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TITLE PAGE

Title

The De-imFAR Phase II Project: A study protocol for a randomized implementation trial to evaluate the effectiveness of de-implementation strategies to reduce low-value statin prescribing in the primary prevention of Cardiovascular Disease.

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ABSTRACT

Introduction

This study aims to reduce potentially inappropriate prescribing (PIP) of statins and foster healthy lifestyle promotion in cardiovascular disease (CVD) primary prevention in low risk patients. To this end, the study will compare the effectiveness and feasibility of several de-implementation strategies developed following the structured design process of the Behavior Change Wheel targeting key determinants of clinical decision-making process in CVD prevention.

Methods and analysis

A randomized implementation trial, with an additional control group, will be launched, involving family physicians (FPs) from 13 Integrated Healthcare Organizations (IHOs) of Osakidetza – Basque Health Service with non-zero incidence rates of PIP of statins in 2021. All FPs will be exposed to a non-reflective decision assistance strategy based on reminders and decision support tools. Additionally, FPs from two of the IHOs will be randomly assigned to one of two increasingly intensive implementation strategies: adding a decision information strategy based on knowledge dissemination, and a reflective decision structure strategy through audit/feedback. The target population comprises 45- to 74-year-old women and 40- to 74-year-old men with moderately elevated cholesterol levels but no diagnosed CVD and a low cardiovascular risk (REGICOR <7.5%), who attend at least one appointment with any of the participating FPs (May 2022-May 2023), and will be followed until May 2024. The main implementation outcome will be the change in the incidence rate of PIP of statins and healthy lifestyle counseling in the study population 12 and 24 months after health professionals' exposure to the strategies. Fidelity of the de-implementation strategies,

FPs' perception of their feasibility and acceptability, and patient experience regarding the quality of treatment received will also be evaluated.

Ethics and dissemination

The study was approved by the Basque Country Clinical Research Ethics Committee and was registered in ClinicalTrials.gov (NCT04022850). The results will be disseminated in scientific peer-reviewed journals.

Keywords: Inappropriate Prescribing, Cardiovascular Diseases / prevention & control, Hypercholesterolemia / drug therapy, Implementation Science, Research Design, Primary care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The goal of the present study is to assess the effectiveness of several de-implementation strategies targeting primary care family physicians' (FPs) decision-making process to reduce potentially inappropriate prescribing (PIP) of statins and to increase healthy lifestyle promotion as the recommended treatment option in cardiovascular disease (CVD) primary prevention through a randomized implementation trial with an additional control group conducted in real-world conditions of Primary Care.
- The present study proposes an efficient design that combines experimental and non-experimental comparisons through two randomized and one non-randomized control (reference) arm that will allow: a) to capture the secular trends across all FPs within the healthcare system that are exposed to a reference intervention and estimating its effect on reducing PIP of statins and increasing healthy lifestyle promotion; and b) to compare this reference strategy with the two experimental de-implementation strategies.
- The main limitation of the study lies in the planned comparisons of the randomized groups with respect to the control arm. Therefore, in addition to

evaluating the change in PIP incidence in all eligible FPs, a matching strategy with the selection of one matched FP from this non-randomized group for each of the randomized FPs will be performed seeking to increase comparability and reduce potential bias.

- In order to better understand from the perspective of the study participants the reasons why (why not) the strategies work, to explain the variations in the results achieved and to identify the essential components and those that will require to be optimized, qualitative methods will also be used to assess i) professionals' perception of the feasibility and acceptability of the de-implementation strategies aimed at reducing their unnecessary prescribing and favoring recommended practice in the primary prevention of CVD in patients with low cardiovascular risk (CVR); and ii) patients' perception and experiences related to receiving clinical care derived from the exposure of their healthcare professionals to the different de-implementation strategies.

INTRODUCTION

Low-value healthcare may be considered a major global problem due to the widespread empirical evidence of its high prevalence across healthcare systems and its impact on patient safety, resource use, and social inefficiency [1,2]. It is becoming a global priority to reduce low-value care, that is, clinical practices (e.g., diagnostic and therapeutic procedures) that are ineffective, have not been shown to be efficient or effective, are not the best available option, or have a poor cost- and/or risk-to-benefit balance.

Nonetheless, reducing or eliminating low-value practices is a complex matter, as drivers fostering or maintaining them seem, in most cases, to operate at multiple levels and be context specific; therefore, there is a need for a careful process of formal analysis of the

problems and their mechanisms of action to design and guide effective and efficient corrective measures. This can be achieved using models or theories that cover a wide range of possible influences or determinants of the clinical behavior in question. In this context, behavior change theory has been extensively applied to understand the factors that may influence clinical behavior, identify and design possible techniques and interventions that could be used to change it, and explain the mechanisms through which such interventions operate [3,4].

The DE-imFAR (from the Spanish for de-implementation of low-value pharmacological prescribing) project [5] aims to apply behavioral science theory within a structured process involving the main stakeholders (health professionals, patients, and researchers) in the design, deployment, and evaluation of targeted de-implementation strategies for reducing potentially inappropriate prescribing (PIP). Specifically, we have applied a combination of the Theoretical Domains Framework and Behavior Change Wheel [6] methods to a) understand the factors that may influence problematic clinical behavior (PIP of statins in low cardiovascular risk (CVR) patients within the context of cardiovascular disease [CVD] primary prevention in primary care), and b) map targeted de-implementation and implementation strategies conducive to reducing or stopping the low-value practice in question.

Briefly, having prioritized a specific target behavior (clinician decision-making on intervention/treatment to be provided based on objective clinical information and subjective schemas and heuristics), identified determinants (facilitators of statin PIP and barriers to recommended activities promoting healthy lifestyles), and mapped specific behavior change techniques, three types of de-implementation/implementation strategies were selected for influencing decision-making through different mechanisms. The behavior change interventions selected were those judged to be the most potentially effective, feasible, and acceptable by the DE-imFAR Phase I working group: a) a non-

reflective decision assistance strategy based on providing evidence-based information communication technology tools to help and guide decision-making; b) a decision information strategy based on the dissemination of the evidence concerning CVD primary prevention framed in a corporate campaign encouraging family physicians (FPs) to move away from PIP; and c) a reflective decision structure strategy encouraging reflection on actual performance based on an audit/feedback system [7].

According to the evidence reviewed in Phase I of the DE-imFAR project [8-17] regarding the evaluation of interventions for the reduction of low-value prescribing, the three prioritized de-implementation strategies seem to be non-innovative interventions but do address the main determinants of clinical decisions processes that perpetuate the PIP of statins in our public healthcare setting (Osakidetza/Basque Health Service). On the other hand, these strategies are supported by evidence as multicomponent interventions that —combining passive dissemination interventions, based on training in or dissemination of clinical practice guidelines (CPGs), with more proactive interventions incorporating decision-making aids or the sending of audit/feedback— achieve the most positive results. Specifically, in the context of PIP of statins, a positive impact has been observed on documentation of CVR and prescription adequacy using a) multi-component dissemination strategies including informative web pages, and implementation of electronic CPGs compared to routine practice and training activities, and b) interventions based on sending clinical scenarios and cases, and audit/feedback to professionals, and decision support tools [12-16]. Research is needed, however, to determine whether these evidence-based and barrier-specific strategies for de-implementation identified in DE-imFAR Phase I are also effective in our context.

Thus, the goal of the present study is 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 (low-risk patients, REGICOR [18] CVR score <7.5%, with moderately

elevated cholesterol levels, low-density lipoprotein (LDL) cholesterol levels between 70 and 189 mg/dL and/or total cholesterol (TC) between 200 and 289 mg/dL, but without ischemic heart disease/CVD). The de-implementation strategies are derived from a systematic theory- and evidence-based intervention design process and composed of a set of active components targeting the facilitators of the non-desired behavior (PIP of statins) while tackling the barriers to applying the recommended clinical practice behavior (healthy lifestyle promotion) [7].

Specifically, we aim to answer the following research questions:

1. Observational comparison questions:

As compared to a reference/control non-reflective decision assistance strategy based on reminders and decision support tools incorporated into the electronic health record (EHR) for helping clinical decision-making, what is the effect on the incidence of PIP of statins in CVD primary prevention and the rate of delivery of healthy lifestyle counseling of a) a decision information strategy comprising a corporate “Stopping Low-Value Prescribing” campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD; b) a reflective decision structure strategy based on an audit/feedback system; and c) any intervention based on a reflective de-implementation strategy (a or b)?

2. Experimental comparison question:

As compared to a decision information strategy comprising a corporate “Stopping Low-Value Prescribing” campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD, together with the non-reflective decision assistance intervention based on reminders and decision support tools incorporated into the EHR for helping clinical decision-making, what is the effect on the incidence of PIP of statins in CVD primary prevention and the rate of delivery of healthy lifestyle counseling of adding a reflective decision structure strategy based on an audit/feedback system?

METHODS AND ANALYSIS

Design

A randomized implementation trial with an additional control group will be conducted for evaluating the potential effectiveness and feasibility of three de-implementation strategies (Figure 1). A mixed methods evaluation will be undertaken: quantitative for assessing the implementation results at the professional level (implementation outcomes regarding changes in rates of PIP and healthy lifestyle counseling) and qualitative for assessing the feasibility and perceived impact of the de-implementation strategies from the FPs' perspective and the experience and satisfaction of patients concerning the clinical care received. The unit of intervention will be the primary care FP, while observation and analysis will be performed at professional and patient levels. The DE-imFAR research protocol was reviewed and approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 28 July 2023).

Osakidetza provides universal coverage and services are free at the point of use, aside from co-payment for drugs, funded through regional general taxation. Primary, specialized, and social health-related service provision is organized around 13 Integrated Healthcare Organizations (IHOs) that cover the 3 provinces of the region of the Basque Country: Araba, Bizkaia, and Gipuzkoa. Each resident is on the list of one FP or pediatrician who offers comprehensive primary care and refers patients for hospital and specialty services. Primary care professionals work in full-time teams, including FPs, pediatricians, nurses, and administrative staff based at local centers providing access to healthcare for users in a defined geographical area.

We used the SPIRIT reporting guidelines and the SPIRIT checklist when writing the present study [19].

Participants

1. Professionals: FPs belonging to any of the 13 IHOs of Osakidetza with a non-zero annual incidence rate of PIP of statins at baseline (2021) with a minimum cluster size of n ≥10 patients

2. Patients: All 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL but without ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% who attend at least one appointment at the participating FPs' practices during the study period from May 2022 to May 2023, and followed until May 2024.

Clinical interventions

According to clinical practice recommendations in Osakidetza and the Spanish National Health System [20], although there is evidence that statins reduce the risk of cardiovascular events in secondary prevention and individuals with high CVR, for primary prevention in low-risk patients (REGICOR <10%), the risk-benefit balance is uncertain. Specifically, in patients with low CVR, preventive activities should be focused on the promotion of healthy lifestyles through optimizing diet, increasing physical activity, and stopping smoking. Moreover, the NICE guideline on CVR management and reduction [21] and the 2019 ACC/AHA guideline on the primary prevention of CVD [22] 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. They also stress the importance of discussing the risks and benefits of pharmacological treatment, taking into account patient preferences and conditions. Similarly, the 2019 ESC/EAS guidelines for the management of dyslipidemias [23] recommend healthy eating, regular exercise, and smoking cessation as the first line of treatment for hyperlipidemia.

