PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of the ONCO-TreC electronic diary compared with a standard paper diary to improve adherence to oral cancer therapy in patients with solid and hematological tumors: protocol for a randomized controlled trial
AUTHORS	Passardi, Alessandro; Serra, Patrizia; Caffo, Orazio; Masini, Carla; Brugugnoli, Erika; Vespignani, Roberto; Giardino, Valeria; Petracci, Elisabetta; Bartolini, Giulia; Sullo, Francesco; Anesi, Cecilia; Dianti, Marco; Eccher, Claudio; Piras, Enrico; Gios, Lorenzo; Campomori, Annalisa; Oberosler, Valentina; Forti, Stefano

VERSION 1 – REVIEW

REVIEWER	Chatelut , Etienne Institut Universitaire du Cancer Toulouse-Oncopole
REVIEW RETURNED	03-Sep-2021

GENERAL COMMENTS	The manuscript describes a planned clinical trial aimed to compare two methods to improve adherence of patients treated by oral anticancer drugs: an electronic diary vs. a paper diary (corresponding to the current practice). This manuscript is original since by looking for previous publications in BMJ Open journal using adherence[title] AND cancer, 22 references can be found but no one that describes similar protocol. However, among these 22 reference, there is the article [Santos Medeiros et al: Impact of mobile applications on adherence to cancer treatment: a systematic review and meta-analysis protocol. BMJ Open 2019 Nov 7;9(11)] which deserves probably to be cited among the (only) 21 references of the current manuscript. The manuscript and the corresponding protocol address an important issue since it is well known that adherence of oral cancer treatment is roughly not better that treatment of other chronic diseases. The main weakness of this protocol is the fact that oral cancer treatment corresponds to very heterogeneous drugs and clinical situations: targeted therapies, hormonal therapies, neo-adjuvant, adjuvant, and palliative settings ... Unbalanced characteristics regarding the drugs or the diseases between the two arms could bias the results. Did the authors consider a stratified approach? It would be interesting to justify the choice of parallel arm design in regards to a crossover design. Specific points: 1. Some sentences are poorly formulated: e.g., “no randomized trials have shown significant differences” (Page 8), thus the

	authors would likely say ".. have been perform to evaluate the difference …" ; later: "a possible benefit … from their intervention" … 2. The limit of the chosen endpoint to quantify the adherence of each included patient (i.e., residual pills) should be better justified in comparison with alternative methods, and combination of several approaches may be considered. 3. Page 7. Does the paper diary used for the control arm corresponds really to "standard clinical practice" in most of the centers? 4. The term "treatment monitoring" is used several times in the manuscript (e.g., on Page 8) without any clear signification. 5. Strangely, the reference corresponding to [Pasardi et al. submitted] (page 9) is a BMJ Open paper of 2017. 6. Not only the ONCO-TreC application should be briefly described (Page 8), but also the paper diary support.

REVIEWER	Lopes, Luciane Universidade de Sorocaba, Pharmaceutical Science
REVIEW RETURNED	12-Oct-2021

GENERAL COMMENTS	Abstract - Why the Advancing strategies title? these strategies are advanced? - The description of the method is incomplete. How will the randomization proportion be? Will it be blind? How will the statistical analysis be? Will the primary statistical analysis be based on intention to treat? - What is the primary outcome? How this will be measure? For how long? - Where is the study registration in the clinical trial or other study registration database? Introduction: - I think the authors should follow a rationale about: the condition (who will benefit from this strategy and why?); a Description of the intervention and how the intervention might work; why this trial needs to be done - The authors themselves state in the introduction that a previous study that was carried out in a prospective multicenter trial in cancer patients treated with oral anticancer drugs, the small sample size and absence of a control arm did not allow any definitive conclusions to be drawn about the efficacy of the system. - However, do you consider only the number of sites as a possible limitation of this study? how many sites are participating? are there other limitations that can overcome the previous study? - Methods - The estimated value for the power of the sample of patients to be recruited would be 136 and not 124 as the authors reported. Review information to maintain consistency. - How will the authors treat loss to follow-up if it is higher than expected? - Blinding, has not been described? How can the lack of blinding bring a result superior to previous studies? How can this interfere with performance bias? Will the allocation be blind? What is the randomization method? How will the outcome evaluator be blinded?

