PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The De-imFAR Phase II Project: A study protocol for a cluster randomized implementation trial to evaluate the effectiveness of de-implementation strategies to reduce low-value statin prescribing in the primary prevention of Cardiovascular Disease.
AUTHORS	Sanchez , Alvaro; Pijoan, Jose Ignacio; Sainz de Rozas, Rita; Lekue, Itxasne; San Vicente, Ricardo; Quindimil, Jose Antonio; Rotaeche, Rafael; Etxeberria, Arritxu; Mozo, Carmela; Martinez-Cengotitabengoa, Monica; Monge, Monica; Gómez-Ramírez, Cristina; Samper, Ricardo; Ogueta Lana, Mikel; Celorrio, Sara; Merino-Inda, Nerea; Llarena, Marta; Gonzalez Saenz de Tejada, Marta; García-Alvarez, Arturo; Grandes, Gonzalo

VERSION 1 – REVIEW

REVIEWER	Douglas Schocken Duke University, Medicine
REVIEW RETURNED	03-Oct-2023

GENERAL COMMENTS	2023 BMJO Review – MS #bmjopen - 2023 - 078692 This is a very interesting manuscript. Prevention of cardiovascular disease is a very important medical goal. A healthy lifestyle is one intervention that can contribute to CVD prevention. In this era, however, instead of prescribing a medication such as statin for everyone, PIP (preventing inappropriate prescribing) in low-risk populations might prevent both financial toxicity and non-evidence-based prescribing of statins in patients with low risk by current guidelines. The investigators have designed a four-pronged experimental approach using behavior change techniques to decrease inappropriate statin use in low-risk patients. The manuscript describes the study and presents the experimental protocol. The study employs behavioral interventions and examines the effects of three types of practitioner interventions, a non-reflective approach (presenting a variety of educational programs “Stopping low-value prescribing Campaign” without interaction with the provider), a reflective approach (presenting educational program that involves interaction with the provider), a combination educational program with components of both non-reflective and reflective approaches. In addition, all patients are provided with healthy lifestyle education. The provider component of the study is a population of primary care providers in the Basque region of Spain. The providers are members of 13 primary health organizations, The subjects are patients within those care networks. The endpoints are the changes in patient behavior at one year and two years following stratified randomization to one of the three intervention groups. Data analysis is by mixed method modeling with adjustments to address

	possible confounders. This manuscript describes the background and the protocol. The hypothesis is reasonable. Because the study has already been approved and implemented, no changes in protocol are applicable at this time, and no preliminary or final data is available. There are several problems with this manuscript. Most of these problems relate to the composition and the content. The manuscript is both too 'wordy' and not informative enough. Especially in the introduction and background, the sentences are too long and leave a sense that they were written by AI software such as Chat-gpt. Another descriptor for the composition might be 'full of redundant wording'. The authors should make their points concisely in crisp, clear language. The flow diagram (figure on P. 29) is good. The interviews described for the family practice providers are too cursory and do not focus on the specific items of interest. In manuscripts designed to describe study protocols, there must be a presentation of the details of the protocol. Those specifics are not provided in enough detail here. For example, which potential confounders are included in the mixed methods models? The informed consent process is unclear to this reviewer. Is there any blinding? How are the patient groups isolated by intent-to-treat? Sample size calculations for the patient outcomes may be reasonable but appear too ambitious. There is no description of the information collected from the very small number of physician and patient interviews. In the definition of the low-risk group from which the experimental group is recruited, how is the absence of CVD determined? The comparison sample of FPs is quite small to measure professional perception of feasibility for the study. How was that approach determined? How will the results be analyzed? The study design was facilitated by focus groups of stakeholders (patients, professionals and researchers). How were the focus groups utilized?

REVIEWER	Michelle Rockwell Virginia Polytechnic Institute & State University, Family and Community Medicine
REVIEW RETURNED	29-Nov-2023

GENERAL COMMENTS	Thank you for the opportunity to review The De-imFAR Phase II Project: A study protocol for a randomized implementation trial to 5 evaluate the effectiveness of de-implementation strategies to reduce low-value statin 6 prescribing in the primary prevention of Cardiovascular Disease. This innovative and well-designed study addresses multiple important issues, including what de-implementation strategies work best and how effective are these strategies for reducing or eliminating potentially inappropriate statin prescribing. This is a nuanced and very detailed study design that is difficult to describe concisely. Below I have recommended three

	MAJOR edits that I perceive as required to clearly communicate the protocol and assure that outcomes are being measured appropriately. I realize that the study is already underway and that few protocol changes can be made at this time. However, I suspect that the team has appropriate data for each specified evaluation domain available and the limitation is in the current description. MAJOR recommended edits- 1) The strong study design and background work are not reflected in the current manuscript as written. Some restructuring of the paper, clarification of terms, and clearer communication about what parts of the study have already been performed is needed. Many components that might typically appear in the Introduction are instead, included in Methods. Most readers will require definitions for terms used in the study. Realizing this is a big task because this study is rich in potentially unfamiliar terms, it seems essential for setting up the study. Some examples I might recommend for the introduction (even a very brief definition): 1. De-implementation 2. Implementation 3. Theoretical Domains Framework 4. Behavior Change Wheel 5. Statin 6. Non-reflective 7. Reflective 8. Decision assistance strategy (decision aid?) 9. Decision information strategy 10. Reflective decision structure strategy 11. Audit & feedback While some of these terms and corresponding study elements are described in Appendices (which is great), a brief descriptor in the text is needed. 2) I particularly appreciate the authors' graceful navigation of de-implementation and implementation language, which can be cumbersome! Further justification for using RE-AIM (an implementation framework) to evaluate de-implementation efforts is needed. Also, might it be more appropriate to say that you are using RE-AIM to evaluate the implementation of de-implementation strategies (as opposed to the effectiveness, which is just one outcome)? Importantly, on pages 12 and 13, the authors describe their approach to evaluating Reach, Adoption, Implementation, and Maintenance. First, it is unclear why Effectiveness is not included and it appears that the planned measures for Implementation should actually be classified as Effectiveness. The Implementation domain should evaluate if the intervention was delivered as intended, what adaptations were made, etc. Further, the Adoption measures described are not appropriate measures of Adoption (which should evaluate if/how the FP's used the de-implementation strategies. 3) There is no description of the methods that will be used for the qualitative analysis, nor how the quantitative and qualitative data will be integrated and analyzed. Additional recommendations: This paper describes the study protocol for a trial to examine the effectiveness and feasibility of different de-implementation strategies, so framing the introduction around de-implementation makes sense. However, additional background about the specific PIP being studied – statins for CVD prevention in low-risk patients –