De-implementation strategies evaluated

There is plenty of evidence demonstrating that it is possible to de-implement inappropriate medical practices through the lens of clinician cognition [24-26]. In this context, the growing field of choice architecture aims to explore how the structure and framing of decision situations influence the choice of certain behaviors over alternative ones. On the one hand, FPs' decision-making ability can be influenced by unconscious processes that occur in response to environmental or emotive cues, that is, through type 1 (or automatic) cognition. On the other, clinicians' conscious intention to change can be promoted by engaging their reflective cognition to consciously evaluate and correct their inappropriate behavior, that is, using type 2 (or reflective) cognition [27].

Within the present study, three types of strategies that purportedly affect FPs' decision-making process will be set up. The strategies can be theoretically differentiated as a function of the way they may affect clinicians' decision-making [28] and will be cumulatively deployed (see Supplemental file 1 for a more detailed description):

1) *A non-reflective decision assistance strategy*, that targets type 1 cognitive processes through decision support systems that prompt and remind FPs about the recommended practice in a simplified way, thereby reducing the cognitive burden. In short, pop-up reminders and alerts with associated messages were incorporated into the REGICOR CVR calculator in OSABIDE (Osakidetza's EHR system) and within the prescription pathway in PRESBIDE (the electronic drug prescribing component). The tools devised include an interactive media-based algorithm stating the recommended practice for the primary prevention of CVD in low-risk patients developed by an expert panel, and a patient information sheet depicting and promoting evidence-based practice for addressing cholesterol in the primary prevention of CVD in low-risk patients.

2) *A both reflective and non-reflective decision information strategy*, targeting both types 1 and 2 cognitive processes, based on the principle of knowledge dissemination and consisting of a "Stopping Low-Value Prescribing" campaign run by the organization that

also eases access (decreasing the physical effort required) to the evidence-based CPGs for the primary prevention of CVD in low-risk patients.

3) *A reflective decision structure strategy*, that targets type 2 cognition through an audit/feedback system reporting data with practice- and organizational-level performance indicators regarding PIP of statins and healthy lifestyle promotion to prompt reflection about their own care practice, provided along with intention formation and goal-setting-focused messages.

Allocation of intervention units to compared groups

All FPs from all 13 IHOs will be exposed to the first of the aforementioned strategies, namely, the provision of non-reflective decision assistance strategy. Further, in addition to this first strategy, FPs belonging to two IHOs (Barakaldo-Sestao and Ezkerraldea-Enkarterri-Cruces) in which the DE-imFAR project has been previously commissioned [7] 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). The allocation sequence within these two groups will be generated using a specific restricted randomization scheme by one member of the research team. The sequence will be concealed at the coordinating center. In all cases, FPs will only be allocated to the study groups after they have provided informed consent to participate through an opt-out strategy. The data analyst and the staff in charge of measurements will be blind to FP allocation to study arms. Given that the audit/feedback strategy will involve regular reports sent privately to individuals, participants in the experimental arms are also expected to be blind to group allocation.

Outcome measures

To assess the effectiveness of the de-implementation strategies compared in terms of public health impact, we will use the following dimensions of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [29]:

Reach

• Percentage of patients in the target population exposed to the recommended CVD primary prevention practice (e.g., assessment and advice regarding healthy lifestyles instead of statins), 12 months following FP's exposure to the experimental or control de-implementation strategies; and their representativeness.

Adoption

• 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.

Implementation

The study's main outcome measures will compare the change in the incidence of both the PIP of statins and the health promotion activities in patients of the target population eligible for CVD primary prevention, from baseline to 12 months after exposure of collaborating FPs to the de-implementation strategies. Specifically, the two following measures will be compared:

• Change in the incidence of PIP of statins

and

• Change in the incidence of provision of advice regarding healthy lifestyles, in both cases, considering the change, from baseline to 12 months after exposure of FPs to the de-implementation strategies compared, in the target population.

As a secondary implementation outcome, we will compare the change in the incidence of CVR score documentation in the EHR, from baseline to 12 months after exposure of FPs to the de-implementation strategies compared, in 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use and without ischemic heart disease/CVD but who have been newly prescribed statins during the fieldwork period.

Maintenance and Spreading

• Change in the incidence of PIP of statins and provision of healthy lifestyle counseling in eligible patients, 24 months after exposure of FPs to the de-implementation strategies compared to levels observed at the 12-month assessment.

Fidelity and Feasibility Evaluation

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 [30].

The professionals' perception of the feasibility of and satisfaction with the de-implementation strategies to enhance the provision of the recommended CVD prevention clinical practice will be assessed through key-informant semi-structured interviews. At least 12 interviews with professionals will be carried out: 6 professionals (3 from each randomized arm) who reduced their PIP and 6 who did not. Exposed patients' perception and experience regarding the quality of CVD prevention care received will also be assessed through key-informant semi-structured interviews: at least five interviews will be carried out with patients who have and five with patients who have not been clinically managed according to recommended practice.

Analysis

Frequencies and proportions along with the corresponding 95% confidence intervals (CIs) will be used to describe the prevalence and cumulative incidence of PIP of statins and healthy lifestyle counseling in the primary prevention of CVD by FPs. The primary effectiveness outcomes will be the changes in the cumulative incidence of PIP of statins

and healthy lifestyle counseling in patients from the target population (individuals with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL without past or current ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% attending at least one clinical appointment with their FP in the study period), from baseline to 12 months after exposure of FPs to the de-implementation strategies. Therefore, to evaluate the impact of the three de-implementation strategies, we will estimate the relative reduction in the risk of receiving PIP of statins in patients from the target population assigned to the experimental interventions over that in patients from the non-randomized group (non-reflective decision assistance strategy group). With respect to this group and seeking to increase comparability and reduce potential bias, in addition to evaluating the change in PIP incidence in all eligible FPs, we will select one matched FP from this non-randomized group for each of the randomized FPs taking into account both FP-related characteristics (e.g., baseline rate of PIP, etc.) and characteristics of the population of patients assigned to the FP (e.g., average socioeconomic status, etc.). Change in PIP incidence rates from baseline to those observed 12 and 24 months after FPs' exposure to the de-implementation strategies and the relative risk reduction will be estimated with the corresponding 95% CIs. To adjust for potential confounding factors, stratified statistical analyses and logistic models will be used. These models will be extended to generalized mixed effects models to take into account the hierarchical structure of data (patients nested in FPs and FPs in primary care teams), with fixed effects (comparison group, effect of time on outcome indicators, and time-group interactions) and random effects on the intercept and the time slope (for each patient, FP, center, etc.). These models will be adjusted for potential confounders, following a backward strategy, guided by the stratified analyses. A similar approach will be taken to analyze the secondary outcomes. The analyses will be carried out with SAS (v. 9.2, SAS Institute, Cary, NC, USA),and R (R Development Core Team, 2014).

Calculation of the required sample size for the most unfavorable scenario, this being the comparison between the two randomized de-implementation strategies, was based on: i) a baseline incidence of statin PIP of 7.4% estimated among the patients of the target population seen in 2021 by FPs with an incidence of PIP > 0% with a minimum cluster size n ≥10 patients, ii) an intra-class correlation coefficient of 0.01, iii) an average cluster size of 39 patients with a coefficient of variation of 0.63, iv) α = 0.05 and statistical power of 80%, and v) hypothetical decreases in annual PIP rates of 20% in the decision information strategy group and 50% in the decision structure strategy group. With these assumptions, it was estimated that at least 58 FPs were required for each experimental arm.

Management, quality, and safety in data processing

This study will be carried out in accordance with the international standards for conducting epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies [31]. This is a prospective intervention study focused mainly on the collection of information from data recorded by health professionals in the Osakidetza EHR (OSABIDE) under routine clinical practice conditions. The process indicators related to the clinical practice of the professionals, and patients' sociodemographic and clinical characteristics (age, sex, socioeconomic status, active health problems, etc.) and clinical outcomes will be extracted from OSABIDE through the corporate Oracle Business Intelligence platform. The Primary Care Research Unit of Bizkaia is formally authorized to extract and use data from the EHR for research purposes by the Healthcare Directorate of Osakidetza. On the other hand, it will be necessary to inform participants about the study and obtain their written informed consent concerning the information collected directly from the professionals and patients under study through the key-informant semi-structured interviews. All the information regarding the study subjects, either extracted from EHRs or collected from the participants expressly for this research, will be protected and treated confidentially for all

purposes, in accordance with the provisions of the Spanish Organic Law 3/2018, of 5 December, on Personal Data Protection and digital rights guarantee (LOPD-GDD) and the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, RGPD). Specifically, all data will be documented anonymously and de-identified, linked to a unique key that is meaningless outside the context of the system. The final resulting database will be exported to a formatted plain text file that will then be compressed and encrypted using a secure algorithm and subsequently be processed and included in a robust and secure database server.

Patient and public involvement

Patients were involved in the DE-imFAR Phase I project as one of the main stakeholders (health professionals, patients, and researchers) in the formative process conducted to map and design de-implementation strategies to reduce PIP, which will be evaluated in the DE-imFAR Phase II project. Specifically, during the Phase I project, a focus group with six patients was conducted to ascertain patients' experience regarding the clinical practice of statin prescription and triangulate physicians discourse.

During the Phase II project, semi-structured interviews will be conducted with patients to assess their perception and experience of the clinical care received as a result of their healthcare professionals´ exposure to the different de-implementation strategies. These interviews will help to better understand from the perspective of the study participants the reasons why the strategies work (or do not work), to explain the variations in the outcomes achieved and to identify the key components and those that need to be optimized.

ETHICS AND DISSEMINATION

The research protocol (version 1; 170221) has been approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 28 July 2023).The Primary Care Research Unit of Bizkaia is explicitly authorized by the Healthcare Directorate of Osakidetza - Basque Health Service to extract and use data from EHRs for research purposes. Since data supporting the present study will mostly concern routine data retrieved from the EHR of the Basque Health Service-Osakidetza, it will be only shared on justified request to the study guarantors. The results of this study will be disseminated via publication in scientific peer-reviewed journals.

LIST OF ABBREVIATIONS

EHR: Electronic health record

CI: Confidence interval

CVD: Cardiovascular disease

CVR: Cardiovascular risk

CPG: Clinical practice guideline

FP: Family physician

IHO: Integrated Healthcare Organization

LDL: Low-density lipoprotein

PIP: Potentially inappropriate prescribing

RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

TC: Total cholesterol

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AUTHORS' CONTRIBUTIONS

AS, JIP, and GG conceived the idea and are the study guarantors. They are primarily responsible for the study design and planning, obtained funding, will be responsible for project coordination and supervision, analysis and interpretation of results, and were responsible for manuscript preparation. RSR, IL, RSV, JAQ, RR, AE, CM, MMC, MM, CGR, RS, MOL, SC, NMI, ML, MGST, and AGA are co-investigators of the projects and collaborated in the study design and/or manuscript preparation; and they will be responsible for study coordination and interpretation of results. AS, JIP, and AGA will be

responsible for the analysis of results. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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WORD COUNT

3763 words excluding title page, abstract, strengths and limitations of this study, list of abbreviations, full references, authors' contributions, funding statement, competing interests statement and acknowledgements.

