualized, semi-supervised, technology-based exercise program)  
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25 141 and the other is a therapeutic patient education intervention. The research hypothesis is that patients  
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27 142 participating in the 6-month connected device or therapeutic education intervention will be more  
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29 143 likely to achieve the international physical activity recommendations, compared to women receiving  
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31 144 physical activity recommendations only (usual care). The international recommendations of the World  
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33 145 Health Organization (WHO) for health are to do at least 150 min of moderate-intensity or 75 min of  
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35 146 vigorous-intensity aerobic physical activity or an equivalent combination each week, and muscle-  
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37 147 strengthening activities at least two days a week.<sup>49</sup> Secondary objectives are: (i) to evaluate the  
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39 148 adherence to the interventions; the impact of the interventions on physical fitness, physical activity  
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41 149 profile, anthropometrics, quality of life, fatigue, biological parameters, occupational status and  
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43 150 lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12 months; the  
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45 151 representations and acceptability of activity tracker and of therapeutic patient education; and ii) to  
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47 152 assess the cost-effectiveness of the interventions. If one of the interventions is individually effective,  
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49 153 the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.  
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## **METHODS AND DESIGN**

## 156 **Trial design**

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

171

## 172 **Eligibility criteria for participants**

173 Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-  
174 metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and  
175 requiring adjuvant treatment (chemotherapy, hormonotherapy, radiotherapy) that will be realised in  
176 one of the investigating centres; providing a medical certificate of no contraindication to exercise;  
177 being available and willing to participate in the study for the duration of the interventions and follow-  
178 up; using a personal smartphone compatible with the application (iOS operating system from version  
179 9.3, Android operating system from version 5.0, no Microsoft operating system) and having a computer  
180 with Internet access; being able to understand, read and write French; and being affiliated with a social  
181 security scheme.

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3 182 Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal history  
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5 183 or co-existence of other primary cancer (except of in situ cancer regardless of the site, basal cell skin  
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7 184 cancer and non-mammary cancer in complete remission for more than 5 years); presenting a  
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10 185 contraindication to exercise according to the investigator (such as cardiorespiratory or bone  
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12 186 pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe  
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14 187 malnutrition according to the criteria of the French National Health Authority (i.e., for women  $\leq 70$   
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16 188 years: weight loss  $\geq 15\%$  in 6 months or  $\geq 10\%$  in 1 month; for women  $> 70$  years: weight loss  $\geq 15\%$  in 6  
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18 189 months or  $\geq 10\%$  in 1 month, and body mass index  $< 18 \text{ kg/m}^2$ );<sup>50</sup> being unable to be followed for  
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20 190 medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or  
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23 191 breastfeeding or of childbearing age without effective contraception for the duration of the study.  
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### 27 193 **Recruitment**

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30 194 Recruitment started on May 2018. Participants will be recruited at several national comprehensive  
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32 195 cancer centres, clinics or hospitals located in France (see ClinicalTrials.gov NCT03529383), which will  
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34 196 ensure adequate participant enrolment to reach the target sample size in a timely manner. Inclusion  
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36 197 of patients will be carried out after surgery and confirmation of the indication of adjuvant treatment.  
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39 198 The study will be proposed to patients at the postoperative, pre-chemotherapy or pre-radiotherapy  
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41 199 consultation (by the surgeon, oncologist or radiotherapist investigator, respectively) depending on the  
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43 200 patient's treatment plan. At this visit, the investigator will check all eligibility criteria and propose to  
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45 201 the eligible patients to participate in the study, explain the objectives and study process and give them  
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48 202 an information notice. After sufficient time for reflection, eligible patients who agree to participate will  
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50 203 date and sign an informed consent and will be included prior to the onset of adjuvant therapy (or  
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52 204 within one month thereafter). The number of eligible patients refusing to participate in the study and  
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55 205 reason for non-participation will be recorded.  
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### 59 207 **Randomisation**

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3 208 Prior to randomisation, participants will be asked to complete the Recent Physical Activity  
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5 209 Questionnaire (RPAQ) to assess their level of physical activity.<sup>51</sup> Their weight, size and prescribed  
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7 210 adjuvant treatments will be collected from the patient's medical record.

9  
10 211 Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris, France)  
11  
12 212 into one of the four arms of the trial, by using the following minimization criteria:<sup>52,53</sup> body mass index  
13  
14 213 (BMI) (<25 kg/m<sup>2</sup>, ≥25 and <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), baseline physical activity level from RPAQ (<150  
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16 214 min/week, ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant  
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18 215 treatments at inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ±  
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20 216 radiotherapy, chemotherapy ± radiotherapy, radiotherapy only).

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## 24 25 218 **INTERVENTIONS**

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28 219 At baseline, all participants will benefit from the international recommendations in terms of physical  
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30 220 activity for promoting health in the general population<sup>49</sup> delivered by a certified exercise instructor.

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### 33 34 222 **Intervention with connected device**

35  
36 223 Participants randomised to the "connected device" arm will benefit from a 6-month exercise program.  
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38 224 The connected device consists of an activity tracker (connected wristband, LS417-F model, CARE  
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40 225 Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application and a  
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42 226 dedicated website proposing an individualized, semi-supervised exercise program adapted to cancer  
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44 227 patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based exercise  
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46 228 program will aim to support participants to enhance physical activity in two ways: doing structured  
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48 229 physical activity sessions and increasing daily physical activity (number of steps). Physical activity  
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50 230 sessions will be automated generated by an algorithm based on the patient profile (described below).  
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52 231 The participants will receive notifications informing them of a new structured physical activity session  
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54 232 available on the website or mobile application, or alerting them when a session was not carried out  
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3 233 and inviting them to execute it when possible. Participants will receive a free 6-month subscription to  
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5 234 the program.

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7 235 —*Setting up the connected device:* At the end of the baseline assessment, the certified exercise  
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9 236 instructor will introduce the participants to the customized exercise program and will give them the  
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11 237 activity tracker and a user guide for the connected device. Then, the certified exercise instructor will  
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13 238 explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated  
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15 239 website, as well as assist the participants to install the application on their smartphone. The  
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17 240 participants will be registered in the customized exercise program by the certified exercise instructor.  
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19 241 The registration will consist of completing a web-based questionnaire about personal and health data  
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21 242 to determine the participant profile (age, weight, height, level of aerobic and muscular strength,  
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23 243 treatment, symptoms, availabilities for exercise sessions and sport materials).

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25 244 —*Baseline level of aerobic and muscular strength for the individualisation of the exercise program:* The  
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27 245 physical fitness tests performed at baseline will be used to classify the participants at the start of the  
28  
29 246 exercise program according to their aerobic level (for the walking sessions) and their muscular strength  
30  
31 247 level (for the strengthening sessions). The aerobic level categories will be determined by the distance  
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33 248 performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2  
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35 249 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level will be determined  
36  
37 250 by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test: muscular  
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39 251 strength group 1 ( $\leq 10$  repetitions), muscular strength group 2 (11 to 14 repetitions) and muscular  
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41 252 strength group 3 ( $\geq 15$  repetitions). Thresholds were based on average values reached by women on  
42  
43 253 treatment for breast cancer for the 6MWT (pooled mean value, 523 m) and the Sit-to-stand test  
44  
45 254 (pooled mean value, 13 repetitions);<sup>54</sup> these values were checked for consistency with percentile  
46  
47 255 scores obtained at the 6MWT and Sit-to-stand test in community-dwelling older women,<sup>55</sup> then the  
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49 256 percentiles were used to determine the thresholds for the three groups.

50  
51 257 —*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise  
52  
53 258 instructor through an individual follow-up of participants (see 'Participant follow-up' part and  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 259 'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using  
4  
5 260 the smartphone application and the website. The program is based on three structured unsupervised  
6  
7 261 sessions per week alternating two types of exercise: two walking sessions (by following oral  
8  
9 262 instructions given via the smartphone application) and one muscle strengthening session (by using  
10  
11 263 videos accessible on the website). The levels of the first walking and muscle strengthening sessions will  
12  
13 264 be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent  
14  
15 265 sessions will be programmed according to the participant's availability days and strengthening  
16  
17 266 exercises will be adapted according to sport materials available to the participants at home (e.g., Swiss  
18  
19 267 ball, sports mat, stick, weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a  
20  
21 268 body session of 10 to 35 minutes of strengthening exercises developing, or 10 to 50 minutes of walking  
22  
23 269 sessions (mixing continuous and/or intermittent effort); 3) a 5-minute recovery period, consisting of  
24  
25 270 stretching and relaxation during strength training sessions, or a cool down during walking sessions.  
26  
27 271 Sessions will be of moderate-to-high intensity ( $\geq 3$  and  $\leq 9$  METs).  
28  
29 272 The three structured unsupervised exercise sessions per week are configured by a unique algorithm  
30  
31 273 hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to  
32  
33 274 plan the exercise sessions and determine the exercise level in an adapted and progressive manner. At  
34  
35 275 the beginning of each session, the duration and intensity of the session will be determined according  
36  
37 276 to the perceived difficulties (evaluated by a Borg scale) and participant's emotional state (recorded by  
38  
39 277 an emoji) in the previous session, and will be modified or postponed according to the level of fatigue  
40  
41 278 (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg scale), the presence or absence  
42  
43 279 of unusual muscle pain and the presence or absence of unusual nausea/diarrhea. In case of a severe  
44  
45 280 adverse event related to disease or treatment (i.e., joint disability, osteoarthritis, cachexia, hand-foot  
46  
47 281 syndrome, aplasia, diuretic, axillary node dissection, pace-maker, chemotherapy, targeted therapy,  
48  
49 282 hormone therapy, radiotherapy, COPD, diabetes) or temporary contraindication to exercise, declared  
50  
51 283 by the participant on her device, the program and sessions will be adapted or suspended until the  
52  
53 284 participant's health improves.  
54  
55  
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57  
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1  
2  
3 285 In addition, participants will have the opportunity to perform additional exercise sessions according to  
4  
5 286 their preferences and lifestyle, outside the program. Participants will be asked to record these sessions  
6  
7 287 through the smartphone application or the website: type of activity (e.g., walking, hiking, cycling) from  
8  
9 288 a list adapted from the Ainsworth's Compendium,<sup>56</sup> duration and intensity.

11  
12 289 —*Number of daily steps*: Participants will be advised to wear the activity tracker daily and regularly  
13  
14 290 (preferably daily) launch the application, which will automatically synchronize with the activity tracker  
15  
16 291 via Bluetooth connection and will collect the number of steps. The target number of steps will be  
17  
18 292 3,000 steps per day at the program onset, and then will be set on the basis of the daily average steps  
19  
20 293 during the first week after inclusion. The target number of daily steps will evolve automatically every  
21  
22 294 three weeks based on the average number of daily steps achieved during the previous three weeks,  
23  
24 295 and will be updated automatically in the application. Consistent with principles of exercise training and  
25  
26 296 progression,<sup>57,58</sup> after each 3-week cycle, if the objective of steps per day is reached by the participant,  
27  
28 297 the target objective will increase by 15% during the following 3-week-cycle, within a maximum target  
29  
30 298 of 10,000 daily steps. If the average number of daily steps does not meet the objective, the target will  
31  
32 299 remain unchanged in the next cycle.

33  
34  
35 300 —*Participant follow-up*: A telephone follow-up will be carried out by the certified exercise instructor  
36  
37 301 at 10 days, 2 months and 4 months after randomisation to ensure the proper functioning of the  
38  
39 302 connected device, review the use of the connected device, review the conduct of the sessions and  
40  
41 303 answer the participants' questions. Participants will be orally encouraged to remain physically active  
42  
43 304 on a daily basis (reminder of the benefits and recommendations of physical activity, success and  
44  
45 305 satisfaction during the exercise sessions). During the 6-month intervention, the participants will have  
46  
47 306 the opportunity to contact the certified exercise instructor or the clinical research assistant at any time,  
48  
49 307 by e-mail (directly through the website) or by telephone for any question or assistance with the  
50  
51 308 connected device.

52  
53  
54 309 —*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device  
55  
56 310 by the participants and their progress in the program through a dedicated professional website that

1  
2  
3 311 provides real-time access to the participants' data. On this website, an automatically generated daily  
4  
5 312 event table will inform the certified exercise instructor of the occurrence of disabilities reported by the  
6  
7 313 participants that may lead to modify their program (e.g., severe fatigue, dyspnea, unusual muscle pain)  
8  
9  
10 314 or if participants have not performed their planned sessions or used their activity tracker for seven  
11  
12 315 consecutive days. Upon these alerts, the certified exercise instructor will contact the participants to  
13  
14 316 precisely analyse the reported disabilities, advice participants, identify the causes of non-use of the  
15  
16 317 connected device, solve possible technical problems or reinforce participant's motivation if necessary.  
17  
18 318 *End of the intervention:* At the end of the 6-month program, participants will keep their activity tracker  
19  
20 319 to be encouraged to continue regularly exercising in autonomy. Upon their request, continued  
21  
22 320 subscription to the dedicated application and website will be offered for six other months, with no  
23  
24 321 individual follow-up anymore.  
25  
26  
27  
28  
29

### 30 323 **Intervention of therapeutic patient education**

31  
32 324 Participants randomised to the therapeutic patient education arm will benefit from a therapeutic  
33  
34 325 patient education intervention, in addition to the international recommendations in terms of physical  
35  
36 326 activity. The intervention is part of the therapeutic patient education program set up at the Léon  
37  
38 327 Bérard cancer centre and validated by the Regional Health Agency ("Agence Régionale de Santé Rhône-  
39  
40 328 Alpes") and will be disseminated in the investigating centres according to the criteria of the Regional  
41  
42 329 Health Agency. The therapeutic patient education intervention consists in four sessions that will be  
43  
44 330 scheduled according to participants' availability during their follow-up visits as part of their usual  
45  
46 331 clinical management over a 6-month period.  
47  
48  
49

50 332 First, participants will be invited to an initial 1-hour individual session of educational diagnosis with a  
51  
52 333 health professional trained in therapeutic patient education. This session will assess their needs and  
53  
54 334 establish a contract of objectives to reach. Then, participants will be invited to participate in two  
55  
56 335 collective educational sessions of 1h30 each (group of 10 patients maximum). These sessions will be  
57  
58 336 composed of theoretical and practical workshops to help them understand their physical activity in  
59  
60

1  
2  
3 337 their daily life and implement the necessary means to practice regular exercise in autonomy. Finally,  
4  
5 338 an educational evaluation will be conducted during a 1-hour individual session, during which the  
6  
7 339 participants will identify whether they have achieved their individual objectives set at the time of the  
8  
9  
10 340 educational diagnosis.

11  
12 341

### 13 14 342 **Combined interventions**

15  
16 343 Participants randomised to the 'combined intervention' arm will benefit from a combination of the  
17  
18 344 connected device intervention and the therapeutic patient education intervention in parallel for  
19  
20  
21 345 6 months.

22  
23 346

### 24 25 347 **STUDY OUTCOMES**

26  
27 348 The primary endpoint will be the proportion of women who achieve at 6 months the internationally  
28  
29 349 recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical  
30  
31 350 activity, i.e., intensity  $\geq 3$  METs) assessed according to the RPAQ self-administered questionnaire.

32  
33  
34 351 Secondary endpoints will be:

35  
36 352 1. Assessment of the efficacy of the programs at 12 months (i.e., proportion of women who achieve  
37  
38 353 the internationally recommended level of physical activity);

39  
40 354 2. Assessment of the adherence to the interventions at 6 months (proportion of participants who are  
41  
42 355 compliant to the program, participation rate in planned sessions);

43  
44 356 3. Assessment of the impact between baseline and 6 months and between 6–12 months of the  
45  
46 357 interventions on physical activity profile (change in time spent in different intensities of physical  
47  
48 358 activity and time spent in sedentary activities), physical fitness (change in results to the 6-minute walk  
49  
50 359 test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test),  
51  
52 360 anthropometrics (change in weight, waist and hip circumferences, BMI, fat mass, lean body mass,  
53  
54 361 muscle mass, dry lean mass and body water), quality of life (change in scores obtained from the EORTC  
55  
56 362 QLQ-C30 questionnaire and its BR-23 module), fatigue condition (change in scores obtained from the  
57  
58  
59  
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2  
3 363 PFS-12 questionnaire), health-related quality of life (change in scores obtained from the EQ-5D-5L  
4  
5 364 questionnaire), social deprivation (change in scores obtained from the EPICES self-administered  
6  
7 365 questionnaire), occupational status (proportion of participants who changed their employment status,  
8  
9  
10 366 with return to work and who perceived difficulty at work obtained from a self-administered  
11  
12 367 questionnaire) and lifestyle factors (proportion of participants who change their tobacco use and  
13  
14 368 alcohol intake obtained from a self-administered questionnaire).

16 369 4. Assessment of the impact of the interventions on biological parameters between baseline and  
17  
18 370 6 months (change in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], change in  
19  
20 371 plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines:  
21  
22 372 adiponectin and leptin], proportion of participants with a modification on vitamin D status).

23  
24 373 5. Assessment of the representations and acceptability of activity tracker and of therapeutic patient  
25  
26 374 education, at baseline, 6 and 12 months (proportion of participants who accept the connected device  
27  
28 375 and who accept the therapeutic program, according to scores obtained from a self-administered  
29  
30 376 qualitative questionnaire used in social psychology science).

31  
32 377 6. Assessment of refusal rate among eligible patients (proportion of patients who refuse to participate).

33  
34 378 7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at  
35  
36 379 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital  
37  
38 380 costs (national data) and benefit in physical activity level.

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41  
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43 381

## 44 382 **EVALUATIONS**

45  
46 383 The initial assessment (T0) will be performed prior to randomisation for minimization purposes. Three  
47  
48 384 evaluations will then be conducted at baseline (T1), 6 months (T2) and 12 months (T3). All study  
49  
50 385 participants will then be followed at 6 months  $\pm 1$  month post-randomisation (corresponding to the  
51  
52 386 end of participation in the interventions for women in the connected device, therapeutic patient  
53  
54 387 education and combined arms) and at 12 months  $\pm 1$  month post-randomisation (corresponding to a  
55  
56 388 follow-up period of 6 months post-interventions). Assessments will be carried out by a clinical research  
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58  
59  
60

1  
2  
3 389 assistant and a certified exercise instructor. The clinical research assistant will contact participants by  
4  
5 390 phone to invite them to follow-up visits and to promote participant retention and complete follow-up.  
6  
7 391 Participants will have no compensation for participation and all study visits will be scheduled on days  
8  
9  
10 392 of medical or health-related appointments.  
11  
12 393 All evaluations (baseline, 6 and 12 months) will include physical fitness tests, anthropometrics  
13  
14 394 measures, self-administered questionnaires and a non-fasting blood draw (baseline and 6 months  
15  
16 395 only). Data will be recorded using an electronic case report form (eCRF).  
17  
18

19 396

## 20 21 397 **DATA COLLECTION**

22  
23 398 The study outcome measures and their schedule are summarised in [Table 1](#).

### 24 25 399 **Socio-demographic and clinical data**

26  
27 400 Demographic and clinical data, including month/year of birth, age at diagnosis, family status, level of  
28  
29 401 education, hormonal status, tumour histology and personal history of breast cancer will be collected  
30  
31 402 at baseline. Family status, potential cancer progression and all treatments received for cancer will be  
32  
33 403 collected at 6 and 12 months. All data will be extracted from patients' electronic medical records,  
34  
35 404 except family status and level of education that will be self-reported in a questionnaire.  
36  
37

38  
39 405 Occupational status will be assessed using a self-administered questionnaire asking employment  
40  
41 406 status, occupation, size of the company, perceived intensity of the physical effort at work, evolution  
42  
43 407 of employment status at return to work.<sup>59</sup>  
44  
45

46 408

### 47 48 409 **Anthropometrics and body composition**

49  
50 410 The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be  
51  
52 411 measured using standardized procedures and BMI will be calculated as the body weight in kilograms  
53  
54 412 divided by the square of the height in meters (kg/m<sup>2</sup>). The waist circumference will be measured  
55  
56 413 midway between the last floating rib and the iliac crest. The hip circumference will be measured at the  
57  
58 414 tip of the pubis. Body composition will be measured by bioelectronic impedancemetry (Biody XPert  
59  
60

1  
2  
3 415 ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle  
4  
5 416 mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid  
6  
7 417 (in L).  
8  
9

10 418

### 11 419 **Physical fitness**

12  
13  
14 420 Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance  
15  
16 421 covered in metres) with perceived difficulty using Borg scale.<sup>60</sup> During this test, participants will be  
17  
18 422 asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes.

19 423 The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a  
20  
21 424 chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as  
22  
23 425 many times as possible during 30 seconds.<sup>61</sup>

24  
25  
26 426 Hand prehensile strength will be measured using hand dynamometry (Jamar Plus Digital Hand  
27  
28 427 Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the isometric strength  
29  
30 428 of the hand and forearm muscles.<sup>62</sup> During this hand-grip test, participants will be asked to squeeze  
31  
32 429 the handgrip as strongly as possible to obtain the maximal force (in kg). Two measures will be  
33  
34 430 performed on each hand and the best performance registered.

35  
36  
37 431 Flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe Baseline  
38  
39 432 flexibility test, 3B Scientific, Bartenheim, France).<sup>63</sup> In this test, participants will be seated on the floor  
40  
41 433 on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as  
42  
43 434 possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering  
44  
45 435 the level of the feet as recording zero, any measure that does not reach the toes is negative and any  
46  
47 436 measure beyond the toes is positive).

48  
49  
50 437 The balance will be measured using the bilateral unipodal equilibrium test.<sup>64</sup> The participants will stand  
51  
52 438 and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same  
53  
54 439 exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).  
55  
56  
57  
58  
59  
60

### 441 **Physical activity level, sitting time and achievement of physical activity recommendations**

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

456 Achievement of international physical activity guidelines will be computed for each individual by  
457 dividing the time spent in moderate-to-vigorous physical activity (i.e.,  $\geq 3$  METs) into two categories:<sup>49</sup>  
458 <150 min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines);  $\geq 150$   
459 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).

460

### 461 **Patient-reported outcomes**

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

1  
2  
3 467 insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score  
4  
5 468 ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds  
6  
7 469 to a better functioning level. For scales related to symptoms, a lower score corresponds to a better  
8  
9  
10 470 functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex  
11  
12 471 enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.

