PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	RATIONALE AND DESIGN OF THE CV-PREVITAL STUDY: AN ITALIAN MULTIPLE COHORT RANDOMISED CONTROLLED TRIAL INVESTIGATING INNOVATIVE DIGITAL STRATEGIES IN PRIMARY CARDIOVASCULAR PREVENTION
AUTHORS	Baldassarre, Damiano; Iacoviello, Licia; Baetta, Roberta; Roncaglioni, Maria; Condorelli, Gianluigi; Remuzzi, Giuseppe; Gensini, Gianfranco; Frati, Luigi; Ricciardi, Walter; Conaldi, Pier Giulio; Uccelli, Antonio; Blandini, Fabio; Bosari, Silvano; Scambia, Giovanni; Fini, Massimo; Di Malta, Antonio; Amato, Mauro; Veglia, Fabrizio; Bonomi, Alice; Klersy, Catherine; Colazzo, Francesca; Pengo, Martino; Gorini, Francesca; Auteri, Luciana; Ferrante, Giuseppe; Baviera, Marta; Ambrosio, Giuseppe; Catapano, Alberico; Gialluisi, Alessandro; Malavazos, Alexis Elias; Castelvecchio, Serenella; Corsi, Massimiliano; Cardani, Rosanna; Rovere, Maria Teresa La; Agnese, Valentina; Pane, Bianca; Prati, Daniele; Spinardi, Laura; Liuzzo, Giovanna; Arbustini, Eloisa; Volterrani, Maurizio; Visconti, Marco; Werba, Pablo; Genovese, Stefano; Bilo, Grzegorz; Invitti, Cecilia; Di Blasio, Anna; Lombardi, Carolina; Faini, Andrea; Rosa, Debora; Ojeda-Fernández, Luisa; Foresta, Andreana; De Curtis, Amalia; Di Castelnuovo, Augusto; Scalvini, Simonetta; Pierobon, Antonia; Gorini, Alessandra; Valenti, Luca; Luzi, Livio; Racca, Annarosa; Bandi, Manuela; Tremoli, Elena; Menicanti, Lorenzo; Parati, Gianfranco; Pompilio, Giulio; Study Group, CV-PREVITAL

VERSION 1 – REVIEW

REVIEWER	Paprica, P. Alison University of Toronto, Institute for Health Policy, Management and Evaluation
REVIEW RETURNED	21-Apr-2023

GENERAL COMMENTS	Overall, the publication of the protocol is recommended, but there is some room for improvement in the study protocol itself, and way it is described in the manuscript under review. Suggestions to strengthen the study protocol/design: • From the protocol it is not clear when the trial will start and end • The authors should provide evidence and or references to justify the statement “A 10% improvement in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App) compared with the score change detected in the control group (Usual care) is regarded indicative of a clinically meaningful intervention effectiveness at short term.” • To enable the comparison of trial results with other studies that do not use the Moli-Sani score as a measure, the authors should

	commit to publishing in their findings data for all the elements of the MOLI-SCAN score, total and for each by biological sex • The text about sample size should state whether the study will have sufficient power for conclusions to be drawn between the experience of men and women participants • The rationale for sample size collection would be strengthened if the authors make explicit reference to, and incorporate, the expected loss to follow-up/ drop out rate • It is not clear from the sample size description if the ancillary studies will have sufficient power Suggestions to strengthen the manuscript: • The acronym IRCCS should be explained • As a non-Italian speaker, I could not review or provide comments on the informed consent material • There are a few minor issues with language which an expert English copyeditor or proof-reader could address and help with, for example o pg. 1 line 9 “CVD are” should be “CVDs are” o pg. 6 line 56 reads “subjects who accepts to compile the questionnaires” which I think means “subjects who agree to complete questionnaires” o pg. 9 line 57 ETICHS vs. ETHICS o most of the outcomes at the bottom of page 6 describe patient/participant outcomes, but the long-term secondary outcomes beginning on line 48 are really outputs of the projects as opposed to outcomes that will be assessed as part of the trial o the text “Participants are not eligible for the study if they: (a) refuse to sign the informed consent” should be revised to read “if they (a) do not sign…” because “refuse” could be interpreted as meaning those people are obstinate/ refusing without justification o In the sentence “The CV risk factors managed by the app include high blood pressure, dyslipidemia… “ it would be better to use a word like “monitored” because “managed” presupposes that the app will work before the trial has been completed o Similarly the sentence “Gamification logic has been proposed … to ensure people's long-term commitment to tasks…” should be revised because before the trial is completed there is no evidence that gamification logic will ensure commitment to task completion

REVIEWER	Chello, Massimo Universita Campus Bio-Medico di Roma, Cardiovascular Surgery
REVIEW RETURNED	22-Apr-2023