FIGURES

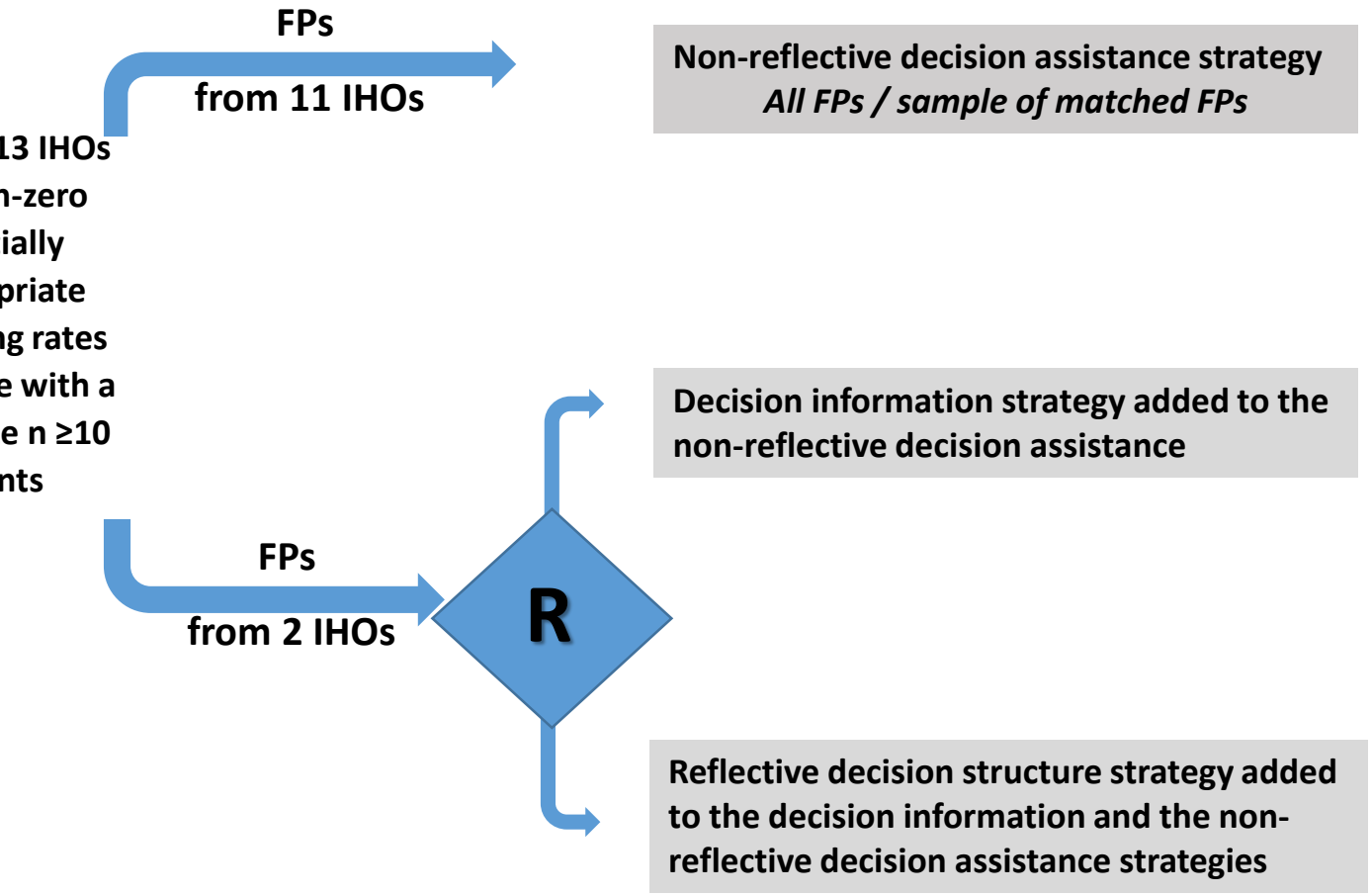
Figure 1. Study design diagram. (PDF format)

Note: FP: Family Physician; IHO: Integrated Healthcare Organization; R: Randomization.

SUPPLEMENTAL FILES

Supplemental File 1 [DE-imFAR de-implementation strategies] (PDF format)

Experimental implementation trial with an additional control group



Change in the incidence of potentially inappropriate prescriptions and provision of lifestyle advice from baseline to 12 months after exposure of physicians to the compared strategies, in 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, with LDL-cholesterol levels between 70 and 189 mg/dl and/or Total Cholesterol between 200 and 289 mg/dl but without ischemic heart/cardiovascular disease and with an estimated cardiovascular risk <7.5% attending during the field-work period

Outcome

The DE-imFAR de-implementation strategies

1. Strategy - *Non-reflective decision assistance strategy*

Support for clinical decision-making on the primary prevention of cardiovascular disease (CVD) in low cardiovascular risk (CVR) patients integrated into the electronic health record (EHR) of the Basque Health Service (Osakidetza), based on pop-up reminders and alerts, together with an interactive media-based algorithm stating the recommended practice and a patient information sheet.

1.1. Target audience

This strategy targets all family phyisicians (FPs) from all 13 Integrated Healthcare Organizations (IHOs) of the Basque Health Service (Osakidetza), both in primary and specialist or hospital care.

1.2. Active components (actions) of the intervention

- "Lighthouse" guiding alert in the REGICOR CVR calculator. Reminders of recommended clinical practice in the primary prevention of CVD that pop-up in the REGICOR CVR calculator when the CVR is estimated in patients aged between 35 and 74 years old. The alert varies depending on the CVR score (<10% or ≥10%).

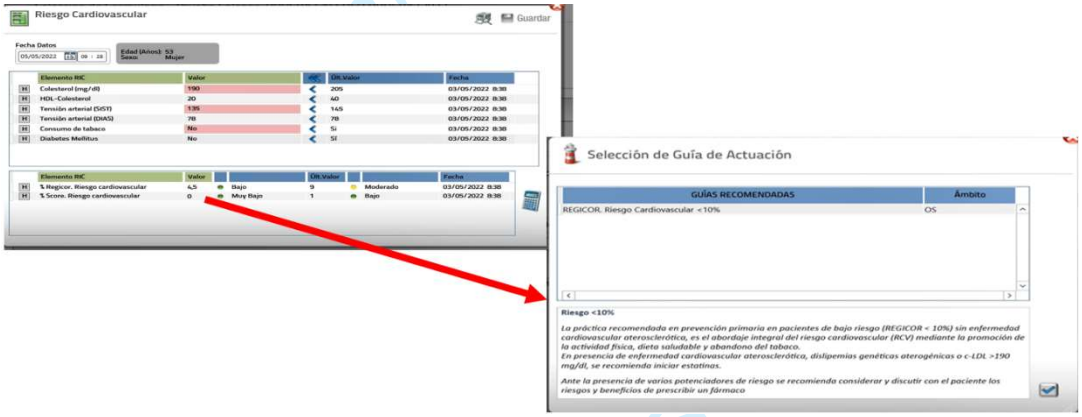


Figure 1. Pop-up reminder ("Lighthouse" guiding alert) in the REGICOR cardiovascular risk calculator when estimated cardiovascular risk score is <10%.

- Alerts in PRESBIDE. Pop-up reminders that appear when the PRESBIDE software is used to prescribe statins. There are three types of alerts depending on the patient's age group (<35, 35-74, and ≥75 years old). Further, links are providedto a decision-making algorithm and a patient information sheet (i-botika).
- Decision-making algorithm: "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease". Clinical decision tree presenting potential courses of action based on clinical practice guidelines (CPGs), specifically for reducing cholesterol for the primary prevention of CVD in patients of different age groups and levels of CVR. Interactive decision-making support tool, developed by researchers collaborating in the DE-imFAR project, that also includes links for downloading two further documents: one providing information on CVD risk factors and the other on the 5As "Ask, Assess, Advise, Assist, Arrange" clinical intervention, recommended for promoting healthy lifestyles.

- Patient information sheet on cholesterol levels (i-botika: "Cholesterol levels are not the only thing", developed in the framework of this project, providing information on high cholesterol levels and their role together with other risk factors associated with CVD)

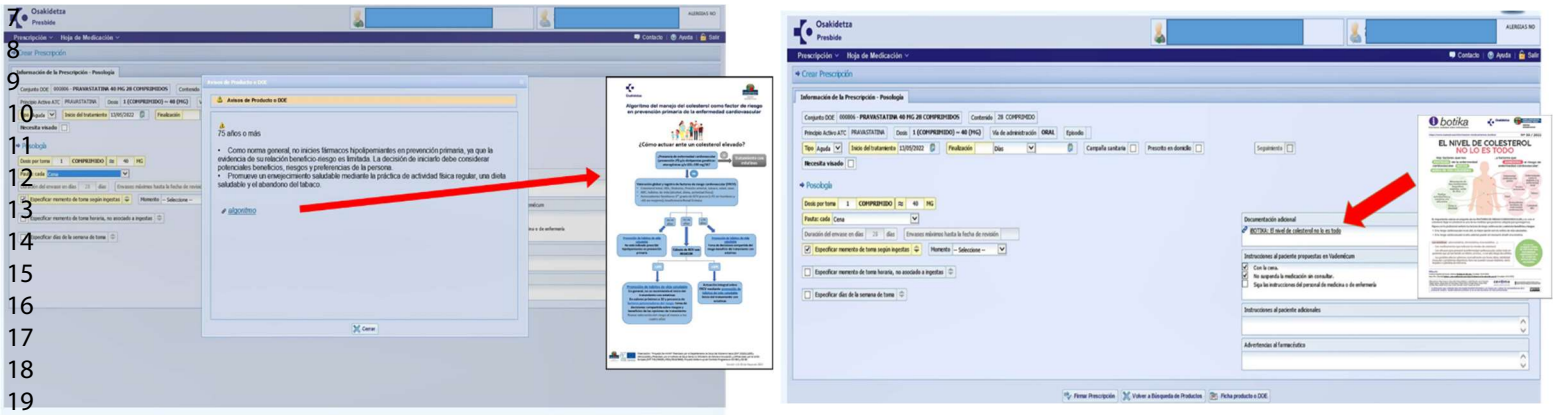


Figure 2. a). Pop-up reminder in the PRESBIDE software with recommendations on the prescribing of statins in people ≥75 years old that includes a link to the "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease" algorithm, b) PRESBIDE form for prescribing statins, with a link to the patient information sheet (i-botika).

1.3. Objectives: *Determinant - What needs to change*

Pop-up alerts, reminders, and an algorithm

Cognitive and interpersonal skills:

✓ Enhance skills to enable appropriate prescribing of statins based on clinical practice recommendations

Attention, memory, and decision-making processes:

✓ Promote recall of recommended clinical practice in the primary prevention of CVD, reducing the impact of therapeutic inertia

Context and resources:

✓ Develop support systems in the EHR as reminders of and to promote the practices recommended in CPGs for the primary prevention of CVD (avoiding statins and encouraging healthy lifestyles)

✓ Restrict or impede inappropriate prescribing of statins due to clinical prescribing behavior driven by simplicity and speed

Emotion/Reinforcement:

✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended practice and this is made evident by alerts

Patient information sheet

Social influence (patient involvement):

✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits

✓ Increase patient knowledge of the criteria and courses of action recommended in CPGs (concerning cholesterol, CVD, and CVR)

1.4. Choice architecture techniques

A. Decision Information

A1. Translate information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., Presenting the contents of CPGs in several different ways (i.e., text within alerts, in the form of an algorithm, etc.).
Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.
A2. Make information visible: make necessary information readily accessible.
Make external information visible: make decision-relevant information visible, e.g., text within alerts recalling the CPGs.