14 472 The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.<sup>67</sup> This standardized  
15  
16 473 self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual activities,  
17  
18 474 pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight, moderate, severe  
19  
20 475 and extreme problems) and comprises a 0-100 visual analogue scale recording the self-rated health  
21  
22  
23 476 (where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can  
24  
25 477 imagine').

27 478 Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported  
28  
29  
30 479 questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of  
31  
32 480 fatigue):<sup>68</sup> the higher the score, the worse the fatigue. All items together will produce a total score for  
33  
34 481 fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3),  
35  
36 482 moderate fatigue (score 4-6) and severe fatigue (score 7-10).

38  
39 483 Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in  
40  
41 484 Health Examination Centres) score.<sup>69</sup> The score will be computed by adding each question coefficient  
42  
43 485 to the intercept whenever the answer is "yes." The score ranges from 0 to 100 (i.e., the higher the  
44  
45 486 score, the greater the deprivation level) with the threshold for deprivation at 30.

47  
48 487 Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e., never,  
49  
50 488 former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol intake  
51  
52 489 over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3  
53  
54 490 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer,  
55  
56 491 cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses).  
57  
58 492 The amount of alcohol will be computed by multiplying the frequency of consumption by the amount  
59  
60



1  
2  
3 493 of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over  
4  
5 494 the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.  
6

7  
8 495

9  
10 496 **Determinants of Physical activity**

11  
12 497 The 21-item self-administered questionnaire “Barriers to Being Active Quiz” will qualitatively assess  
13  
14 498 barriers to regular practice of physical activity.<sup>70</sup>

15  
16 499 Uses, representations and motivation towards physical activity will be assessed within the study  
17  
18 500 population using a self-administered questionnaire available online. Acceptability of connected  
19  
20 501 devices and acceptability of therapeutic patient education will be assessed among participants  
21  
22 502 randomised to the corresponding arms using a paper-based self-administered questionnaire. These  
23  
24 503 questionnaires will be built in accordance with the Unified Theory of Acceptance and Use of  
25  
26 504 Technology (UTAUT),<sup>71</sup> which is a specification of the Theory of Planned Behaviour<sup>72</sup> designed to  
27  
28 505 explain and predict the probability of behaviour change among individuals faced with new  
29  
30 506 technologies. The Theory of Planned Behaviour has been massively used during the last two decades  
31  
32 507 to promote health behaviours such as physical activity. Besides, items wording will be based on the  
33  
34 508 results of individual and collective interviews conducted for that purpose and designed to identify  
35  
36 509 social representations<sup>73</sup> of health protection and physical activity incentive devices.  
37  
38  
39  
40

41 510

42  
43 511 **Biological assessments**

44  
45 512 A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at baseline  
46  
47 513 and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant treatments,  
48  
49 514 otherwise the two blood samples will not be collected. The following biological factors will be assessed  
50  
51 515 in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol), circulating  
52  
53 516 plasma levels of inflammatory cytokines (IL-6, TNF $\alpha$ , CRP) and circulating plasma levels of adipokines  
54  
55  
56 517 (adiponectin, leptin).  
57  
58

59 518  
60

## 519 STATISTICAL ANALYSIS

### 520 Sample size determination

521 The efficacy rate assumptions are  $\mu=40\%$ ,  $\mu+\mu_A=55\%$  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).<sup>22</sup>

527 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:

$$533 [\mu + (\mu+\mu_B)] / 2, \text{ versus } [(\mu+\mu_A) + (\mu + \mu_A + \mu_B)/2]$$

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

535 With a first species risk  $\alpha=0.025$  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  $\alpha =0.025$  in bilateral situation.

540

### 541 Data analysis plan

542 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

1  
2  
3 545 followed the procedure for the duration of the study. Analyses in the ITT population will be performed  
4  
5 546 for all the study endpoints; analysis in the per-protocol population will be performed for exploratory  
6  
7 547 purposes. The randomisation date will be considered as the reference date in all delay calculations,  
8  
9  
10 548 unless otherwise specified.

11  
12 549 Baseline data will be described in the ITT population and presented by randomisation arm. For the  
13  
14 550 primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who  
15  
16 551 received the connective device vs. participants who did not; (ii) participants who benefited from the  
17  
18 552 therapeutic patient education intervention vs. participants who did not. Results will be presented with  
19  
20 553 their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the  
21  
22  
23 554 efficacy of the intervention with a connected device (compared to the absence of a connected device);  
24  
25 555 the efficacy of the therapeutic patient education intervention (compared to no therapeutic patient  
26  
27 556 education); and the interest of combining the two intervention modalities (i.e., connected device and  
28  
29 557 therapeutic patient education) compared to the intervention with the connected device only or the  
30  
31  
32 558 intervention with therapeutic patient education only. The analysis strategy will therefore be as  
33  
34 559 follows:<sup>74</sup> 1) searching first for an interaction by a specific interaction test, performed at the  
35  
36 560 significance level of 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the  
37  
38 561 absence of interaction, testing each of the two bilateral interest comparisons at the 0.025 threshold,  
39  
40 562 namely the efficacy of the intervention with connected device and the efficacy of the therapeutic  
41  
42 563 patient education intervention; 3) in case of efficacy of either one of the intervention modalities,  
43  
44 564 evaluating the interest of the combination of the two interventions compared to the intervention with  
45  
46 565 connected device only or the intervention with therapeutic patient education only.

47  
48 566 For secondary outcome variables, the efficacy of the program at 12 months, as well as according to  
49  
50 567 stratification criteria, will be analysed similarly to the primary outcome. The adherence to the  
51  
52 568 interventions will be studied by the proportion of compliant participants and participation rate in  
53  
54 569 planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life,  
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56 570 fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative  
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3 571 variations of each of these endpoints; these variations will be compared between an intervention and  
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5 572 the absence of this intervention, for each intervention, and between their combination and either  
6  
7 573 intervention, using a parametric test. Occupational status and lifestyle factors will be analysed by  
8  
9 574 comparing proportion of participants between interventions or their combination. Representations  
10  
11 575 and acceptability of activity tracker and of therapeutic patient education will be analysed by comparing  
12  
13 576 proportion of participants between randomisation and follow-up assessments. A method for imputing  
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15 577 missing data will be considered if necessary.

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19 578 Statistical analyses will be performed using SAS<sup>®</sup> software version 9.4 or later.  
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#### 23 24 580 **Medico-economic analysis**

25  
26 581 The cost-effectiveness analysis will be conducted alongside the trial using the French national health  
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28 582 insurance perspective. The time horizon will be 12 months. Hence, neither costs nor effectiveness will  
29  
30 583 be discounted. Mean costs and effectiveness will be derived for all four strategies under consideration:  
31  
32 584 connected device, therapeutic patient education, combined and control arms. Incremental Cost-  
33  
34 585 Effectiveness Ratios (ICERs) will be expressed in cost per quality-adjusted life year (QALY) gained using  
35  
36 586 EQ-5D-5L to estimate utility, cost per life year gained, cost per BMI unit lost and cost per centimetre  
37  
38 587 of waist-to-hip circumference lost. One-way sensitivity analyses will be conducted by varying resource  
39  
40 588 consumption and unit cost parameters and graphically illustrated in a Tornado diagram. The  
41  
42 589 uncertainty surrounding the ICERs will be also captured by a probabilistic analysis using non-parametric  
43  
44 590 bootstrap methods as recommended by the French National Authority for Health.<sup>75</sup>  
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#### 50 51 52 592 **ADVERSE EVENTS**

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54 593 All participants will continuously report the occurrence of adverse events regarding neuropathies and  
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56 594 joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped with  
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58 595 the connected device will also report potential adverse events before and after each session of their  
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3 596 exercise program (see *Connected device*). Due to the low risks associated with the interventions,<sup>15</sup> data  
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5 597 monitoring will not be conducted for other adverse events.  
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10 599 **DATA MANAGEMENT**

11  
12 600 The database for clinical data and randomisation will be created using EnnovClinical® software. Its  
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14 601 access will be secured (personal identification and password protection) for maintaining confidentiality  
15  
16 602 at all times. Individual participants will not be identified in any reports of this trial. All data from the  
17  
18 603 connected device will be merge to the clinical database at the end of the study. Investigators and data  
19  
20 604 analysts will have access to the final dataset.  
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23 605 Data monitoring will be provided by the trial steering committee, including overall project supervision,  
24  
25 606 progress monitoring, advice on scientific credibility, and ensuring the integrity and appropriate running  
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27 607 of the project. The clinical research assistant will verify all consent forms, compliance with established  
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29 608 protocol and procedures, and data quality in the eCRF. The research team will make biannual reports  
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31 609 to the trial steering committee.  
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36 611 **PATIENT AND PUBLIC INVOLVEMENT**

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39 612 An association of breast cancer patients' representatives (Europa Donna France,  
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41 613 <http://www.europadonna.fr/>) was involved in preparing the conduct of interventions and evaluations,  
42  
43 614 in particular by considering patients' expectations, experience and desire for global care. The  
44  
45 615 association will be involved in plans to disseminate the study results to breast cancer patients, study  
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47 616 participants and wider patient communities concerned.  
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52 618 **ETHICS AND DISSEMINATION**

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54 619 The study protocol was approved by the French ethics committee (Comité de Protection des Personnes  
55  
56 620 Est I, ID RCB 2017-A03360-53, 1<sup>st</sup> February 2018) and its database was reported to the French National  
57  
58 621 Commission for Data Protection and Liberties (CNIL, ref. MR-001 no. 2016177, 13<sup>th</sup> December 2016).  
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3 622 Substantial protocol modifications will be submitted to the ethics committee for approval and protocol  
4  
5 623 amendment. The trial is prospectively registered on <http://www.ClinicalTrials.gov> (NCT number:  
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7 624 NCT03529383, 17<sup>th</sup> May 2018).

9  
10 625 The study findings will be widely disseminated through the clinical community by publications in  
11  
12 626 international, peer-reviewed journals and by presentations at national and international conferences.  
13  
14 627 They will also be communicated to patients through associations of patients' representatives and  
15  
16 628 science-based information websites. They will be useful for improving clinical care of cancer patients  
17  
18 629 and provide health professionals, institutions and public authorities with useful information for  
19  
20 630 implementing exercise programs for cancer patients. The study sponsors will disseminate the study  
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22 631 findings to their stakeholders.

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## 26 27 633 **DISCUSSION**

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30 634 This article presents the protocol for the DISCO trial, which aims to evaluate the efficacy of a web-  
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32 635 based connected device intervention and of a therapeutic patient education intervention, either alone  
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34 636 or combined, on the physical activity levels of breast cancer patients undergoing adjuvant treatment,  
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36 637 as well as to assess the cost-effectiveness of the interventions. In the short term, the expected results  
37  
38 638 are to develop autonomy of breast cancer patients in their practice of physical activity, as well as to  
39  
40 639 identify the best strategies of physical activity during breast cancer adjuvant treatments to increase  
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42 640 and sustain physical activity levels in patients, overall or in specific subgroups according to BMI,  
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44 641 baseline physical activity level and type of adjuvant treatment. In the medium term, the goal of the  
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46 642 DISCO trial is to disseminate innovative programs in supportive cancer care, based on evidence-based  
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48 643 practice, to systematically integrate exercise in breast cancer cares.

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51 644 While an increasing number of studies have demonstrated the benefits of exercise in breast cancer  
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53 645 patients, the routine implementation in the cancer care process lacks behind evidence and practice  
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55 646 guidelines.<sup>76-78</sup> While the prescription of physical activity in supervised programs have been shown  
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57 647 superior compared to non-supervised programs,<sup>21,79</sup> semi-supervised interventions seem to yield  
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3 648 comparable or superior benefits than supervised programs.<sup>80</sup> Therefore, the semi-supervised exercise  
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5 649 program of the DISCO trial through continuous follow-up has been designed according to the  
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7 650 preferences of women with breast cancer so as not to leave patients in total autonomy.<sup>35,81</sup> Connected  
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10 651 devices are tools developed over the last 10 years that are very promising for promoting physical  
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12 652 activity in the general population and in chronic diseases such as cancer<sup>82,83</sup> and for developing  
13  
14 653 distance-based physical activity interventions.<sup>84</sup>

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16 654 The semi-supervised home-based physical activity program of the DISCO trial using the connected  
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18 655 device provides flexibility to patients that may facilitate adherence, as well as to overcome barriers  
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20 656 due to distance of facilities from women's home and spatial inequalities of access.<sup>26</sup> Connected devices  
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22  
23 657 allow proposing a tailored physical activity program to patients regardless of their place of residence,  
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25 658 and enable patients to practice physical activities of their choice, at a time that suits them. Therefore,  
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27 659 they may reduce geographical and organisational barriers in the access of patients to exercise, a key  
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29 660 issue to improve their engagement in regular and sustained physical activity.<sup>26</sup> To overcome  
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31 661 motivational barriers to physical activity in oncology, the use of mobile devices has reported benefits  
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33 662 such as patient's engagement, as they can help patients staying physically active over the medium and  
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35 663 long term.<sup>85,86</sup> Moreover, while some studies have shown that breast cancer patients achieve higher  
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37 664 fitness levels during supervised training compared to unsupervised training, low and medium levels of  
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39 665 supervision have been shown to be effective and may represent less resource-intensive options for  
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41 666 effective and longer term behaviour change strategies based on exercise in cancer patients and  
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43 667 survivors.<sup>80,87</sup>

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47 668 Activity trackers have become increasingly popular in recent years. They have been reported to be  
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49 669 pleasant to wear, with positive patients' experience, easy to use and to have a strongly motivational  
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51 670 role through real-time display of the number of steps.<sup>88</sup> Also, walking is an inexpensive activity that  
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53 671 can be performed anywhere and does not require specific skills. A study that assessed preferences for  
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55 672 technology-supported interventions in breast cancer survivors has reported that 63% would like to use  
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3 673 a physical activity mobile application and 90% would find a physical activity tracker useful to monitor  
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5 674 and increase physical activity.<sup>34</sup>  
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7 675 Despite the potential benefits of connected devices in cancer care, their use may face important issues.  
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9 676 First, their use raises important ethical challenges, related to the sensitivity of data and the security of  
10 677 data storage.<sup>89</sup> To ensure that data transfer and storage guarantee informational privacy and patient  
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12 678 safety,<sup>90</sup> an activity tracker made in France (i.e., allowing storing health data in France) and an  
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14 679 accredited national health data host were chosen for the DISCO trial. Particularly, insuring medical  
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16 680 data security is a reassuring choice for patients to participate in this new kind of medical research.  
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18 681 Second, connected devices may raise technical challenges, related to technological robustness,  
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20 682 reliability of data collection and processing, and ease of use. Therefore, an activity tracker with step  
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22 683 display on the screen, user-friendly interface, good reliability and good price-performance ratio was  
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24 684 chosen in the DISCO trial. Third, connected devices may create or exacerbate access disparities related  
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26 685 to technological literacy and economic means, as well as reliable access to internet in rural or isolated  
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28 686 areas.<sup>89</sup> Fourth, medical reasons are usually not easy to control in patients' adherence to exercise  
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30 687 programs. Reliance upon self-assessment of the participant's fatigue, evaluation of the participant  
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32 688 before and after each session on the remote monitoring, up as the source of information about the  
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34 689 participant's health, can result in the ignorance of aspects of the participant's health that cannot easily  
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36 690 be monitored.<sup>89</sup>  
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41 691 Therapeutic patient education has been suggested to increase physical activity in patients with chronic  
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43 692 diseases<sup>45</sup> and to improve multiple health outcomes, including behavioural interventions combined  
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45 693 with physical activity.<sup>91</sup> Therapeutic patient education interventions might be promising for promoting  
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47 694 a physically active lifestyle in cancer patients as it helps patients establish changes in lifestyle and  
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49 695 reinforce self-management.<sup>91</sup> Therapeutic patient education differs from patient education in its  
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51 696 intrinsic structure. Patient education is directed towards informing and teaching patients how to  
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53 697 manage their condition or disease. In contrast, by its structure, therapeutic patient education differs  
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55 698 from patient education in the self-management conferred on the patient.<sup>39</sup> Therefore, therapeutic  
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3 699 patient education is more broadly directed towards how the patient accepts his/her condition and  
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5 700 manages his/her problems on a daily basis and the impact of the disease on personal, family,  
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7 701 professional and social life. Yet, in oncology, few therapeutic patient education studies targeting pain,  
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9 702 fatigue, toxicities or treatment adherence are ongoing, and evaluations are rarely published.<sup>40</sup> To our  
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11 703 knowledge, only one program of therapeutic patient education specific to physical activity have been  
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13 704 evaluated in cancer patients.<sup>44</sup> However, a recent qualitative study has shown the value of promoting  
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15 705 therapeutic patient education to better understand the attitudes towards physical activity of women  
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17 706 with breast cancer to promote regular exercise, which is a guarantee of a better quality of life.<sup>92</sup>  
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19 707 As the DISCO trial was designed to evaluate the efficacy of two interventions, the primary outcome  
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21 708 was based on the physical activity level of the participants comparatively to international  
22  
23 709 recommendations. The primary outcome measure was chosen according to the RPAQ questionnaire  
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25 710 for its easy implementation. The authors acknowledge that this declarative evaluation confers  
26  
27 711 methodological limits to the study. But the RPAQ questionnaire has been validated against objective  
28  
29 712 methods (i.e., combined accelerometry and heart rate monitoring)<sup>65</sup> to evaluate moderate-to-vigorous  
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31 713 physical activities, which is relevant for the primary outcome. No objective measures of physical  
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33 714 activity were planned because of organisational and logistic difficulties to equip and follow participants  
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35 715 for one week (i.e., the usual duration of monitoring with an accelerometer such as Actigraph™).<sup>93</sup> Such  
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37 716 a test would even be particularly overwhelming for cancer patients during the demanding period of  
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39 717 adjuvant treatment onset. Additionally, the number of daily steps reported by the activity tracker was  
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41 718 not chosen as primary outcome because the activity tracker used in the study was not validated for  
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43 719 monitoring physical activity in research or for medical purposes when the study was designed,  
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45 720 although its reliability was checked against other devices (data not shown). However, the performance  
46  
47 721 and reliability of smart devices tends to be increasingly validated.<sup>94</sup>  
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49 722 To understand results of the DISCO clinical study, it is essential to study beliefs about connected  
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51 723 devices and their appropriation by the patients, in order to understand why behaviours tend to fade  
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53 724 over time. In therapeutic education, beliefs and representations are essential to the success of the  
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3 725 intervention. Moreover, with connected devices, only technical dimensions are not sufficient to  
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5 726 understand and highlight why individuals adopt or misuses connected devices.<sup>71,72</sup>  
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7 727 There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of  
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10 728 interventions promoting physical activity among women with breast cancer from studies conducted in  
11  
12 729 France, the Netherland and Australia.<sup>95-100</sup> In various chronic conditions other than cancer, there is  
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14 730 now clear evidence in favour of exercise-based programs for the treatment of various chronic  
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16 731 conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.<sup>101</sup> As more  
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18 732 research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers,  
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21 733 particularly breast cancer, the economic evaluation planned in the DISCO trial will add useful  
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23 734 information.  
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25 735 In conclusion, the study findings will provide valuable information on the efficacy of exercise  
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27 736 interventions during breast cancer treatments, overcoming current barriers of access to facilities. They  
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30 737 will further guide the development of evidence-based innovative interventions, to systematically  
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32 738 include physical activity in the breast cancer care process. Finally, the economic evaluation planned in  
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34 739 the DISCO trial will provide useful information for decision makers.  
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39 741 **Supplementary file 1:** SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.