	- What is the follow-up time? - What are the primary and secondary outcomes? Describe how they will be accurately measured. It is not clear how the outcome will be measured in each group. - What is the definition of adherence? - Are the authors using surrogate outcomes? What outcomes in oncology matter to patients? - What clinical difference between groups will be considered? This is a superiority study so the analyzes must be done considering this aspect. Please explain how this will be considered. - If the aspects of blinding, outcomes, measurement method, loss to follow-up and analysis are not well defined, this trial will face the same problems described by the authors themselves in the introduction to previous trials. - Please use a proper checklist to describe a trial protocol appropriately: consort P etc. - It is important to state in the study whether the main investigator, second author and senior have a conflict of interest with the main intervention to be tested.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Etienne Chatelut, Institut Universitaire du Cancer Toulouse-Oncopole
Comments to the Author:
The manuscript describes a planned clinical trial aimed to compare two methods to improve adherence of patients treated by oral anticancer drugs: an electronic diary vs. a paper diary (corresponding to the current practice).
This manuscript is original since by looking for previous publications in BMJ Open journal using adherence [title] AND cancer, 22 references can be found but no one that describes similar protocol. However, among these 22 references, there is the article [Santos Medeiros et al: Impact of mobile applications on adherence to cancer treatment: a systematic review and meta-analysis protocol. BMJ Open 2019 Nov 7;9(11)] which deserves probably to be cited among the (only) 21 references of the current manuscript.
Reply: thank you for the comment; we added the reference (N 22).

The manuscript and the corresponding protocol address an important issue since it is well known that adherence of oral cancer treatment is roughly not better that treatment of other chronic diseases.
The main weakness of this protocol is the fact that oral cancer treatment corresponds to very heterogeneous drugs and clinical situations: targeted therapies, hormonal therapies, neo-adjuvant, adjuvant, and palliative settings ... Unbalanced characteristics regarding the drugs or the diseases between the two arms could bias the results. Did the authors consider a stratified approach? It would be interesting to justify the choice of parallel arm design in regards to a crossover design.
Reply: we thank the reviewer for this comment.
With regard to the use of stratified randomization, this is generally implemented to better balance two (or more) groups of interest with respect to factors known to have a large effect on the primary outcome (eg, prognostic factors), especially in trials with less than 100 patients. To date, there is no consistent evidence about factors related to non-adherence to oral anticancer therapy. Moreover, non-adherence is a complex phenomenon and drug-taking barriers (eg, treatment related adverse events – that however are not baseline factors) and patient beliefs significantly affect patient's non-compliance; more studies exploring this aspects/processes are needed. With stratified randomization, attention should be paid not only on which "prognostic" factors to use but also to both the number of

such factors and the number of their levels. A limited number of strata is recommended also for not incurring in the so-called “overstratification”, especially when stratified randomization is used together with permuted block procedures. Other than not having a clear picture of which factors play a key role in non-adherence, choosing a limited number of factors is not an easy task in a pragmatic trial, such as the proposed one, including a heterogeneous target population. For these reasons, we weighted pros and cons and opted for a permuted block unstratified procedure.
With respect to the choice of the study design worth remember that a cross-over design even if generally requires a lower sample size as compared to a parallel design, may be more complex from an organizational point of view, longer, and more problematic from a methodological point of view. Especially with respect to the latter point, patient prematurely abandoning the study (eg, due to disease progression), before the last intervention of the sequence, should be eliminated from the analysis. In this case missing imputation procedures such as the last observation carried forward, are useless. Thus, given the heterogeneous settings considered in this study (eg, adjuvant and advanced) and the belief that 6 therapy cycles (and not less) could represent an appropriate window for the evaluation of the two diaries with respect to treatment adherence, we opted for a parallel design.

