PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Touillaud, Marina; Fournier, Baptiste; Pérol, Olivia; Delrieu, Lidia; Maire, Aurélia; Belladame, Elodie; Pérol, David; Perrier, Lionel; Preau, Marie; LEROY, Tanguy; Fassier, Jean-Baptiste; Fillol, Florie; Pascal, Sébastien; Durand, Thierry; Fervers, Béatrice

VERSION 1 – REVIEW

REVIEWER	Joaquim, Ana Centro Hospitalar de Vila Nova de Gaia Espinho EPE
REVIEW RETURNED	06-Dec-2020

GENERAL COMMENTS	I think it's important to explain how the international recomendations are going to be recomended (verbally, with a flyer, etc). In the figure 1, in the flowchart, before the randomization, it should be counted, also, the reffusing patients. I would also like to know why the curable inflamatory breast cancer (the T4d tumors) is an exclusion criteria? In the adjuvant treatments, are you considering the anti-HER2 for the HER2 tumors, like trastuzumab, pertuzumab and TDM1? How will be monitorized the adverse events and with wich grading system? How will be managed the adverse events? I don't think the only adverse events to report are neuropathies and joint pain. We are talking of patients who may be treated with anthracyclines, anti HER2 and left wall thoracic radiotherapy... those that the American Heart Association considers of risk to cardiovascular complications (vide their position paper of 2019 on the Cardio-oncology rehabilitation). So, I think other adverse events, such as cardiac, respiratory and, also, from others systems, must be recorded, just like in the clinical trials of any medication. Why do you use both the EORTC QLQ and the 5Q-5D-5L questionnaires for the Health Related Quality of Life? It seemed to me that you will not compare the control arm with any of the interventions... why?

REVIEWER	Campbell, Kristin University of British Columbia, Department of Physical Therapy
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	Line 122: Consider adding one additional sentence on the limitations of research to date on therapeutic patient education in the breast cancer and exercise context. This is a key argument for why the trial needs to be done and the reader is not clear on what the gap is. Line 123 - 129 - is this a separate paragraph? It seems odd to go from therapeutic patient education into biological mechanisms with no transition. Also this information seems a bit out of place. The trial is focused on increasing physical activity levels, and this is linked to survival outcomes but consider providing this insight earlier in the background (around line 95) and potentially reduce the text. Distracts reader from thread of the argument for why the trial is needed. Or if biomarkers are being collected, which it appears they are once you read to line 369, a more robust paragraph on what is known about impact of physical activity during adjuvant treatment on these biomarkers is warranted such that reader can understand what is be collected and why, and what the gap is that these biomarkers will help to answer. Line 133 – consider alternate word to “propose”, maybe “encourage engagement in exercise”….. and consider one line that defines physical activity and exercise somewhere in the background so the distinction is clear to the reader, or use one term only. Line 144 – Meeting the physical activity guidelines for health from WHO are outlined as the aim of the intervention. Consider adding one statement about why the current international physical activity guidelines to manage common side effects of cancer treatment (published by ACSM) is not the goal for the individuals while on treatment. Methods Overall – tense used for statements could be confusing. Recruitment stated in 2018, but all the language is written in future tense, as “will be”. Consider reconciling this by including status of when recruitment started perhaps later in the manuscript perhaps the start of the discussion as no data about recruitment to date is provided. Line 166 – what is the rationale for only on session of muscle strengthening per week? This is less than that stated WHO Guidelines? Line 175 – consider another word for “be realized”; perhaps “that present at one of the investigating centres”. Line 191 – eligibility criteria – consider what questions will be asked for the criteria “of childbearing age without effective contraception for the duration of the study”. This may result needlessly in lower recruitment rates; review cost/risk balance of this criteria if recruitment has been a challenge. Line 223 – consider change form “will benefit from” to “will receive”; it is hypothesized that there will be benefit but not the goal of this statement from my point of view. It is explaining what the individuals in this group will receive. Line 229 – “structured physical activity settings” – is this exercise or physical activity; the terms are being used interchangeably. Line 2248- 256: Interesting approach to individualizing the exercise program, can more detail be provided on how the “groups” will inform the exercise prescription provided to an individual? Stated later the target will be 3,000 steps at program onset. Line 271 – any insight on how the intervention will be progressive? Line 332 – is this education session completed in-person? Consider stating this.