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### 743 **Abbreviations**

744 BMI: body mass index;

745 eCRF: electronic case report form;

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

747 Questionnaire;

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

749 ITT: intent-to-treat;

750 MET: metabolic equivalent of task;

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3 751 PFS-12: Piper Fatigue Scale-12;  
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5 752 RPAQ: Recent Physical Activity Questionnaire;  
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7 753 WHO: World Health Organization;  
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10 754 6MWT: six-minute walk test.  
11  
12 755

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29

### 32 764 **Authors' contributions**

34 765 BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the  
36 766 research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological  
38 767 aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise  
40 768 training. LP, MT, OP, AM and EB designed the medico-economic study and eCRF. MP, TL, MT, OP and  
42 769 AM designed the part on uses and representations. J-BF, MT and OP designed the part on occupational  
44 770 status. All authors were involved in in planning the methods and measurement and a priori analysis  
46 771 planning. MT and BFo wrote initial draft of the manuscript. All authors reviewed and provided  
48 772 comprehensive contribution to the manuscript, and approved the final manuscript.  
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52 773

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8  
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11  
12 781 **Competing interests**

13  
14 782 None declared.  
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19 784 **Ethics approval**

20  
21 785 Ethics approval was provided by the French Ethics Committee (Comité de Protection des Personnes  
22  
23 786 Est I).  
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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
<b>Demographic and clinical data</b>	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
<b>Anthropometrics</b>				
- 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
<b>Physical fitness</b>		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			
<b>Physical activity level, sitting time and achievement of physical activity recommendations</b>	RPAQ Questionnaire	X	X	X
<b>Patient-reported outcomes</b>				
- 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
<b>Determinants of physical activity</b>				
- 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
<b>Biological data</b>	Blood sample	X	X	
- Serum endocrine factors (IGF-1, insulin, estradiol)				

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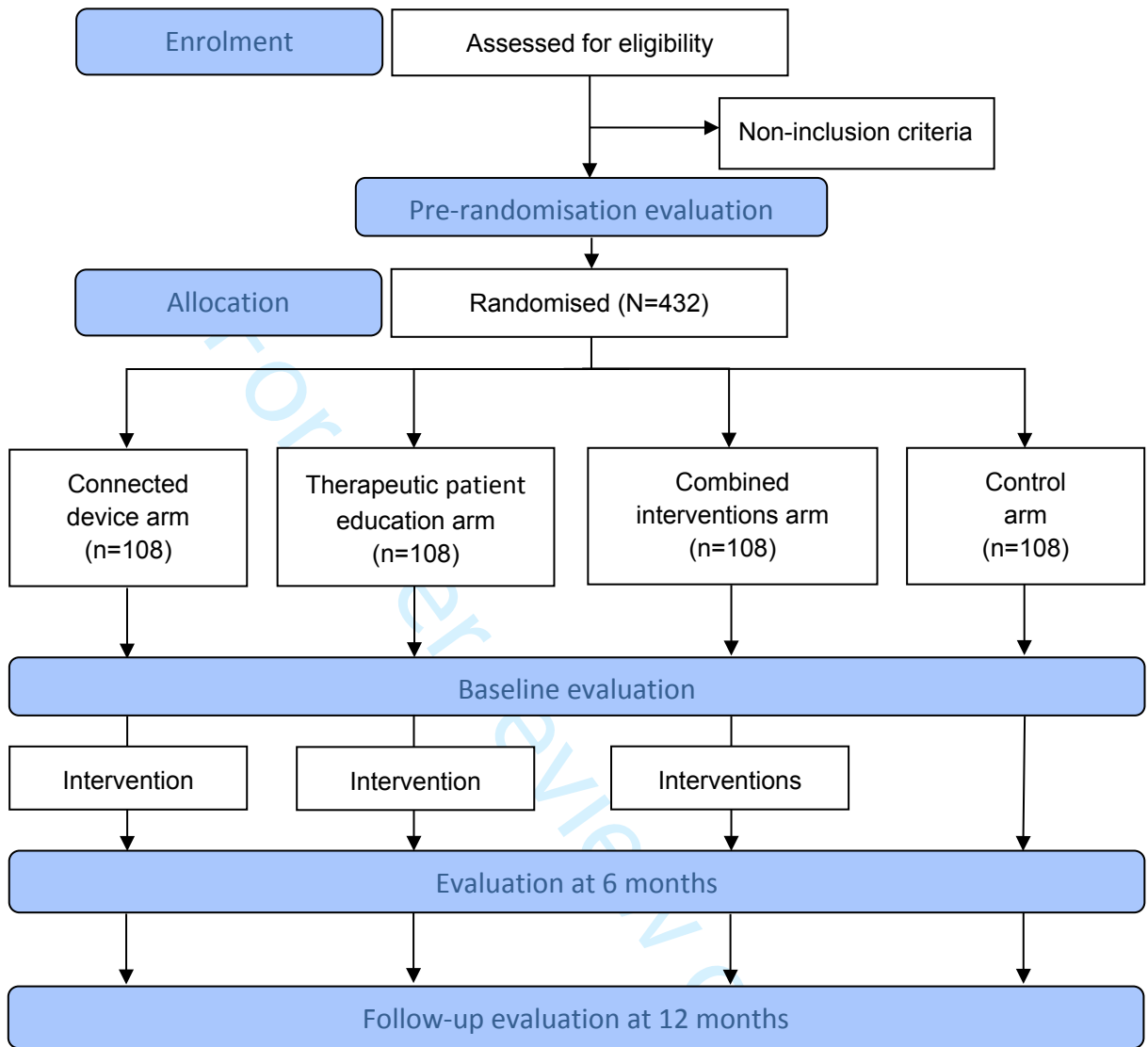
Assessments	Tools	Baseline +1month	6 months ±1month	12 months ±1month
- Plasmatic inflammatory cytokines (IL-6, TNF $\alpha$ , CRP)				
- Plasmatic adipokines (adiponectin, leptin)				
- Vitamin D status				
<b>Compliance with each intervention</b> (only for patients in the “connected device”, “therapeutic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

1099 Notes. 6MWT: six-minute walk test

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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
<b>Administrative information</b>			
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_____



1 **Introduction**

2

3 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 \_\_\_\_\_

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6 6b Explanation for choice of comparators 7 \_\_\_\_\_

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8 Objectives 7 Specific objectives or hypotheses 7 \_\_\_\_\_

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10 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 \_\_\_\_\_

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14 **Methods: Participants, interventions, and outcomes**

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16 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 \_\_\_\_\_

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19 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 \_\_\_\_\_

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 9-15 \_\_\_\_\_

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25 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 \_\_\_\_\_

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 13-14 \_\_\_\_\_

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A \_\_\_\_\_

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34 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\_\_

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40 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\_\_

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1	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_____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8_____
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7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	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_____
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16	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_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_____
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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_____
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39		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_____
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1	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_____
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5	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_____
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24_____
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10		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_____
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14	<b>Methods: Monitoring</b>			
15				
16	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_____
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22		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_____
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25	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_____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25_____
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32__
35				
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37	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_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8_____
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A_____
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7	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_____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32_____
11				
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13	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_____
14				
15				
16	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_____
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20	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_____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	31_____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A_____
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29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9_____
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34	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_____
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# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045448.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Mar-2021
Complete List of Authors:	<p>Touillaud, Marina; Centre Léon Bérard, Department of Prevention Cancer Environment; UMR1296, INSERM-Centre Léon Bérard-Ministère des Armées "Radiations: Defense, Health and Environment"</p> <p>Fournier, Baptiste; Centre Léon Bérard, Department of Prevention Cancer Environment</p> <p>Pérol, Olivia; Centre Léon Bérard, Department of Prevention Cancer Environment; UMR1296, INSERM-Centre Léon Bérard-Ministère des Armées "Radiations: Defense, Health and Environment"</p> <p>Delrieu, Lidia; Centre Léon Bérard, Department of Prevention Cancer Environment; Université Claude Bernard Lyon 1, Inter-University Laboratory of Human Movement Biology EA7424</p> <p>Maire, Aurélia; Centre Léon Bérard, Department of Prevention Cancer Environment</p> <p>Belladame, Elodie; Centre Léon Bérard, Department of Prevention Cancer Environment</p> <p>Pérol, David; Centre Léon Bérard, Department of of Clinical Research and Innovation</p> <p>Perrier, Lionel; Centre Léon Bérard, Direction of Clinical Research and Innovation; GATE, UMR-CNRS 5824, University of Lyon</p> <p>Preau, Marie; Lumière University Lyon 2, GRePS EA4163 Institute of Psychology</p> <p>LEROY, Tanguy; Lumière University Lyon 2, GRePS EA4163 Institute of Psychology</p> <p>Fassier, Jean-Baptiste; Hospices Civils de Lyon, UMRESTTE UMR T9405, Université Claude Bernard Lyon 1</p> <p>Fillol, Florie; Biomouv</p> <p>Pascal, Sébastien; Biomouv</p> <p>Durand, Thierry; Centre Léon Bérard, Department of Hospital Information</p> <p>Fervers, Béatrice; Centre Léon Bérard, Department of Prevention Cancer Environment; UMR1296, INSERM-Centre Léon Bérard-Ministère des Armées "Radiations: Defense, Health and Environment"</p>
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Sports and exercise medicine, Nutrition and metabolism, Health economics, Sociology

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

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3 1 **Connected device and therapeutic patient education to promote physical activity among women**  
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5 2 **with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised**  
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7 3 **controlled trial**  
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12 5 Marina Touillaud<sup>1,2</sup>, Baptiste Fournier<sup>1</sup>, Olivia Pérol<sup>1,2</sup>, Lidia Delrieu<sup>1,3</sup>, Aurélia Maire<sup>1</sup>, Elodie

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16 7 Fillol<sup>8</sup>, Sébastien Pascal<sup>8</sup>, Thierry Durand<sup>9</sup>, Béatrice Fervers<sup>1,2</sup>  
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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, hormone therapy 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.

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

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12 54 **Word count:** 8445

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16 56 **Strengths and limitations of this study**

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19 57 - This randomized clinical trial with four arms has the advantage to evaluate the efficacy of two  
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21 58 interventions, either single or their combination, using a 2x2 factorial design, ensuring a higher  
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23 59 statistical power than a classic trial with three arms, for a similar sample size.
- 24  
25 60 - While the connected device intervention is semi-supervised, the exercise program has been  
26  
27 61 designed according to the preferences of women with breast cancer so as not to leave patients  
28  
29 62 in total autonomy and to provide organisational flexibility to patients to facilitate adherence.
- 30  
31 63 - Despite the potential benefits of connected devices in cancer care, their use may face  
32  
33 64 important issues, such as ethical challenges related to the security of sensitive data storage,  
34  
35 65 technical challenges related to technological robustness and reliability, exacerbating access  
36  
37 66 disparities, and self-assessment of the participant's fatigue or health condition.
- 38  
39 67 - The primary outcome measure is based on a declarative evaluation of physical activity that  
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41 68 confers methodological limits to the study, but the validated questionnaire was chosen  
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43 69 according for its easy implementation for cancer patients compared to accelerometer  
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45 70 monitoring and its relevance for the primary outcome.  
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## 71 INTRODUCTION

72 Breast cancer is the leading cause of cancer in women worldwide with 1.6 million new cases  
73 diagnosed each year,<sup>1</sup> representing more than a third of all new cancer cases in women. In France,  
74 breast cancer also represents the leading cause of cancer incidence and mortality among women, with  
75 approximately 58,000 new cases and 12,000 breast cancer deaths estimated in 2018.<sup>2</sup> Despite a very  
76 good prognosis worldwide with overall survival of 85% at 5 years (87% in France) and 71% at 10 years  
77 (78% in France) for all stages combined,<sup>3-5</sup> a large number of patients with breast cancer experience  
78 adverse effects of cancer and its treatments such as fatigue, impaired quality of life, anxiety or weight  
79 gain.<sup>6-8</sup>

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

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3 96 from home constitutes a barrier to regular exercise during cancer treatments.<sup>26</sup> Successful exercise  
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5 97 strategies during and beyond cancer treatment remain to be determined in clinical trials.<sup>28</sup>  
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7 98 The recent development of connected devices such as activity trackers offers a real opportunity in  
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10 99 oncology to promote and monitor patients' physical activity.<sup>29</sup> While adherence to lifestyle  
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12 100 interventions is a major challenge, connected activity trackers and smartphone applications enable  
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14 101 structured monitoring of health parameters and provide feedback to patients. A systematic review of  
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16 102 randomised controlled trials of physical activity interventions using new technologies such as activity  
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18 103 trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly  
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20 104 increased their number of steps per day in the majority of the studies.<sup>30</sup> Recent reviews of intervention  
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23 105 studies conducted among breast cancer patients have also shown that patients increased their physical  
24  
25 106 activity when they used activity trackers.<sup>31,32</sup> Overall, connected activity trackers receive increasing  
26  
27 107 interest for being systematically integrated into clinical oncology practice.<sup>33,34</sup> Yet, more research is  
28  
29 108 needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the  
30  
31 109 preferences of breast cancer patients.<sup>35-37</sup>  
32  
33

34 110 Therapeutic patient education has emerged in the 1990s in response to the recognition of the need  
35  
36 111 to support patients in the self-management of their chronic diseases, such as diabetes and asthma.<sup>38,39</sup>  
37  
38 112 According to the World Health Organization (WHO), therapeutic patient education aims to "help  
39  
40 113 patients acquire or maintain the skills they need to best manage their lives with a chronic disease".<sup>40</sup>  
41  
42 114 In the cancer field, several cancer-specific programs of therapeutic patient education have been set up  
43  
44 115 to manage pain, fatigue, side effects of treatment (chemotherapy, surgery) or compliance to  
45  
46 116 treatment.<sup>41-44</sup> By enhancing relevant knowledge and skills, therapeutic patient education may greatly  
47  
48 117 contribute to increasing patients' autonomy in their disease management. Despite the performance in  
49  
50 118 modifying long-term individual behaviours and adherence to cancer treatments,<sup>44</sup> the benefits of  
51  
52 119 therapeutic patient education on physical activity levels in cancer patients early after diagnosis has  
53  
54 120 been poorly investigated.<sup>45,46</sup> The research on therapeutic patient education in the breast cancer and  
55  
56 121 exercise context is limited to date and warrants further research.  
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3 122 Several biological mechanisms have been proposed to explain the effects of physical activity on  
4  
5 123 breast cancer risk and outcome. Preclinical and human studies have shown the influence of physical  
6  
7 124 activity on several signalling pathways involved in tumour development, growth and progression,  
8  
9  
10 125 including the insulin signalling pathway (IGF-1, insulin), chronic inflammation (involving inflammatory  
11  
12 126 cytokines such as IL-6, TNF $\alpha$ , CRP) and endocrine hormone regulation (estrogens, adipokines).<sup>47-49</sup> By  
13  
14 127 affecting the endogenous systemic milieu, physical activity is believed to influence cellular processes  
15  
16 128 and tumour growth, and therefore reduce the risk of recurrence, increase treatment efficacy and  
17  
18 129 improve survival.<sup>50</sup> Also, because vitamin D alters mechanisms implicated in cellular growth and  
19  
20 130 proliferation, accumulating evidence suggests that normal-to-high ranges of serum vitamin D levels  
21  
22 131 improve breast cancer prognosis and outcome.<sup>51</sup> Based on the data in the literature, it is not possible  
23  
24 132 to conclude a causal relationship between the metabolic effects of physical activity and the impact on  
25  
26 133 breast cancer risk and survival. Biological effects of physical activity on these biomarkers of  
27  
28 134 endogenous mechanisms interfering in cancer suppression or proliferation remain to be elucidated in  
29  
30 135 order to better understand the benefit of physical activity during adjuvant treatment.<sup>49</sup>

31  
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33  
34 136 In this context, given the accumulating evidence for the benefits and safety of regular exercise  
35  
36 137 during treatments of localized breast cancer, it is necessary to systematically encourage patients to  
37  
38 138 remain or become physically active from the time of diagnosis and to implement and assess the most  
39  
40 139 appropriate strategies of physical activity in clinical practice. The aim of the DISCO trial is to encourage  
41  
42 140 engagement in exercise during breast cancer treatment through two innovative types of interventions,  
43  
44 141 that is to say a web-based connected device and therapeutic patient education, which aim to develop  
45  
46 142 patients' autonomy in their practice of physical activity. The primary objective of the DISCO trial is to  
47  
48 143 evaluate the efficacy of two interventions, either single or combined, concomitant to adjuvant  
49  
50 144 treatments, on the physical activity level of breast cancer patients at the end of the 6-month  
51  
52 145 interventions, compared to usual care: one is an exercise program using a connected device  
53  
54 146 (comprising an activity tracker linked to a smartphone application and a website and providing an  
55  
56 147 individualized, semi-supervised, technology-based exercise program) and the other is a therapeutic  
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3 148 patient education intervention. The research hypothesis is that patients participating in the 6-month  
4  
5 149 exercise program using the connected device or therapeutic education intervention are more likely to  
6  
7 150 achieve the international physical activity recommendations, compared to women receiving physical  
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9  
10 151 activity recommendations only (usual care). The WHO recommendations to maintain or improve  
11  
12 152 health, which applied when the study protocol was developed, are to do at least 150 min of moderate-  
13  
14 153 intensity or 75 min of vigorous-intensity aerobic physical activity or an equivalent combination each  
15  
16 154 week, and muscle-strengthening activities at least two days a week.<sup>11</sup> Secondary objectives are: (i) to  
17  
18 155 evaluate the adherence to the interventions; the impact of the interventions on physical fitness,  
19  
20 156 physical activity profile, anthropometrics, quality of life, fatigue, biological parameters, occupational  
21  
22 157 status and lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12  
23  
24 158 months; the representations and acceptability of activity tracker and therapeutic patient education;  
25  
26 159 and ii) to assess the cost-effectiveness of the interventions. If one of the interventions is individually  
27  
28 160 effective, the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.  
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## 34 162 **METHODS AND DESIGN**

### 36 163 **Trial design**

38  
39 164 The DISCO (an acronym for “dispositif connecté”, i.e., connected device in English) trial is a 2x2  
40  
41 165 prospective, multicentre, factorial, randomised, controlled and open-label study (phase III), conducted  
42  
43 166 by the Léon Bérard comprehensive cancer centre (Lyon, France) among women receiving treatment  
44  
45 167 for localized breast cancer. The clinical protocol was designed and written according to the SPIRIT  
46  
47 168 (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Supplementary  
48  
49 169 file 1). The flowchart of the study is presented in **Figure 1**. Patients will be randomly assigned to one  
50  
51 170 of the four arms of the study according to the 2x2 factorial design (1:1:1:1 ratio). They will all receive  
52  
53 171 international recommendations on physical activity,<sup>11</sup> and: (i) women allocated to the “connected  
54  
55 172 device” arm will benefit from a 6-month individualized, semi-supervised exercise program carried out  
56  
57 173 autonomously. The program consists of an evolving goal of daily numbers of steps using an activity  
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3 174 tracker and two sessions of brisk walking and one session of muscle strengthening per week, using  
4  
5 175 dedicated smartphone application and website; (ii) women allocated to the “therapeutic patient  
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7 176 education” arm will benefit from four therapeutic education sessions on exercise; (iii) women  
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9 177 allocated to the “combined” arm will benefit from both interventions in parallel; (iv) women allocated  
10  
11  
12 178 to the “control” arm will receive usual care.  
13

14 179

### 16 180 **Eligibility criteria for participants**

18 181 Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-  
19  
20 182 metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and  
21  
22 183 requiring adjuvant treatment (chemotherapy, hormonotherapy and/or radiotherapy) that present at  
23  
24 184 one of the investigating centres; providing a medical certificate of no contraindication to exercise;  
25  
26 185 being available and willing to participate in the study for the duration of the interventions and follow-  
27  
28 186 up; using a personal smartphone compatible with an application used for the intervention (iOS  
29  
30 187 operating system from version 9.3, Android operating system from version 5.0, no Microsoft operating  
31  
32 188 system) and having a computer with Internet access; being able to understand, read and write French;  
33  
34 189 and being affiliated with a social security scheme.  
35  
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38 190 Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal  
39  
40 191 history or co-existence of other primary cancer (except for in situ cancer regardless of the site, basal  
41  
42 192 cell skin cancer and non-mammary cancer in complete remission for more than 5 years); presenting a  
43  
44 193 contraindication to exercise according to the investigator (such as cardiorespiratory or bone  
45  
46 194 pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe  
47  
48 195 malnutrition according to the criteria of the French National Health Authority (i.e., for women  $\leq 70$   
49  
50 196 years: weight loss  $\geq 15\%$  in 6 months or  $\geq 10\%$  in 1 month; for women  $> 70$  years: weight loss  $\geq 15\%$  in 6  
51  
52 197 months or  $\geq 10\%$  in 1 month, and body mass index (BMI)  $< 18 \text{ kg/m}^2$ );<sup>52</sup> being unable to be followed for  
53  
54 198 medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or  
55  
56 199 breastfeeding or of childbearing age without effective contraception for the duration of the study.  
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200

**201 Recruitment**

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

214

**215 Randomisation**

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

219 Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris,  
220 France) into one of the four arms of the trial, by using the following minimization criteria:<sup>54,55</sup> BMI (<25  
221 kg/m<sup>2</sup>, ≥25 and <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), baseline physical activity level from RPAQ (<150 min/week,  
222 ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant treatments at  
223 inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ± radiotherapy,  
224 chemotherapy ± radiotherapy, radiotherapy only).

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3 226 **INTERVENTIONS**  
4

5 227 At baseline, all participants will receive the international recommendations in terms of physical  
6  
7 228 activity for promoting health in the general population<sup>11</sup>, which will be delivered orally by a certified  
8  
9 229 exercise instructor with the help of a leaflet.  
10

11  
12 230

13  
14 231 **Intervention with a connected device**  
15

16 232 Participants randomised to the “connected device” arm will benefit from a 6-month exercise  
17  
18 233 program. The connected device consists of an activity tracker (connected wristband, LS417-F model,  
19  
20 234 CARE Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application  
21  
22 235 and a dedicated website proposing an individualized, semi-supervised exercise program adapted to  
23  
24 236 cancer patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based  
25  
26 237 exercise program will aim to support participants to enhance physical activity in two ways: doing  
27  
28 238 structured exercise sessions and increasing daily physical activity (number of steps). Exercise sessions  
29  
30 239 will be automatically generated by an algorithm based on the patient profile (described below). The  
31  
32 240 participants will receive notifications informing them of a new structured exercise session available on  
33  
34 241 the website or mobile application, or alerting them when a session was not carried out, and inviting  
35  
36 242 them to execute it when possible. Participants will receive a free 6-month subscription to the program.  
37  
38 243 —*Setting up the connected device:* At the end of the baseline assessment, the certified exercise  
39  
40 244 instructor will introduce the customized exercise program to the participants and will give them the  
41  
42 245 activity tracker and a user guide for the connected device. Then, the certified exercise instructor will  
43  
44 246 explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated  
45  
46 247 website, as well as assist the participants to install the application on their smartphone. The  
47  
48 248 participants will be registered in the customized exercise program by the certified exercise instructor.  
49  
50 249 The registration will consist of completing a web-based questionnaire about personal and health data  
51  
52 250 to determine the participant profile (age, weight, height, level of aerobic and muscular strength,  
53  
54 251 treatment, symptoms, availabilities for exercise sessions and sports materials).  
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3 252 —*Baseline level of aerobic and muscular strength for the individualised exercise program:* The physical  
4  
5 253 fitness tests performed at baseline will be used to classify the participants at the start of the exercise  
6  
7 254 program according to their aerobic level (for the walking sessions) and their muscular strength level  
8  
9  
10 255 (for the strengthening sessions). The aerobic level categories will be determined by the distance  
11  
12 256 performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2  
13  
14 257 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level categories will be  
15  
16 258 determined by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test:  
17  
18 259 muscular strength group 1 ( $\leq 10$  repetitions), muscular strength group 2 (11 to 14 repetitions) and  
19  
20 260 muscular strength group 3 ( $\geq 15$  repetitions). Thresholds were based on average values reached by  
21  
22 261 women receiving breast cancer treatments for the 6MWT (pooled mean value, 523 m) and the Sit-to-  
23  
24 262 stand test (pooled mean value, 13 repetitions) from a previous study;<sup>56</sup> these values were checked for  
25  
26 263 consistency with percentile scores obtained at the 6MWT and Sit-to-stand test in community-dwelling  
27  
28 264 older women,<sup>57</sup> then the interquartile range was used to determine the thresholds for the three groups  
29  
30 265 of this study. The level categories assigned will be entered by the exercise instructor in the baseline  
31  
32 266 patient profile and will be used by the automated algorithm to set up the level of the first walking and  
33  
34 267 muscle strengthening sessions.

35  
36  
37  
38 268 —*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise  
39  
40 269 instructor through an individual follow-up of participants (see 'Participant follow-up' part and  
41  
42 270 'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using  
43  
44 271 the smartphone application and the website. The program is based on three structured unsupervised  
45  
46 272 sessions per week alternating two types of exercise: two walking sessions (by following oral  
47  
48 273 instructions given via the smartphone application) and one muscle strengthening session (by using  
49  
50 274 videos accessible on the website). The levels of the first walking and muscle strengthening sessions will  
51  
52 275 be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent  
53  
54 276 sessions will be planned according to the available days of the participant. Strengthening exercises will  
55  
56 277 be adapted according to sports materials available at their home (e.g., Swiss ball, sports mat, stick,  
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3 278 weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a body session of 10 to 35  
4  
5 279 minutes of strengthening exercises, or 10 to 50 minutes of walking (mixing continuous and/or  
6  
7 280 intermittent effort); 3) a 5-minute recovery period, consisting of stretching and relaxation during  
8  
9  
10 281 strengthening sessions or a cool down during walking sessions. Sessions will be of moderate-to-high  
11  
12 282 intensity ( $\geq 3$  and  $\leq 9$  METs).