	would be very helpful, in addition to a plain language interpretation of when statins are high vs. low-value. What professional recommendation informs this? What is the scope of the problem? How often does PIP statin prescribing occur in primary care? What are the potential harms of PIP of statins? Some of this is included in the Methods section but is foundational to understanding the goals and research questions. What do the recommendations advise as related to healthy lifestyle counseling? And how will the authors measure FP's provision of this? Chart review? This method should be added. Can you provide an estimate of how many FPs belong to these 13 IHOs? What is the likely n of the study? Was there a power analysis/sample size calculation? If not, explain why that was unnecessary and how it will impact analysis and interpretation. A conclusion that describes the expected impact of the study would be nice. Minor: Consider new references for #1 and 2. While these are seminal publications about healthcare quality, they don't particularly address the prevalence and impact of low-value care (particularly on a global basis as the intro sentence suggests). Intro- Paragraph 1- also potential harm Consider a figure that shows TDF and behavior change wheel Line 183- CVR? I believe this should be CVD. Line 209- can you reference "Stopping Low-Value Prescribing"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Douglas Schocken, Duke University Comments to the Author:
2023 BMJO Review – MS #bmjopen - 2023 - 078692

This is a very interesting manuscript. Prevention of cardiovascular disease is a very important medical goal. A healthy lifestyle is one intervention that can contribute to CVD prevention. In this era, however, instead of prescribing a medication such as statin for everyone, PIP (preventing inappropriate prescribing) in low-risk populations might prevent both financial toxicity and non-evidence-based prescribing of statins in patients with low risk by current guidelines. The investigators have designed a four-pronged experimental approach using behavior change techniques to decrease inappropriate statin use in low-risk patients.
The manuscript describes the study and presents the experimental protocol. The study employs behavioral interventions and examines the effects of three types of practitioner interventions, a non-reflective approach (presenting a variety of educational programs "Stopping low-value prescribing Campaign" without interaction with the provider), a reflective approach (presenting educational program that involves interaction with the provider), a combination educational program with components of both non-reflective and reflective approaches. In addition, all patients are provided with healthy lifestyle education. The provider component of the study is a population of primary care providers in the Basque region of Spain. The providers are members of 13 primary health organizations, The subjects are patients within those care networks. The endpoints are the changes in patient behavior at one year and two years following stratified randomization to one of the three

intervention groups. Data analysis is by mixed method modeling with adjustments to address possible confounders.
This manuscript describes the background and the protocol. The hypothesis is reasonable. Because the study has already been approved and implemented, no changes in protocol are applicable at this time, and no preliminary or final data is available.
There are several problems with this manuscript. Most of these problems relate to the composition and the content.
1. The manuscript is both too 'wordy' and not informative enough. Especially in the introduction and background, the sentences are too long and leave a sense that they were written by AI software such as Chat-gpt. Another descriptor for the composition might be 'full of redundant wording'. The authors should make their points concisely in crisp, clear language.
In this regard, trying to combine both the suggestions of Reviewer #1 and #2, we have carried out important changes in the layout of the manuscript. On the one hand, we have lightened

excess or repetitive content. On the other hand, we have moved contents that, although more appropriate for the introduction as Reviewer #2 points out, were in the methodology section. Given the accomplished modifications, it is advisable to carry out a detailed review based on the new documents that we send: the corrected version with tracked changes and the clean version.

2. The flow diagram (figure on P. 29) is good.
Thank you

3. A) The interviews described for the family practice providers are too cursory and do not focus on the specific items of interest. In manuscripts designed to describe study protocols, there must be a presentation of the details of the protocol. Those specifics are not provided in enough detail here.
A more detailed description of the semi-structured interviews with family physicians and patients has been included in the section "Feasibility Evaluation" (line 397) of the reviewed version of the manuscript. This description adds information regarding how the interviews will be conducted and how the analysis of the qualitative study will be performed.

Semi-structured interviews with family physicians, Line 403: "The interview script will contain open-ended questions that will focus on the perceived value of the de-implementation strategies and recommendations for their optimization."

Semi-structured interviews with patients, Line 411: "The interview script will contain open- ended questions that will focus on the perceived CVD primary prevention care received. "

Line 414:
"Both professional and patient interviews will be conducted by two researchers with experience in qualitative research methods, as well as knowledge of the clinical field and the project. The interviews will be audio-recorded, with prior informed consent, and transcribed verbatim. Regarding the analysis of the qualitative study, the responses will be extracted from the transcript of the interviews. Several members of the research team will participate in the analysis, promoting the exchange of perspectives and consensus, with the aim of triangulating the analysis. A deductive and an inductive perspective will be combined. For the deductive perspective, the discourse of each professional and patient interviewed will be associated with constructs derived from the behavior changes theories (TDF, BCW, etc.) [3, 11-13]. The inductive analysis will be based on the postulates of grounded theory [35]. Researchers will use coding techniques, or line-by-line analysis, looking for words and phrases that identify explanatory concepts. Subsequently, thematic connections between the basic theoretical concepts and the data will be developed."

B) For example, which potential confounders are included in the mixed methods models? The potential confounders that will be measured have been added in the reviewed version of the manuscript (line 388).
Line 388:
“Other study covariates
In addition, and informed by the cross-sectional observational study performed in the Phase I of the DE-imFAR study [10], potential confounders that may bias the estimated effect of the

de-implementation strategies on the change in PIP of statins will be measured, both at a) health professional level: sociodemographic variables (age, sex), baseline rate of PIP of statins; and b) patient level: socio-demographic variables (age, sex, socioeconomic status) and clinical variables (baseline cholesterol level, presence of hypertension, prescribed anti- hypertensive, tobacco use).”

4. A) The informed consent process is unclear to this reviewer
We would like to clarify that the informed consent process do only apply to the conduction of the semi-structured interviews to the selected healthcare professionals (FP) and patients as it is described for the qualitative study (line 416). The informed consent forms include information about the study and request FP and/or patient to provide their consent to carry out and audio record the interview as well as reviewing the transcripts. Please, see also page 18 (lines 489-492).
“The interviews will be audio-recorded, with prior informed consent, and transcribed verbatim” (line 416) has been add in the reviewed version of the manuscript.
These interviews will be performed once the implementation trial is finished, that is, at 12 months after exposure of the FP to the de-implementation strategies.