Specific points:

1. Some sentences are poorly formulated: eg, “no randomized trials have shown significant differences” (Page 8), thus the authors would likely say “… have been perform to evaluate the difference …”; later: “a possible benefit … from their intervention” …
Reply: we corrected the sentences as suggested.

2. The limit of the chosen endpoint to quantify the adherence of each included patient (ie, residual pills) should be better justified in comparison with alternative methods, and combination of several approaches may be considered.
Reply: we are aware of the lack of a gold-standard measure of adherence and of a standardized definition of non adherence. Several techniques for measuring adherence exist. These include objective methods such as pill counts, electronic monitoring systems, prescription database analysis, assessment of serum and urine drug levels, self-report questionnaires, and drug diaries. In the present trial the pill count will be the tool that will address the primary endpoint, anyway we will also consider what the patients report in the electronic/paper diary and what the healthcare professionals will report in the medical record as well. For example, as stated in the “Outcome measures” paragraph, patients who take fewer tablets than prescribed due to toxicity or medical decision will be considered adherent if this decision is recorded in the medical records. We created a new paragraph (Outcome measures) to better explain the outcomes of the trial and how we will measure them (Pages 11-13).

3. Page 7. Does the paper diary used for the control arm correspond really to “standard clinical practice” in most of the centers?
Reply: the use of the paper diary is the standard clinical practice in both the oncology units that are involved in the trial, as it is a mandatory ministerial measure. The presence of the counselor is also standard practice in the 2 recruiting centers. As stated in the discussion, not all cancer centers have a counselor available and this aspect might limit the applicability of the model to the general population. Anyway, since the involved oncology units have been using the counselor for some time it did not seem ethical that the patients enrolled in the study would lose the possibility of being followed and trained as outside the trial.

4. The term “treatment monitoring” is used several times in the manuscript (eg, on Page 8) without any clear signification.
Reply: we integrated the introduction to better clarify the meaning of this term (page 6, lines 98-100).

5. Strangely, the reference corresponding to [Passardi et al. submitted] (page 9) is a BMJ Open paper of 2017.
Reply: the BMJ Open paper of 2017 was the study protocol description, while the trial results have been submitted to another Journal and currently under review (with some delay). To avoid confusion we moved the sentence [Passardi et al. submitted] at the end of the paragraph (line 124).

6. Not only the ONCO-TreC application should be briefly described (Page 8), but also the paper diary support.
Reply: thank you for the comment; we added a paragraph describing briefly the paper diary support (lines 185-188).

Reviewer: 2
Prof. Luciane Lopes, Universidade de Sorocaba Comments to the Author:

Abstract
- Why the Advancing strategies title? These strategies are advanced?
Reply: the paper title have been completely modified.

- The description of the method is incomplete. How will the randomization proportion be? Will it be blind? How will the statistical analysis be? Will the primary statistical analysis be based on intention to treat?
Reply: thank you for the comment. We modified the “Methods and analysis” section of the abstract, adding details about randomization, blinding and statistical analysis.

- What is the primary outcome? How this will be measure? For how long?
Reply: thank you for the comment. We modified the “Methods and analysis” section of the abstract adding details about the primary outcome.

- Where is the study registration in the clinical trial or other study registration database?
Reply: this information was already specified at the end of the Abstract. “Trial registration number: ClinicalTrials.gov NCT04826458”.

Introduction:
- I think the authors should follow a rationale about: the condition (who will benefit from this strategy and why?); a Description of the intervention and how the intervention might work; why this trial needs to be done
Reply: we think that the rationale is clear in the introduction: adherence is a major issue for patients receiving oral cancer treatments. mHealth is promising in improving adherence but data are still lacking. The intervention has been already described in previous publications; a brief description is present in the ONCO-TreC and paper diary paragraph (Pages 178-184). We added a brief description of the intervention also in the Abstract (introduction).