13  
14 283 The three structured unsupervised exercise sessions per week are configured by a unique algorithm  
15  
16 284 hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to  
17  
18 285 plan the exercise sessions and determine the exercise level in an adapted and progressive manner by  
19  
20 286 increasing the duration and then intensity in accordance with principles of exercise training and  
21  
22 287 progression.<sup>58,59</sup> At the beginning of each session, the duration and intensity of the session will be  
23  
24 288 determined according to the perceived difficulties (evaluated by a Borg scale) and emotional state  
25  
26 289 (recorded by an emoji) of the participant in the previous session, and will be modified or postponed  
27  
28 290 according to the level of fatigue (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg  
29  
30 291 scale), the presence or absence of unusual muscle pain and the presence or absence of unusual  
31  
32 292 nausea/diarrhea. In case of a severe adverse event related to disease or treatment (i.e., joint disability,  
33  
34 293 osteoarthritis, cachexia, hand-foot syndrome, aplasia, diuretic, axillary node dissection, pace-maker,  
35  
36 294 chemotherapy, targeted therapy, hormone therapy, radiotherapy, COPD, diabetes) or temporary  
37  
38 295 contraindication to exercise, declared by the participant on her device, the program and sessions will  
39  
40 296 be adapted or suspended until the participant's health improves.

41  
42 297 In addition, participants will have the opportunity to perform additional exercise sessions according  
43  
44 298 to their preferences and lifestyle, outside the program. Participants will be asked to record these  
45  
46 299 sessions through the smartphone application or the website: type of activity (e.g., walking, hiking,  
47  
48 300 cycling) from a list adapted from Ainsworth's Compendium,<sup>60</sup> and its duration and intensity.

49  
50 301 —*Number of daily steps*: Participants will be advised to wear the activity tracker daily and to launch  
51  
52 302 the application regularly (preferably daily), which will automatically synchronize with the activity  
53  
54 303 tracker via Bluetooth connection and will collect the number of steps. The target number of steps will  
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3 304 be 3,000 steps per day at the program onset, and then will be re-set based on the average number of  
4  
5 305 daily steps during the first week after inclusion. The target number of daily steps will evolve  
6  
7 306 automatically every three weeks based on the average number of daily steps achieved during the  
8  
9 307 previous three weeks, and will be updated automatically in the application. Consistent with principles  
10  
11 308 of exercise training and progression,<sup>58,59</sup> after each 3-week cycle, if the goal of steps per day is reached  
12  
13 309 by the participant, the target goal will increase by 15% during the following 3-week-cycle, within a  
14  
15 310 maximum target of 10,000 daily steps. If the average number of daily steps does not meet the goal,  
16  
17 311 the target will remain unchanged in the next cycle.

20  
21 312 —*Participant follow-up*: Telephone follow-ups will be carried out by the certified exercise instructor at  
22  
23 313 10 days, 2 months and 4 months after the intervention onset to ensure the proper functioning of the  
24  
25 314 connected device, review the use of the connected device, review the conduct of the sessions and  
26  
27 315 answer the participants' questions if they may have. Participants will be orally encouraged to remain  
28  
29 316 physically active on a daily basis (reminder of the benefits and recommendations of physical activity,  
30  
31 317 success and satisfaction during the exercise sessions). During the 6-month intervention, the  
32  
33 318 participants will have the opportunity to contact the certified exercise instructor or the clinical  
34  
35 319 research assistant at any time, by e-mail (directly through the website) or by telephone for any  
36  
37 320 question or assistance with the connected device.

40  
41 321 —*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device  
42  
43 322 by the participants and their progress in the program through a dedicated professional website that  
44  
45 323 provides real-time access to the participants' data. On this website, an automatically generated daily  
46  
47 324 event table will inform the certified exercise instructor of the occurrence of disabilities reported by the  
48  
49 325 participants that may lead to modifying their program (e.g., severe fatigue, dyspnea, unusual muscle  
50  
51 326 pain) or if participants have not performed their planned sessions or used their activity tracker for  
52  
53 327 seven consecutive days. Upon these alerts, the certified exercise instructor will contact the participants  
54  
55 328 to precisely analyse the reported disabilities, advise participants, identify the causes of non-use of the  
56  
57 329 connected device, solve possible technical problems or reinforce participant's motivation if necessary.  
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3 330 —*End of the intervention*: At the end of the 6-month program, participants will keep their activity  
4  
5 331 tracker to be encouraged to continue regularly exercising in autonomy. Upon their request, continued  
6  
7 332 subscription to the dedicated application and website will be offered for another six months, with no  
8  
9 333 individual follow-up anymore.  
10  
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12 334

### 14 335 **Intervention of therapeutic patient education**

16 336 Participants randomised to the therapeutic patient education arm will benefit from a therapeutic  
17  
18 337 patient education intervention, in addition to receiving the international physical activity  
19  
20 338 recommendations. The intervention is part of the therapeutic patient education program set up at the  
21  
22 339 Léon Bérard cancer centre and validated by the Regional Health Agency (“Agence Régionale de Santé  
23  
24 340 Rhône-Alpes”). It will be disseminated in the investigating centres according to the criteria of the  
25  
26 341 Regional Health Agency. The therapeutic patient education intervention consists of four sessions that  
27  
28 342 will be scheduled according to participants’ availability during their follow-up visits as part of their  
29  
30 343 usual clinical management over a 6-month period.  
31  
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34 344 First, participants will be invited to an initial 1-hour individual face-to-face session of educational  
35  
36 345 diagnosis with a health professional trained in therapeutic patient education. This session will assess  
37  
38 346 their needs and establish a contract of objectives to reach. Then, participants will be invited to  
39  
40 347 participate in two collective educational sessions (1h30 each with a group of 10 patients maximum per  
41  
42 348 session). These sessions will be composed of theoretical and practical workshops to help them  
43  
44 349 understand their physical activity in their daily life and implement the necessary means to practice  
45  
46 350 regular exercise in autonomy. Finally, participants will be invited to another 1-hour individual session,  
47  
48 351 where an educational evaluation will be conducted to identify whether they achieve their individual  
49  
50 352 objectives set at the time of the educational diagnosis.  
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### 354 **Combined interventions**

355 Participants randomised to the 'combined intervention' arm will benefit from a combination of the  
356 connected device intervention and the therapeutic patient education intervention in parallel for  
357 6 months.

### 360 **EVALUATIONS**

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

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

### 375 **DATA COLLECTION**

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

#### 377 **Socio-demographic and clinical data**

378 Socio-demographic and clinical data, including month/year of birth, age at diagnosis of breast  
379 cancer, family status, level of education, hormonal status, tumour histology and personal history of  
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1  
2  
3 380 breast cancer will be collected at baseline. Family status, potential cancer progression and all  
4  
5 381 treatments received for cancer will be collected at 6 and 12 months. All data will be extracted from  
6  
7 382 patients' electronic medical records, except family status and level of education that will be self-  
8  
9 383 reported in a questionnaire.

11 384 The occupational status will be assessed using a self-administered questionnaire asking  
12  
13 385 employment status, occupation, size of the company, the perceived intensity of the physical effort at  
14  
15 386 work, the evolution of employment status at return to work in case of sick leave.<sup>61</sup>  
16  
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### 21 388 **Anthropometrics and body composition**

22  
23 389 The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be  
24  
25 390 measured using standardized procedures and BMI will be calculated as the body weight in kilograms  
26  
27 391 divided by the square of the height in meters (kg/m<sup>2</sup>). The waist circumference will be measured  
28  
29 392 midway between the last floating rib and the iliac crest. The hip circumference will be measured at the  
30  
31 393 tip of the pubis. Body composition will be measured by a bioelectrical impedance meter (Biody XPert  
32  
33 394 ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle  
34  
35 395 mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid  
36  
37 396 (in L).  
38  
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### 43 398 **Physical fitness**

44  
45 399 Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance  
46  
47 400 covered in metres) with perceived difficulty using the Borg scale.<sup>62</sup> During this test, participants will be  
48  
49 401 asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes.

50  
51 402 The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a  
52  
53 403 chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as  
54  
55 404 many times as possible during 30 seconds.<sup>63</sup>  
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3 405 Hand prehensile strength will be measured by the handgrip test using hand dynamometry (Jamar  
4  
5 406 Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the  
6  
7 407 isometric strength of the hand and forearm muscles.<sup>64</sup> During this hand-grip test, participants will be  
8  
9  
10 408 asked to squeeze the handgrip as strongly as possible to obtain the maximal force (in kg). Two  
11  
12 409 measures will be performed on each hand and the best performance will be registered.

13  
14 410 The flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe  
15  
16 411 Baseline flexibility test, 3B Scientific, Bartenheim, France).<sup>65</sup> In this test, participants will sit on the floor  
17  
18 412 on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as  
19  
20 413 possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering  
21  
22 414 the level of the feet as recording zero, any measure that does not reach the toes is negative and any  
23  
24 415 measure beyond the toes is positive).

25  
26  
27 416 The balance will be measured using the bilateral single-leg stance test.<sup>66</sup> The participants will stand  
28  
29 417 and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same  
30  
31 418 exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).

32  
33  
34 419

#### 35 36 420 **Physical activity level, sitting time and achievement of physical activity recommendations**

37  
38 421 The validated self-administered questionnaire RPAQ will be used to measure the self-reported  
39  
40 422 physical activity.<sup>53,67</sup> The RPAQ was designed to assess usual physical activity in the last four weeks,  
41  
42 423 covering three activity domains: domestic physical activity, including sitting time that is a good proxy  
43  
44 424 of sedentary behaviour; occupational physical activity, including transportation to and from work; and  
45  
46 425 recreational physical activity. The RPAQ gives specific scores in the metabolic equivalent of task (MET)  
47  
48 426 unit for activities of very low intensity (<1.5 METs, i.e., sedentary activities), low intensity (1.5 to  
49  
50 427 <3 METs), moderate intensity (3 to <6 METs) and high intensity (≥6 METs, i.e., vigorous activities)  
51  
52 428 within each domain during the past four weeks. Questions will be coded and converted in MET-minute  
53  
54 429 per four weeks according to the Compendium of Physical Activities<sup>60</sup> by multiplying the number of  
55  
56 430 METs by the duration and frequency of each activity. Then, the global score of physical activity will be  
57  
58  
59  
60



1  
2  
3 431 obtained by adding the number of MET-minutes per four weeks in each intensity and each domain.  
4  
5 432 The physical activity profile will be defined as the time spent in physical activities of low, moderate and  
6  
7 433 high intensities. The physical activity level will be defined by the overall weekly physical activity  
8  
9  
10 434 (average expressed in MET-hour/week).

11  
12 435 Achievement of international physical activity guidelines will be computed for each individual by  
13  
14 436 dividing the time spent in moderate-to-vigorous physical activity (i.e.,  $\geq 3$  METs) into two categories:<sup>11</sup>  
15  
16 437  $<150$  min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines);  $\geq 150$   
17  
18 438 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).

19  
20  
21 439

#### 22 23 440 **Patient-reported outcomes**

24  
25 441 The quality of life will be measured using the European Organization for Research and Treatment  
26  
27 442 of Cancer (EORTC) Quality-Of-Life Questionnaire (QLQ-C30) and its specific module for breast cancer  
28  
29 443 (BR-23).<sup>68</sup> The QLQ-C30 is a 30-item validated self-administered questionnaire that evaluates five  
30  
31 444 functioning domains (i.e., physical, role, emotional, cognitive and social), a global quality-of-life  
32  
33 445 domain, three symptom domains (i.e., pain, fatigue and nausea) and six single items (i.e., dyspnea,  
34  
35 446 insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score  
36  
37 447 ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds  
38  
39 448 to a better functioning level. For scales related to symptoms, a lower score corresponds to a better  
40  
41 449 functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex  
42  
43 450 enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.

44  
45  
46  
47 451 The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.<sup>69</sup> This  
48  
49 452 standardized self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual  
50  
51 453 activities, pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight,  
52  
53 454 moderate, severe and extreme problems), and comprises a 0-100 visual analogue scale recording the  
54  
55 455 self-rated health (where the endpoints are labelled 'The best health you can imagine' and 'The worst  
56  
57 456 health you can imagine').  
58  
59  
60

1  
2  
3 457 Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported  
4  
5 458 questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of  
6  
7 459 fatigue):<sup>70</sup> the higher the score, the worse the fatigue. All items together will produce a total score for  
8  
9 460 fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3),  
10  
11 461 moderate fatigue (score 4-6) and severe fatigue (score 7-10).

12  
13  
14 462 Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in  
15  
16 463 Health Examination Centres) score.<sup>71</sup> The score will be computed by adding each question coefficient  
17  
18 464 to the intercept whenever the answer is “yes.” The score ranges from 0 to 100 (i.e., the higher the  
19  
20 465 score, the greater the deprivation level) with the threshold for deprivation at 30.

21  
22  
23 466 Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e.,  
24  
25 467 never, former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol  
26  
27 468 intake over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3  
28  
29 469 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer,  
30  
31 470 cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses).  
32  
33 471 The amount of alcohol will be computed by multiplying the frequency of consumption by the number  
34  
35 472 of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over  
36  
37 473 the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.  
38  
39  
40

41 474

### 42 43 475 **Determinants of Physical activity**

44  
45 476 The 21-item self-administered questionnaire “Barriers to Being Active Quiz” will be used to  
46  
47 477 qualitatively assess barriers to the regular practice of physical activity.<sup>72</sup>

48  
49 478 Uses, representations and motivation towards physical activity will be assessed within the study  
50  
51 479 population using a self-administered questionnaire available online. Acceptability of connected  
52  
53 480 devices and acceptability of therapeutic patient education will be assessed among participants  
54  
55 481 randomised to the corresponding arms using a paper-based self-administered questionnaire. These  
56  
57 482 questionnaires will be developed following the Unified Theory of Acceptance and Use of Technology  
58  
59  
60

1  
2  
3 483 (UTAUT),<sup>73</sup> which is a specification of the Theory of Planned Behaviour<sup>74</sup> designed to explain and  
4  
5 484 predict the probability of behaviour change among individuals faced with new technologies. The  
6  
7 485 Theory of Planned Behaviour has been massively used during the last two decades to promote health  
8  
9 486 behaviours such as physical activity. Besides, item wording will be based on the results of individual  
10  
11 487 and collective interviews conducted for that purpose and designed to identify social representations<sup>75</sup>  
12  
13  
14 488 of health protection and physical activity incentive devices.  
15  
16  
17 489

### 18 19 490 **Compliance with interventions**

20  
21 491 Compliance with each intervention will be assessed at the 6-month evaluation only for patients  
22  
23 492 randomized to the “connected device”, “therapeutic patient education” and “combined” arms.  
24  
25 493 Compliance will be assessed by the number of days of use of the activity tracker, the participation rate  
26  
27 494 in scheduled exercise sessions, the participation rate in scheduled therapeutic education sessions and  
28  
29 495 the proportion of compliant patients, depending on the intervention allocated, following the  
30  
31 496 recommendations of the protocol. Patients’ compliance and reasons for non-compliance during the  
32  
33 497 intervention period (6 months) will be described for each arm.  
34  
35  
36  
37 498

### 38 39 499 **Biological assessments**

40  
41 500 A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at  
42  
43 501 baseline and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant  
44  
45 502 treatments, otherwise no blood samples will be collected. The following biological factors will be  
46  
47 503 assessed in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol),  
48  
49 504 circulating plasma levels of inflammatory cytokines (IL-6, TNF $\alpha$ , CRP), circulating plasma levels of  
50  
51 505 adipokines (adiponectin, leptin) and vitamin D status.  
52  
53  
54  
55 506

### 56 57 507 **STUDY OUTCOMES**

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1  
2  
3 508 The primary endpoint will be the proportion of women who achieve at 6 months the internationally  
4  
5 509 recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical  
6  
7 510 activity, i.e., intensity  $\geq 3$  METs) assessed by the RPAQ self-administered questionnaire.

9  
10 511 Secondary endpoints will be:

11  
12 512 1. Assessment of the efficacy of the programs at 12 months (i.e., the proportion of women who achieve  
13  
14 513 the internationally recommended level of physical activity);

15  
16 514 2. Assessment of the adherence to the interventions at 6 months (the proportion of participants who  
17  
18 515 are compliant to the program, participation rate in planned sessions);

19  
20 516 3. Assessment of the impact between baseline and 6 months and between 6–12 months of the  
21  
22 517 interventions on physical activity profile (changes in time spent in different intensities of physical  
23  
24 518 activity and time spent in sedentary activities), physical fitness (changes in results to the 6-minute walk  
25  
26 519 test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test),  
27  
28 520 anthropometrics (changes in weight, waist and hip circumferences, BMI, fat mass, lean body mass,  
29  
30 521 muscle mass, dry lean mass and body water), quality of life (changes in scores obtained from the EORTC  
31  
32 522 QLQ-C30 questionnaire and its BR-23 module), fatigue condition (changes in scores obtained from the  
33  
34 523 PFS-12 questionnaire), health-related quality of life (changes in scores obtained from the EQ-5D-5L  
35  
36 524 questionnaire), social deprivation (changes in scores obtained from the EPICES self-administered  
37  
38 525 questionnaire), occupational status (the proportion of participants who changed their employment  
39  
40 526 status, with return to work and who perceived difficulty at work obtained from a self-administered  
41  
42 527 questionnaire) and lifestyle factors (the proportion of participants who change their tobacco use and  
43  
44 528 alcohol intake obtained from a self-administered questionnaire).

45  
46 529 4. Assessment of the impact of the interventions on biological parameters between baseline and  
47  
48 530 6 months (changes in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], changes in  
49  
50 531 plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines:  
51  
52 532 adiponectin and leptin], the proportion of participants with a modification on vitamin D status).

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

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

539 7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at  
 540 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital  
 541 costs (national data) and benefit in physical activity level.

542

## 543 **STATISTICAL ANALYSIS**

### 544 **Sample size determination**

545 The efficacy rate assumptions are  $\mu=40\%$ ,  $\mu+\mu_A=55\%$  and  $\mu+\mu_B=65\%$  for the "control",  
 546 "therapeutic patient education" and "connected device" arm modalities, respectively. The expected  
 547 benefit in the "therapeutic patient education" arm compared to the "control" arm is 15% (40% efficacy  
 548 in the "control" arm versus 55% efficacy in the "therapeutic patient education" arm). The expected  
 549 benefit in the "connected device" arm compared to the "control" arm is 25% (40% efficacy in the  
 550 "control" arm versus 65% efficacy in the "connected device" arm).<sup>23</sup>

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

$$557 \left[ \mu + (\mu + \mu_B) \right] / 2, \text{ versus } \left[ (\mu + \mu_A) + (\mu + \mu_A + \mu_B) \right] / 2$$

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

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2  
3 559 With a first species risk  $\alpha=0.025$  and a power of 80% in the bilateral situation, the number of  
4  
5 560 patients to include per treatment arm to demonstrate the efficacy of the therapeutic patient education  
6  
7 561 will be 108 (or 432 for the four treatment arms) (nQuery V6.0, Chi-two test with continuity correction).  
8  
9  
10 562 This number of patients will also allow a power greater than 95% to evaluate the efficacy of the  
11  
12 563 "connected device" intervention, always with a risk  $\alpha = 0.025$  in the bilateral situation.  
13  
14  
15 564

#### 16 565 **Data analysis plan**

17  
18  
19 566 The following populations will be defined for statistical analyses: i) the intent-to-treat (ITT)  
20  
21 567 population, which includes all randomised participants in the study; ii) the per-protocol population,  
22  
23 568 which consists of a subgroup of participants from the ITT population, who has no major protocol  
24  
25 569 violations and who follows the procedure for the duration of the study. Analyses in the ITT population  
26  
27 570 will be performed for all the study endpoints; analyses in the per-protocol population will be  
28  
29 571 performed for exploratory purposes. The randomisation date will be considered as the reference date  
30  
31 572 in all delay calculations, unless any other way is specified.  
32  
33

34 573 Baseline data will be described in the ITT population and presented by randomised arms. For the  
35  
36 574 primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who  
37  
38 575 received the connected device vs. participants who did not; (ii) participants who benefited from the  
39  
40 576 therapeutic patient education intervention vs. participants who did not. Results will be presented with  
41  
42 577 their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the  
43  
44 578 efficacy of the intervention with a connected device (compared to without a connected device); the  
45  
46 579 efficacy of the therapeutic patient education intervention (compared to no therapeutic patient  
47  
48 580 education); and the interest of two combined intervention modalities (i.e., connected device and  
49  
50 581 therapeutic patient education) compared to the single intervention with the connected device only or  
51  
52 582 with therapeutic patient education only. The analysis strategy will therefore be as follows:<sup>76</sup>  
53  
54 583 1) searching first for an interaction by a specific interaction test, performed at the significance level of  
55  
56 584 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the absence of interaction,  
57  
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59  
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1  
2  
3 585 testing each of the two bilateral interest comparisons at the threshold of 0.025, namely the efficacy of  
4  
5 586 the intervention with the connected device and the efficacy of the therapeutic patient education  
6  
7 587 intervention; 3) in case of the efficacy of either one of the intervention modalities, evaluating the  
8  
9 588 interest of the combination of the two interventions compared to the single intervention with the  
10  
11  
12 589 connected device only or with therapeutic patient education only.

13  
14 590 For secondary outcome variables, the efficacy of the program at 12 months, as well as according to  
15  
16 591 stratification criteria, will be analysed similarly to the primary outcome. The adherence to the  
17  
18 592 interventions will be evaluated by the proportion of compliant participants and participation rate in  
19  
20 593 planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life,  
21  
22 594 fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative  
23  
24 595 variations in each of these endpoints; these variations will be compared between with and without  
25  
26 596 each intervention, for each intervention, and between combined interventions and the single one,  
27  
28 597 using a parametric test. Occupational status and lifestyle factors will be analysed by comparing the  
29  
30 598 proportion of participants between interventions or their combination. Representations and  
31  
32 599 acceptability of activity tracker and therapeutic patient education will be analysed by comparing the  
33  
34 600 proportion of participants between randomisation and follow-up assessments. A method for imputing  
35  
36 601 missing data will be considered if necessary.