B) Is there any blinding?
Having reached this point at the response to the Reviewers’ comments, we would like to add the following detailed explanation that we do hope could be useful for understanding some issues raised at several Reviewers’ comments.
The DE-imFAR study is a cluster randomized implementation trial conducted under real world conditions of primary prevention of CVD in Primary Care (PC) where both clinical practices, i.e., inappropriate statin prescription and substandard promotion of healthy lifestyles, occur. The DE-imFAR study aims to evaluate the feasibility and effectiveness of a set of strategies to reduce low-value practice and increase the recommended practice of PC healthcare professionals.
To this end, the designed de-implementation strategies will be cumulatively deployed in the routine conditions of health care service provision in Osakidetza-Basque Health Service. Specifically, the decision support tools integrated in the electronic health records (EHR) (“non-reflective decision assistance strategy”) will be applied to all the family physicians (FPs) from the 13 integrated healthcare organizations (IHOs) of Osakidetza. Further, in addition to this first strategy, eligible FPs belonging to two out of the 13 IHOs (Barakaldo-Sestao and Ezkerraldea-Enkarterri-Cruces), will be randomly assigned to exposure to either the second (“decision information strategy”) or second and third (“decision information” and “reflective decision structure” strategies).
However, the evaluation of the results, taking into account the eligibility criteria, the randomization of FPs to intervention arms due to the study design, and the sample size calculation, will not be carried out in all the healthcare professionals. First, according to the professionals’ eligibility criteria, only those FPs who at baseline performed the low-value practice to some degree (potentially inappropriate statins prescription rate > 0) will be subject to evaluation. Second, it is a cluster randomized clinical trial with an additional, non- randomly generated control group in which we would like to evaluate, on the one hand, whether a strategy that additionally contains an audit/feedback system is more effective

than a strategy based on decision support tools and a campaign (experimental comparison). Thus, in the two IHOs in which the experimental trial is set up, all FPs receive the campaign in addition to the aids and it is randomly decided who also receives the audit/feedback. Hence, all FPs from these two

IHOs are informed and offered to indicate whether they would like to participate or not through an opt-out strategy. Those who agree to participate are randomly assigned to be exposed to a second ("decision information strategy") or a second- and-third strategy ("decision information strategy" and "reflective decision structure strategy"). To detect the hypothesized effect in this experimental comparison, we would only require at least 58 FPs for each of the two experimental arms.
On the other hand, we intend to evaluate whether these two experimental strategies are more effective than the strategy that relies solely on clinical decision support tools ("non- reflective decision assistance strategy"). This is an observational comparison since, as we have mentioned before, this strategy is being implemented in Osakidetza on all healthcare professionals and no one is randomly assigned to receive it. Thus, on the one hand, we will make a matched observational comparison by selecting two FPs -with the same characteristics- for each FP in the randomized arms. On the other hand, a comparison will be made between all the FPs who meet the eligibility criteria from the 11 IHOs, in which they only receive the decision support tools, and the FPs from two IHOs included in the randomized groups.
All of these contents have been clarified as suggested by both reviewers in different comments and in the reviewed version of the manuscript as follows:
Line 331:
"The DE-imFAR study is a cluster randomized implementation trial conducted under real world conditions of primary prevention of CVD in Primary Care (PC) where both clinical practices, i.e., inappropriate statin prescription and substandard promotion of healthy lifestyles, occur. The aforementioned de-implementation strategies will be cumulatively deployed in the routine conditions of health care service provision in Osakidetza to reduce the low-value practice and increase the recommended practice of PC healthcare professionals. Specifically, the decision support tools integrated in the EHR (non-reflective decision assistance strategy) will be applied to all FPs from the 13 IHOs of Osakidetza. Further, in addition to this first strategy, eligible FPs belonging to two IHOs (Barakaldo-Sestao and Ezkerraldea-Enkarterri- Cruces) will be randomly assigned to exposure to either the second (provision of decision information strategy) or second and third (provision of decision information and reflective decision structure strategies)."
Line 345:
"In all cases, FPs will only be allocated to the study groups after they have agreed to participate through an opt-out strategy."

C) How are the patient groups isolated by intent-to-treat?
We have further clarified throughout the manuscript (as well as in the title) that the DE- imFAR study is a cluster randomized implementation trial. As it was already specified in line 248: "The unit of randomization and intervention will be the primary care FP, while observation and analysis will be performed at professional and patient levels".

Regarding the isolation of patient groups by intention-to-treat (analysis at patient level), we would like to clarify that all patients who meet the eligibility criteria and who attend for consultation to their corresponding FP during the study period, will be considered in the analysis within the corresponding comparison group according to their FP allocation.

5. A) Sample size calculations for the patient outcomes may be reasonable but appear too ambitious.
As commented, we have further clarified throughout the manuscript that the study is a cluster randomized implementation trial. Thus, as explained in the "Analysis section", sample size calculation was performed at cluster level but considering both cluster size and a cluster effect (intra-class correlation coefficient) for a correct calculation of the required sample size of FPs. This calculation was focused on the "worst scenario" of the comparison between the two randomized arms. For the comparison of those randomized arms with the non- randomized one (observational comparison) we have doubled the required size of the matched comparison group.

B) There is no description of the information collected from the very small number of physician and patient interviews.
As already mentioned in point #3, we have added specific information regarding the information to be collected in the family physicians and patients semi-structured interviews in the reviewed version of the manuscript.
For family physicians: Line 403: “The interview script will contain open-ended questions that will focus on the perceived value of the de-implementation strategies and recommendations for their optimization.”