B. Decision structure
B1. Change choice defaults
Prompted choice: avoid the status quo bias or default effects because of inertia or assumed recommendations, e.g., pop-up alerts.
B2. Change option-related effort: change physical effort.
Increase physical effort: e.g., pop-up alerts.

C. Decision assistance
C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., Pop-up alerts with the recommendation to not prescribe statins.

1.5. Exposure
- "Lighthouse" guiding alert in the REGICOR CVR calculator: by clicking to "save" the result after estimating CVR
- Alerts in PRESBIDE: by starting to prescribe statins or clicking on the links to the algorithm or the patient information sheet

2. Strategy - *Reflective/non-reflective decision information strategy*

Corporate campaign entitled "Stopping low-value prescribing" (in Spanish: "*Abandono de prescripciones farmacológicas de escaso valor*"), promoted through a knowledge dissemination strategy based on circulars and notifications (e.g., mass mailing and internal newsletters) concerning content, informative material and documents on recommended clinical practice and improving the appropriateness and/or optimization in prescribing drug treatments, including that of statins for the primary prevention of CVD, made available to FPs on the corporate intranets of the Ezkerraldea-Enkarterri-Cruces (EEC) and Barakaldo-Sestao (BS) IHOs, part of the Basque Health Service (Osakidetza).

2.1. Target audience

This strategy targets all FPs from the EEC and BS IHOs, who will also be exposed to the first strategy, namely, non-reflective decision assistance.

2.2. Active components (actions) of the intervention

- Adherence to and implementation of best practice pages on the EEC and BS IHO intranets which have dedicated sections focused on improving the appropriateness of the use of statins providing easy access to the CPGs and recommended practice for the primary prevention of CVD.

Figure 3. Main page of the adherence to and implementation of best practice ("A*decuación e Implementación de Buenas Prácticas*") section on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet and main page of the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section. Equivalent pages were also created on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Corporate dissemination campaign: activities aimed at attracting FPs to the pages created on the EEC and BS IHO intranets, in order that they access the information and documents available
  - News story on the launch of the campaign with links to the pages on the corporate intranets, e.g.,

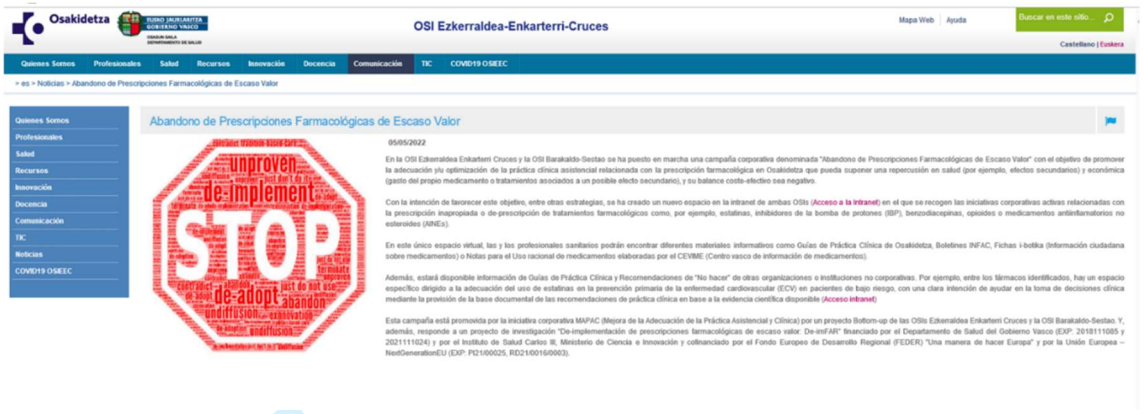


Figure 4. News story published on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet to announce the launch of the corporate "Stopping low-value prescribing" campaign and the development of pages on its intranet and that of the Barakaldo-Sestao Integrated Healthcare Organization, on May 5, 2022. The story was also published on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Monthly newsletter: reporting of the launch of the campaign in the monthly newsletter circulated by the BS IHO to all its employees
- Mass mailing on the launch of the campaign with links to the pages on the corporate intranets
- Revitalization of the corporate campaign: periodic publication of news stories on the EEC and BS IHO intranets with content related to the campaign informing FPsof the updating of content/informative materials (for example, any changes in the recommendations in CPGs and INFAC [pharmacotherapy information] newsletters) on the dedicated pages on the intranets of both IHOs, aimed at improving the appropriateness of the use of statins in primary prevention of CVD, including links to these pages.

- Justification email from the Healthcare Management of the Basque Health Service, telling all FPs about the initiatives being put in place to improve the approach to the prevention of CVD, improving the appropriateness of statin prescribing, and encouraging the provision of healthy lifestyle advice, among other components.

2.3. Objectives: Determinant - *What needs to change*

Knowledge:
- ✓ Increase awareness of the problem of the inappropriate prescribing of statins
- ✓ Increase knowledge of the CPGs on the primary prevention of CVD, in particular, the appropriate or recommended care as a function of the estimated CVR
- ✓ Provide evidence-based standardized and up-to-date clinical guidelines

Behavior regulation:
- ✓ Encourage reflection on practice/performance in relation to inappropriate prescribing of statins in the primary prevention of CVD

Beliefs about capabilities:
- ✓ Strengthen the belief that the prescribing of statins is not as straightforward and safe as might be thought
- ✓ Strengthen the belief that statin treatment is not easy for patients (dosage)

Beliefs about consequences:

- ✓ Strengthen the belief that not prescribing statins for the primary prevention of CVD is not the same as "not treating".
- ✓ Strengthen the belief that statins are not more effective in reducing cardiovascular events than healthy lifestyle promotion in the primary prevention of CVD
- ✓ Strengthen the belief that statins, in the primary prevention of CVD, may have adverse effects and are not risk-free.

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers.
- ✓ Strengthen understanding that the role of FPs goes beyond that of prescribing drugs.

Social influence:

- ✓ Increase awareness of the organizational goals for reducing inappropriate prescribing of statins in the primary prevention of CVD.
- ✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits
- ✓ Increase patient knowledge of the criteria and recommended courses of action (concerning cholesterol, CVD, and CVR)

Emotion/reinforcement:

- ✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended clinical practice and this is made evident by alerts.

Cognitive and interpersonal skills:

- ✓ Enhance skills to enable the appropriate prescribing of statins based on CPGs.

2.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., clinical guidelines, algorithm, patient information leaflet.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.

A2. Make information visible: make necessary information readily accessible.

Make external information visible: make decision-relevant information visible, e.g., Links about inappropriate statin prescription in the Basque Health Service (Osakidetza), adverse effects of statins and cholesterol treatment, and promotion of the campaign through emails and news.

A3. Provide social reference point: influence decision-making through other's behavior.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., links about inappropriate statin prescription in the Basque Health Service (Osakidetza).

B. Decision structure

B2. Change option-related effort: modify the physical or financial effort involved in the decision-making process.

Change physical effort, e.g., decreasing physical effort by making all theme-related information accessible on the same website and including links to the website in the text of emails and news stories.

C. Decision assistance

C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., links to clinical guidelines with recommended practice about CVD primary prevention, and information about adverse effects of statins.

C2. Provide social reference point: influence decision-making through other's behavior.

Refer to opinion leader: use them as information disseminators to improve the impact of the campaign, e.g., Setting of goals in an email sent by an opinion leader, using the source as much as the content of the message to improve the impact of the campaign.

2.5. Exposure

- By accessing the pages of the EEC and BS IHO corporate intranet and clicking on the links to the CPGs, INFAC newsletters, i-botika patient information sheets, recommendations, etc. available in the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section
- By accessing the news section on the dedicated pages on the intranets of EEC and BS IHOs

3. Strategy - *Reflective decision structure strategy*

Sending of regular personalized *Audit & Feedback (A&F)* reports with practice- and organizational-level performance indicators of the FPsregarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of CVD in low-risk patients in the Basque Health Service

3.1. Target audience

This strategy targets a randomly selected set of FPs from the EEC and BS IHOs, who will also be exposed to the previously described interventions, namely, *non-reflective decision assistance and decision information*.

3.2. Active components (actions) of the intervention

- Informative email concerning the sending of A&F reports, including the possibility to opt out: email with information for primary care FPs of the EEC and BS IHOs on the sending of regular personalized A&F reports, in the framework of the corporate campaign, with the goal of encouraging adherence to recommendations and stopping inappropriate prescribing of statins

- A&F reports mailing: periodic A&F reports with indicators describing global performance across the Basque Health Service: a) rate of new potentially inappropriate prescribing of statins to people without CVD and with REGICOR CVR scores <7.5% and practice in the promotion of healthy habits in these patients; b) rate of documentation of CVR (in the 2 years before the prescription date) in all 40- to 75-year-olds with no clinical history of CVR who are newly prescribed statins. Future A&F reports are expected to contain a link to a short voluntary exercise on goal setting for improving the appropriateness of statin prescribing for the primary prevention of CVD

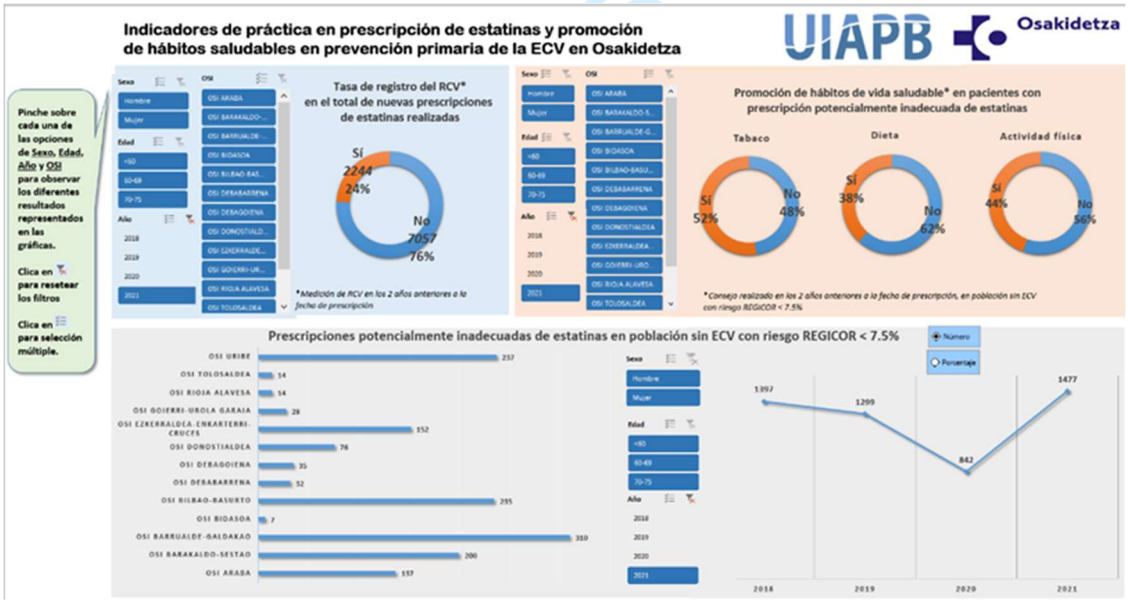


Figure 5. Draft of the Audit & Feedback report with practice- and organizational-level performance indicators of the family physicians regarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of cardiovascular disease in low-risk patients in the Basque Health Service

3.3. Objectives: Determinant - What needs to change

Knowledge:

- ✓ Increase awareness of the problem of the inappropriate prescribing of statins

Behavior regulation:

- ✓ Make data available on inappropriate prescribing of statins for the primary prevention of CVD
- ✓ Provide tools for the setting of clear specific goals, at personal and organizational levels, regarding the reduction of inappropriate prescribing of statins for the primary prevention of CVD

Active reflection on personal practice:

- ✓ Encourage further reflection on practice/performance in relation to inappropriate prescribing of statins for the primary prevention of CVD

Intentions:

- ✓ Reduce the intention to prescribe statins inappropriately and increase the intention to promote healthy lifestyles for the primary prevention of CVD

Goals:

- ✓ Encourage commitment to practice in the primary prevention of CVD that is in accordance with recommendations
- ✓ Increase the motivation to promote healthy lifestyles in the primary prevention of CVD

Beliefs about capabilities:

- ✓ Strengthen self-efficacy and enhance the skills required for promoting healthy lifestyles

Emotion:

- ✓ Strengthen self-confidence about not prescribing statins for the primary prevention of CVD
- ✓ Foster belief in the safety of and trust in the courses of action recommended in the guidelines
- ✓ Experience a negative emotion after inappropriate prescribing

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers
- ✓ Strengthen understanding that the role of FPs goes beyond prescribing drugs

Reinforcement:

- ✓ Generate positive/negative reinforcement related to good/poor performance in the primary prevention of CVD.