- The authors themselves state in the introduction that a previous study that was carried out in a prospective multicenter trial in cancer patients treated with oral anticancer drugs, the small sample size and absence of a control arm did not allow any definitive conclusions to be drawn about the efficacy of the system.
However, do you consider only the number of sites as a possible limitation of this study? How many sites are participating? Are there other limitations that can overcome the previous study?
Reply: the centers participating in the study are two (we added this information both in the "Abstract" and in the "Methods and analysis", lines 153-155). Another limitation of the study is the presence of a counselor that does not represent the standard in all cancer centers. We accepted the suggestion and implemented the discussion section with more details about strengths and limitations of the trial (Page 16).

Methods
- The estimated value for the power of the sample of patients to be recruited would be 136 and not 124 as the authors reported. Review information to maintain consistency.
Reply: thank you for the comment; we modified the text accordingly.

- How will the authors treat loss to follow-up if it is higher than expected?
Reply: we do not expect much patients lost to follow-up as they are recruited after they have accepted the oncologic treatment. Anyway, recruitment will continue until 124 evalable patients will be available.

- Blinding, has not been described? How can the lack of blinding bring a result superior to previous studies? How can this interfere with performance bias? Will the allocation be blind? What is the randomization method? How will the outcome evaluator be blinded?
Reply: we added these informations in the text. Given the peculiarities of study, it was not possible to implement the blinding for the patient and the clinicians. The investigators do not have access to the randomization list that is implemented through Open Clinica by the Biostatistics and Clinical Trials Unit of the study promoter (See Page 9).

- What is the follow-up time?
Reply: as reported in the protocol, the intervention will last 6 treatment cycles. Adherence data will be collected during this period of time.

- What are the primary and secondary outcomes? Describe how they will be accurately measured. It is not clear how the outcome will be measured in each group.
Reply: We added a paragraph reporting details about primary and secondary outcomes ("Outcome measures", Pages 11-13)

- What is the definition of adherence?
- Are the authors using surrogate outcomes? What outcomes in oncology matter to patients?
Reply: the definition of adherence is now reported in the "Outcome measures" paragraph. We are aware of the lack of a gold-standard measure of adherence and of a standardized definition of nonadherence. Several techniques for measuring adherence exist. These include objective methods such as pill counts, electronic monitoring systems, prescription database analysis, assessment of serum and urine drug levels, self-report questionnaires, and drug diaries. In the present trial, the pill count will be the tool that will address the primary outcome; anyway, we will also consider what the patients report in the electronic/paper diary and what the healthcare professionals will report in the medical record as well. For example, as stated in the statistical analysis paragraph, patients who take fewer tablets than prescribed due to toxicity or medical decision will be considered adherent if this decision is recorded in the medical records.

- What clinical difference between groups will be considered? This is a superiority study so the analyzes must be done considering this aspect. Please explain how this will be considered.
Reply: This information can be found in the “Statistical analysis” paragraph. We added them also in the abstract.

- If the aspects of blinding, outcomes, measurement method, loss to follow-up and analysis are not well defined, this trial will face the same problems described by the authors themselves in the introduction to previous trials.
Reply: thank you for this important contribution. We hope that, after the above clarifications as well as the changes made to the manuscript, these aspects will be clearer.

- Please use a proper checklist to describe a trial protocol appropriately: consort P etc.
Reply: we included the Spirit checklist.

- It is important to state in the study whether the main investigator, second author and senior have a conflict of interest with the main intervention to be tested.
Reply: we confirm that there is no conflict of interest to be declared, as stated at page 17.

VERSION 2 – REVIEW

REVIEWER	Chatelut , Etienne Institut Universitaire du Cancer Toulouse-Oncopole
REVIEW RETURNED	15-Nov-2021

GENERAL COMMENTS	Authors revised adequately the manuscript.