	Line 354 – no information on how adherence will be calculated is provided in the methods; add this information so this secondary outcome can be assessed by readers. Line 378 – no information on how the cost effectiveness data will be collected is provided in the protocol. This then appears at Line 580 – why is this not part of the data analysis section? Line 397 – Data collection section is placed in an odd section after aims; if this is the template of why reporting is required that is fine, but distracting to read about cost-effectiveness and biomarkers with no prior information on how this data will be collected. Line 535 – is there any loss to follow up (10-20%) accounted for in the sample size calculation? Line 678 – "ensuring" versus insuring. Consider a thorough review for English spelling and phrases. Overall good, but a few areas

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ana Joaquim, Centro Hospitalar de Vila Nova de Gaia Espinho EPE
Comments to the Author:
I think it's important to explain how the international recomendations are going to be recomended (verbally, with a flyer, etc).

Answer 3: The physical activity recommendations are delivered orally with the help of a leaflet. This has been added on lines 242-243.

In the figure 1, in the flowchart, before the randomization, it should be counted, also, the reffusing patients.

Answer 4: In the flowchart, a box "Refusal to participate" has been added before randomization.

I would also like to know why the curable inflamatory breast cancer (the T4d tumors) is an exclusion criteria?

Answer 5: Inflammatory breast cancers are always treated with neoadjuvant chemotherapy and had been excluded at first when women receiving adjuvant treatment were considered for this protocol. When we decided to make women receiving neoadjuvant chemotherapy eligible, we did not re-include inflammatory breast cancer because it is an uncommon, very specific and aggressive tumour that is often detected at an advanced stage (with a very high rate of initially metastatic tumours at diagnosis), which would introduce heterogeneity in the sample.

In the adjuvant treatments, are you considering the anti-HER2 for the HER2 tumors, like trastuzumab, pertuzumab and TDM1?

Answer 6: The anti-HER2 for the HER2 tumors, like trastuzumab, pertuzumab and TDM1, are recorded in the therapeutic data as part of adjuvant treatments when they are taken combined to chemotherapy, hormonotherapy or radiotherapy. For inclusion purposes, chemotherapy,

hormonotherapy and radiotherapy are considered as adjuvant treatment (as specified in part ‘Eligibility criteria for participants’, line 193), but anti-HER2 alone is not.

How will be monitorized the adverse events and with wich grading system?
How will be managed the adverse events?
I don't think the only adverse events to report are neuropathies and joint pain. We are talking of patients who may be treated with anthracyclines, anti HER2 and left wall thoracic radiotherapy... those that the American Heart Association considers of risk to cardiovascular complications (vide their position paper of 2019 on the Cardio-oncology rehabilitation). So, I think other adverse events, such as cardiac, respiratory and, also, from others systems, must be recorded, just like in the clinical trials of any medication.

Answer 7: Details on the management of adverse events have been added in the Adverse Events section (lines 697-703). Because this study is considered as “intervention research with minimal risks and constraints” (category 2 in the French legislation), only adverse events arising within the framework of the study will be reported. In particular, adverse events related to cancer therapeutics (chemotherapy, radiotherapy, …) will not be recorded as they would not be related to the interventions and not be useful to test the efficacy of the interventions.

Why do you use both the EORTC QLQ and the 5Q-5D-5L questionnaires for the Health Related Quality of Life?

Answer 8: The EORTC QLQ-C30 and its BR-23 module are used for specific scores of quality of life, including functioning and symptoms domains. As it is a widely used questionnaire, it will allow comparisons to other populations on multiple dimensions. The 5Q-5D-5L evaluates five dimensions that are specifically used for the cost-effectiveness analysis and will also allow comparisons to other studies.

It seemed to me that you will not compare the control arm with any of the interventions... why?

Answer 9: The 2×2 factorial design will allow testing the efficacy of each intervention (compared to without that intervention) and the interest of the combination of the two interventions compared to each intervention alone (as mentioned on lines 635-640). Indeed, the control group is not compared alone and this plan does not allow a direct comparison between the two interventions. However, the control group contributes to testing the efficacy of each intervention and this type of experimental design has the advantage of ensuring a higher statistical power than in a classic trial with three arms (intervention A, intervention B and standard care, where the standard care arm would be used for two comparisons). As a consequence of higher power, this design allows to test the efficacy of two interventions instead of one with a similar sample size.

Reviewer: 2
Dr. Kristin Campbell, University of British Columbia
Comments to the Author:
Line 122: Consider adding one additional sentence on the limitations of research to date on therapeutic patient education in the breast cancer and exercise context. This is a key argument for why the trial needs to be done and the reader is not clear on what the gap is.

Answer 10: A sentence has been added on lines 131-132.