3.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., presenting prescription rate data in a simple, user-friendly way, namely, on a dashboard.

A2. Make information visible: make necessary information readily accessible.

Make own behavior visible: feedback.

Make external information visible: make decision-relevant information visible, e.g., showing the prescription rates of other FPs and other IHOs.

A3. Provide social reference point: influence decision-making through the behavior of others.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., showing other FPs' prescribing behavior.

B. Decision structure

B2. Change opinion-related effort: modify the physical or financial effort involved in the decision-making process.

Decrease physical effort: collect all prescribing data in one file, e.g., dashboard.

C. Decision assistance

C2. Facilitate commitment: overcome constrained self-control and bridge the intention-behavior gap.

Support self-commitment: arrange with the aim of helping fulfill a plan, e.g., self-commitment questionnaire

3.5. Exposure

By opening the A&F reports received by email.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9, 12

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12,17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Reference: Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200-207. doi: 10.7326/0003-4819-158-3-201302050-00583.

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Keywords:	Primary Care < Primary Health Care, Clinical Decision-Making, Clinical Trial, PREVENTIVE MEDICINE, Implementation Science, Cardiovascular Disease

TITLE PAGE

Title

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.

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ABSTRACT

Introduction

This study aims to reduce potentially inappropriate prescribing (PIP) of statins and foster healthy lifestyle promotion in cardiovascular disease (CVD) primary prevention in low-risk patients. To this end, we will compare the effectiveness and feasibility of several de-implementation strategies developed following the structured design process of the Behavior Change Wheel targeting key determinants of clinical decision-making process in CVD prevention.

Methods and analysis

A cluster randomized implementation trial, with an additional control group, will be launched, involving family physicians (FPs) from 13 Integrated Healthcare Organizations (IHOs) of Osakidetza-Basque Health Service with non-zero incidence rates of PIP of statins in 2021. All FPs will be exposed to a non-reflective decision assistance strategy based on reminders and decision support tools. Additionally, FPs from two of the IHOs will be randomly assigned to one of two increasingly intensive de-implementation strategies: adding a decision information strategy based on knowledge dissemination, and a reflective decision structure strategy through audit/feedback. The target population comprises 45- to 74-year-old women and 40- to 74-year-old men with moderately elevated cholesterol levels but no diagnosed CVD and low cardiovascular risk (REGICOR <7.5%), who attend at least one appointment with any of the participating FPs (May 2022-May 2023), and will be followed until May 2024. We use the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework to evaluate outcomes. The main outcome will be the change in the incidence rate of PIP of statins and healthy lifestyle counseling in the study population 12 and 24 months after FPs' exposure to the strategies. Moreover, FPs' perception of their feasibility and

acceptability, and patient experience regarding quality of treatment received will be evaluated.

Ethics and dissemination

The study was approved by the Basque Country Clinical Research Ethics Committee and was registered in ClinicalTrials.gov (NCT04022850). Results will be disseminated in scientific peer-reviewed journals.

Keywords: Inappropriate Prescribing, Cardiovascular Diseases / prevention & control, Hypercholesterolemia / drug therapy, Implementation Science, Research Design, Primary care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- An strength of the DE-imFAR study is that it involves an efficient design that combines experimental and non-experimental comparisons through two randomly assigned intervention arms and one non-randomized control arm to test the comparative effectiveness on reducing potentially inappropriate prescribing (PIP) of statins and increasing healthy lifestyle promotion of several de-implementation strategies deployed in real-world settings.
- Counting with one non-randomized control arm is a strength because it allows capturing the effect of temporal trends, regression to the mean, and the learning curve due to the reference/background strategy to which all targeted family physicians (FPs) are exposed, when comparing this reference strategy with the two experimental de-implementation strategies.
- Another strength is the use of qualitative methods to better understand from the perspective of the study participants the reasons why (why not) the strategies work, to explain the variations in the results achieved and to identify the essential components of the strategy and those that will require to be optimized.

- To the best of our knowledge, the DE-imFAR study is one of the firsts of its kind that specifically uses the RE-AIM framework for the evaluation of the study results in terms of public health impacts.
- The main limitation lies in the planned comparisons of the randomized groups with respect to the control arm, likely to differ to some extent at baseline because of the non-random process of generation. To tackle this limitation, in addition to evaluating the change in PIP incidence in all eligible FPs, a matching strategy with the selection of one matched FP from this non-randomized group for each of the randomized FPs will be performed seeking to increase comparability and reduce potential bias.

INTRODUCTION

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].

Nonetheless, reducing or eliminating low-value practices is a complex matter, as drivers fostering or maintaining them seem to operate at multiple levels and be context specific. Therefore, in order to design effective and efficient corrective measures, a careful process of formal analysis of the determinants of the clinical behavior in question is needed. In this context, behavior change theory has been extensively applied to understand the factors that may influence clinical behavior, identify and design possible techniques and interventions that could be used to change it, and explain the mechanisms through which such interventions operate [3,4].

The DE-imFAR study (from the Spanish for de-implementation of low-value pharmacological prescribing) is a two-phase project [5] that aims to apply behavioral

science theory within a structured process involving the main stakeholders (health professionals, patients, and researchers) in the design, deployment, and evaluation of targeted de-implementation strategies for reducing potentially inappropriate prescribing (PIP). 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].

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].

Secondly, we applied two of the most successfully used behavior change theories in field of Implementation Science, the Theoretical Domains Framework (TDF) [3,11,12] and Behavior Change Wheel (BCW) [13], to a) understand and define the problem (low-value practice) in behavioral terms and to select and specify the target behaviors; b) identify

the factors that may influence it; and c) map targeted de-implementation and implementation strategies conducive to reducing the low-value practice in question. Briefly, after having prioritized our specific target behavior (that is "clinician decision-making on intervention/treatment to be provided based on objective clinical information and subjective schemas and heuristics"), identified determinants (facilitators of the non-desired behavior of PIP of statins and barriers to applying the recommended clinical practice behavior of promoting healthy lifestyles), and mapped specific behavior change techniques, three types of de-implementation strategies were selected based on being the most potentially effective, feasible, and acceptable for influencing decision-making through different mechanisms [14]. Hence, the three strategies derived from the systematic theory- and evidence-based intervention design process were: a) a non-reflective decision assistance strategy based on providing evidence-based information communication technology tools to help and guide decision-making; b) a decision information strategy based on the dissemination of the evidence concerning CVD primary prevention framed in a corporate campaign encouraging family physicians (FPs) to move away from PIP; and c) a reflective decision structure strategy encouraging reflection on actual performance based on an audit/feedback system [14].

According to the literature review performed in Phase I of the DE-imFAR project [14] regarding the evaluation of effective intervention strategies for the reduction of low-value prescribing [15-24], multicomponent interventions—combining passive dissemination interventions, based on training in or dissemination of clinical practice guidelines (CPGs), with more proactive interventions incorporating decision-making aids or the sending of audit/feedback— achieve the most positive results. Specifically, in the context of PIP of statins, a positive impact has been observed on documentation of CVR and prescription adequacy using a) multi-component dissemination strategies including informative web pages, and implementation of electronic CPGs compared to routine practice and training activities, and b) interventions based on sending clinical scenarios and cases, and

audit/feedback to professionals, and decision support tools [19-23]. All these strategies can be conceived and theoretically differentiated as a function of the way they may affect clinicians' decision-making [25]. There is plenty of evidence demonstrating that it is possible to de-implement inappropriate medical practices through the lens of clinician cognition using audit/feedback, decision support tools, etc. [26-28]. In this context, the growing field of choice architecture aims to explore how the structure and framing of decision situations influence the choice of certain behaviors over alternative ones. On the one hand, FPs' decision-making ability can be influenced by unconscious processes that occur in response to environmental or emotive cues, that is, through type 1 (or non-reflective) cognition. On the other, clinicians' conscious intention to change can be promoted by engaging their reflective cognition to consciously evaluate and correct their inappropriate behavior, that is, using type 2 (or reflective) cognition [29]. However, further research is needed to determine whether these evidence-based and barrier-specific strategies for de-implementation identified in DE-imFAR Phase I are also effective in our context.

Thus, the goal of the present Phase II of the DE-imFAR study is to assess the potential effectiveness and feasibility of this set of de-implementation strategies to reduce the PIP of statins in the primary prevention of CVD (low-risk patients, REGICOR [30] CVR score <7.5%, with moderately elevated cholesterol levels, low-density lipoprotein (LDL) cholesterol levels between 70 and 189 mg/dL and/or total cholesterol (TC) between 200 and 289 mg/dL, but without ischemic heart disease/CVD).

Specifically, we aim to answer the following research questions:

1. Observational comparison questions:

As compared to a reference non-reflective decision assistance strategy based on reminders and decision support tools incorporated into the electronic health record (EHR) for helping clinical decision-making, what is the effect on the incidence of PIP of

statins in CVD primary prevention and the rate of delivery of healthy lifestyle counseling of a) a decision information strategy comprising a corporate "Stopping Low-Value Prescribing" campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD; b) a reflective decision structure strategy based on an audit/feedback system; and c) any intervention based on a reflective de-implementation strategy (a or b)?

2. Experimental comparison question:

As compared to a decision information strategy comprising a corporate "Stopping Low-Value Prescribing" campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD, together with the non-reflective decision assistance intervention based on reminders and decision support tools incorporated into the EHR for helping clinical decision-making, what is the effect on the incidence of PIP of statins in CVD primary prevention and the rate of delivery of healthy lifestyle counseling of adding a reflective decision structure strategy based on an audit/feedback system?