37  
38  
39 602 Statistical analyses will be performed using SAS® software version 9.4 or later.

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43 603

#### 44 45 604 **Medico-economic analysis**

46  
47 605 The cost-effectiveness analysis will be conducted alongside the trial using the French national  
48  
49 606 health insurance perspective. Quantities of resources used [external consultations, hospital stays  
50  
51 607 including Diagnosis-related groups, drugs with extra payments and other healthcare-related costs] will  
52  
53 608 be collected on the eCRF and multiplied by the respective unit costs. The intervention with therapeutic  
54  
55 609 patient education and the intervention with connected device will be evaluated using a bottom-up  
56  
57 610 micro-costing approach.<sup>77,78</sup> Using the Diagnosis-related group, hospital stays will be evaluated based  
58  
59  
60

1  
2  
3 611 on the French National hospital costs study database. External consultations and wider examinations,  
4  
5 612 community care (general practitioner visits, nurse visits, etc.) will be valued on the basis of the General  
6  
7 613 Nomenclature of Professional Treatments (NGAP, “Nomenclature Générale des Actes  
8  
9 614 Professionnels”). The cost of biological treatments will be estimated using the Nomenclature of  
10  
11 615 Biological Medical Treatments (NABM, “Nomenclature des Actes de Biologie Médicale”). The cost of  
12  
13 616 technical treatments (e.g., imaging) will be estimated using the Common Classification of Medical  
14  
15 617 Treatments (CCAM, “Classification Commune des Actes Médicaux”). Acquisition costs for the most  
16  
17 618 expansive drugs will be based on the list of common units of dispensation for supplementary medicines  
18  
19 619 (“liste des unités communes de dispensation prise en charge en sus”). Finally, costs of medical  
20  
21 620 transport will be derived from the French Court of Audit's report on medical transport expenses  
22  
23 621 covered by the French National Health insurance. The time horizon will be 12 months. Hence, neither  
24  
25 622 costs nor effectiveness will be discounted. Mean costs and effectiveness will be derived for all four  
26  
27 623 strategies under consideration: connected device, therapeutic patient education, combined and  
28  
29 624 control arms. Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per quality-  
30  
31 625 adjusted life year (QALY) gained using EQ-5D-5L to estimate utility, cost per life year gained, cost per  
32  
33 626 BMI unit lost and cost per centimetre of waist-to-hip circumference lost. One-way sensitivity analyses  
34  
35 627 will be conducted by varying resource consumption and unit cost parameters and graphically  
36  
37 628 illustrated in a Tornado diagram. The uncertainty surrounding the ICERs will be also captured by a  
38  
39 629 probabilistic analysis using non-parametric bootstrap methods as recommended by the French  
40  
41 630 National Authority for Health.<sup>79</sup>

631

## 632 **ADVERSE EVENTS**

51  
52 633 All participants will continuously report the occurrence of adverse events regarding neuropathies  
53  
54 634 and joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped  
55  
56 635 with the connected device will also report potential adverse events before and after each session of  
57  
58 636 their exercise program (see *Connected device*). Due to the low risks associated with the interventions,<sup>16</sup>  
59  
60



1  
2  
3 637 this study is part of the so-called “intervention research with minimal risks and constraints” in the  
4  
5 638 French legislation and therefore only these adverse events arising within the framework of the study  
6  
7 639 will be reported.  
8  
9

10 640 In the occurrence of an adverse event regarding neuropathies and joint pain, the principal  
11  
12 641 investigator will report it to the health authorities responsible for vigilance without delay. The  
13  
14 642 promotor will also report the adverse events, as well as any safety measures to be proposed, to the  
15  
16 643 French Ethics Committee and the investigators without delay.  
17  
18

19 644

#### 20 21 645 **DATA MANAGEMENT**

22  
23 646 The database for clinical data and randomisation will be created using EnnovClinical® software. Its  
24  
25 647 access will be secured (personal identification and password protection) for maintaining confidentiality  
26  
27 648 at all times. Individual participants will not be identified in any reports of this trial. All data from the  
28  
29 649 connected device will be merged to the clinical database at the end of the study. Investigators and  
30  
31  
32 650 data analysts will have access to the final dataset.  
33

34 651 Data monitoring will be provided by the trial steering committee, including overall project  
35  
36 652 supervision, progress monitoring, advice on scientific credibility, and ensuring the integrity and  
37  
38 653 appropriate running of the project. The clinical research assistant will verify all consent forms,  
39  
40 654 compliance with established protocol and procedures, and data quality in the eCRF. The research team  
41  
42  
43 655 will make biannual reports to the trial steering committee.  
44  
45

46 656

#### 47 48 657 **PATIENT AND PUBLIC INVOLVEMENT**

49  
50 658 An association of breast cancer patients' representatives (Europa Donna France,  
51  
52 659 <http://www.europadonna.fr/>) was involved in preparing the conduct of interventions and evaluations,  
53  
54 660 in particular by considering patients' expectations, experience and desire for global care. The  
55  
56 661 association will be involved in plans to disseminate the study results to breast cancer patients, study  
57  
58  
59 662 participants and wider patient communities concerned.  
60

663

**664 ETHICS AND DISSEMINATION**

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

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

678

**679 DISCUSSION**

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

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2  
3 689 the goal of the DISCO trial is to disseminate innovative programs in supportive cancer care, based on  
4  
5 690 scientific evidence, to systematically integrate exercise in breast cancer cares.  
6

7 691 While an increasing number of studies have demonstrated the benefits of exercise in breast cancer  
8  
9 692 patients, the routine implementation in the cancer care process lacks behind evidence and practice  
10  
11 693 guidelines.<sup>80–82</sup> While the prescription of physical activity in supervised programs has been shown  
12  
13 694 superior compared to non-supervised programs,<sup>22,83</sup> semi-supervised interventions seem to yield  
14  
15 695 comparable or superior benefits to supervised programs.<sup>84</sup> Therefore, the semi-supervised exercise  
16  
17 696 program of the DISCO trial through continuous follow-up has been designed according to the  
18  
19 697 preferences of women with breast cancer so as not to leave patients in total autonomy.<sup>36,85</sup> Connected  
20  
21 698 devices are tools developed over the last 10 years that are very promising for promoting physical  
22  
23 699 activity in the general population and in patients with chronic diseases such as cancer<sup>86,87</sup> and for  
24  
25 700 developing distance-based physical activity interventions.<sup>88</sup>  
26  
27  
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29

30 701 The semi-supervised home-based physical activity program of the DISCO trial using the connected  
31  
32 702 device provides flexibility to patients that may facilitate adherence and to overcome barriers due to  
33  
34 703 distance of facilities from women's home and spatial inequalities of access.<sup>27</sup> Connected devices allow  
35  
36 704 proposing a tailored physical activity program to patients regardless of their place of residence, and  
37  
38 705 enable patients to practice physical activities of their choice, at any time that suits them. Therefore,  
39  
40 706 they may reduce geographical and organisational barriers in the access of patients to exercise, a key  
41  
42 707 issue to improve their engagement in regular and sustained physical activity.<sup>27</sup> Previous studies in  
43  
44 708 oncology have reported that the use of mobile devices has benefits to overcome motivational barriers  
45  
46 709 to physical activity, which can help patients staying physically active over the medium and long  
47  
48 710 term.<sup>89,90</sup> Moreover, some studies have shown that breast cancer patients achieved higher fitness  
49  
50 711 levels during supervised training compared to unsupervised training, even low and medium levels of  
51  
52 712 supervision have been effective, as less resource-intensive options for effective and longer-term  
53  
54 713 behaviour change strategies based on exercises in cancer patients and survivors.<sup>84,91</sup>  
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3 714 Activity trackers have become increasingly popular in recent years. Patients have reported positive  
4  
5 715 feedback on using activity trackers such as pleasant to wear, easy to use and a strong motivational role  
6  
7 716 through the real-time display of daily number of steps.<sup>92</sup> Also, walking is an inexpensive activity that  
8  
9  
10 717 can be performed anywhere and does not require specific skills. A study on preferences for technology-  
11  
12 718 supported interventions in breast cancer survivors has reported that 63% would like to use a physical  
13  
14 719 activity mobile application and 90% would find a physical activity tracker useful to monitor and  
15  
16 720 increase physical activity.<sup>35</sup>

17  
18  
19 721 Despite the potential benefits of connected devices in cancer care, their use may face several  
20  
21 722 important issues. First, ethical challenges related to the security of sensitive data storage have been  
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23 723 raised.<sup>93</sup> To ensure that data transfer and storage guarantee informational privacy and patient safety,<sup>94</sup>  
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25 724 an activity tracker made in France (i.e., allowing storing health data only in France) and an accredited  
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27 725 national health data host were chosen for the DISCO trial. Particularly, ensuring medical data security  
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29 726 is a reassuring choice for patients to participate in this new kind of medical research. Second, technical  
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31 727 challenges have been raised, related to technological robustness, reliability of data collection and  
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33 728 processing, and ease of use. Therefore, an activity tracker with a step display on the screen, a user-  
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35 729 friendly interface, good reliability and a good price-performance ratio was chosen in the DISCO trial.  
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39 730 Third, connected devices may create or exacerbate access disparities related to technological literacy  
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41 731 and economic means, as well as reliable access to the internet in rural or isolated areas.<sup>93</sup> Fourth,  
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43 732 medical reasons are usually not easy to control in patients' adherence to exercise programs. Reliance  
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45 733 upon self-assessment of the participant's fatigue, evaluation of the participant before and after each  
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47 734 session on the remote monitoring, up as the source of information about the participant's health, can  
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49 735 result in the ignorance of aspects of the participant's health that cannot easily be monitored.<sup>93</sup>

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52 736 Therapeutic patient education has been suggested to increase physical activity level in patients with  
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54 737 chronic diseases<sup>46</sup> and to improve multiple health outcomes, together with behavioural interventions  
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56 738 including physical activity.<sup>95</sup> Therapeutic patient education interventions might be promising for  
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58 739 promoting a physically active lifestyle in cancer patients as it helps patients establish lifestyle changes  
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3 740 and reinforce self-management.<sup>95</sup> Therapeutic patient education differs from traditional patient  
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5 741 education in its intrinsic structure. Traditional patient education is directed towards informing and  
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7 742 teaching patients how to manage their condition or disease. In contrast, therapeutic patient education  
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9 743 differs from traditional patient education in the self-management conferred on the patient.<sup>40</sup>  
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11 744 Therefore, therapeutic patient education is more broadly directed towards how the patient accepts  
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13 745 his/her condition and manages his/her problems on a daily basis and the impact of the disease on  
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15 746 personal, family, professional and social life. Yet, in oncology, few therapeutic patient education  
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17 747 studies targeting pain, fatigue, toxicities or treatment adherence are ongoing, and evaluations are  
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19 748 rarely conducted.<sup>41</sup> To our knowledge, only one program of therapeutic patient education specific to  
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21 749 physical activity has been evaluated in cancer patients.<sup>45</sup> However, a recent qualitative study has  
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23 750 shown the value of therapeutic patient education on the attitudes towards the physical activity of  
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25 751 women with breast cancer to promote regular exercise, which is a guarantee of a better quality of  
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27 752 life.<sup>96</sup>

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32 753 In order to evaluate the efficacy of two interventions in the DISCO trial, the primary outcome  
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34 754 measure will be based on the physical activity level of the participants with or without interventions  
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36 755 compared to international recommendations. The RPAQ questionnaire will be used for the primary  
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38 756 outcome measure on account of its easy implementation. The authors acknowledge that this  
39  
40 757 declarative evaluation confers methodological limits to the study. But the RPAQ questionnaire has  
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42 758 been validated against objective methods (i.e., combined accelerometry and heart rate monitoring)<sup>67</sup>  
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44 759 to evaluate moderate-to-vigorous physical activities, which is relevant for the primary outcome. No  
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46 760 objective measures of physical activity have been planned because of organisational and logistic  
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48 761 difficulties to equip and follow participants for one week (i.e., the usual duration of monitoring with  
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50 762 an accelerometer such as Actigraph™).<sup>97</sup> Such a test would even be particularly overwhelming for  
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52 763 cancer patients during the demanding period of adjuvant treatment onset. Additionally, the number  
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54 764 of daily steps reported by the activity tracker was not chosen as the primary outcome because the  
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56 765 activity tracker used in the study was not validated for monitoring physical activity in research or for  
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3 766 medical purposes when the study was designed, although its reliability was evaluated against other  
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5 767 devices (data not shown). However, recently the performance and reliability of smart devices tend to  
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7 768 be increasingly validated.<sup>98</sup>  
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10 769 To understand the results of the DISCO clinical study, it is essential to study beliefs about connected  
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12 770 devices and their appropriation by the patients, particularly to understand why behaviours of the  
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14 771 patients tend to fade over time. In therapeutic education, beliefs and representations are essential to  
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16 772 the success of the intervention. Moreover, with the connected devices, only technical dimensions are  
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18 773 not sufficient to understand and highlight why individuals adopt or misuse the connected devices.<sup>73,74</sup>  
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21 774 There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of  
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23 775 interventions promoting physical activity among women with breast cancer from studies conducted in  
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25 776 France, the Netherland and Australia.<sup>99-104</sup> In various chronic conditions other than cancer, there is  
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27 777 now clear evidence in favour of exercise-based programs for the treatment of various chronic  
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29 778 conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.<sup>105</sup> As more  
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31 779 research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers,  
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33 780 particularly breast cancer, the economic evaluation planned in the DISCO trial will fill in the gap by  
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35 781 adding useful information.  
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39 782 In conclusion, the study findings will provide valuable information on the efficacy of exercise  
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41 783 interventions during breast cancer treatments, overcoming current barriers of access to facilities. They  
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43 784 will further guide the development of evidence-based innovative interventions, to systematically  
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45 785 include physical activity in the breast cancer care process. Finally, the economic evaluation planned in  
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47 786 the DISCO trial will provide useful information for decision-makers.  
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52 788 **Supplementary file 1:** SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.  
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54 789 **Supplementary file 2:** English language example of the patient consent  
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3 791 **Abbreviations**  
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5 792 BMI: body mass index;

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7 793 eCRF: electronic case report form;

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10 794 EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-Of-Life  
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12 795 Questionnaire;

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14 796 EPICES: Evaluation of Deprivation and Inequalities in Health Examination Centres (questionnaire);

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16 797 ITT: intent-to-treat;

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18 798 MET: metabolic equivalent of task;

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20 799 PFS-12: Piper Fatigue Scale-12;

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22 800 RPAQ: Recent Physical Activity Questionnaire;

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24 801 WHO: World Health Organization;

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26 802 6MWT: six-minute walk test.  
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31  
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52 813 **Authors' contributions**  
53

54 814 BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the  
55  
56 815 research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological  
57  
58 816 aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise  
59  
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3 817 training. LP, MT, OP, AM and EB designed the medico-economic study and eCRF. MP, TL, MT, OP and  
4  
5 818 AM designed the part on uses and representations. J-BF, MT and OP designed the part on occupational  
6  
7 819 status. All authors were involved in in planning the methods and measurement and a priori analysis  
8  
9  
10 820 planning. MT and BFo wrote the initial draft of the manuscript. All authors reviewed and provided  
11  
12 821 comprehensive contribution to the manuscript, and approved the final manuscript.  
13

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28

29 829

31 830 **Competing interests**

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34 831 None declared.  
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37 833 **Ethics approval**

38  
39 834 Ethics approval was provided by the French Ethics Committee (Comité de Protection des Personnes  
40  
41 835 Est I).  
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43 836

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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
<b>Demographic and clinical data</b>	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
<b>Anthropometrics</b>				
- 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
<b>Physical fitness</b>		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			
<b>Physical activity level, sitting time and achievement of physical activity recommendations</b>	RPAQ Questionnaire	X	X	X
<b>Patient-reported outcomes</b>				
- 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
<b>Determinants of physical activity</b>				
- 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
<b>Biological data</b>	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, TNF $\alpha$ , CRP)				
- Plasmatic adipokines (adiponectin, leptin)				
- Vitamin D status				
<b>Compliance with each intervention</b> (only for patients in the "connected device", "therapeutic patient education" and "combined" arms)	Connected device and/or patient's record		X	
<b>Adverse events</b> (neuropathies, joint pain)	Patient's diary		X	X

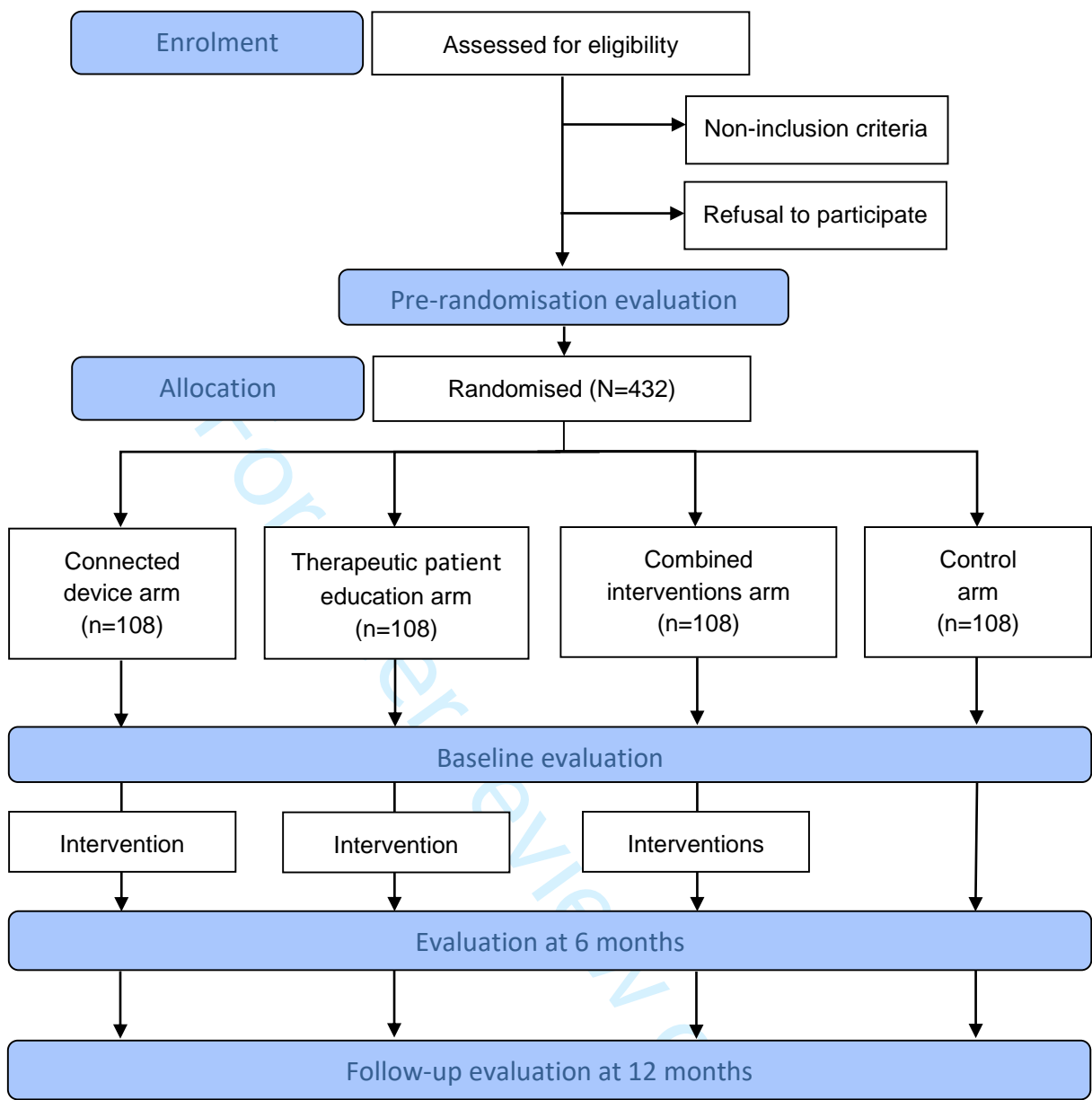
1159 Notes. 6MWT: six-minute walk test

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3 1161 **Figure 1:** Flow chart of participants through the DISCO trial.  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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_____

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 7 \_\_\_\_\_

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators 7 \_\_\_\_\_

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8 Objectives 7 Specific objectives or hypotheses 7 \_\_\_\_\_

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 8 \_\_\_\_\_

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 8 \_\_\_\_\_

17 be collected. Reference to where list of study sites can be obtained

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 8-9 \_\_\_\_\_

20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 9-15 \_\_\_\_\_

23 administered

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25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 12-13 \_\_\_\_\_

26 change in response to harms, participant request, or improving/worsening disease)

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 13-14 \_\_\_\_\_

29 (eg, drug tablet return, laboratory tests)

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A \_\_\_\_\_

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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 17, Table 1\_\_

35 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

36 efficacy and harm outcomes is strongly recommended

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40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 9, 16-17, Figure1,

41 participants. A schematic diagram is highly recommended (see Figure) Table1\_\_

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1	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_____
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3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8_____
5				
6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	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_____
11				
12				
13				
14				
15				
16	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_____
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_____
28				
29				
30				
31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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_____
34				
35				
36				
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38				
39		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_____
40				
41				
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1	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_____
2				
3				
4				
5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24_____
9				
10		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_____
11				
12				
13				

14 **Methods: Monitoring**

15				
16	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_____
17				
18				
19				
20				
21				
22		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_____
23				
24				
25	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_____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25_____
29				
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31				

32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32__
35				
36				
37	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_____
38				
39				
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42				



1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8_____
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A_____
5				
6				
7	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_____
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9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32_____
11				
12				
13	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_____
14				
15				
16	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_____
17				
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19				
20	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_____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	31_____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A_____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9, Suppl file 2 ___
32				
33				
34	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_____
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36				

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Sports and exercise medicine, Nutrition and metabolism, Health economics, Sociology