For patients: Line 411: “The interview script will contain open-ended questions that will focus on the perceived CVD primary prevention care received. “

6. In the definition of the low-risk group from which the experimental group is recruited, how is the absence of CVD determined?
The absence of cardiovascular disease (CVD) is one of the “eligibility criteria” for all the patients analyzed in the study; both in the control non-randomized group and in the experimental randomized groups.
The absence of CVD is determined by the fact that there is no registry in the patients’ Osakidetza electronic health record (EHR) of any of the following ICD-9 codes that are related to cardiovascular diseases.
List of ICD-9 codes used in our study: 042; 250; 250.0; 250.00; 250.01; 250.02; 250.03; 250.1; 250.11; 250.12; 250.13; 250.2; 250.20; 250.21; 250.30; 250.4; 250.40; 250.41; 250.42; 250.43; 250.5; 250.50; 250.51; 250.52; 250.6; 250.60; 250.61; 250.62; 250.63; 250.7; 250.70; 250.71; 250.72; 250.73; 250.8; 250.80; 250.81; 250.82; 250.9; 250.90; 250.91; 250.92; 250.93; 256.31; 272; 272.0; 272.1; 272.2; 272.4; 272.6; 272.7; 272.8; 272.9; 278.0; 278.00; 278.01; 278.02; 390; 391; 394; 395; 396; 401; 402; 403; 404; 405; 410; 411; 412; 413; 414; 415; 416; 417; 420; 422; 423; 424; 425; 426; 427; 428; 429; 430; 431; 432; 434; 435; 436; 437; 438; 440; 441; 442; 443; 444; 447; 451; 452; 453; 459; 580; 580.0; 580.4; 580.81; 580.89; 580.9; 581; 581.1; 581.3; 581.89; 581.9; 582; 582.1; 582.2; 582.4; 582.81; 582.89; 582.9; 583;

583.0; 583.1; 583.8; 583.81; 583.89; 583.9; 584; 584.5; 584.8; 584.9; 585; 585.1; 585.2; 585.3; 585.4; 585.5; 585.6; 585.9; 586; 587; 588; 588.0; 588.1; 588.8; 588.81; 588.89; 588.9; 589; 589.0; 589.9; 590; 590.0; 590.00; 590.1; 590.10; 590.2; 590.8; 590.80; 590.81; 590.9; 591; 592; 592.0; 592.1; 592.9; 593; 593.1; 593.2; 593.3; 593.4; 593.6; 593.73; 593.8; 593.81; 593.82; 593.89; 593.9; 594; 594.1; 594.2; 595; 595.0; 595.1; 595.2; 595.3; 595.4; 595.82; 595.89; 595.9; 596; 596.0; 596.1; 596.3; 596.5; 596.51; 596.52; 596.53; 596.54; 596.55; 596.59; 596.8; 596.89; 596.9; 597; 597.8; 597.80; 597.81; 597.89; 598; 598.00; 598.01; 598.2; 598.8; 598.9; 599; 599.0; 599.1; 599.2; 599.3; 599.6; 599.60; 599.7; 599.70; 599.71; 599.72; 599.8; 599.81; 599.83; 599.84; 599.89; 599.9; 696; 696.0; 696.1; 696.2; 696.3; 696.4; 696.5; 696.8; 710.0; 714; 714.0; 714.2; 714.3; 714.30; 714.31; 714.32; 714.33; 714.4; 714.8; 714.9; 720; 720.0; 720.1; 720.2; 720.8; 720.81; 720.89; 720.9.

7. The comparison sample of FPs is quite small to measure professional perception of feasibility for the study. How was that approach determined? How will the results be analyzed?
With regard to the sample of FPs for the feasibility evaluation, we have clarified in the reviewed version of the manuscript that the number of interviews will be at least 12 until data saturation is reached. Saturation refers to the point in data collection when no additional issues or insights are identified and data begin to repeat so that further data collection is redundant, signifying that an adequate sample size is reached. Saturation is an important indicator that a sample is adequate for the phenomenon studied – that data collected have captured the diversity, depth, and nuances of the

issues studied – and thereby demonstrates content validity. Reaching saturation has become a critical component of qualitative research that helps make data collection robust and valid.
For healthcare professionals: line 401 “Interviews will be carried out with at least 12 professionals until data saturation is reached: at least six (three from each randomized arm) who reduced their PIP and at least six who did not, as informed by the quantitative results.” The same clarification for patients: line 409 “The interviews will be carried out with at least ten patients until data saturation is reached: at least five interviews will be carried out with patients who have been clinically managed according to recommended practice and five with patients who have not.”

With regard to the analysis of the results, as already mentioned in point #3, we have added a more detailed description of how the analysis of the qualitative study will be performed in the section “Feasibility Evaluation” (line 417) of the reviewed version of the manuscript.
Line 417:
“Regarding the analysis of the qualitative study, the responses will be extracted from the transcript of the interviews. Several members of the research team will participate in the analysis, promoting the exchange of perspectives and consensus, with the aim of triangulating the analysis. A deductive and an inductive perspective will be combined. For the deductive perspective, the discourse of each professional and patient interviewed will be associated with constructs derived from the behavior changes theories (TDF, BCW, etc.) [3, 11-13]. The inductive analysis will be based on the postulates of grounded theory [35]. Researchers will use coding techniques, or line-by-line analysis, looking for words and phrases that identify explanatory concepts. Subsequently, thematic connections between the basic theoretical concepts and the data will be developed.”

8. The study design was facilitated by focus groups of stakeholders (patients, professionals and researchers). How were the focus groups utilized?
During Phase I of the DE-imFAR, we conducted a qualitative study comprising focus groups with Family Physicians and patients in order to identify the determinants (barriers and facilitators) of the selected target behaviors related to potentially inappropriate statin prescription (low-value practice) and of healthy lifestyle promotion practice (the recommended clinical practice). These results were already published in Sanchez et al., 2022. Therefore, we have included the reference number of this paper [14] in the corresponding section “Patient and public involvement” of the reviewed manuscript (line 512).
Please find below a summary of the focus groups results that were already published [reference 14]:
“Numerous determinants, facilitators of the inappropriate statin prescription and barriers toward healthy lifestyle promotion emerged from the focus groups with healthcare professionals. The script of these focus groups was developed to explore in-depth potential determinants with questions covering each of the TDF dimensions. Then, with the main goal of designing and developing targeted strategies that address the specific determinants of CVD prevention practice, we carried out a mapping process of de- implementation/implementation strategies in order to reduce the low-value practice and promote the implementation of the recommended practice, based on the determinants of routine practice reported by FPs in the focus groups, following the procedure established by the BCW. In addition, a patient focus group was conducted to ascertain patients’ experience regarding the clinical practice of statin prescription and triangulate physicians discourse. The following aspects were explored: how the pharmacological treatment was started; whether it was a decision made in conjunction with the FP; how they were informed; what factors could determine this action (preference or health problem, and at patient, professional, health center level), patient comfort with treatment, and so on.”