GENERAL COMMENTS	authors should be congratulated for their work. in my opinion, this article deserves publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 We thank the Reviewer for the positive comment and valuable suggestions, and hope to have profitably used them to improve the manuscript. For helping the review process, the sentences modified according to reviewers’ suggestions in the revised version of the manuscript are highlighted with the word track-change tool. A point-by-point response to each issue raised by the Reviewer is

given below. Suggestions to strengthen the study protocol/design: • Reviewer's comment: From the protocol it is not clear when the trial will start and end Author's reply: We thank the Reviewer for noticing this lack of information, which has now been added. Please see page 5, lines 19-20 of the tracked change manuscript file (corresponding to page 23 of the bmjopen-2023- 072040.R1 pdf file) • Reviewer's comment: The authors should provide evidence and or references to justify the statement "A 10% improvement in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App) compared with the score change detected in the control group (Usual care) is regarded indicative of a clinically meaningful intervention effectiveness at short term." Author's reply: We appreciate the reviewer for this suggestion. In order to enhance the interpretability of the Moli-Sani Risk Score (MRS), we divided it by 0.06859 before of using it. This value (0.06859) represents the natural logarithm of the hazard ratio for each additional year of age, as measured in the derivation cohort (Moli-Sani population). By employing this approach, a one-unit increase in the rescaled MRS becomes associated with the same outcome as one additional year of age at baseline. Essentially, a one-point increase in the MRS corresponds to an equivalent increase in cardiovascular risk as that of one year of age. As the MRS value increases, so does the cardiovascular risk. The median MRS value in the derivation cohort is -3. Therefore, a 2 33% reduction in the MRS is nearly equivalent to reducing the score by one unit, which corresponds to a decrease in cardiovascular risk equivalent to one year of age less at baseline. In the Moli-Sani population, one year more at baseline was associated with 6% to 8% higher rate of cardiovascular events. Then, we believe that a gain of one year can be considered a clinically meaningful intervention effectiveness in the short term. Consequently, we made the following change in the manuscript: "An improvement of one unit (approximately 33% reduction) in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App), compared to the score change observed in the control group (Usual care), is indicative of a clinically meaningful intervention effectiveness in the short term. This is because, according to the construction of the Moli-Sani risk score, a one-point improvement in the Moli-Sani risk score is equivalent (in terms of cardiovascular risk) to an increase of one year of age". Please see page 7, lines 18-26 of the tracked change manuscript file (corresponding to page 25 of the bmjopen-2023-072040.R1 pdf file). • Reviewer's comment: To enable the comparison of trial results with other studies that do not use the Moli-Sani score as a measure, the authors should commit to publishing in their findings data for all the elements of the MOLI-SCAN score, total and for each by biological sex Author's reply: We thank the reviewer for this suggestion. The essential data of the Moli-Sani Risk Score (and of its elements) needed for comparison with other studies that do not use the Moli-Sani score as a measure are indeed in the Online-Supplemental Material in the paragraph named "RISK SCORE USED AS PRIMARY OUTCOME". Comprehensive data regarding the development and validation of the Moli-Sani Risk Score are currently being reviewed for publication in a scientific peer-reviewed journal. Due to this circumstance, we face limitations in providing an extensive description of the Moli-Sani risk score in this context. We provide here the association (hazard ratio) between age, sex, and all components of the Moli-Sani Risk Score with the occurrence of fatal or non-fatal cardiovascular events. Association of age, sex and 9 modifiable risk factors with incidence of fatal or non-fatal cardiovascular events, in the Moli-Sani (derivation) cohort Non-modifiable risk factors HR* 95% CI Age (for 1 year more) 1.071 1.062 to 1.080 Men vs women 2.577 2.205 to 3.011 Modifiable risk factors No. of cigarettes (1-unit increase) 1.029 1.022 to 1.037 Mediterranean Diet score (1-point increase) 0.941 0.901 to 0.983 LDL, z-score (1-unit increase) 1.219 1.135 to 1.309 HDL, z-score (1-unit increase) 0.857 0.789 to 0.932 Triglycerides, z-score (1-unit increase) 1.015 0.941 to 1.096 Mean Arterial Pressure, z-score (1-unit increase) 1.204 1.125 to 1.289 Glucose, z-score (1-unit increase) 1.144 1.083 to 1.209 Leisure time physical activity, z-score (1-unit increase) 0.956 0.890 to 1.027 Relative Fat Mass, z-score (1-unit increase) 1.036 0.925 to 1.162 *HR means hazard ratio; CI means confidence interval; HR and 95%CI are calculated from a multivariable Cox survival regression including all the variables in the Table plus educational level (2-level variable), household income (4-level variable), body mass index (3-level variable), history of cancer (no/yes), diabetes (no/yes), hypertension (no/yes) and hyperlipidaemia (no/yes). 3 We believe that it is not necessary to add this table to the text. However, should the reviewer disagree, we are prepared

