PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	THE MyPal Adult STUDY PROTOCOL: A RANDOMIZED CLINICAL TRIAL OF THE MyPal ePRO-BASED EARLY PALLIATIVE CARE SYSTEM IN ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES
AUTHORS	Scarfò, Lydia; Karamanidou, Christina; Doubek, Michael; Garani-Papadatos, Tina; Didi, Jana; Pontikoglou, Charalampos; Ling, J.; Payne, Cathy; Papadaki, Helen A.; Rosenquist, Richard; Stavroyianni, Niki; Payne, Sheila; Ghia, Paolo; Natsiavas, Pantelis; Maramis, Christos; Stamatopoulos, Kostas

VERSION 1 – REVIEW

REVIEWER	Krakauer, Eric Harvard Medical School
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	Confidential information should be protected better. The protocol states that links to the identity of study participants are not possible, but elsewhere it states that such links will indeed exist. It mentions a number of people who will have access to the codes to identify research subjects. The protocol should: 1) reduce to absolute minimum the number of persons who will have access to the code (ideally ONLY the PI), and 2) State in the consent forms who will have access to the code. The protocol also should state specifically which RECs (IRBs) will review the protocol and that the study will not proceed unless the REC at each involved institution approves the same protocol. Finally, the consent form should state that one disadvantage of being in the intervention group might be the weekly and monthly notifications that could be perceived as bothersome.

REVIEWER	Taylor, Sally The Christie NHS Foundation Trust, Christie Patient Centred Research
REVIEW RETURNED	25-May-2021

GENERAL COMMENTS	The authors present the protocol of an interesting and worthwhile study. The study is well designed and using appropriate methodology. Generally the manuscript is well written, there are just a few minor areas where the text could be updated to improve clarity. Page 5, lines 42-46 do not read well and would benefit from rewording

	Page 5, line 57. The authors refer to PROs playing a role in palliative care by improving the quality, efficiency and availability. The use of PROs may improve quality and efficiency of palliative care although the reference mentioned does not seem to support this. The Temel paper explores the impact of early palliative care versus standard care but does not seem to include PROs as part of this intervention. I am unsure how the use of PROs would play a role in improving the availability of palliative care. Accurate references are needed to support the points made in this sentence. Page 6, lines 5-7 do not read well and would benefit from rewording There are references missing on page 6 Page 19, lines 30-44. This whole paragraph is one long sentence. The section needs restructuring and should be broken down into shorter sentences as at present it is difficult to follow and the point the author is trying to make is lost.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Eric Krakauer, Harvard Medical School
Comments to the Author:
Confidential information should be protected better.
REPLY: Thank you for your comments.
Indeed, we agree with patient privacy being a top priority for our MyPal consortium; the technical details regarding the specific information security measures to protect patient data have been elaborated in detail in the two Data Protection Impact Assessments (DPIAs) which are explicitly mentioned in the manuscript in the following snippet:
The privacy-by-design paradigm [27] has been employed to install appropriate data protection measures as early as possible in the development of the MyPal platform, in compliance with the General Data Protection Regulation (EU) 2016/679 (GDPR) [28]. To this end, the necessary Data Protection Impact Assessments (DPIAs, n=2) were conducted. The first focusing on the management of data on local clinical sites (mobile apps etc.), and the second on the management of aggregated data for further analysis (anonymization of data etc.) These were thoroughly reviewed by the respective Data Protection Officers (DPOs). The data protection security measures include (1) the storage of personally identifiable data only in the premises of clinical sites, (2) role-based data access, (3) password encryption, (4) use of the OAuth protocol (to minimize password-based authentication whenever possible), (5) network data transfer via the secure HTTPs protocol, etc.

The protocol states that links to the identity of study participants are not possible, but elsewhere it states that such links will indeed exist.
REPLY: We apologize for creating confusion on this. Indeed, the link between the ID of the patient used in the context of MyPal study and the patient identification information (name, address, age etc.) exists, but this link never leaves the local clinical site environment. This has now been clarified in the manuscript (page 15, row 28).

It mentions a number of people who will have access to the codes to identify research subjects. The protocol should: 1) reduce to absolute minimum the number of persons who will have access to the code (ideally ONLY the PI), and 2) State in the consent forms who will have access to the code.

REPLY: We thank the reviewer for giving us the opportunity to clarify this issue which is of utmost importance for all of us. The code/patient ID exposure does not by any means imply a privacy risk for the patient per se. It is an ID identifying the patient data record per se and does not by any means contain information which could identify the patient as a person. As such, the MyPal consortium decided that there is no need to explicitly mention it in the consent form as it could also lead to more confusion to the patient. This decision was also validated by the respective Data Protection Officer (an independent consultant) who validated the respective DPIAs and the respective consent forms.

The protocol also should state specifically which RECs (IRBs) will review the protocol and that the study will not proceed unless the REC at each involved institution approves the same protocol.
REPLY: The MyPal Adult study protocol has been reviewed by the respective REC/RIBs in all the MyPal clinical sites. This is reported in the manuscript (Page 3 and 21) as follows: "The MyPal-Adult study protocol has received ethical approval from the Ethics Committee of San Raffaele Hospital (05Feb2020, registry number 8/2020), the Ethics Committee of General Hospital of Thessaloniki 'George Papanikolaou' (20.5.2020, registry number 849), Ethics Committee of Karolinska Institutet (20.10.2020), Ethics Committee of the University General Hospital of Heraklion (07/15.4.2020) as well as the Ethics Committee of the University of Brno (01-120220/EK).

Finally, the consent form should state that one disadvantage of being in the intervention group might be the weekly and monthly notifications that could be perceived as bothersome.
REPLY: Thank you for pointing this out. The repeated notifications were not considered as risks or burdens but as characterizing part of the methodology which is indeed the subject of the study. On this, the patient has been and will be informed in detail by the respective clinician before registering. The MyPal consortium aimed at providing a consent form which would keep a balance between the provided information to sufficiently inform the patient/end user for the respective risks and burdens while also keeping the consent form to a reasonable length to maintain readability, thus we deliberately avoided repeating each detail in the consent form.

Reviewer: 2
Dr. Sally Taylor, The Christie NHS Foundation Trust
Comments to the Author:
The authors present the protocol of an interesting and worthwhile study. The study is well designed and using appropriate methodology. Generally the manuscript is well written, there are just a few minor areas where the text could be updated to improve clarity.

Page 5, lines 42-46 do not read well and would benefit from rewording.
REPLY: thank you for your suggestion, this has been now rephrased.

Page 5, line 57. The authors refer to PROs playing a role in palliative care by improving the quality, efficiency and availability. The use of PROs may improve quality and efficiency of palliative care although the reference mentioned does not seem to support this. The Temel paper explores the impact of early palliative care versus standard care but does not seem to include PROs as part of this intervention. I am unsure how the use of PROs would play a role in improving the availability of palliative care. Accurate references are needed to support the points made in this sentence.
REPLY: This sentence has now been rephrased in order to improve its accuracy and a more appropriate reference has replaced Temel et al. There is evidence that PROs are indeed improving the quality of palliative care and this has now been clarified to specify 'facilitation of physician –patient communication' and 'symptom management'.

Page 6, lines 5-7 do not read well and would benefit from rewording
REPLY: thank you for your suggestion, this has been now rephrased.

There are references missing on page 6.
REPLY: we apologize for the inconvenience. We have now fixed them.

Page 19, lines 30-44. This whole paragraph is one long sentence. The section needs restructuring and should be broken down into shorter sentences as at present it is difficult to follow and the point the author is trying to make is lost.
REPLY: thank you for your suggestion, this has been now rephrased.