Reviewer: 2
Dr. Michelle Rockwell, Virginia Polytechnic Institute & State University Comments to the Author:

Thank you for the opportunity to review The De-imFAR Phase II Project: A study protocol for a randomized implementation trial to 5 evaluate the effectiveness of de-implementation strategies to reduce low-value statin 6 prescribing in the primary prevention of Cardiovascular Disease. This innovative and well-designed study addresses multiple important issues, including what de-implementation strategies work best and how effective are these strategies for reducing or eliminating potentially inappropriate statin prescribing. This is a nuanced and very detailed study design that is difficult to describe concisely. Below I have recommended three MAJOR edits that I perceive as required to clearly communicate the protocol and assure that outcomes are being measured appropriately. I realize that the study is already underway and that few protocol changes can be made at this time. However, I suspect that the team has

appropriate data for each specified evaluation domain available and the limitation is in the current description.
MAJOR recommended edits-
1) The strong study design and background work are not reflected in the current manuscript as written. Some restructuring of the paper, clarification of terms, and clearer communication about what parts of the study have already been performed is needed. Many components that might typically appear in the Introduction are instead, included in Methods. Most readers will require definitions for terms used in the study. Realizing this is a big task because this study is rich in potentially unfamiliar terms, it seems essential for setting up the study. Some examples I might recommend for the introduction (even a very brief definition):

1. De-implementation
2. Implementation
3. Theoretical Domains Framework
4. Behavior Change Wheel
5. Statin
6. Non-reflective
7. Reflective
8. Decision assistance strategy (decision aid?)
9. Decision information strategy
10. Reflective decision structure strategy
11. Audit & feedback

While some of these terms and corresponding study elements are described in Appendices (which is great), a brief descriptor in the text is needed.
Trying to combine the suggestions of Reviewers #1 and #2, we have carried out an important modification of the layout of the manuscript. Given the accomplished changes, it is advisable to carry out a detailed review based on the new documents that we send: the corrected version with tracked changes and the clean version.

On the one hand, we have lightened excess or repetitive content. On the other hand, we have moved contents that, although more related to the introduction as the reviewer points out, were in the methodology section. That is: i) the paragraph that describes the clinical practice guidelines and recommendations for CVD primary prevention recommendations (Lines 144- 153); and ii) the paragraph regarding that the designed de-implementation strategies can be conceived and theoretically differentiated based on how they influence clinicians' decision making (Lines 195-206).

Moreover, in the reviewed version of the manuscript, we have clarified that DE-imFAR study is a two-phase project (Phase I and Phase II) (lines 137-138); and therefore, we have better stated which parts of the study were already performed during the Phase I (results already published) (lines 155, 185, 208, 306, 390, 507, 510) and which ones correspond to the present Phase II (lines 211, 305, 510, 513). In addition to this, we have included additional background information (see also Reviewer

#2 additional recommendation point 4) describing the magnitude of the problem in our setting (line 155) whose results were published (reference [10]).
Line 155 “Within the Phase I of the DE-imFAR study, we first conducted a cross-sectional observational study on the incidence of PIP of statins and provision of advice for changing

lifestyles in the Basque Health Service-Osakidetza in 2018. The results showed that the prescription of statins had increased notably in the Basque Country (Spain) with an estimated incidence of new PIP of 10.5 per 100,000 persons/year in patients aged 40 to 75 years, without CVD, with moderately elevated cholesterol levels but with a CVR <5% [10].”

With regard to Reviewer #2’s suggestion of including a definition of several terms in the Introduction section, we consider that it would not be strictly possible due to word count and space limitations. On the other hand, the definition of some of the suggested terms, such as statins or non-reflective/reflective, are more or less implicitly stated in the manuscript. However, as suggested, we have prepared a glossary of these terms to be included at the end of the Supplemental File 1 [DE-imFAR de-implementation strategies]. This new pdf file has been also uploaded.

2) I particularly appreciate the authors’ graceful navigation of de-implementation and implementation language, which can be cumbersome! Further justification for using RE-AIM (an implementation framework) to evaluate de-implementation efforts is needed. Also, might it be more appropriate to say that you are using RE-AIM to evaluate the implementation of de-implementation strategies (as opposed to the effectiveness, which is just one outcome)? Importantly, on pages 12 and 13, the authors describe their approach to evaluating Reach, Adoption, Implementation, and Maintenance. First, it is unclear why Effectiveness is not included and it appears that the planned measures for Implementation should actually be classified as Effectiveness. The Implementation domain should evaluate if the intervention was delivered as intended, what adaptations were made, etc. Further, the Adoption measures described are not appropriate measures of Adoption (which should evaluate if/how the FP’s used the de-implementation strategies.
The RE-AIM planning and evaluation framework is used as a framework for the consistent evaluation and communication of results related to the implementation of programs or initiatives (public health, health promotion, chronic disease self-management, etc…) and to facilitate the translation of research into practice and help plan programs and improve their chances of success in "real world" settings. Thus, in order to facilitate the evaluation of the impact of the present (research) initiative of de-implementation of low-value pharmacological prescribing in terms of public health, to the best of our knowledge, we have innovatively adopted the RE-AIM framework. Since there are no examples (or at least we have not been able to find any) of de-implementation studies using the RE-AIM framework, it has been difficult for us to operationalize the dimensions adequately. As it is therefore an innovative application, we consider this a strength of the study, which will serve as an example for future de-implementation studies.
We would like to thank Reviewer #2 for this comment; thanks to it, we have thoroughly reviewed the section of the evaluation of the de-implementation strategies using the RE-AIM framework; and in consequence, we have corrected and clarified some of the dimensions (please read below). In addition, as suggested by the reviewer, we have changed to “evaluate the implementation of the de-implementation strategies…” instead of “evaluate the effectiveness” (Line 353). It may be advisable to read our reply to Reviewer #1 point 4B, where we have provided a more detailed explanation of the Phase II study; thus, Reviewer #2 could assess whether she agrees with the definitions for the RE-AIM dimensions given below.