to add it to the online material. • Reviewer's comment: The text about sample size should state whether the study will have sufficient power for conclusions to be drawn between the experience of men and women participants Author's reply: Modified accordingly. Please see page 9, lines 17-18 of the tracked change manuscript file (corresponding to page 27 of the bmjopen-2023-072040.R1 pdf file) • Reviewer's comment: The rationale for sample size collection would be strengthened if the authors make explicit reference to, and incorporate, the expected loss to follow-up/drop out rate Author's reply: Modified accordingly. Please see page 9, lines 9-14 of the tracked change manuscript file (corresponding to page 27 of the bmjopen-2023-072040.R1 pdf file). • Reviewer's comment: It is not clear from the sample size description if the ancillary studies will have sufficient power Author's reply: According to the Reviewer's request, for each ancillary study additional information about of sample size has now been provided. Please see in the Ancillary Studies section of the Online Supplemental Material file. Suggestions to strengthen the manuscript: • Reviewer's comment The acronym IRCCS should be explained Author's reply: Modified accordingly thorough the text. • Reviewer's comment: As a non-Italian speaker, I could not review or provide comments on the informed consent material Author's reply: The authors apologise for forgetting to include the English version of the informed consent material. Such document has now been added as an additional supplemental file (Online Supplemental file 3b - Informed consent materials). • Reviewer's comment: There are a few minor issues with language which an expert English copyeditor or proof-reader could address and help with, for example • pg. 1 line 9 "CVD are" should be "CVDs are" • pg. 6 line 56 reads "subjects who accepts to compile the questionnaires" which I think means "subjects who agree to complete questionnaires" • pg. 9 line 57 ETICHS vs. ETHICS 4 Author's reply: As suggested by the reviewer, an editing of the entire manuscript was made to improve style and correct spelling errors. The changes made are highlighted in track change mode throughout the text. • Reviewer's comment: Most of the outcomes at the bottom of page 6 describe patient/participant outcomes, but the longterm secondary outcomes beginning on line 48 are really outputs of the projects as opposed to outcomes that will be assessed as part of the trial Author's reply: We agree with the Reviewer. The text has been modified accordingly. Please see page 7, lines 37-41 of the tracked change manuscript file (corresponding to page 25 of the bmjopen-2023-072040.R1 pdf file). • Reviewer's comment: The text "Participants are not eligible for the study if they: (a) refuse to sign the informed consent" should be revised to read "if they (a) do not sign…" because "refuse" could be interpreted as meaning those people are obstinate/ refusing without justification Author's reply: Modified accordingly. Please see page 5, line 31 of the tracked change manuscript file (corresponding to page 23 of the bmjopen-2023-072040.R1 pdf file). • Reviewer's comment: In the sentence "The CV risk factors managed by the app include high blood pressure, dyslipidemia… "it would be better to use a word like "monitored" because "managed" presupposes that the app will work before the trial has been completed Author's reply: Modified accordingly. Please see page 6, line 18 of the tracked change manuscript file (corresponding to page 24 of the bmjopen-2023-072040.R1 pdf file). • Reviewer's comment: Similarly, the sentence "Gamification logic has been proposed … to ensure people's long-term commitment to tasks…" should be revised because before the trial is completed there is no evidence that gamification logic will ensure commitment to task completion Author's reply: Modified accordingly. Please see page 6, lines 45-50 of the tracked change manuscript file (corresponding to page 24 of the bmjopen-2023-072040.R1 pdf file). Reviewer: 2 • Reviewer's comment: Authors should be congratulated for their work. in my opinion, this article deserves publication. Author's reply: We would like to thank the Reviewer for the positive comment. 5 Other • Formatting Amendments: 1. Kindly place your Patient and Public Involvement statement under Methods section on the main document. 2. Please re-upload your supplementary files in PDF format. Author's reply: Required formatting changes have been made. • Word Count The main text word count limit is 4000 words. Should the word count exceed this number, please state this in the cover letter upon submission. Author's reply: As requested, we have added a statement about word count in the cover letter. • Provide detailed contributorship statement Please provide a more detailed contributorship statement. It needs to mention all the names/initials of authors along with their specific contribution/participation for the article. This should be stating how each author contributed to the article. It should discuss on the planning, conduct and reporting of the

work in your paper. You may also consider the conception and design, acquisition of data or analysis and interpretation of data, etc. The statement in the ScholarOne system and main document should matched. Author's reply: As requested, we have added more details about contributorship in the paragraph entitled "Authors contribution".

VERSION 2 – REVIEW

REVIEWER	Paprica, P. Alison University of Toronto, Institute for Health Policy, Management and Evaluation
REVIEW RETURNED	23-Jun-2023

GENERAL COMMENTS	I think the authors for addressing my concerns from a previous review of this manuscript. I do recommend that the details of the MOLI SAN score are included as supplemental material.