METHODS AND ANALYSIS

Design

A cluster randomized implementation trial with an additional control group will be conducted for evaluating the potential effectiveness and feasibility of three de-implementation strategies (Figure 1). A mixed methods evaluation will be undertaken: quantitative for assessing the implementation results at the professional level (effectiveness outcomes regarding changes in rates of PIP and healthy lifestyle counseling) and qualitative for assessing the feasibility and perceived impact of the de-implementation strategies from the FPs' perspective and the experience and satisfaction of patients concerning the clinical care received. The unit of randomization and intervention will be the primary care FP, while observation and analysis will be performed at professional and patient levels. The DE-imFAR research protocol was reviewed and

approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 31 January 2024).

Osakidetza-Basque Health Service provides universal coverage and services are free at the point of use, aside from co-payment for drugs, funded through regional general taxation. Primary, specialized, and social health-related service provision is organized around 13 Integrated Healthcare Organizations (IHOs) that cover the 3 provinces of the region of the Basque Country: Araba, Bizkaia, and Gipuzkoa. Each resident is on the list of one FP or pediatrician who offers comprehensive primary care and refers patients for hospital and specialty services. Primary care professionals work in full-time teams, including FPs, pediatricians, nurses, and administrative staff based at local centers providing access to healthcare for users in a defined geographical area.

We used the SPIRIT reporting guidelines and the SPIRIT checklist when writing the present study [31].

Participants

Eligibility criteria for the study will be:

1. Professionals: FPs belonging to any of the 13 IHOs of Osakidetza with a non-zero annual incidence rate of PIP of statins at baseline (2021) with a minimum cluster size of n ≥10 patients

2. Patients: All 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL but without ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% who attend at least one appointment at the participating FPs' practices during the study period from May 2022 to May 2023, and followed until May 2024.

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.

De-implementation strategies evaluated

Within the present Phase II of the DE-imFAR study, the three types of strategies that were derived from Phase I systematic theory- and evidence-based intervention design process will be set up (see Supplemental file 1 for a more detailed description):

1) *A non-reflective decision assistance strategy*, that targets type 1 cognitive processes through decision support systems that prompt and remind FPs about the recommended practice in a simplified way, thereby reducing the cognitive burden. In short, pop-up reminders and alerts with associated messages will be incorporated into the REGICOR CVR calculator in OSABIDE (Osakidetza's EHR system) and within the prescription pathway in PRESBIDE (the electronic drug prescribing component). The tools devised include an interactive media-based algorithm stating the recommended practice for the primary prevention of CVD in low-risk patients developed by an expert panel, and a patient information sheet depicting and promoting evidence-based practice for addressing cholesterol in the primary prevention of CVD in low-risk patients.

2) *A both reflective and non-reflective decision information strategy***,** targeting both types 1 and 2 cognitive processes, based on the principle of knowledge dissemination and consisting of a "Stopping Low-Value Prescribing" campaign run by the organization (Osakidetza- Basque Health Service) that also eases access (decreasing the physical effort required) to the evidence-based CPGs for the primary prevention of CVD in low-risk patients.

3) *A reflective decision structure strategy*, that targets type 2 cognition through an audit/feedback system reporting data with practice- and organizational-level performance indicators regarding PIP of statins and healthy lifestyle promotion to prompt reflection about their own care practice, provided along with intention formation and goal-setting-focused messages.

Allocation of intervention units to compared groups

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). The allocation sequence within these two groups will be generated using a specific restricted randomization scheme by one member of the research team. The sequence will be concealed at the coordinating center. In all cases, FPs will only be allocated to the study groups after they have agreed to participate through an opt-out strategy. The data analyst and the staff in charge of measurements will be blind to FP allocation to study arms. Given that the audit/feedback strategy will involve regular reports sent privately to individuals, participants in the experimental arms are also expected to be blind to group allocation.

Outcome measures

To evaluate the implementation of the de-implementation strategies compared in terms of public health impact, we will use the following dimensions of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [33]:

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.

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.

As a secondary outcome, we will measure the change in the incidence of CVR (REGICOR) documentation in the EHR, from baseline to 12 months after exposure of FPs to the de-implementation strategies compared, in 40- to 74-year-old men and 45- to 74-year-old women without ischemic heart disease/CVD.

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 reduce PIP of statins and/or increase health promotion activities in the target population; and their representativeness.

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].

Maintenance

Change in the incidence of PIP of statins and provision of healthy lifestyle counseling in eligible patients, 24 months after exposure of FPs to the de-implementation strategies compared to levels observed at the 12-month assessment.

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).

Feasibility Evaluation

The professionals' perception of the feasibility of and satisfaction with the de-implementation strategies to enhance the provision of the recommended CVD prevention clinical practice will be assessed through key-informant semi-structured individual interviews. 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 interview script will contain open-ended questions that will focus on the perceived value of the de-implementation strategies and recommendations for their optimization.

Exposed patients' perception and experience regarding the quality of CVD prevention care received will also be assessed through key-informant semi-structured interviews. The interviews will be carried out with at least ten patients until data saturation is reached: at least five with patients who have been clinically managed according to recommended practice and five who have not. The interview script will contain open-ended questions that will focus on the perceived CVD primary prevention care received.

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.

Analysis

Frequencies and proportions along with the corresponding 95% confidence intervals (CIs) will be used to describe the prevalence and cumulative incidence of PIP of statins and healthy lifestyle counseling in the primary prevention of CVD by FPs. The primary effectiveness outcomes will be the changes in the cumulative incidence of PIP of statins and healthy lifestyle counseling in patients from the target population (individuals with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL without past or current ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% attending at least one clinical appointment with their FP in the study period), from baseline to 12 months after exposure of FPs to the de-implementation strategies. Therefore, to evaluate the impact of the three de-implementation strategies, we will estimate the relative reduction in the risk of receiving PIP of statins in patients from the target population assigned to the experimental strategies over that in patients from the non-randomized group (non-reflective decision assistance strategy group). 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 taking into account both FP-related characteristics (e.g., baseline rate of PIP of statins, etc.) and characteristics of the population of patients assigned to the FP (e.g., average socioeconomic status, etc.). Change in PIP of statins incidence rates from baseline to those observed 12 and 24 months after FPs' exposure to the de-implementation strategies and the relative risk reduction will be estimated with the corresponding 95% CIs. To adjust for potential confounding factors, stratified statistical analyses and logistic models will be used. These models will be extended to generalized mixed effects models to take into account the hierarchical structure of data (patients nested in FPs and FPs in primary care teams), with fixed effects (comparison group, effect of time on outcome indicators, and time-group interactions) and random effects on the intercept and the time slope (for each patient, FP, center, etc.). These models will be adjusted for potential confounders, following a backward strategy, guided by the stratified analyses. A similar approach will be taken to analyze the secondary outcomes. The analyses will be carried out with SAS (v. 9.2, SAS Institute, Cary, NC, USA), and R (R Development Core Team, 2014).

Calculation of the required sample size for the most unfavorable scenario, this being the comparison between the two randomized de-implementation strategies, was based on: i) a baseline incidence of statin PIP of 7.4% estimated among the patients of the target population seen in 2021 by FPs with an incidence of PIP > 0% with a minimum cluster size n ≥10 patients, ii) an intra-class correlation coefficient of 0.01, iii) an average cluster size of 39 patients with a coefficient of variation of 0.63, iv) $\alpha = 0.05$ and statistical power of 80%, and v) hypothetical decreases in annual PIP rates of 20% in the decision information strategy group and 50% in the decision structure strategy group. With these assumptions, it was estimated that at least 58 FPs were required for each experimental arm.

Management, quality, and safety in data processing

This study will be carried out in accordance with the international standards for conducting epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies [36]. This is a prospective intervention study focused mainly on the collection of information from data recorded by health professionals in the Osakidetza EHR (OSABIDE) under routine clinical practice conditions. 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), patients' sociodemographic and clinical characteristics (age, sex, CVR, active health problems recorded in EHR, socioeconomic status, etc.) and clinical outcomes 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. The Primary Care Research Unit of Bizkaia is formally authorized to extract and use data from the EHR for research purposes by the Healthcare Directorate of Osakidetza. On the other hand, it will be necessary to inform participants about the study and obtain their written informed consent concerning the information collected directly from the professionals and patients under study through the key-informant semi-structured interviews (Supplemental File 2 and 3). All the information regarding the study subjects, either extracted from EHRs or collected from the participants expressly for this research, will be protected and treated confidentially for all purposes, in accordance with the provisions of the Spanish Organic Law 3/2018, of 5 December, on Personal Data Protection and digital rights guarantee (LOPD-GDD) and the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, RGPD). Specifically, all data will be documented anonymously

and de-identified, linked to a unique key that is meaningless outside the context of the system. The final resulting database will be exported to a formatted plain text file that will then be compressed and encrypted using a secure algorithm and subsequently be processed and included in a robust and secure database server.

Patient and public involvement

Patients were involved in the DE-imFAR Phase I project as one of the main stakeholders (health professionals, patients, and researchers) in the formative process conducted to map and design de-implementation strategies to reduce PIP, which will be evaluated in the DE-imFAR Phase II project. Specifically, during the Phase I project, a focus group with six patients was conducted to ascertain patients' experience regarding the clinical practice of statin prescription and triangulate physicians discourse [14].

During the Phase II project, semi-structured interviews will be conducted with patients to assess their perception and experience of the clinical care received as a result of their healthcare professionals´ exposure to the different de-implementation strategies. These interviews will help to better understand from the perspective of the study participants the reasons why the strategies work (or do not work), to explain the variations in the outcomes achieved and to identify the key components and those that need to be optimized as well as triangulating the analysis.

ETHICS AND DISSEMINATION

The research protocol (version 1; 170221) has been approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 31 January 2024).The Primary Care Research Unit of Bizkaia is explicitly authorized by the Healthcare Directorate of Osakidetza - Basque Health Service to extract and use data from EHRs

for research purposes. Since data supporting the present study will mostly concern routine data retrieved from the EHR of the Basque Health Service-Osakidetza, it will be only shared on justified request to the study guarantors. The results of this study will be disseminated via publication in scientific peer-reviewed journals.

LIST OF ABBREVIATIONS

EHR: Electronic health record

BCW: Behavior Change Wheel

CI: Confidence interval

CVD: Cardiovascular disease

CVR: Cardiovascular risk

CPG: Clinical practice guideline

FP: Family physician

IHO: Integrated Healthcare Organization

LDL: Low-density lipoprotein

PIP: Potentially inappropriate prescribing

PC: Primary care

RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

TC: Total cholesterol

TDF: Theoretical Domains Framework

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AUTHORS' CONTRIBUTIONS

AS, JIP, and GG conceived the idea and are the study guarantors. They are primarily responsible for the study design and planning, obtained funding, will be responsible for project coordination and supervision, analysis and interpretation of results, and were responsible for manuscript preparation. RSR, IL, RSV, JAQ, RR, AE, CM, MMC, MM, CGR, RS, MOL, SC, NMI, ML, MGST, and AGA are co-investigators of the projects and collaborated in the study design and/or manuscript preparation; and they will be responsible for study coordination and interpretation of results. AS, JIP, and AGA will be responsible for the analysis of results. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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WORD COUNT

4353 words excluding title page, abstract, strengths and limitations of this study, list of abbreviations, full references, authors' contributions, funding statement, competing interests statement and acknowledgements.

FIGURES

Figure 1. Study design diagram. (PDF format)

Note: FP: Family Physician; IHO: Integrated Healthcare Organization; R: Randomization.