1. Effectiveness: as indicated by Reviewer #2, we have corrected the “Effectiveness” dimension, whose definition was incorrectly under the “Implementation” dimension (line 360).
Line 360 “Effectiveness

The study's main outcome will measure both the change in the incidence of the PIP of statins and the change in the incidence of the provision of advice regarding healthy lifestyles in patients of the target population eligible for CVD primary prevention, from baseline to 12 months after exposure of target FPs to the de-implementation strategies."

2. Adoption: taking account the explanation provided in point 4.B (Reviewer #1), we consider that in our study the "Adoption" dimension should evaluate whether the FPs adopt or not the recommended CVD primary prevention clinical intervention. Therefore, we would disagree with the Reviewer #2 in this respect. However, it is true that our previous definition for "Adoption" was not entirely correct, and so we have modified it in the reviewed version of the manuscript (line 370) as follows:

Line 370 "Adoption

Degree to which the recommended CVD primary prevention clinical intervention is adopted by the FPs 12 months after exposure to the de-implementation strategies, that will be measured by the percentage of FPs who improve their CVD prevention practice, by reducing PIP of statins and/or increasing health promotion activities in the target population eligible for CVD prevention, 12 months following FP's exposure to the allocated or control de-implementation strategies; and their representativeness."

3. Implementation: taking account the explanation provided in point 4.B (Reviewer #1), we consider that in our study, the implementation dimension should evaluate the fidelity of the de-implementation strategies, i.e. if the strategies were delivered as intended. This information was included in a different section of the submitted manuscript. We have changed the position of this paragraph to the Implementation dimension of the RE-AIM (line 375).

Line 375: "Implementation

The fidelity of the delivery of each de-implementation strategy under study (i.e., the degree to which they have been executed as planned) will be evaluated. To this end, a complete record and subsequent description of the execution process, documentation of adaptations made to the planned strategies, and process indicators of the delivery of and exposure to the interventions (see Supplemental file 1 for specification of the exposure to each strategy), will be used to assess the following components of fidelity: adherence, dose, quality of delivery, professionals' responsiveness and program differentiation [34]."

4. Reach: after having thoroughly reviewed this section of the RE-AIM evaluation, we have made a slight change (only for clarification) in the "Reach" dimension ["who received the recommended CVD primary prevention clinical intervention" (line 356)]. The definition will be as follows:

Line 356: "Reach: Absolute number and percentage of patients in the target population who received the recommended CVD primary prevention clinical intervention 12 months following FP's exposure to the de-implementation strategies compared; and their representativeness."

3) There is no description of the methods that will be used for the qualitative analysis, nor how the quantitative and qualitative data will be integrated and analyzed.

As requested, we have improved the description of the methods for the qualitative analysis in the section "Feasibility Evaluation" of the reviewed version of the manuscript (lines 397-427). See our reply to the Reviewer #1 comments number 3.A, 5.B and 7.

On the other hand, as we have clarified in page 15 (line 403) the qualitative methods are linked to the quantitative results since we have already decided to perform the qualitative interviews stratified by the study results. Specifically, we have planned to perform semi-structured interviews with a group of family physicians who improve their practice and with a group of those who do not, expecting different discourses. Similar methods will be applied with patients' semi-structured interviews, trying to ascertain whether those who receive the recommended CVD primary prevention clinical practice have a different discourse compared to those who have not.

Lines 401-403

“Interviews will be carried out with at least 12 professionals until data saturation is reached: at least six (three from each randomized arm) who reduced their PIP and at least six who did not, as informed by the quantitative results.”
In addition, in order to provide validity to the qualitative methods, as stated within the new added clarification (line 420), we will triangulate both physicians and patient discourse analyses.
Line 417-420
“Regarding the analysis of the qualitative study, the responses will be extracted from the transcript of the interviews. Several members of the research team will participate in the analysis, promoting the exchange of perspectives and consensus, with the aim of triangulating the analysis.”

Additional recommendations:

4) This paper describes the study protocol for a trial to examine the effectiveness and feasibility of different de-implementation strategies, so framing the introduction around de- implementation makes sense. However, additional background about the specific PIP being studied – statins for CVD prevention in low-risk patients – would be very helpful, in addition to a plain language interpretation of when statins are high vs. low-value. What professional recommendation informs this? What is the scope of the problem? How often does PIP statin prescribing occur in primary care? What are the potential harms of PIP of statins? Some of this is included in the Methods section but is foundational to understanding the goals and research questions.
As suggested by Reviewer #2 and #1, we have carried out important modifications of the Introduction section in the reviewed version of the manuscript (see also response to point 1). As recommended by Reviewer #2, we have included additional text in order to describe the targeted low-value practice of the DE-imFAR study (lines 142-144). In doing so, as indicated by the reviewer, we have moved contents from the methodology section to the introduction section, in particular those that describe the clinical practice guidelines and recommendations for CVD primary prevention (lines 144-153).

Lines 142-153 “Specifically, the targeted low-value practice of the DE-imFAR study is the pharmacological prescription of statins in the primary prevention of cardiovascular disease (CVD) in low-risk patients. In order to prevent CVD, one of the leading causes of morbidity and death worldwide, there is general agreement on the indication of lipid-lowering treatment, mainly with statins, in patients with a cardiovascular risk (CVR) greater than 10% over 10 years or in secondary prevention [6-9]. Whereas, for primary prevention in patients with low CVR (<10%), preventive activities should be focused on the promotion of healthy lifestyles through optimizing diet, increasing physical activity, and stopping smoking [6-9]. Moreover, international guidelines encourage discussion with patients concerning the benefits of lifestyle modification for the prevention of CVD, as well as other modifiable risk factors, before considering pharmacological treatment [7-9].”
As a consequence of this movement, in the reviewed version of the manuscript we have improved the Methods section of “Clinical interventions” (line 279) by defining more in detail which is the recommended CVD primary prevention clinical intervention for the DE-imFAR study. We have included the new reference [32]: “32. COLESTEROL Y PREVENCIÓN PRIMARIA DE LA ENFERMEDAD CARDIOVASCULAR: El debate continúa. INFAC. 2022;30(7):65-75.”

Line 279-302:
“Clinical interventions
The DE-imFAR study, with regard to the prescription of statins in primary prevention of CVD, follows the clinical practice recommendations in Osakidetza-Basque Health Service and the Spanish National Health System [6] as well as several international guidelines [7-9]. Thus, these are the recommendations concerning when to initiate treatment in primary prevention of CVD [6, 32]:
 For individuals aged 40 to 75 years with an estimated 10-year CVR REGICOR >10%, initiation of statin therapy is recommended.