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

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3 1 **Connected device and therapeutic patient education to promote physical activity among women**  
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5 2 **with localized breast cancer (DISCO trial): Protocol for a multicentre 2x2 factorial randomised**  
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7 3 **controlled trial**  
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3 24 **ABSTRACT**  
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5 25 **Introduction:** Despite safety and benefits of physical activity during treatment of localized breast  
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7 26 cancer, successful exercise strategies remain to be determined. The primary objective of the DISCO  
8  
9 27 trial is to evaluate the efficacy of two 6-month exercise interventions, either single or combined,  
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11 28 concomitant to adjuvant treatments, on the physical activity level of breast cancer patients, compared  
12  
13 29 to usual care: an exercise program using a connected device (activity tracker, smartphone application,  
14  
15 30 website) and a therapeutic patient education intervention. Secondary objectives are to evaluate  
16  
17 31 adherence to interventions, their impact at 6 and 12 months, representations and acceptability of  
18  
19 32 interventions, and to assess the cost-effectiveness of the interventions using quality-adjusted life years.  
20  
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22

23 33 **Methods and analysis:** This is a 2x2 factorial, multicentre, phase III randomised controlled trial. The  
24  
25 34 study population (with written informed consent) will consist of 432 women diagnosed with primary  
26  
27 35 localized invasive breast carcinoma and eligible for adjuvant chemotherapy, hormonotherapy and/or  
28  
29 36 radiotherapy. They will be randomly allocated between one of four arms: (i) web-based connected  
30  
31 37 device (evolving target number of daily steps and an individualized, semi-supervised, adaptive program  
32  
33 38 of two walking and one muscle strengthening sessions per week in autonomy), (ii) therapeutic patient  
34  
35 39 education (one educational diagnosis, two collective educational sessions, one evaluation), (iii)  
36  
37 40 combination of both interventions, (iv) control. All participants will receive the international physical  
38  
39 41 activity recommendations. Assessments (baseline, 6 and 12 months) will include physical fitness tests,  
40  
41 42 anthropometrics measures, body composition (CT-scan, bioelectrical impedance), self-administered  
42  
43 43 questionnaires [physical activity profile (RPAQ), quality of life (EORTC QLQ-C30, EQ-5D-5L), fatigue  
44  
45 44 (PFS-12), social deprivation (EPICES), lifestyle, physical activity barriers, occupational status] and  
46  
47 45 biological parameters (blood draw).  
48  
49  
50

51  
52 46 **Ethics and dissemination:** This study was reviewed and approved by the French Ethics Committee. The  
53  
54 47 findings will be disseminated to the scientific and medical community via publications in peer-reviewed  
55  
56 48 journals and conference presentations.  
57

58  
59 49 **Registration:** ClinicalTrials.gov NCT03529383; 05/17/2018.  
60

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51 **Keywords:** Breast cancer, Physical activity, Sitting time, Activity tracker, Connected device, Web-  
6 based, eHealth, Therapeutic patient education, Randomised controlled trial  
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12 54 **Word count:** 8445  
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14 55  
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16 56 **Strengths and limitations of this study**

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18  
19 57 - This randomized clinical trial with four arms has the advantage to evaluate the efficacy of two  
20  
21 58 interventions, either single or their combination, using a 2x2 factorial design, ensuring a higher  
22  
23 59 statistical power than a classic trial with three arms, for a similar sample size.  
24  
25 60 - While the connected device intervention is semi-supervised, the exercise program has been  
26  
27 61 designed according to the preferences of women with breast cancer so as not to leave patients  
28  
29 62 in total autonomy and to provide organisational flexibility to patients to facilitate adherence.  
30  
31 63 - Despite the potential benefits of connected devices in cancer care, their use may face  
32  
33 64 important issues, such as ethical challenges related to the security of sensitive data storage,  
34  
35 65 technical challenges related to technological robustness and reliability, exacerbating access  
36  
37 66 disparities, and self-assessment of the participant's fatigue or health condition.  
38  
39 67 - The primary outcome measure is based on a declarative evaluation of physical activity that  
40  
41 68 confers methodological limits to the study, but the validated questionnaire was chosen  
42  
43 69 according for its easy implementation for cancer patients compared to accelerometer  
44  
45 70 monitoring and its relevance for the primary outcome.  
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## 71 INTRODUCTION

72 Breast cancer is the leading cause of cancer in women worldwide with 1.6 million new cases  
73 diagnosed each year,<sup>1</sup> representing more than a third of all new cancer cases in women. In France,  
74 breast cancer also represents the leading cause of cancer incidence and mortality among women, with  
75 approximately 58,000 new cases and 12,000 breast cancer deaths estimated in 2018.<sup>2</sup> Despite a very  
76 good prognosis worldwide with overall survival of 85% at 5 years (87% in France) and 71% at 10 years  
77 (78% in France) for all stages combined,<sup>3-5</sup> a large number of patients with breast cancer experience  
78 adverse effects of cancer and its treatments such as fatigue, impaired quality of life, anxiety or weight  
79 gain.<sup>6-8</sup>

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



1  
2  
3 96 from home constitutes a barrier to regular exercise during cancer treatments.<sup>26</sup> Successful exercise  
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5 97 strategies during and beyond cancer treatment remain to be determined in clinical trials.<sup>28</sup>  
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7 98 The recent development of connected devices such as activity trackers offers a real opportunity in  
8  
9 99 oncology to promote and monitor patients' physical activity.<sup>29</sup> While adherence to lifestyle  
10  
11 100 interventions is a major challenge, connected activity trackers and smartphone applications enable  
12  
13 101 structured monitoring of health parameters and provide feedback to patients. A systematic review of  
14  
15 102 randomised controlled trials of physical activity interventions using new technologies such as activity  
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17 103 trackers in cancer patients (including five studies in breast cancer) has shown that patients significantly  
18  
19 104 increased their number of steps per day in the majority of the studies.<sup>30</sup> Recent reviews of intervention  
20  
21 105 studies conducted among breast cancer patients have also shown that patients increased their physical  
22  
23 106 activity when they used activity trackers.<sup>31,32</sup> Overall, connected activity trackers receive increasing  
24  
25 107 interest for being systematically integrated into clinical oncology practice.<sup>33,34</sup> Yet, more research is  
26  
27 108 needed, especially clinical trials, to demonstrate the effectiveness of these tools and to respond to the  
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29 109 preferences of breast cancer patients.<sup>35-37</sup>  
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34 110 Therapeutic patient education has emerged in the 1990s in response to the recognition of the need  
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36 111 to support patients in the self-management of their chronic diseases, such as diabetes and asthma.<sup>38,39</sup>  
37  
38 112 According to the World Health Organization (WHO), therapeutic patient education aims to "help  
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40 113 patients acquire or maintain the skills they need to best manage their lives with a chronic disease".<sup>40</sup>  
41  
42 114 In the cancer field, several cancer-specific programs of therapeutic patient education have been set up  
43  
44 115 to manage pain, fatigue, side effects of treatment (chemotherapy, surgery) or compliance to  
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46 116 treatment.<sup>41-44</sup> By enhancing relevant knowledge and skills, therapeutic patient education may greatly  
47  
48 117 contribute to increasing patients' autonomy in their disease management. Despite the performance in  
49  
50 118 modifying long-term individual behaviours and adherence to cancer treatments,<sup>44</sup> the benefits of  
51  
52 119 therapeutic patient education on physical activity levels in cancer patients early after diagnosis has  
53  
54 120 been poorly investigated.<sup>45,46</sup> The research on therapeutic patient education in the breast cancer and  
55  
56 121 exercise context is limited to date and warrants further research.  
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3 122 Several biological mechanisms have been proposed to explain the effects of physical activity on  
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5 123 breast cancer risk and outcome. Preclinical and human studies have shown the influence of physical  
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7 124 activity on several signalling pathways involved in tumour development, growth and progression,  
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9  
10 125 including the insulin signalling pathway (IGF-1, insulin), chronic inflammation (involving inflammatory  
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12 126 cytokines such as IL-6, TNF $\alpha$ , CRP) and endocrine hormone regulation (estrogens, adipokines).<sup>47-49</sup> By  
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14 127 affecting the endogenous systemic milieu, physical activity is believed to influence cellular processes  
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16 128 and tumour growth, and therefore reduce the risk of recurrence, increase treatment efficacy and  
17  
18 129 improve survival.<sup>50</sup> Also, because vitamin D alters mechanisms implicated in cellular growth and  
19  
20 130 proliferation, accumulating evidence suggests that normal-to-high ranges of serum vitamin D levels  
21  
22 131 improve breast cancer prognosis and outcome.<sup>51</sup> Based on the data in the literature, it is not possible  
23  
24 132 to conclude a causal relationship between the metabolic effects of physical activity and the impact on  
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26 133 breast cancer risk and survival. Biological effects of physical activity on these biomarkers of  
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28 134 endogenous mechanisms interfering in cancer suppression or proliferation remain to be elucidated in  
29  
30 135 order to better understand the benefit of physical activity during adjuvant treatment.<sup>49</sup>

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34 136 In this context, given the accumulating evidence for the benefits and safety of regular exercise  
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36 137 during treatments of localized breast cancer, it is necessary to systematically encourage patients to  
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38 138 remain or become physically active from the time of diagnosis and to implement and assess the most  
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40 139 appropriate strategies of physical activity in clinical practice. The aim of the DISCO trial is to encourage  
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42 140 engagement in exercise during breast cancer treatment through two innovative types of interventions,  
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44 141 that is to say a web-based connected device and therapeutic patient education, which aim to develop  
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46 142 patients' autonomy in their practice of physical activity. The primary objective of the DISCO trial is to  
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48 143 evaluate the efficacy of two interventions, either single or combined, concomitant to adjuvant  
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50 144 treatments, on the physical activity level of breast cancer patients at the end of the 6-month  
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52 145 interventions, compared to usual care: one is an exercise program using a connected device  
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54 146 (comprising an activity tracker linked to a smartphone application and a website and providing an  
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56 147 individualized, semi-supervised, technology-based exercise program) and the other is a therapeutic  
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3 148 patient education intervention. The research hypothesis is that patients participating in the 6-month  
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5 149 exercise program using the connected device or therapeutic education intervention are more likely to  
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7 150 achieve the international physical activity recommendations, compared to women receiving physical  
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10 151 activity recommendations only (usual care). The WHO recommendations to maintain or improve  
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12 152 health, which applied when the study protocol was developed, are to do at least 150 min of moderate-  
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14 153 intensity or 75 min of vigorous-intensity aerobic physical activity or an equivalent combination each  
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16 154 week, and muscle-strengthening activities at least two days a week.<sup>11</sup> Secondary objectives are: (i) to  
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18 155 evaluate the adherence to the interventions; the impact of the interventions on physical fitness,  
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20 156 physical activity profile, anthropometrics, quality of life, fatigue, biological parameters, occupational  
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22 157 status and lifestyle factors; the efficacy of the 6-month interventions on physical activity level at 12  
23  
24 158 months; the representations and acceptability of activity tracker and therapeutic patient education;  
25  
26 159 and ii) to assess the cost-effectiveness of the interventions. If one of the interventions is individually  
27  
28 160 effective, the efficacy of the combination of both interventions at 6 and 12 months will be evaluated.  
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## 34 162 **METHODS AND DESIGN**

### 36 163 **Trial design**

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39 164 The DISCO (an acronym for “dispositif connecté”, i.e., connected device in English) trial is a 2x2  
40  
41 165 prospective, multicentre, factorial, randomised, controlled and open-label study (phase III), conducted  
42  
43 166 by the Léon Bérard comprehensive cancer centre (Lyon, France) among women receiving treatment  
44  
45 167 for localized breast cancer. The clinical protocol was designed and written according to the SPIRIT  
46  
47 168 (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Supplementary  
48  
49 169 file 1). The flowchart of the study is presented in **Figure 1**. Patients will be randomly assigned to one  
50  
51 170 of the four arms of the study according to the 2x2 factorial design (1:1:1:1 ratio). They will all receive  
52  
53 171 international recommendations on physical activity,<sup>11</sup> and: (i) women allocated to the “connected  
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55 172 device” arm will benefit from a 6-month individualized, semi-supervised exercise program carried out  
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57 173 autonomously. The program consists of an evolving goal of daily numbers of steps using an activity  
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3 174 tracker and two sessions of brisk walking and one session of muscle strengthening per week, using  
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5 175 dedicated smartphone application and website; (ii) women allocated to the “therapeutic patient  
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7 176 education” arm will benefit from four therapeutic education sessions on exercise; (iii) women  
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9 177 allocated to the “combined” arm will benefit from both interventions in parallel; (iv) women allocated  
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11  
12 178 to the “control” arm will receive usual care.  
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14 179

### 16 180 **Eligibility criteria for participants**

18  
19 181 Inclusion criteria include: being a female 18 to 75 years old; diagnosed with a first primary non-  
20  
21 182 metastatic invasive breast carcinoma histologically confirmed; treated with curative surgery and  
22  
23 183 requiring adjuvant treatment (chemotherapy, hormonotherapy and/or radiotherapy) that present at  
24  
25 184 one of the investigating centres; providing a medical certificate of no contraindication to exercise;  
26  
27 185 being available and willing to participate in the study for the duration of the interventions and follow-  
28  
29 186 up; using a personal smartphone compatible with an application used for the intervention (iOS  
30  
31 187 operating system from version 9.3, Android operating system from version 5.0, no Microsoft operating  
32  
33 188 system) and having a computer with Internet access; being able to understand, read and write French;  
34  
35 189 and being affiliated with a social security scheme.  
36  
37

38  
39 190 Non-inclusion criteria include: recurrent, metastatic or inflammatory breast cancer; personal  
40  
41 191 history or co-existence of other primary cancer (except for in situ cancer regardless of the site, basal  
42  
43 192 cell skin cancer and non-mammary cancer in complete remission for more than 5 years); presenting a  
44  
45 193 contraindication to exercise according to the investigator (such as cardiorespiratory or bone  
46  
47 194 pathologies, non-stabilized chronic diseases such as diabetes, malnutrition, etc.); presenting severe  
48  
49 195 malnutrition according to the criteria of the French National Health Authority (i.e., for women  $\leq 70$   
50  
51 196 years: weight loss  $\geq 15\%$  in 6 months or  $\geq 10\%$  in 1 month; for women  $> 70$  years: weight loss  $\geq 15\%$  in 6  
52  
53 197 months or  $\geq 10\%$  in 1 month, and body mass index (BMI)  $< 18 \text{ kg/m}^2$ );<sup>52</sup> being unable to be followed for  
54  
55 198 medical, social, family, geographic or psychological reasons for the duration of the study; pregnant or  
56  
57 199 breastfeeding or of childbearing age without effective contraception for the duration of the study.  
58  
59  
60

200

**201 Recruitment**

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

214

**215 Randomisation**

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

219 Participants will be randomised using EnnovClinical® software (version 7.5.710.4, Ennov, Paris,  
220 France) into one of the four arms of the trial, by using the following minimization criteria:<sup>54,55</sup> BMI (<25  
221 kg/m<sup>2</sup>, ≥25 and <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), baseline physical activity level from RPAQ (<150 min/week,  
222 ≥150 min/week of moderate-to-vigorous physical activity) and prescribed adjuvant treatments at  
223 inclusion (i.e., chemotherapy + hormone therapy ± radiotherapy, hormone therapy ± radiotherapy,  
224 chemotherapy ± radiotherapy, radiotherapy only).

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3 226 **INTERVENTIONS**  
4

5 227 At baseline, all participants will receive the international recommendations in terms of physical  
6  
7 228 activity for promoting health in the general population<sup>11</sup>, which will be delivered orally by a certified  
8  
9 229 exercise instructor with the help of a leaflet.  
10

11  
12 230

13  
14 231 **Intervention with a connected device**  
15

16 232 Participants randomised to the “connected device” arm will benefit from a 6-month exercise  
17  
18 233 program. The connected device consists of an activity tracker (connected wristband, LS417-F model,  
19  
20 234 CARE Fitness, Bobigny, France) that participants will wear daily, a dedicated smartphone application  
21  
22 235 and a dedicated website proposing an individualized, semi-supervised exercise program adapted to  
23  
24 236 cancer patients (developed by BIOMOUV, Paris, France). This automated web- and mobile-based  
25  
26 237 exercise program will aim to support participants to enhance physical activity in two ways: doing  
27  
28 238 structured exercise sessions and increasing daily physical activity (number of steps). Exercise sessions  
29  
30 239 will be automatically generated by an algorithm based on the patient profile (described below). The  
31  
32 240 participants will receive notifications informing them of a new structured exercise session available on  
33  
34 241 the website or mobile application, or alerting them when a session was not carried out, and inviting  
35  
36 242 them to execute it when possible. Participants will receive a free 6-month subscription to the program.  
37  
38 243 —*Setting up the connected device:* At the end of the baseline assessment, the certified exercise  
39  
40 244 instructor will introduce the customized exercise program to the participants and will give them the  
41  
42 245 activity tracker and a user guide for the connected device. Then, the certified exercise instructor will  
43  
44 246 explain the functioning of the activity tracker, the dedicated smartphone application and the dedicated  
45  
46 247 website, as well as assist the participants to install the application on their smartphone. The  
47  
48 248 participants will be registered in the customized exercise program by the certified exercise instructor.  
49  
50 249 The registration will consist of completing a web-based questionnaire about personal and health data  
51  
52 250 to determine the participant profile (age, weight, height, level of aerobic and muscular strength,  
53  
54 251 treatment, symptoms, availabilities for exercise sessions and sports materials).  
55  
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57  
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3 252 —*Baseline level of aerobic and muscular strength for the individualised exercise program:* The physical  
4  
5 253 fitness tests performed at baseline will be used to classify the participants at the start of the exercise  
6  
7 254 program according to their aerobic level (for the walking sessions) and their muscular strength level  
8  
9  
10 255 (for the strengthening sessions). The aerobic level categories will be determined by the distance  
11  
12 256 performed during the 6-minute walk test (6MWT): aerobic group 1 (<460 meters), aerobic group 2  
13  
14 257 (460 to 580 meters) and aerobic group 3 (>580 meters). The muscular strength level categories will be  
15  
16 258 determined by the number of sit-ups performed on a chair in 30 seconds during the Sit-to-stand test:  
17  
18 259 muscular strength group 1 ( $\leq 10$  repetitions), muscular strength group 2 (11 to 14 repetitions) and  
19  
20 260 muscular strength group 3 ( $\geq 15$  repetitions). Thresholds were based on average values reached by  
21  
22 261 women receiving breast cancer treatments for the 6MWT (pooled mean value, 523 m) and the Sit-to-  
23  
24 262 stand test (pooled mean value, 13 repetitions) from a previous study;<sup>56</sup> these values were checked for  
25  
26 263 consistency with percentile scores obtained at the 6MWT and Sit-to-stand test in community-dwelling  
27  
28 264 older women,<sup>57</sup> then the interquartile range was used to determine the thresholds for the three groups  
29  
30 265 of this study. The level categories assigned will be entered by the exercise instructor in the baseline  
31  
32 266 patient profile and will be used by the automated algorithm to set up the level of the first walking and  
33  
34 267 muscle strengthening sessions.

35  
36  
37  
38 268 —*Exercise program:* The 6-month exercise program will be semi-supervised by the certified exercise  
39  
40 269 instructor through an individual follow-up of participants (see 'Participant follow-up' part and  
41  
42 270 'Continuous monitoring' part). It will be carried out autonomously by the participants at home by using  
43  
44 271 the smartphone application and the website. The program is based on three structured unsupervised  
45  
46 272 sessions per week alternating two types of exercise: two walking sessions (by following oral  
47  
48 273 instructions given via the smartphone application) and one muscle strengthening session (by using  
49  
50 274 videos accessible on the website). The levels of the first walking and muscle strengthening sessions will  
51  
52 275 be determined by the fitness tests performed at baseline (see 'Baseline level' part). Then, subsequent  
53  
54 276 sessions will be planned according to the available days of the participant. Strengthening exercises will  
55  
56 277 be adapted according to sports materials available at their home (e.g., Swiss ball, sports mat, stick,  
57  
58  
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1  
2  
3 278 weight, etc.). Each session will include: 1) a warm-up period of 5 minutes; 2) a body session of 10 to 35  
4  
5 279 minutes of strengthening exercises, or 10 to 50 minutes of walking (mixing continuous and/or  
6  
7 280 intermittent effort); 3) a 5-minute recovery period, consisting of stretching and relaxation during  
8  
9  
10 281 strengthening sessions or a cool down during walking sessions. Sessions will be of moderate-to-high  
11  
12 282 intensity ( $\geq 3$  and  $\leq 9$  METs).

13  
14 283 The three structured unsupervised exercise sessions per week are configured by a unique algorithm  
15  
16 284 hosted by an accredited personal healthcare data host (Orange Business Services, Paris, France), to  
17  
18 285 plan the exercise sessions and determine the exercise level in an adapted and progressive manner by  
19  
20 286 increasing the duration and then intensity in accordance with principles of exercise training and  
21  
22 287 progression.<sup>58,59</sup> At the beginning of each session, the duration and intensity of the session will be  
23  
24 288 determined according to the perceived difficulties (evaluated by a Borg scale) and emotional state  
25  
26 289 (recorded by an emoji) of the participant in the previous session, and will be modified or postponed  
27  
28 290 according to the level of fatigue (evaluated by a Borg scale), the level of dyspnea (evaluated by a Borg  
29  
30 291 scale), the presence or absence of unusual muscle pain and the presence or absence of unusual  
31  
32 292 nausea/diarrhea. In case of a severe adverse event related to disease or treatment (i.e., joint disability,  
33  
34 293 osteoarthritis, cachexia, hand-foot syndrome, aplasia, diuretic, axillary node dissection, pace-maker,  
35  
36 294 chemotherapy, targeted therapy, hormone therapy, radiotherapy, COPD, diabetes) or temporary  
37  
38 295 contraindication to exercise, declared by the participant on her device, the program and sessions will  
39  
40 296 be adapted or suspended until the participant's health improves.

41  
42 297 In addition, participants will have the opportunity to perform additional exercise sessions according  
43  
44 298 to their preferences and lifestyle, outside the program. Participants will be asked to record these  
45  
46 299 sessions through the smartphone application or the website: type of activity (e.g., walking, hiking,  
47  
48 300 cycling) from a list adapted from Ainsworth's Compendium,<sup>60</sup> and its duration and intensity.

49  
50 301 —*Number of daily steps*: Participants will be advised to wear the activity tracker daily and to launch  
51  
52 302 the application regularly (preferably daily), which will automatically synchronize with the activity  
53  
54 303 tracker via Bluetooth connection and will collect the number of steps. The target number of steps will  
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3 304 be 3,000 steps per day at the program onset, and then will be re-set based on the average number of  
4  
5 305 daily steps during the first week after inclusion. The target number of daily steps will evolve  
6  
7 306 automatically every three weeks based on the average number of daily steps achieved during the  
8  
9 307 previous three weeks, and will be updated automatically in the application. Consistent with principles  
10  
11 308 of exercise training and progression,<sup>58,59</sup> after each 3-week cycle, if the goal of steps per day is reached  
12  
13 309 by the participant, the target goal will increase by 15% during the following 3-week-cycle, within a  
14  
15 310 maximum target of 10,000 daily steps. If the average number of daily steps does not meet the goal,  
16  
17 311 the target will remain unchanged in the next cycle.