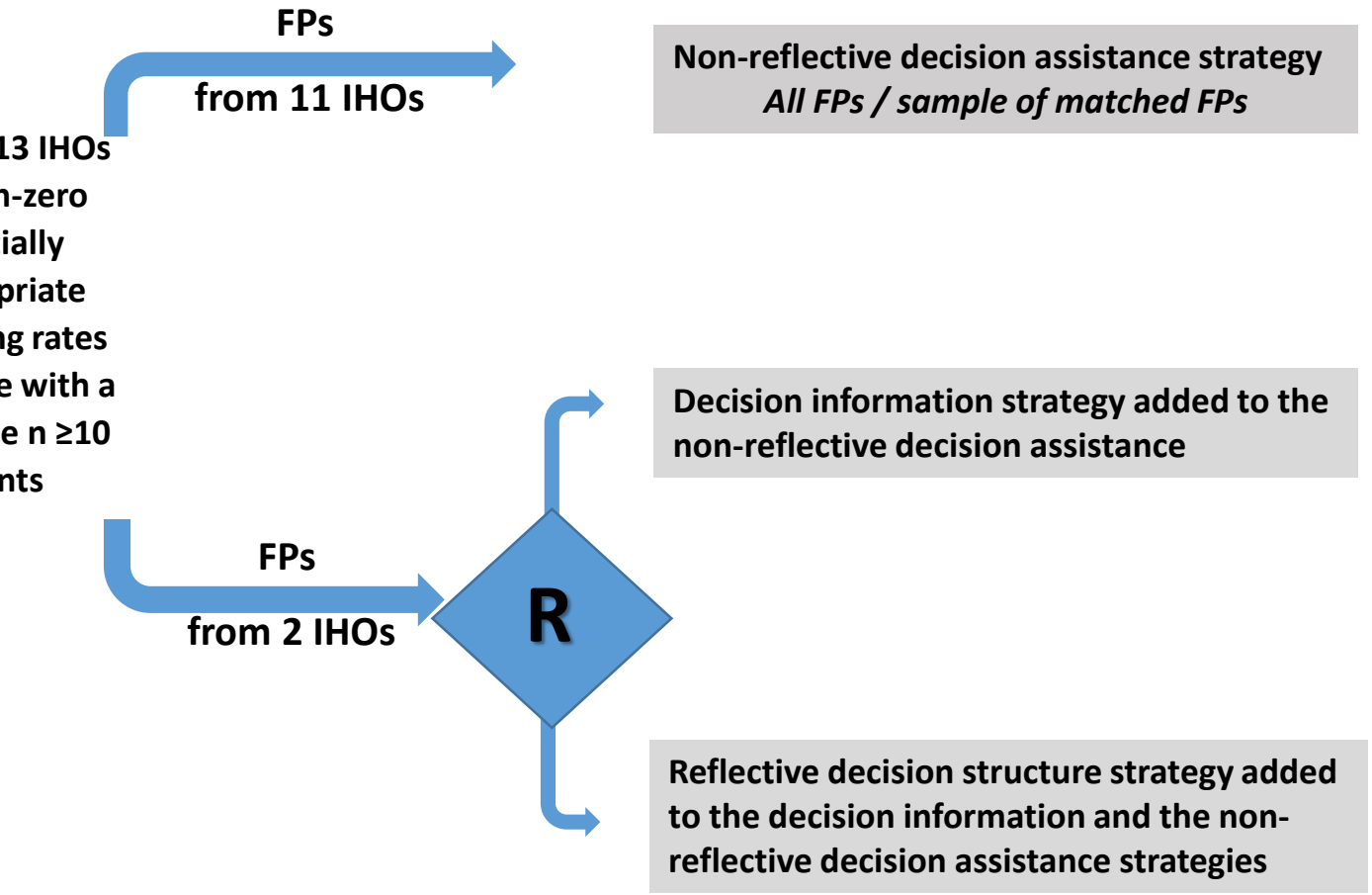
SUPPLEMENTAL FILES

Supplemental File 1 [DE-imFAR de-implementation strategies] (PDF format)

Supplemental File 2 [DE-imFAR Phase II - Informed Consent Form for Family Physicians (Spanish)] (PDF format)

Supplemental File 3 [DE-imFAR Phase II - Informed Consent Form for Patients (Spanish)] (PDF format)

Experimental implementation trial with an additional control group



Change in the incidence of potentially inappropriate prescriptions and provision of lifestyle advice from baseline to 12 months after exposure of physicians to the compared strategies, in 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, with LDL-cholesterol levels between 70 and 189 mg/dl and/or Total Cholesterol between 200 and 289 mg/dl but without ischemic heart/cardiovascular disease and with an estimated cardiovascular risk <7.5% attending during the field-work period

Outcome

The DE-imFAR de-implementation strategies

1. Strategy - *Non-reflective decision assistance strategy*

Support for clinical decision-making on the primary prevention of cardiovascular disease (CVD) in low cardiovascular risk (CVR) patients integrated into the electronic health record (EHR) of the Basque Health Service (Osakidetza), based on pop-up reminders and alerts, together with an interactive media-based algorithm stating the recommended practice and a patient information sheet.

1.1. Target audience

This strategy targets all family phyisicians (FPs) from all 13 Integrated Healthcare Organizations (IHOs) of the Basque Health Service (Osakidetza), both in primary and specialist or hospital care.

1.2. Active components (actions) of the intervention

- "Lighthouse" guiding alert in the REGICOR CVR calculator. Reminders of recommended clinical practice in the primary prevention of CVD that pop-up in the REGICOR CVR calculator when the CVR is estimated in patients aged between 35 and 74 years old. The alert varies depending on the CVR score (<10% or ≥10%).

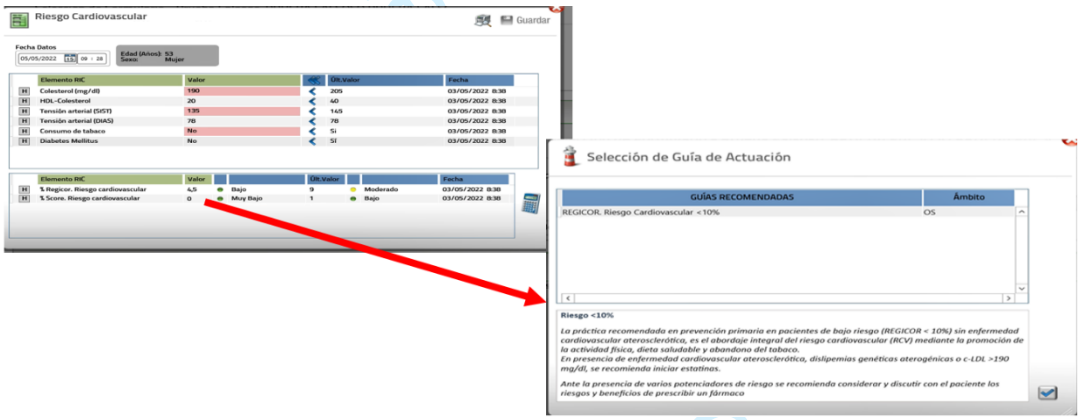


Figure 1. Pop-up reminder ("Lighthouse" guiding alert) in the REGICOR cardiovascular risk calculator when estimated cardiovascular risk score is <10%.

- Alerts in PRESBIDE. Pop-up reminders that appear when the PRESBIDE software is used to prescribe statins. There are three types of alerts depending on the patient's age group (<35, 35-74, and ≥75 years old). Further, links are providedto a decision-making algorithm and a patient information sheet (i-botika).
- Decision-making algorithm: "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease". Clinical decision tree presenting potential courses of action based on clinical practice guidelines (CPGs), specifically for reducing cholesterol for the primary prevention of CVD in patients of different age groups and levels of CVR. Interactive decision-making support tool, developed by researchers collaborating in the DE-imFAR project, that also includes links for downloading two further documents: one providing information on CVD risk factors and the other on the 5As "Ask, Assess, Advise, Assist, Arrange" clinical intervention, recommended for promoting healthy lifestyles.

- Patient information sheet on cholesterol levels (i-botika: "Cholesterol levels are not the only thing", developed in the framework of this project, providing information on high cholesterol levels and their role together with other risk factors associated with CVD)

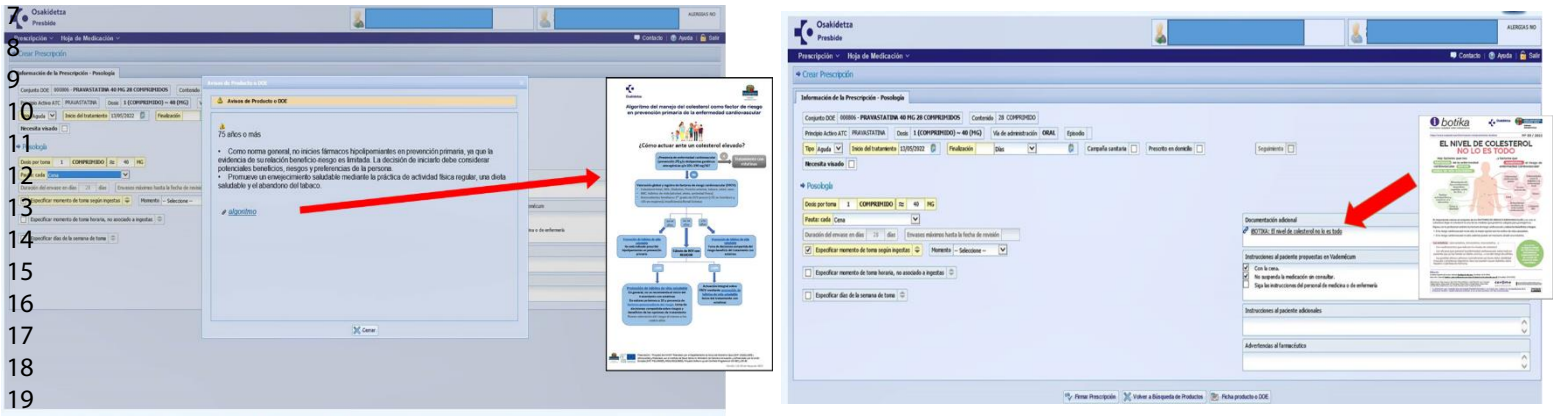


Figure 2. a). Pop-up reminder in the PRESBIDE software with recommendations on the prescribing of statins in people ≥75 years old that includes a link to the "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease" algorithm, b) PRESBIDE form for prescribing statins, with a link to the patient information sheet (i-botika).

1.3. Objectives: *Determinant - What needs to change*

Pop-up alerts, reminders, and an algorithm

Cognitive and interpersonal skills:

✓ Enhance skills to enable appropriate prescribing of statins based on clinical practice recommendations

Attention, memory, and decision-making processes:

✓ Promote recall of recommended clinical practice in the primary prevention of CVD, reducing the impact of therapeutic inertia

Context and resources:

✓ Develop support systems in the EHR as reminders of and to promote the practices recommended in CPGs for the primary prevention of CVD (avoiding statins and encouraging healthy lifestyles)

✓ Restrict or impede inappropriate prescribing of statins due to clinical prescribing behavior driven by simplicity and speed

Emotion/Reinforcement:

✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended practice and this is made evident by alerts

Patient information sheet

Social influence (patient involvement):

✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits

✓ Increase patient knowledge of the criteria and courses of action recommended in CPGs (concerning cholesterol, CVD, and CVR)

1.4. Choice architecture techniques

A. Decision Information

A1. Translate information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., Presenting the contents of CPGs in several different ways (i.e., text within alerts, in the form of an algorithm, etc.).