Line 123 - 129 - is this a separate paragraph? It seems odd to go from therapeutic patient education into biological mechanisms with no transition. Also this information seems a bit out of place. The trial is focused on increasing physical activity levels, and this is linked to survival outcomes but consider providing this insight earlier in the background (around line 95) and potentially reduce the text. Distracts reader from thread of the argument for why the trial is needed. Or if biomarkers are being collected, which it appears they are once you read to line 369, a more robust paragraph on what is known about impact of physical activity during adjuvant treatment on these biomarkers is warranted such that reader can understand what is be collected and why, and what the gap is that these biomarkers will help to answer.

Answer 11: This is a separate paragraph, although the layout did not make it appear (the previous paragraph ended at the end of the line); an indentation has been added on the first line of each paragraph. The knowledge of the impact of physical activity on these biomarkers and how it can help understanding effects on the disease have been developed in the paragraph (lines 134-147, line 562).

Line 133 – consider alternate word to “propose”, maybe “encourage engagement in exercise”….. and consider one line that defines physical activity and exercise somewhere in the background so the distinction is clear to the reader, or use one term only.

Answer 12: “Propose exercise” has been changed into “encourage engagement in exercise” as suggested (line 152).
Also, a definition of physical activity and exercise has been added in the Introduction section, lines 91-94: “Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, including any daily life activity of household, occupation, recreation (e.g., sports) or transportation. Exercise is a subset of physical activity that is planned, structured and repetitive, in the purpose of improving or maintaining physical fitness.”
The use of the term exercise has been modified when needed (line 105, also see Answer 19).

Line 144 – Meeting the physical activity guidelines for health from WHO are outlined as the aim of the intervention. Consider adding one statement about why the current international physical activity guidelines to manage common side effects of cancer treatment (published by ACSM) is not the goal for the individuals while on treatment.

Answer 13: The international WHO recommendations for physical activity were applied at the time the study protocol was developed and submitted for regulatory authorization, that is in 2017, before the ACSM roundtable in 2018 et the publication of the recommendations in 2019 (Campbell et al. 2019, Patel et al. 2019). A statement has been added on line 164.

Methods
Overall – tense used for statements could be confusing. Recruitment stated in 2018, but all the language is written in future tense, as “will be”. Consider reconciling this by including status of when recruitment started perhaps later in the manuscript perhaps the start of the discussion as no data about recruitment to date is provided.

Answer 14: A sentence has been added with the status of recruitment at the beginning of the discussion (lines 744-5): “This multicentre study opened in May 2018 and recruitment is expected to end in Summer 2021.”

Line 166 – what is the rationale for only on session of muscle strengthening per week? This is less than that stated WHO Guidelines?

Answer 15: The exercise program includes three structured sessions per week, including two walking sessions and one muscular strength session, to leave a day off between sessions for after-exercise recovery. Two walking sessions were favoured because there are easy to do in the daily life of cancer patients and walking mixes both aerobic and muscular strength of lower limbs.

Line 175 – consider another word for “be realized”; perhaps “that present at one of the investigating centres”.

Answer 16: The text has been modified accordingly (lines 197).

Line 191 – eligibility criteria – consider what questions will be asked for the criteria “of childbearing age without effective contraception for the duration of the study”. This may result needlessly in lower recruitment rates; review cost/risk balance of this criteria if recruitment has been a challenge.

Answer 17: We ask each patient if she is on contraception and intends to remain on it for at least one year (duration of the study). This criterion was not added to protect the patient and the baby (because this is not a therapeutic study), but to limit the bias due to the impact of pregnancy on the practice of physical activity. The study is ongoing and this non-inclusion criterium is not limiting recruitment as only 0,2% of screened patients have been concerned so far.

Line 223 – consider change form “will benefit from” to “will receive”; it is hypothesized that there will be benefit but not the goal of this statement from my point of view. It is explaining what the individuals in this group will receive.

Answer 18: The text has been modified accordingly (text line 241 and abstract line 41).

Line 229 – “structured physical activity settings” – is this exercise or physical activity; the terms are being used interchangeably.

Answer 19: “physical activity” has been changed into “exercise” on lines 252-255 (also, see Answer 12).

Line 2248- 256: Interesting approach to individualizing the exercise program, can more detail be provided on how the “groups” will inform the exercise prescription provided to an individual? Stated later the target will be 3,000 steps at program onset.