20  
21 312 —*Participant follow-up*: Telephone follow-ups will be carried out by the certified exercise instructor at  
22  
23 313 10 days, 2 months and 4 months after the intervention onset to ensure the proper functioning of the  
24  
25 314 connected device, review the use of the connected device, review the conduct of the sessions and  
26  
27 315 answer the participants' questions if they may have. Participants will be orally encouraged to remain  
28  
29 316 physically active on a daily basis (reminder of the benefits and recommendations of physical activity,  
30  
31 317 success and satisfaction during the exercise sessions). During the 6-month intervention, the  
32  
33 318 participants will have the opportunity to contact the certified exercise instructor or the clinical  
34  
35 319 research assistant at any time, by e-mail (directly through the website) or by telephone for any  
36  
37 320 question or assistance with the connected device.

40  
41 321 —*Continuous monitoring*: The certified exercise instructor will monitor the use of the connected device  
42  
43 322 by the participants and their progress in the program through a dedicated professional website that  
44  
45 323 provides real-time access to the participants' data. On this website, an automatically generated daily  
46  
47 324 event table will inform the certified exercise instructor of the occurrence of disabilities reported by the  
48  
49 325 participants that may lead to modifying their program (e.g., severe fatigue, dyspnea, unusual muscle  
50  
51 326 pain) or if participants have not performed their planned sessions or used their activity tracker for  
52  
53 327 seven consecutive days. Upon these alerts, the certified exercise instructor will contact the participants  
54  
55 328 to precisely analyse the reported disabilities, advise participants, identify the causes of non-use of the  
56  
57 329 connected device, solve possible technical problems or reinforce participant's motivation if necessary.  
58  
59  
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3 330 —*End of the intervention*: At the end of the 6-month program, participants will keep their activity  
4  
5 331 tracker to be encouraged to continue regularly exercising in autonomy. Upon their request, continued  
6  
7 332 subscription to the dedicated application and website will be offered for another six months, with no  
8  
9 333 individual follow-up anymore.  
10  
11

12 334

### 14 335 **Intervention of therapeutic patient education**

16 336 Participants randomised to the therapeutic patient education arm will benefit from a therapeutic  
17  
18 337 patient education intervention, in addition to receiving the international physical activity  
19  
20 338 recommendations. The intervention is part of the therapeutic patient education program set up at the  
21  
22 339 Léon Bérard cancer centre and validated by the Regional Health Agency (“Agence Régionale de Santé  
23  
24 340 Rhône-Alpes”). It will be disseminated in the investigating centres according to the criteria of the  
25  
26 341 Regional Health Agency. The therapeutic patient education intervention consists of four sessions that  
27  
28 342 will be scheduled according to participants’ availability during their follow-up visits as part of their  
29  
30 343 usual clinical management over a 6-month period.  
31  
32

34 344 First, participants will be invited to an initial 1-hour individual face-to-face session of educational  
35  
36 345 diagnosis with a health professional trained in therapeutic patient education. This session will assess  
37  
38 346 their needs and establish a contract of objectives to reach. Then, participants will be invited to  
39  
40 347 participate in two collective educational sessions (1h30 each with a group of 10 patients maximum per  
41  
42 348 session). These sessions will be composed of theoretical and practical workshops to help them  
43  
44 349 understand their physical activity in their daily life and implement the necessary means to practice  
45  
46 350 regular exercise in autonomy. Finally, participants will be invited to another 1-hour individual session,  
47  
48 351 where an educational evaluation will be conducted to identify whether they achieve their individual  
49  
50 352 objectives set at the time of the educational diagnosis.  
51  
52

53 353

### 354 **Combined interventions**

355 Participants randomised to the 'combined intervention' arm will benefit from a combination of the  
356 connected device intervention and the therapeutic patient education intervention in parallel for  
357 6 months.

### 360 **EVALUATIONS**

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

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

### 375 **DATA COLLECTION**

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

#### 377 **Socio-demographic and clinical data**

378 Socio-demographic and clinical data, including month/year of birth, age at diagnosis of breast  
379 cancer, family status, level of education, hormonal status, tumour histology and personal history of  
60

1  
2  
3 380 breast cancer will be collected at baseline. Family status, potential cancer progression and all  
4  
5 381 treatments received for cancer will be collected at 6 and 12 months. All data will be extracted from  
6  
7 382 patients' electronic medical records, except family status and level of education that will be self-  
8  
9 383 reported in a questionnaire.

11 384 The occupational status will be assessed using a self-administered questionnaire asking  
12  
13 385 employment status, occupation, size of the company, the perceived intensity of the physical effort at  
14  
15 386 work, the evolution of employment status at return to work in case of sick leave.<sup>61</sup>  
16  
17  
18  
19

### 20 21 388 **Anthropometrics and body composition**

22  
23 389 The standing height (cm), body weight (kg) and waist (cm) and hip (cm) circumferences will be  
24  
25 390 measured using standardized procedures and BMI will be calculated as the body weight in kilograms  
26  
27 391 divided by the square of the height in meters (kg/m<sup>2</sup>). The waist circumference will be measured  
28  
29 392 midway between the last floating rib and the iliac crest. The hip circumference will be measured at the  
30  
31 393 tip of the pubis. Body composition will be measured by a bioelectrical impedance meter (Biody XPert  
32  
33 394 ZM II, eBiody, eBIODY SAS, La Ciotat, France) to assess fat mass (in kg), lean body mass (in kg), muscle  
34  
35 395 mass (in kg), dry lean mass (in kg), total body water (in L), intracellular fluid (in L) and extracellular fluid  
36  
37 396 (in L).  
38  
39  
40  
41  
42

### 43 398 **Physical fitness**

44  
45 399 Cardiorespiratory fitness will be evaluated by the walking endurance during the 6MWT (distance  
46  
47 400 covered in metres) with perceived difficulty using the Borg scale.<sup>62</sup> During this test, participants will be  
48  
49 401 asked to perform the maximum walk shuttle distance on a 30-metre long flat corridor in 6 minutes.

50  
51 402 The lower limb muscle strength will be measured using the sit-to-stand test (number of sit-ups on a  
52  
53 403 chair in 30 seconds). During this test, participants will be asked to sit down on a chair and get up as  
54  
55 404 many times as possible during 30 seconds.<sup>63</sup>  
56  
57  
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2  
3 405 Hand prehensile strength will be measured by the handgrip test using hand dynamometry (Jamar  
4  
5 406 Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, UK), which is a validated index of the  
6  
7 407 isometric strength of the hand and forearm muscles.<sup>64</sup> During this hand-grip test, participants will be  
8  
9  
10 408 asked to squeeze the handgrip as strongly as possible to obtain the maximal force (in kg). Two  
11  
12 409 measures will be performed on each hand and the best performance will be registered.

13  
14 410 The flexibility of lower limbs will be measured using the sit-and-reach flexibility test (Deluxe  
15  
16 411 Baseline flexibility test, 3B Scientific, Bartenheim, France).<sup>65</sup> In this test, participants will sit on the floor  
17  
18 412 on a mat with their legs stretched out straight ahead. They will be asked to lean forward as far as  
19  
20 413 possible and the distance between fingertips and toes will be measured (in cm) (i.e., by considering  
21  
22 414 the level of the feet as recording zero, any measure that does not reach the toes is negative and any  
23  
24 415 measure beyond the toes is positive).

25  
26  
27 416 The balance will be measured using the bilateral single-leg stance test.<sup>66</sup> The participants will stand  
28  
29 417 and be asked to lift a foot and hold the position for a maximum of 60 seconds, then to do the same  
30  
31 418 exercise on the other foot (duration held in equilibrium, 2 times 60 seconds).

32  
33  
34 419

### 35 36 420 **Physical activity level, sitting time and achievement of physical activity recommendations**

37  
38 421 The validated self-administered questionnaire RPAQ will be used to measure the self-reported  
39  
40 422 physical activity.<sup>53,67</sup> The RPAQ was designed to assess usual physical activity in the last four weeks,  
41  
42 423 covering three activity domains: domestic physical activity, including sitting time that is a good proxy  
43  
44 424 of sedentary behaviour; occupational physical activity, including transportation to and from work; and  
45  
46 425 recreational physical activity. The RPAQ gives specific scores in the metabolic equivalent of task (MET)  
47  
48 426 unit for activities of very low intensity (<1.5 METs, i.e., sedentary activities), low intensity (1.5 to  
49  
50 427 <3 METs), moderate intensity (3 to <6 METs) and high intensity ( $\geq$ 6 METs, i.e., vigorous activities)  
51  
52 428 within each domain during the past four weeks. Questions will be coded and converted in MET-minute  
53  
54 429 per four weeks according to the Compendium of Physical Activities<sup>60</sup> by multiplying the number of  
55  
56 430 METs by the duration and frequency of each activity. Then, the global score of physical activity will be  
57  
58  
59  
60

1  
2  
3 431 obtained by adding the number of MET-minutes per four weeks in each intensity and each domain.  
4  
5 432 The physical activity profile will be defined as the time spent in physical activities of low, moderate and  
6  
7 433 high intensities. The physical activity level will be defined by the overall weekly physical activity  
8  
9 434 (average expressed in MET-hour/week).

11 435 Achievement of international physical activity guidelines will be computed for each individual by  
12  
13 436 dividing the time spent in moderate-to-vigorous physical activity (i.e.,  $\geq 3$  METs) into two categories:<sup>11</sup>  
14  
15 437  $<150$  min/week of moderate-to-vigorous physical activity (i.e., under physical activity guidelines);  $\geq 150$   
16  
17 438 min/week of moderate-to-vigorous physical activity (i.e., reaching physical activity guidelines).  
18  
19 439

#### 23 440 **Patient-reported outcomes**

25 441 The quality of life will be measured using the European Organization for Research and Treatment  
26  
27 442 of Cancer (EORTC) Quality-Of-Life Questionnaire (QLQ-C30) and its specific module for breast cancer  
28  
29 443 (BR-23).<sup>68</sup> The QLQ-C30 is a 30-item validated self-administered questionnaire that evaluates five  
30  
31 444 functioning domains (i.e., physical, role, emotional, cognitive and social), a global quality-of-life  
32  
33 445 domain, three symptom domains (i.e., pain, fatigue and nausea) and six single items (i.e., dyspnea,  
34  
35 446 insomnia, anorexia, diarrhea, constipation and financial impact). Each item is associated with a score  
36  
37 447 ranging from 0 to 100. For the functioning and global quality-of-life scales, a higher score corresponds  
38  
39 448 to a better functioning level. For scales related to symptoms, a lower score corresponds to a better  
40  
41 449 functioning level. The BR-23 module gathers data about perceived body image, sexual functioning, sex  
42  
43 450 enjoyment, arm symptoms, breast symptoms and systemic therapy side effects.  
44  
45 451

47 451 The health-related quality of life will be assessed using the EQ-5D-5L questionnaire.<sup>69</sup> This  
48  
49 452 standardized self-administered questionnaire describes five dimensions (i.e., mobility, self-care, usual  
50  
51 453 activities, pain/discomfort and anxiety/depression) being rated using five levels (i.e., no, slight,  
52  
53 454 moderate, severe and extreme problems), and comprises a 0-100 visual analogue scale recording the  
54  
55 455 self-rated health (where the endpoints are labelled 'The best health you can imagine' and 'The worst  
56  
57 456 health you can imagine').  
58  
59  
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3 457 Fatigue will be assessed using the Piper Fatigue Scale-12 (PFS-12), a 12-item self-reported  
4  
5 458 questionnaire with four subscales (i.e., behavioural, affective, sensory and cognitive/mood aspects of  
6  
7 459 fatigue):<sup>70</sup> the higher the score, the worse the fatigue. All items together will produce a total score for  
8  
9 460 fatigue that will be used to define categories as follows: no fatigue (score=0), mild fatigue (score 1-3),  
10  
11 461 moderate fatigue (score 4-6) and severe fatigue (score 7-10).

12  
13  
14 462 Social deprivation will be assessed using the EPICES (Evaluation of Deprivation and Inequalities in  
15  
16 463 Health Examination Centres) score.<sup>71</sup> The score will be computed by adding each question coefficient  
17  
18 464 to the intercept whenever the answer is “yes.” The score ranges from 0 to 100 (i.e., the higher the  
19  
20 465 score, the greater the deprivation level) with the threshold for deprivation at 30.

21  
22  
23 466 Lifestyle factors, assessed using a self-administered questionnaire, include tobacco status (i.e.,  
24  
25 467 never, former, current smoker), lifetime and current tobacco use (expressed in pack-years) and alcohol  
26  
27 468 intake over the past 6 months (usual frequency of consumption [i.e., never, less than 1/month, 1-3  
28  
29 469 times/month, 1-6 times/week, daily] of different categories of alcoholic beverages [i.e., wine, beer,  
30  
31 470 cider, aperitif wine, cocktail/punch, aniseed alcohol, spirits] as well as the usual number of glasses).  
32  
33 471 The amount of alcohol will be computed by multiplying the frequency of consumption by the number  
34  
35 472 of glasses and alcohol content of each type of alcoholic beverage. The average daily alcohol intake over  
36  
37 473 the past 6 months (in g/day) will be computed by summing the amount of alcohol from each beverage.  
38  
39  
40

41 474

#### 42 43 475 **Determinants of Physical activity**

44  
45 476 The 21-item self-administered questionnaire “Barriers to Being Active Quiz” will be used to  
46  
47 477 qualitatively assess barriers to the regular practice of physical activity.<sup>72</sup>

48  
49 478 Uses, representations and motivation towards physical activity will be assessed within the study  
50  
51 479 population using a self-administered questionnaire available online. Acceptability of connected  
52  
53 480 devices and acceptability of therapeutic patient education will be assessed among participants  
54  
55 481 randomised to the corresponding arms using a paper-based self-administered questionnaire. These  
56  
57 482 questionnaires will be developed following the Unified Theory of Acceptance and Use of Technology  
58  
59  
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1  
2  
3 483 (UTAUT),<sup>73</sup> which is a specification of the Theory of Planned Behaviour<sup>74</sup> designed to explain and  
4  
5 484 predict the probability of behaviour change among individuals faced with new technologies. The  
6  
7 485 Theory of Planned Behaviour has been massively used during the last two decades to promote health  
8  
9 486 behaviours such as physical activity. Besides, item wording will be based on the results of individual  
10  
11 487 and collective interviews conducted for that purpose and designed to identify social representations<sup>75</sup>  
12  
13  
14 488 of health protection and physical activity incentive devices.  
15  
16  
17 489

### 18 19 490 **Compliance with interventions**

20  
21 491 Compliance with each intervention will be assessed at the 6-month evaluation only for patients  
22  
23 492 randomized to the “connected device”, “therapeutic patient education” and “combined” arms.  
24  
25 493 Compliance will be assessed by the number of days of use of the activity tracker, the participation rate  
26  
27 494 in scheduled exercise sessions, the participation rate in scheduled therapeutic education sessions and  
28  
29 495 the proportion of compliant patients, depending on the intervention allocated, following the  
30  
31 496 recommendations of the protocol. Patients’ compliance and reasons for non-compliance during the  
32  
33 497 intervention period (6 months) will be described for each arm.  
34  
35  
36  
37 498

### 38 39 499 **Biological assessments**

40  
41 500 A non-fasting blood sample (one 10-ml EDTA tube and one 10-ml dry tube) will be collected at  
42  
43 501 baseline and 6 months. In particular, blood will be drawn at baseline before the onset of adjuvant  
44  
45 502 treatments, otherwise no blood samples will be collected. The following biological factors will be  
46  
47 503 assessed in the blood samples: circulating serum levels of endocrine factors (IGF-1, insulin, estradiol),  
48  
49 504 circulating plasma levels of inflammatory cytokines (IL-6, TNF $\alpha$ , CRP), circulating plasma levels of  
50  
51 505 adipokines (adiponectin, leptin) and vitamin D status.  
52  
53  
54  
55 506

### 56 57 507 **STUDY OUTCOMES**

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2  
3 508 The primary endpoint will be the proportion of women who achieve at 6 months the internationally  
4  
5 509 recommended level of physical activity (at least 150 min/week of moderate-to-vigorous physical  
6  
7 510 activity, i.e., intensity  $\geq 3$  METs) assessed by the RPAQ self-administered questionnaire.

9  
10 511 Secondary endpoints will be:

11  
12 512 1. Assessment of the efficacy of the programs at 12 months (i.e., the proportion of women who achieve  
13  
14 513 the internationally recommended level of physical activity);

15  
16 514 2. Assessment of the adherence to the interventions at 6 months (the proportion of participants who  
17  
18 515 are compliant to the program, participation rate in planned sessions);

19  
20 516 3. Assessment of the impact between baseline and 6 months and between 6–12 months of the  
21  
22 517 interventions on physical activity profile (changes in time spent in different intensities of physical  
23  
24 518 activity and time spent in sedentary activities), physical fitness (changes in results to the 6-minute walk  
25  
26 519 test, hand-grip test, sit-to-stand test, sit-and-reach flexibility test and single-leg stance test),  
27  
28 520 anthropometrics (changes in weight, waist and hip circumferences, BMI, fat mass, lean body mass,  
29  
30 521 muscle mass, dry lean mass and body water), quality of life (changes in scores obtained from the EORTC  
31  
32 522 QLQ-C30 questionnaire and its BR-23 module), fatigue condition (changes in scores obtained from the  
33  
34 523 PFS-12 questionnaire), health-related quality of life (changes in scores obtained from the EQ-5D-5L  
35  
36 524 questionnaire), social deprivation (changes in scores obtained from the EPICES self-administered  
37  
38 525 questionnaire), occupational status (the proportion of participants who changed their employment  
39  
40 526 status, with return to work and who perceived difficulty at work obtained from a self-administered  
41  
42 527 questionnaire) and lifestyle factors (the proportion of participants who change their tobacco use and  
43  
44 528 alcohol intake obtained from a self-administered questionnaire).

45  
46 529 4. Assessment of the impact of the interventions on biological parameters between baseline and  
47  
48 530 6 months (changes in serum circulating levels of endocrine factors [insulin, IGF1, estradiol], changes in  
49  
50 531 plasma circulating levels of cytokines [inflammatory cytokines: IL-6, TNF, and CRP; adipokines:  
51  
52 532 adiponectin and leptin], the proportion of participants with a modification on vitamin D status).

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

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

539 7. Assessment of the cost-utility and the cost-effectiveness of implementing each intervention at  
 540 12 months, using clinical data (treatments received, patients' diary on medical consultations), hospital  
 541 costs (national data) and benefit in physical activity level.

542

## 543 **STATISTICAL ANALYSIS**

### 544 **Sample size determination**

545 The efficacy rate assumptions are  $\mu=40\%$ ,  $\mu+\mu_A=55\%$  and  $\mu+\mu_B=65\%$  for the "control",  
 546 "therapeutic patient education" and "connected device" arm modalities, respectively. The expected  
 547 benefit in the "therapeutic patient education" arm compared to the "control" arm is 15% (40% efficacy  
 548 in the "control" arm versus 55% efficacy in the "therapeutic patient education" arm). The expected  
 549 benefit in the "connected device" arm compared to the "control" arm is 25% (40% efficacy in the  
 550 "control" arm versus 65% efficacy in the "connected device" arm).<sup>23</sup>

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

$$557 \left[ \mu + (\mu + \mu_B) \right] / 2, \text{ versus } \left[ (\mu + \mu_A) + (\mu + \mu_A + \mu_B) \right] / 2$$

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

1  
2  
3 559 With a first species risk  $\alpha=0.025$  and a power of 80% in the bilateral situation, the number of  
4  
5 560 patients to include per treatment arm to demonstrate the efficacy of the therapeutic patient education  
6  
7 561 will be 108 (or 432 for the four treatment arms) (nQuery V6.0, Chi-two test with continuity correction).  
8  
9  
10 562 This number of patients will also allow a power greater than 95% to evaluate the efficacy of the  
11  
12 563 "connected device" intervention, always with a risk  $\alpha = 0.025$  in the bilateral situation.  
13

14 564

#### 16 565 **Data analysis plan**

17  
18  
19 566 The following populations will be defined for statistical analyses: i) the intent-to-treat (ITT)  
20  
21 567 population, which includes all randomised participants in the study; ii) the per-protocol population,  
22  
23 568 which consists of a subgroup of participants from the ITT population, who has no major protocol  
24  
25 569 violations and who follows the procedure for the duration of the study. Analyses in the ITT population  
26  
27 570 will be performed for all the study endpoints; analyses in the per-protocol population will be  
28  
29 571 performed for exploratory purposes. The randomisation date will be considered as the reference date  
30  
31 572 in all delay calculations, unless any other way is specified.  
32  
33

34 573 Baseline data will be described in the ITT population and presented by randomised arms. For the  
35  
36 574 primary outcome, proportions will be estimated for the two targeted comparisons: (i) participants who  
37  
38 575 received the connected device vs. participants who did not; (ii) participants who benefited from the  
39  
40 576 therapeutic patient education intervention vs. participants who did not. Results will be presented with  
41  
42 577 their 95% confidence interval. The use of a 2x2 factorial design will allow to test, respectively: the  
43  
44 578 efficacy of the intervention with a connected device (compared to without a connected device); the  
45  
46 579 efficacy of the therapeutic patient education intervention (compared to no therapeutic patient  
47  
48 580 education); and the interest of two combined intervention modalities (i.e., connected device and  
49  
50 581 therapeutic patient education) compared to the single intervention with the connected device only or  
51  
52 582 with therapeutic patient education only. The analysis strategy will therefore be as follows:<sup>76</sup>  
53  
54 583 1) searching first for an interaction by a specific interaction test, performed at the significance level of  
55  
56 584 0.05 (Chi-square test or use of an interaction term in a logistic model); 2) in the absence of interaction,  
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1  
2  
3 585 testing each of the two bilateral interest comparisons at the threshold of 0.025, namely the efficacy of  
4  
5 586 the intervention with the connected device and the efficacy of the therapeutic patient education  
6  
7 587 intervention; 3) in case of the efficacy of either one of the intervention modalities, evaluating the  
8  
9 588 interest of the combination of the two interventions compared to the single intervention with the  
10  
11 589 connected device only or with therapeutic patient education only.