- In general, for individuals aged 40 to 75 years with CVR REGICOR <10% and LDL cholesterol levels <190 mg/dL, it is recommended not to initiate statin therapy, with the following considerations:
  - with CVR close to 10%, consider the presence of risk-enhancing factors in decision-making.
  - with CVR <5%, it is recommended not to initiate statin therapy.
- For patients with LDL cholesterol levels ≥190 mg/dL, it is recommended to assess the presence of genetic dyslipidemia and potential cardiovascular risk-enhancing factors. It is suggested to initiate statin therapy, together with healthy lifestyle recommendations, regardless of cardiovascular risk.

In any case, the indication for treatment should be preceded and/or accompanied by promotion of healthy lifestyles through healthful diet, regular physical activity and smoking cessation. Moreover, it is recommended that the decision to initiate statin therapy should consider individual baseline risk, absolute risk reduction and whether the risk reduction justifies the potential harms and undesirable consequences of taking a lifelong daily medication."

As suggested by Reviewer #2, we have also added background information describing the magnitude of the problem in our setting (line 155). The reference of the published results have been added (reference [10]): "10. Elizondo-Alzola U, Sánchez A, Pijoan JI, et al. Statins in primary prevention of cardiovascular disease: incidence of potentially inappropriate prescriptions in very low risk primary care patients and associated factors. J Gen Prac. 2022;10:456. doi: 10.37421/2329-9126.22. 10.461"

Line 155 "Within the Phase I of the DE-imFAR study, we first conducted a cross-sectional observational study on the incidence of PIP of statins and provision of advice for changing lifestyles in the Basque Health Service-Osakidetza in 2018. The results showed that the prescription of statins had increased notably in the Basque Country (Spain) with an estimated incidence of new PIP of 10.5 per 100,000 persons/year in patients aged 40 to 75 years, without CVD, with moderately elevated cholesterol levels but with a CVR <5% [10]."

5) What do the recommendations advise as related to healthy lifestyle counseling? And how will the authors measure FP's provision of this? Chart review? This method should be added.

With regard to provision of healthy lifestyles counseling, clinical practice recommendations and guidelines suggest that a personalized medical advice tailored to the patient specific circumstances should be provided. It should include suggestions for lifestyle change with plans for modifying physical activity, dietary habits and stopping smoking. These recommendations are included in both "Introduction" (line 147) and "Methods" sections of the manuscript (line 297).

Introduction section - Line 147: "Whereas, for primary prevention in patients with low CVR (<10%), preventive activities should be focused on the promotion of healthy lifestyles through optimizing diet, increasing physical activity, and stopping smoking [6-9]."

Methods section – Clinical interventions - Line 297: "In any case, the indication for treatment should be preceded and/or accompanied by promotion of healthy lifestyles through healthful diet, regular physical activity and smoking cessation."

As stated in lines 477-478 and 483-484, the collection of information will be from data recorded by healthcare professionals in the Osakidetza's electronic health records (EHR) (OSABIDE) under routine clinical practice conditions, and extracted through the corporate Oracle Business Intelligence platform. Thus, the provision of healthy lifestyles advice will be measure by the fact that there is a record registered in the EHR, since OSABIDE includes a specific electronic form to check that each single piece of advice (diet, exercise, tobacco quitting) has/has not been provided. This has been added in the "Management, quality, and safety in data processing" section of the reviewed version of the manuscript (lines 480-481 and 484-487).

Lines 478-487:
“The process indicators related to the clinical practice of the professionals (prescription of statins and record in the EHR of provision of personalized healthy lifestyles advice concerning the need to increase physical activity, eat a healthy diet and smoking cessation), , will be extracted from OSABIDE through the corporate Oracle Business Intelligence platform. In particular, for the provision of healthy lifestyles advice, OSABIDE includes a specific electronic form to check that each single piece of advice (diet, exercise, tobacco quitting) has/has not been provided.”

6) Can you provide an estimate of how many FPs belong to these 13 IHOs? What is the likely n of the study? Was there a power analysis/sample size calculation? If not, explain why that was unnecessary and how it will impact analysis and interpretation.
In the Osakidetza-Basque Health Service there are approximately 1498 FPs distributed in the 13 Integrated Healthcare Organizations (IHOs). As stated in the calculation of the sample size and in the Analysis section, we will require at least 58 FPs in each of the two randomized arms for the experimental comparisons. For the observational comparison among the non-randomized

arm and those randomized, we will consider at least 232 FPs for the matched comparison and all of the eligible FPs from the 11 IHOs where the two randomized strategies are not being set up.
Line 443 “…With respect to this group and seeking to increase comparability and reduce potential bias, in addition to evaluating the change in PIP of statins incidence in all eligible FPs, we will select two matched FP from this non-randomized group for each of the randomized FPs….”.

7) A conclusion that describes the expected impact of the study would be nice.
We would like to point out that following BMJ Open Submission Guidelines for Study Protocol, we did not include a “Discussion” section in the submitted version of the manuscript. Further, as indicated by the Editor, a “Conclusions” section should not be implemented in a protocol study. However, the Editor suggests, that authors’ expectations and recommendations for future research could be discussed in a “Discussion” section instead.
Taking guidelines, Editor’s comments and Reviewer’s #2 request, we have prepared the below paragraph as “Discussion section”, that we will include in the protocol study, only in the case that both the Editor and Reviewer #2 consider and agree that it is appropriate. Please note that this new Discussion section has not been included yet in the reviewed version of the manuscript.
“DISCUSSION
The goal of the present study is to improve CVD primary prevention clinical practice in a real- world setting in primary care by putting into practice procedures and methods for the design, deployment, and evaluation of implementation/de-implementation strategies informed by behavioral and implementation sciences. Specifically, the Phase II of the DE-imFAR study focuses on reducing PIP of statins in CVD primary prevention in patients with moderate hypercholesterolemia and low CVR and fostering healthy lifestyle promotion as the recommended treatment option. To do so, the study will deploy several de-implementation strategies derived from the Phase I formative study that targets key determinants of the decision- making process involved in the provision of CVD primary prevention by FPs. If the results are successful, policymakers and health managers and professionals will have valid and robust, locally relevant evidence that will support the need to introduce these innovations in methods and procedures informed by implementation science to tackle the hard task of reducing the burden of low-value pharmacological prescription in clinical care services.”