Answer 20: The aerobic and muscular strength level categories determined at inclusion are used to set up the levels of the first walking and muscle strengthening sessions, as indicated later on line 292. For adding clarity to lines 272-281 (formerly 248-256), a sentence has been added on line 281-284: “The level categories assigned will be entered by the exercise instructor in the baseline patient profile and will be used by the automated algorithm to set up the level of the first walking and muscle strengthening sessions”.

Similarly, the target number of daily steps is set up at 3,000 at day 1, then will be personalized based on the average number of steps of the first week, then will evolve automatically every 3 weeks depending on the patient's average number of steps (see lines 322-326).
Also, the text has been modified for more precision:
line 274, "categories" was added in "muscular strength level categories";
line 280, "percentiles" was changed into "interquartile range".

Line 271 – any insight on how the intervention will be progressive?

Answer 21: The algorithm has the sessions evolved in an individualized manner to follow the principles of exercise training and progression. The sentence has been developed on lines 303-305: "…in an adapted and progressive manner by increasing duration and then intensity in accordance with principles of exercise training and progression".

Line 332 – is this education session completed in-person? Consider stating this.

Answer 22: Indeed, the session is completed face-to-face. This has been added on line 364.

Line 354 – no information on how adherence will be calculated is provided in the methods; add this information so this secondary outcome can be assessed by readers.

Answer 23: A paragraph has been added on lines 547-554:
"Compliance with interventions
Compliance with each intervention will be assessed at the 6-month evaluation only for patients randomized to the "connected device", "therapeutic patient education" and "combined" arms. Compliance will be assessed by the number of days of use of the activity tracker, the participation rate in scheduled exercise sessions, the participation rate in scheduled therapeutic education sessions and the proportion of compliant patients, depending on the intervention allocated, following the recommendations of the protocol. Patients' compliance and reasons for non-compliance during the intervention period (6 months) will be described for each arm."

Line 378 – no information on how the cost effectiveness data will be collected is provided in the protocol. This then appears at Line 580 – why is this not part of the data analysis section?

Answer 24: More information on cost effectiveness data collection have been added in the "Medico-economic analysis" section (lines 666-681).

Line 397 – Data collection section is placed in an odd section after aims; if this is the template of why reporting is required that is fine, but distracting to read about cost-effectiveness and biomarkers with no prior information on how this data will be collected.

Answer 25: The Study Outcomes section (formerly starting on line 380 in the revised manuscript) has been moved after the Data Collection section (starting on line 564).

Line 535 – is there any loss to follow up (10-20%) accounted for in the sample size calculation?

Answer 26: For the intervention with connected device, the sample size calculation provides a power greater than 95%, which allows for loss to follow-up while maintaining a sufficient power. For the intervention with therapeutic patient education, the loss to follow-up was not accounted for in the sample size calculation and the authors acknowledge that this might be limiting in case of important loss to follow-up with this intervention. However, every effort is made to limit loss to follow-up, contact is attempted with women in case of no response and women often come to the hospital for their adjuvant treatment during the 6-month interventions (time frame of primary endpoint).

Line 678 – “ensuring” versus insuring.

Answer 27: insuring has been replaced by ensuring (now line 790).

Consider a thorough review for English spelling and phrases. Overall good, but a few areas

Answer 28: The manuscript has been edited for English. Changes have been done all over the manuscript.
Other modifications:
- The label of Team #2 recently changed into UMR 1296. It has been modified on line 10.
- The text on therapeutic education has been clarified on lines 807-809.

Reviewer: 1
Competing interests of Reviewer: None declared

Reviewer: 2
Competing interests of Reviewer: None

VERSION 2 – REVIEW

REVIEWER	Joaquim, Ana Centro Hospitalar de Vila Nova de Gaia Espinho EPE
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	The authors manage to improve the manuscript after the first revision and I congrat them for that. However, I still think that the adverse events should be graduated using, for example, the universal CTCAE v.5, or other graduation system that would allow their systematic identification and graduation.

VERSION 2 – AUTHOR RESPONSE

Reviewer's comment:

"The authors manage to improve the manuscript after the first revision and I congrat them for that.

However, I still think that the adverse events should be graduated using, for example, the universal CTCAE v.5, or other graduation system that would allow their systematic identification and graduation."

Author's reponse : We have taken into consideration the comment of the reviewer. The adverse events will be graduated according to the CTCAE v5. This information has been added to the article.

VERSION 3 – REVIEW

REVIEWER	Joaquim, Ana Centro Hospitalar de Vila Nova de Gaia Espinho EPE
REVIEW RETURNED	27-Jul-2021

GENERAL COMMENTS	Congrats. I do believe this will be a great study.