14 590 For secondary outcome variables, the efficacy of the program at 12 months, as well as according to  
15  
16 591 stratification criteria, will be analysed similarly to the primary outcome. The adherence to the  
17  
18 592 interventions will be evaluated by the proportion of compliant participants and participation rate in  
19  
20 593 planned sessions. Changes in physical activity profile, physical fitness, anthropometrics, quality of life,  
21  
22 594 fatigue, social deprivation and biological parameters will be analysed by the absolute and/or relative  
23  
24 595 variations in each of these endpoints; these variations will be compared between with and without  
25  
26 596 each intervention, for each intervention, and between combined interventions and the single one,  
27  
28 597 using a parametric test. Occupational status and lifestyle factors will be analysed by comparing the  
29  
30 598 proportion of participants between interventions or their combination. Representations and  
31  
32 599 acceptability of activity tracker and therapeutic patient education will be analysed by comparing the  
33  
34 600 proportion of participants between randomisation and follow-up assessments. A method for imputing  
35  
36 601 missing data will be considered if necessary.

41 602 Statistical analyses will be performed using SAS® software version 9.4 or later.

43 603

#### 45 604 **Medico-economic analysis**

47  
48 605 The cost-effectiveness analysis will be conducted alongside the trial using the French national  
49  
50 606 health insurance perspective. Quantities of resources used [external consultations, hospital stays  
51  
52 607 including Diagnosis-related groups, drugs with extra payments and other healthcare-related costs] will  
53  
54 608 be collected on the eCRF and multiplied by the respective unit costs. The intervention with therapeutic  
55  
56 609 patient education and the intervention with connected device will be evaluated using a bottom-up  
57  
58 610 micro-costing approach.<sup>77,78</sup> Using the Diagnosis-related group, hospital stays will be evaluated based  
59  
60

1  
2  
3 611 on the French National hospital costs study database. External consultations and wider examinations,  
4  
5 612 community care (general practitioner visits, nurse visits, etc.) will be valued on the basis of the General  
6  
7 613 Nomenclature of Professional Treatments (NGAP, “Nomenclature Générale des Actes  
8  
9 614 Professionnels”). The cost of biological treatments will be estimated using the Nomenclature of  
10  
11 615 Biological Medical Treatments (NABM, “Nomenclature des Actes de Biologie Médicale”). The cost of  
12  
13 616 technical treatments (e.g., imaging) will be estimated using the Common Classification of Medical  
14  
15 617 Treatments (CCAM, “Classification Commune des Actes Médicaux”). Acquisition costs for the most  
16  
17 618 expansive drugs will be based on the list of common units of dispensation for supplementary medicines  
18  
19 619 (“liste des unités communes de dispensation prise en charge en sus”). Finally, costs of medical  
20  
21 620 transport will be derived from the French Court of Audit's report on medical transport expenses  
22  
23 621 covered by the French National Health insurance. The time horizon will be 12 months. Hence, neither  
24  
25 622 costs nor effectiveness will be discounted. Mean costs and effectiveness will be derived for all four  
26  
27 623 strategies under consideration: connected device, therapeutic patient education, combined and  
28  
29 624 control arms. Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per quality-  
30  
31 625 adjusted life year (QALY) gained using EQ-5D-5L to estimate utility, cost per life year gained, cost per  
32  
33 626 BMI unit lost and cost per centimetre of waist-to-hip circumference lost. One-way sensitivity analyses  
34  
35 627 will be conducted by varying resource consumption and unit cost parameters and graphically  
36  
37 628 illustrated in a Tornado diagram. The uncertainty surrounding the ICERs will be also captured by a  
38  
39 629 probabilistic analysis using non-parametric bootstrap methods as recommended by the French  
40  
41 630 National Authority for Health.<sup>79</sup>

631

## 632 **ADVERSE EVENTS**

51  
52 633 All participants will continuously report the occurrence of adverse events regarding neuropathies  
53  
54 634 and joint pain in their patient's notebook, which will be collected at 6 and 12 months. Those equipped  
55  
56 635 with the connected device will also report potential adverse events before and after each session of  
57  
58  
59 636 their exercise program (see *Connected device*). The reported adverse events will then be graduated  
60

1  
2  
3 637 according the CTCAE v5. Due to the low risks associated with the interventions,<sup>16</sup> this study is part of  
4  
5 638 the so-called “intervention research with minimal risks and constraints” in the French legislation and  
6  
7 639 therefore only these adverse events arising within the framework of the study will be reported.  
8  
9

10 640 In the occurrence of an adverse event regarding neuropathies and joint pain, the principal  
11  
12 641 investigator will report it to the health authorities responsible for vigilance without delay. The  
13  
14 642 promotor will also report the adverse events, as well as any safety measures to be proposed, to the  
15  
16 643 French Ethics Committee and the investigators without delay.  
17  
18

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#### 20 21 645 **DATA MANAGEMENT**

22  
23 646 The database for clinical data and randomisation will be created using EnnovClinical® software. Its  
24  
25 647 access will be secured (personal identification and password protection) for maintaining confidentiality  
26  
27 648 at all times. Individual participants will not be identified in any reports of this trial. All data from the  
28  
29 649 connected device will be merged to the clinical database at the end of the study. Investigators and  
30  
31 650 data analysts will have access to the final dataset.  
32  
33

34 651 Data monitoring will be provided by the trial steering committee, including overall project  
35  
36 652 supervision, progress monitoring, advice on scientific credibility, and ensuring the integrity and  
37  
38 653 appropriate running of the project. The clinical research assistant will verify all consent forms,  
39  
40 654 compliance with established protocol and procedures, and data quality in the eCRF. The research team  
41  
42 655 will make biannual reports to the trial steering committee.  
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#### 46 47 48 657 **PATIENT AND PUBLIC INVOLVEMENT**

49  
50 658 An association of breast cancer patients' representatives (Europa Donna France,  
51  
52 659 <http://www.europadonna.fr/>) was involved in preparing the conduct of interventions and evaluations,  
53  
54 660 in particular by considering patients' expectations, experience and desire for global care. The  
55  
56 661 association will be involved in plans to disseminate the study results to breast cancer patients, study  
57  
58 662 participants and wider patient communities concerned.  
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663

**664 ETHICS AND DISSEMINATION**

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

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

678

**679 DISCUSSION**

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

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2  
3 689 the goal of the DISCO trial is to disseminate innovative programs in supportive cancer care, based on  
4  
5 690 scientific evidence, to systematically integrate exercise in breast cancer cares.  
6

7 691 While an increasing number of studies have demonstrated the benefits of exercise in breast cancer  
8  
9 692 patients, the routine implementation in the cancer care process lacks behind evidence and practice  
10  
11 693 guidelines.<sup>80–82</sup> While the prescription of physical activity in supervised programs has been shown  
12  
13 694 superior compared to non-supervised programs,<sup>22,83</sup> semi-supervised interventions seem to yield  
14  
15 695 comparable or superior benefits to supervised programs.<sup>84</sup> Therefore, the semi-supervised exercise  
16  
17 696 program of the DISCO trial through continuous follow-up has been designed according to the  
18  
19 697 preferences of women with breast cancer so as not to leave patients in total autonomy.<sup>36,85</sup> Connected  
20  
21 698 devices are tools developed over the last 10 years that are very promising for promoting physical  
22  
23 699 activity in the general population and in patients with chronic diseases such as cancer<sup>86,87</sup> and for  
24  
25 700 developing distance-based physical activity interventions.<sup>88</sup>  
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30 701 The semi-supervised home-based physical activity program of the DISCO trial using the connected  
31  
32 702 device provides flexibility to patients that may facilitate adherence and to overcome barriers due to  
33  
34 703 distance of facilities from women's home and spatial inequalities of access.<sup>27</sup> Connected devices allow  
35  
36 704 proposing a tailored physical activity program to patients regardless of their place of residence, and  
37  
38 705 enable patients to practice physical activities of their choice, at any time that suits them. Therefore,  
39  
40 706 they may reduce geographical and organisational barriers in the access of patients to exercise, a key  
41  
42 707 issue to improve their engagement in regular and sustained physical activity.<sup>27</sup> Previous studies in  
43  
44 708 oncology have reported that the use of mobile devices has benefits to overcome motivational barriers  
45  
46 709 to physical activity, which can help patients staying physically active over the medium and long  
47  
48 710 term.<sup>89,90</sup> Moreover, some studies have shown that breast cancer patients achieved higher fitness  
49  
50 711 levels during supervised training compared to unsupervised training, even low and medium levels of  
51  
52 712 supervision have been effective, as less resource-intensive options for effective and longer-term  
53  
54 713 behaviour change strategies based on exercises in cancer patients and survivors.<sup>84,91</sup>  
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2  
3 714 Activity trackers have become increasingly popular in recent years. Patients have reported positive  
4  
5 715 feedback on using activity trackers such as pleasant to wear, easy to use and a strong motivational role  
6  
7 716 through the real-time display of daily number of steps.<sup>92</sup> Also, walking is an inexpensive activity that  
8  
9  
10 717 can be performed anywhere and does not require specific skills. A study on preferences for technology-  
11  
12 718 supported interventions in breast cancer survivors has reported that 63% would like to use a physical  
13  
14 719 activity mobile application and 90% would find a physical activity tracker useful to monitor and  
15  
16 720 increase physical activity.<sup>35</sup>

17  
18  
19 721 Despite the potential benefits of connected devices in cancer care, their use may face several  
20  
21 722 important issues. First, ethical challenges related to the security of sensitive data storage have been  
22  
23 723 raised.<sup>93</sup> To ensure that data transfer and storage guarantee informational privacy and patient safety,<sup>94</sup>  
24  
25 724 an activity tracker made in France (i.e., allowing storing health data only in France) and an accredited  
26  
27 725 national health data host were chosen for the DISCO trial. Particularly, ensuring medical data security  
28  
29 726 is a reassuring choice for patients to participate in this new kind of medical research. Second, technical  
30  
31 727 challenges have been raised, related to technological robustness, reliability of data collection and  
32  
33 728 processing, and ease of use. Therefore, an activity tracker with a step display on the screen, a user-  
34  
35 729 friendly interface, good reliability and a good price-performance ratio was chosen in the DISCO trial.  
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38  
39 730 Third, connected devices may create or exacerbate access disparities related to technological literacy  
40  
41 731 and economic means, as well as reliable access to the internet in rural or isolated areas.<sup>93</sup> Fourth,  
42  
43 732 medical reasons are usually not easy to control in patients' adherence to exercise programs. Reliance  
44  
45 733 upon self-assessment of the participant's fatigue, evaluation of the participant before and after each  
46  
47 734 session on the remote monitoring, up as the source of information about the participant's health, can  
48  
49 735 result in the ignorance of aspects of the participant's health that cannot easily be monitored.<sup>93</sup>

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51  
52 736 Therapeutic patient education has been suggested to increase physical activity level in patients with  
53  
54 737 chronic diseases<sup>46</sup> and to improve multiple health outcomes, together with behavioural interventions  
55  
56 738 including physical activity.<sup>95</sup> Therapeutic patient education interventions might be promising for  
57  
58 739 promoting a physically active lifestyle in cancer patients as it helps patients establish lifestyle changes  
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2  
3 740 and reinforce self-management.<sup>95</sup> Therapeutic patient education differs from traditional patient  
4  
5 741 education in its intrinsic structure. Traditional patient education is directed towards informing and  
6  
7 742 teaching patients how to manage their condition or disease. In contrast, therapeutic patient education  
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9  
10 743 differs from traditional patient education in the self-management conferred on the patient.<sup>40</sup>  
11  
12 744 Therefore, therapeutic patient education is more broadly directed towards how the patient accepts  
13  
14 745 his/her condition and manages his/her problems on a daily basis and the impact of the disease on  
15  
16 746 personal, family, professional and social life. Yet, in oncology, few therapeutic patient education  
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18 747 studies targeting pain, fatigue, toxicities or treatment adherence are ongoing, and evaluations are  
19  
20 748 rarely conducted.<sup>41</sup> To our knowledge, only one program of therapeutic patient education specific to  
21  
22 749 physical activity has been evaluated in cancer patients.<sup>45</sup> However, a recent qualitative study has  
23  
24 750 shown the value of therapeutic patient education on the attitudes towards the physical activity of  
25  
26 751 women with breast cancer to promote regular exercise, which is a guarantee of a better quality of  
27  
28  
29 752 life.<sup>96</sup>

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31  
32 753 In order to evaluate the efficacy of two interventions in the DISCO trial, the primary outcome  
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34 754 measure will be based on the physical activity level of the participants with or without interventions  
35  
36 755 compared to international recommendations. The RPAQ questionnaire will be used for the primary  
37  
38 756 outcome measure on account of its easy implementation. The authors acknowledge that this  
39  
40 757 declarative evaluation confers methodological limits to the study. But the RPAQ questionnaire has  
41  
42 758 been validated against objective methods (i.e., combined accelerometry and heart rate monitoring)<sup>67</sup>  
43  
44 759 to evaluate moderate-to-vigorous physical activities, which is relevant for the primary outcome. No  
45  
46 760 objective measures of physical activity have been planned because of organisational and logistic  
47  
48 761 difficulties to equip and follow participants for one week (i.e., the usual duration of monitoring with  
49  
50 762 an accelerometer such as Actigraph™).<sup>97</sup> Such a test would even be particularly overwhelming for  
51  
52 763 cancer patients during the demanding period of adjuvant treatment onset. Additionally, the number  
53  
54 764 of daily steps reported by the activity tracker was not chosen as the primary outcome because the  
55  
56 765 activity tracker used in the study was not validated for monitoring physical activity in research or for  
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2  
3 766 medical purposes when the study was designed, although its reliability was evaluated against other  
4  
5 767 devices (data not shown). However, recently the performance and reliability of smart devices tend to  
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7 768 be increasingly validated.<sup>98</sup>  
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9

10 769 To understand the results of the DISCO clinical study, it is essential to study beliefs about connected  
11  
12 770 devices and their appropriation by the patients, particularly to understand why behaviours of the  
13  
14 771 patients tend to fade over time. In therapeutic education, beliefs and representations are essential to  
15  
16 772 the success of the intervention. Moreover, with the connected devices, only technical dimensions are  
17  
18 773 not sufficient to understand and highlight why individuals adopt or misuse the connected devices.<sup>73,74</sup>  
19  
20

21 774 There is still limited evidence or contrasting conclusions surrounding the cost-effectiveness of  
22  
23 775 interventions promoting physical activity among women with breast cancer from studies conducted in  
24  
25 776 France, the Netherland and Australia.<sup>99-104</sup> In various chronic conditions other than cancer, there is  
26  
27 777 now clear evidence in favour of exercise-based programs for the treatment of various chronic  
28  
29 778 conditions such as musculoskeletal, rheumatologic disorders, and cardiovascular diseases.<sup>105</sup> As more  
30  
31 779 research is needed to evaluate the cost-effectiveness of physical activity in the treatment of cancers,  
32  
33 780 particularly breast cancer, the economic evaluation planned in the DISCO trial will fill in the gap by  
34  
35 781 adding useful information.  
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39 782 In conclusion, the study findings will provide valuable information on the efficacy of exercise  
40  
41 783 interventions during breast cancer treatments, overcoming current barriers of access to facilities. They  
42  
43 784 will further guide the development of evidence-based innovative interventions, to systematically  
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45 785 include physical activity in the breast cancer care process. Finally, the economic evaluation planned in  
46  
47 786 the DISCO trial will provide useful information for decision-makers.  
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51 787  
52 788 **Supplementary file 1:** SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol.  
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54 789 **Supplementary file 2:** English language example of the patient consent  
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1  
2  
3 791 **Abbreviations**  
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5 792 BMI: body mass index;

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7 793 eCRF: electronic case report form;

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9  
10 794 EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-Of-Life  
11  
12 795 Questionnaire;

13  
14 796 EPICES: Evaluation of Deprivation and Inequalities in Health Examination Centres (questionnaire);

15  
16 797 ITT: intent-to-treat;

17  
18 798 MET: metabolic equivalent of task;

19  
20 799 PFS-12: Piper Fatigue Scale-12;

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23 800 RPAQ: Recent Physical Activity Questionnaire;

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25 801 WHO: World Health Organization;

26  
27 802 6MWT: six-minute walk test.  
28  
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30 803

31  
32 804 **Acknowledgments**  
33

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52 813 **Authors' contributions**  
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54 814 BFe (principal investigator), MT, LD and TD conceived the study. BFe and MT obtained funding for the  
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56 815 research. BFe, MT, BFo and OP designed the protocol. DP and OP conceived the methodological  
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58 816 aspects of the trial. BFe, MT, BFo, LD, FF, SP and TD conceived the connected device and exercise  
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37 833 **Ethics approval**

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44 837 **References**

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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
<b>Demographic and clinical data</b>	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
<b>Anthropometrics</b>				
- 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
<b>Physical fitness</b>		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			
<b>Physical activity level, sitting time and achievement of physical activity recommendations</b>	RPAQ Questionnaire	X	X	X
<b>Patient-reported outcomes</b>				
- 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
<b>Determinants of physical activity</b>				
- 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
<b>Biological data</b>	Blood sample	X	X	
- Serum endocrine factors (IGF-1, insulin, estradiol)				

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

1159 Notes. 6MWT: six-minute walk test

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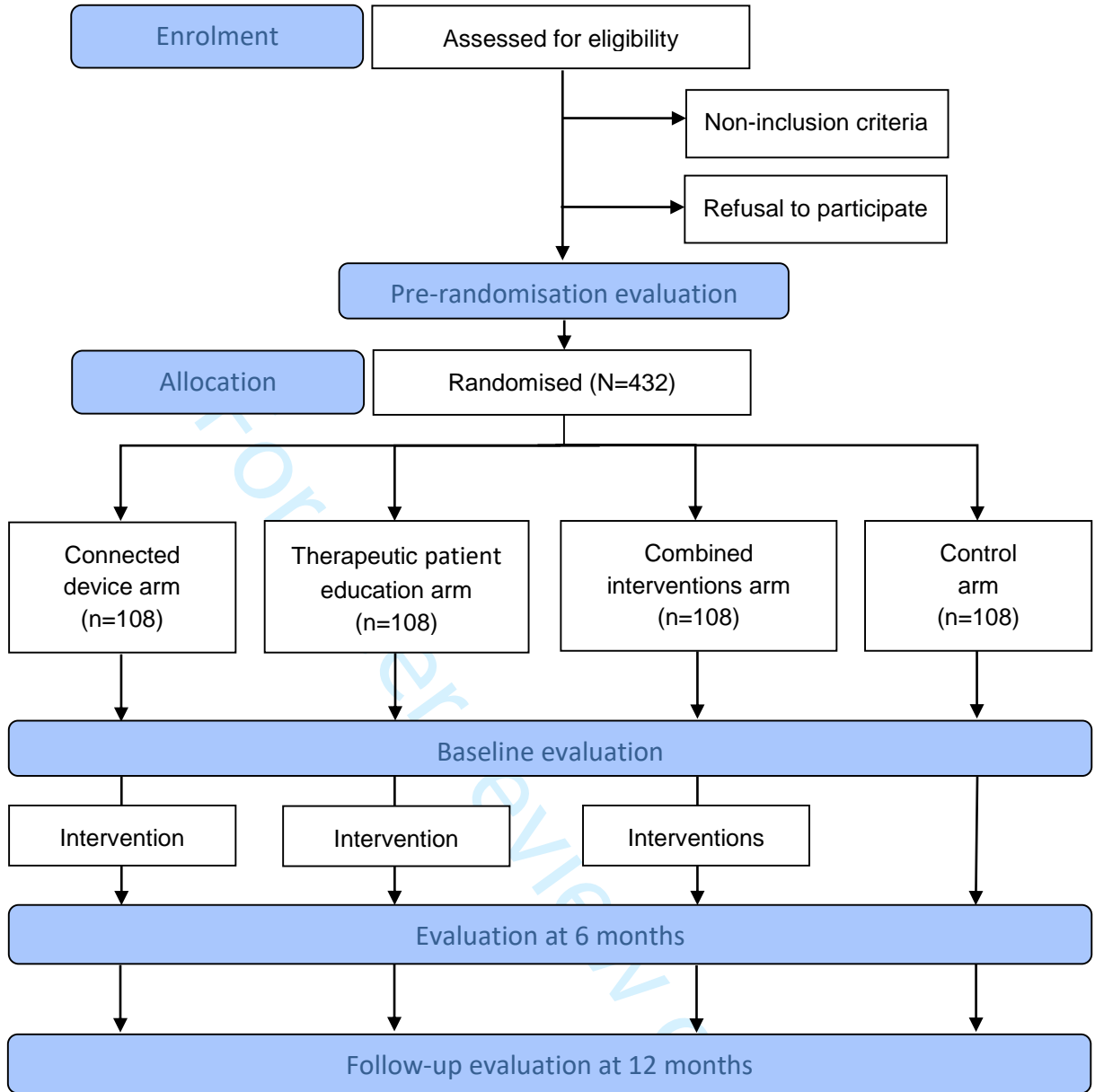
For peer review only

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3 1161 **Figure 1** Flow chart of participants through the DISCO trial.  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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_____

1	<b>Introduction</b>			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	7_____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	7_____
7				
8	Objectives	7	Specific objectives or hypotheses	7_____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8_____
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	8_____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	8-9_____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	9-15_____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	12-13_____
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	13-14_____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A_____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	17, Table 1__
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	9, 16-17, Figure1,
39			participants. A schematic diagram is highly recommended (see Figure)	Table1__
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1	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_____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8_____
5				
6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7				
8	Allocation:			
9				
10	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_____
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16	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_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_____
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_____
28				
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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_____
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39		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_____
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1	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_____
2				
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5	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_____
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10, 23-24_____
9				
10		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_____
11				
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14 **Methods: Monitoring**

15				
16	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_____
17				
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22		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_____
23				
24				
25	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_____
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25_____
29				
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32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 25-26, 32__
35				
36				
37	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_____
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A_____
5				
6				
7	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_____
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9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32_____
11				
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13	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_____
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16	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_____
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20	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_____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	31_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A_____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9, Suppl file 2 ___
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33				
34	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_____
35				
36				

\*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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) 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](mailto: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**

**Surname, first name:** \_\_\_\_\_

**Done in:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Patient's signature:**

### **The Investigator**

**Surname, first name:** \_\_\_\_\_

**Done in:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Physician's signature:**