Minor:

8) Consider new references for #1 and 2. While these are seminal publications about healthcare quality, they don’t particularly address the prevalence and impact of low-value care (particularly on a global basis as the intro sentence suggests).
We have restructured paragraph 1 as follows:

Lines 123-126. “Reducing low-value healthcare, that is, clinical practices that have not been shown to be efficient or effective, is becoming a global priority due to the widespread empirical evidence of its high prevalence across healthcare systems, potential harm and its impact on patient safety, resource use, and social inefficiency [1,2].”
Accordingly, these are the new references for # 1 and #2:
“1. Morgan DJ, Brownlee S, Leppin AL, et al. Setting a research agenda for medical overuse. BMJ. 2015;351:h4534. doi: 10.1136/bmj.h4534.
2. Niven DJ, Mrklas KJ, Holodinsky JK, et al. Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC Med. 2015;13:255. doi: 10.1186/s12916-015-0488-z.”

9) Intro- Paragraph 1- also potential harm
We have done it as suggested (Line 125. Please, see above the response to point 8).

10) Consider a figure that shows TDF and behavior change wheel
The Theoretical Domains Framework (TDF) and Behavior Change Wheel (BCW) were used during the Phase I of the DE-imFAR study for the design of the de-implementation strategies. Moreover, the results of this Phase I study using these behavior change theories have already been published [reference 14]. In the published article, we have explained in detail all the systematic theory- and evidence-based intervention design process. Furthermore, in order to understand the main objective of the Phase II study (“to assess the potential effectiveness and feasibility of a set of de-implementation strategies to reduce the PIP of statins in the primary prevention of CVD”), we consider that a figure that shows the TDF and the BCW would not be required.

In the reviewed version of the manuscript, we have added in lines 164-165 the corresponding references to the TDF [3,11,12]; please note that the reference for the BCW was already mentioned [13]. Therefore, the reader can refer to these articles to find the most relevant information, tables and/or figures of the TDF or the BCW.

Bearing all this in mind, we consider that it would not be necessary to include a figure of the BCW and the TDF in the protocol of the Phase II study.

11) Line 183- CVR? I believe this should be CVD.
We would like to clarify that “CVR” as cardiovascular risk in line 183 was correct. What we mean is that the CVR is being calculated (for example using the REGICOR calculator) and its score is being documented/recorded in patients’ medical records.

12) Line 209- can you reference “Stopping Low-Value Prescribing”
The website for the “Stopping low-value prescribing” campaign and its contents is available only at the corporate intranets of the Ezkerraldea-Enkarterri-Cruces and Barakaldo-Sestao IHOs of the Osakidetza-Basque Health Service. The Osakidetza’s intranet is a private website URL with no access to the public outside of our organization. Hence, the access is only granted to those healthcare professionals who belong to Osakidetza.

For this reason, it is not possible providing a website URL to reference the “Stopping low-value prescribing” campaign in our manuscript. Instead, several screenshots of the main page of the intranet are displayed at the Supplemental File 1 [DE-imFAR de-implementation strategies] for illustration. Moreover, we are planning to include more screenshots in our next paper when we publish the results of the Phase II of the DE-imFAR study.

VERSION 2 – REVIEW

REVIEWER	Douglas Schocken Duke University, Medicine
REVIEW RETURNED	24-Feb-2024

GENERAL COMMENTS	A healthy lifestyle is one intervention that can contribute to CVD prevention. In this era, however, instead of prescribing a medication such as statin for everyone, PIP (preventing inappropriate prescribing) in low-risk populations might prevent both financial toxicity and non-evidence-based prescribing of statins in patients with low risk by current guidelines. The investigators have designed a four-pronged experimental approach using behavior change techniques to decrease inappropriate statin use in low-risk patients. The investigators' responses to this reviewer's comments are excellent. They have considered the stated concerns and have addressed them properly. Specifically, the authors have markedly improved the introduction. The content and style continue 'wordy' but are much more informative. The description of the methods has been improved especially the description of the clinical interventions. Evaluation protocols for the de-implementation strategies have been expanded with a better explanation of the implementation allocation. Implementation variables have been expanded, and examination of other potential confounders has been added. In particular, outcome measures are described in more detail. The feasibility evaluation has been re-written and is significantly improved. Analysis, data management, and QA sections have also been expanded. Patient and public involvement queried by this reviewer continue unaddressed except for the addition of the relevant reference. Problems with translation into English continue, suggesting a larger role for the copy editor.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Douglas Schocken, Duke University Comments to the Author:

A healthy lifestyle is one intervention that can contribute to CVD prevention. In this era, however, instead of prescribing a medication such as statin for everyone, PIP (preventing inappropriate prescribing) in low-risk populations might prevent both financial toxicity and non-evidence-based prescribing of statins in patients with low risk by current guidelines. The investigators have designed a four-pronged experimental approach using behavior change techniques to decrease inappropriate statin use in low-risk patients.

The investigators' responses to this reviewer's comments are excellent. They have considered the stated concerns and have addressed them properly. Specifically, the authors have markedly improved the introduction. The content and style continue 'wordy' but are much more informative.

The description of the methods has been improved especially the description of the clinical interventions. Evaluation protocols for the de-implementation strategies have been expanded with a better explanation of the implementation allocation. Implementation variables have been expanded, and examination of other potential confounders has been added. In particular, outcome measures are described in more detail. The feasibility evaluation has been re-written and is significantly improved.

Analysis, data management, and QA sections have also been expanded.

We would like to take this opportunity to express our gratitude to the reviewer for his feedback and helpful comments that supported the revision of the manuscript, which contributed to a substantial improvement of it.

Patient and public involvement queried by this reviewer continue unaddressed except for the addition of the relevant reference.

We would like to point out that the results of the qualitative study comprising focus groups with family physicians and patients were already published in Sanchez et al., 2022. That is why, due to word count and space limitations, we only included the reference to our paper in the corresponding section “Patient and public involvement” [reference 14], which was initially missing in the first draft of the manuscript. We hoped that providing the reviewer with a summary of the focus groups in the point-by-point response would have been adequate.

Problems with translation into English continue, suggesting a larger role for the copy editor. As requested by the Editor, a proofread of the manuscript has been completed and several spelling and grammar errors have been identified and corrected.