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.

A2. Make information visible: make necessary information readily accessible.

Make external information visible: make decision-relevant information visible, e.g., text within alerts recalling the CPGs.

B. Decision structure

B1. Change choice defaults

Prompted choice: avoid the status quo bias or default effects because of inertia or assumed recommendations, e.g., pop-up alerts.

B2. Change option-related effort: change physical effort.

Increase physical effort: e.g., pop-up alerts.

C. Decision assistance

C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., Pop-up alerts with the recommendation to not prescribe statins.

1.5. Exposure

- "Lighthouse" guiding alert in the REGICOR CVR calculator: by clicking to "save" the result after estimating CVR
- Alerts in PRESBIDE: by starting to prescribe statins or clicking on the links to the algorithm or the patient information sheet

2. Strategy - *Reflective/non-reflective decision information strategy*

Corporate campaign entitled "Stopping low-value prescribing" (in Spanish: "*Abandono de prescripciones farmacológicas de escaso valor*"), promoted through a knowledge dissemination strategy based on circulars and notifications (e.g., mass mailing and internal newsletters) concerning content, informative material and documents on recommended clinical practice and improving the appropriateness and/or optimization in prescribing drug treatments, including that of statins for the primary prevention of CVD, made available to FPs on the corporate intranets of the Ezkerraldea-Enkarterri-Cruces (EEC) and Barakaldo-Sestao (BS) IHOs, part of the Basque Health Service (Osakidetza).

2.1. Target audience

This strategy targets all FPs from the EEC and BS IHOs, who will also be exposed to the first strategy, namely, non-reflective decision assistance.

2.2. Active components (actions) of the intervention

- Adherence to and implementation of best practice pages on the EEC and BS IHO intranets which have dedicated sections focused on improving the appropriateness of the use of statins providing easy access to the CPGs and recommended practice for the primary prevention of CVD.

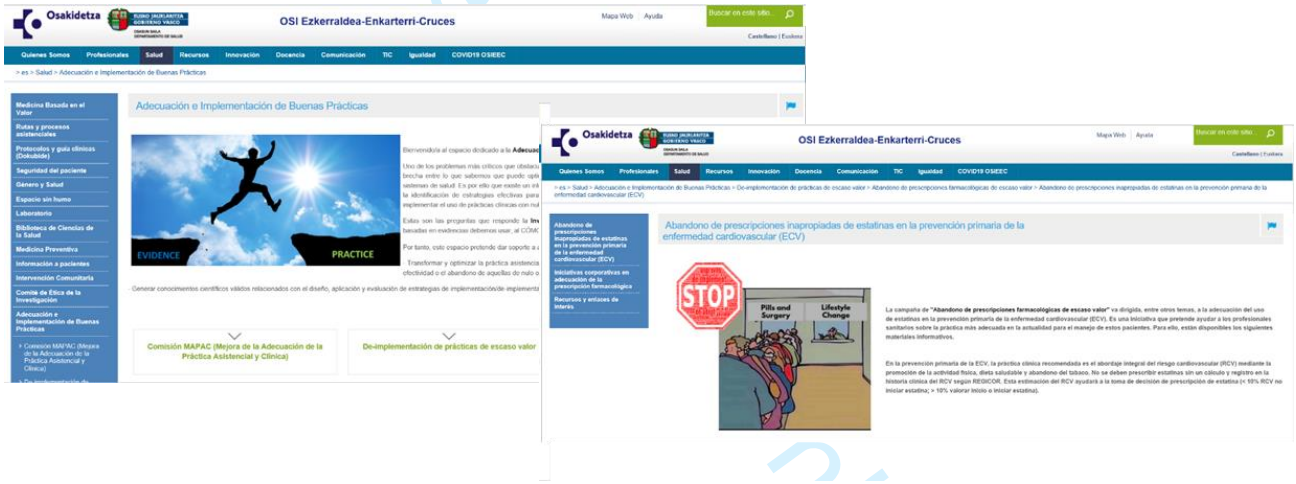


Figure 3. Main page of the adherence to and implementation of best practice ("A*decuación e Implementación de Buenas Prácticas*") section on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet and main page of the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section. Equivalent pages were also created on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Corporate dissemination campaign: activities aimed at attracting FPs to the pages created on the EEC and BS IHO intranets, in order that they access the information and documents available
  - ➢ News story on the launch of the campaign with links to the pages on the corporate intranets, e.g.,

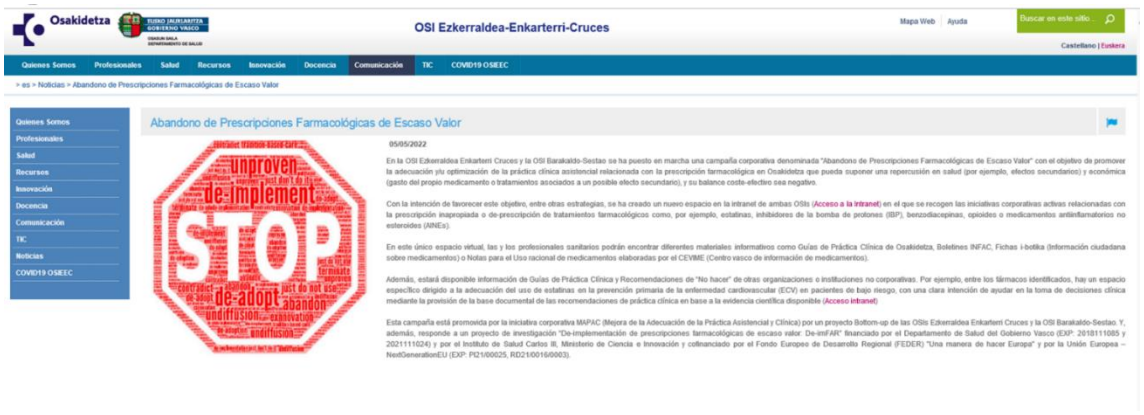


Figure 4. News story published on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet to announce the launch of the corporate "Stopping low-value prescribing" campaign and the development of pages on its intranet and that of the Barakaldo-Sestao Integrated Healthcare Organization, on May 5, 2022. The story was also published on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Monthly newsletter: reporting of the launch of the campaign in the monthly newsletter circulated by the BS IHO to all its employees
- Mass mailing on the launch of the campaign with links to the pages on the corporate intranets
- Revitalization of the corporate campaign: periodic publication of news stories on the EEC and BS IHO intranets with content related to the campaign informing FPsof the updating of content/informative materials (for example, any changes in the recommendations in CPGs and INFAC [pharmacotherapy information] newsletters) on the dedicated pages on the intranets of both IHOs, aimed at improving the appropriateness of the use of statins in primary prevention of CVD, including links to these pages.

- Justification email from the Healthcare Management of the Basque Health Service, telling all FPs about the initiatives being put in place to improve the approach to the prevention of CVD, improving the appropriateness of statin prescribing, and encouraging the provision of healthy lifestyle advice, among other components.

2.3. Objectives: Determinant - *What needs to change*

Knowledge:

- ✓ Increase awareness of the problem of the inappropriate prescribing of statins
- ✓ Increase knowledge of the CPGs on the primary prevention of CVD, in particular, the appropriate or recommended care as a function of the estimated CVR
- ✓ Provide evidence-based standardized and up-to-date clinical guidelines

Behavior regulation:

- ✓ Encourage reflection on practice/performance in relation to inappropriate prescribing of statins in the primary prevention of CVD

Beliefs about capabilities:

- ✓ Strengthen the belief that the prescribing of statins is not as straightforward and safe as might be thought
- ✓ Strengthen the belief that statin treatment is not easy for patients (dosage)

Beliefs about consequences:

- ✓ Strengthen the belief that not prescribing statins for the primary prevention of CVD is not the same as "not treating".
- ✓ Strengthen the belief that statins are not more effective in reducing cardiovascular events than healthy lifestyle promotion in the primary prevention of CVD
- ✓ Strengthen the belief that statins, in the primary prevention of CVD, may have adverse effects and are not risk-free.

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers.
- ✓ Strengthen understanding that the role of FPs goes beyond that of prescribing drugs.

Social influence:

- ✓ Increase awareness of the organizational goals for reducing inappropriate prescribing of statins in the primary prevention of CVD.
- ✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits
- ✓ Increase patient knowledge of the criteria and recommended courses of action (concerning cholesterol, CVD, and CVR)

Emotion/reinforcement:

- ✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended clinical practice and this is made evident by alerts.

Cognitive and interpersonal skills:

- ✓ Enhance skills to enable the appropriate prescribing of statins based on CPGs.

2.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., clinical guidelines, algorithm, patient information leaflet.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.

A2. Make information visible: make necessary information readily accessible.

Make external information visible: make decision-relevant information visible, e.g., Links about inappropriate statin prescription in the Basque Health Service (Osakidetza), adverse effects of statins and cholesterol treatment, and promotion of the campaign through emails and news.

A3. Provide social reference point: influence decision-making through other's behavior.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., links about inappropriate statin prescription in the Basque Health Service (Osakidetza).

Refer to opinion leader: use them as information disseminators to improve the impact of the campaign, e.g., Setting of goals in an email sent by an opinion leader, using the source as much as the content of the message to improve the impact of the campaign.

B. Decision structure

B2. Change option-related effort: modify the physical or financial effort involved in the decision-making process.

Change physical effort, e.g., decreasing physical effort by making all theme-related information accessible on the same website and including links to the website in the text of emails and news stories.

C. <u>Decision assistance</u>

C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., links to clinical guidelines with recommended practice about CVD primary prevention, and information about adverse effects of statins.

2.5. Exposure

- By accessing the pages of the EEC and BS IHO corporate intranet and clicking on the links to the CPGs, INFAC newsletters, i-botika patient information sheets, recommendations, etc. available in the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section
- By accessing the news section on the dedicated pages on the intranets of EEC and BS IHOs

3. Strategy - *Reflective decision structure strategy*

Sending of regular personalized *Audit & Feedback (A&F)* reports with practice- and organizational-level performance indicators of the FPsregarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of CVD in low-risk patients in the Basque Health Service

3.1. Target audience

This strategy targets a randomly selected set of FPs from the EEC and BS IHOs, who will also be exposed to the previously described interventions, namely, *non-reflective decision assistance and decision information*.

3.2. Active components (actions) of the intervention

- Informative email concerning the sending of A&F reports, including the possibility to opt out: email with information for primary care FPs of the EEC and BS IHOs on the sending of regular personalized A&F reports, in the framework of the corporate campaign, with the goal of encouraging adherence to recommendations and stopping inappropriate prescribing of statins

- A&F reports mailing: periodic A&F reports with indicators describing global performance across the Basque Health Service: a) rate of new potentially inappropriate prescribing of statins to people without CVD and with REGICOR CVR scores <7.5% and practice in the promotion of healthy habits in these patients; b) rate of documentation of CVR (in the 2 years before the prescription date) in all 40- to 75-year-olds with no clinical history of CVR who are newly prescribed statins. Future A&F reports are expected to contain a link to a short voluntary exercise on goal setting for improving the appropriateness of statin prescribing for the primary prevention of CVD

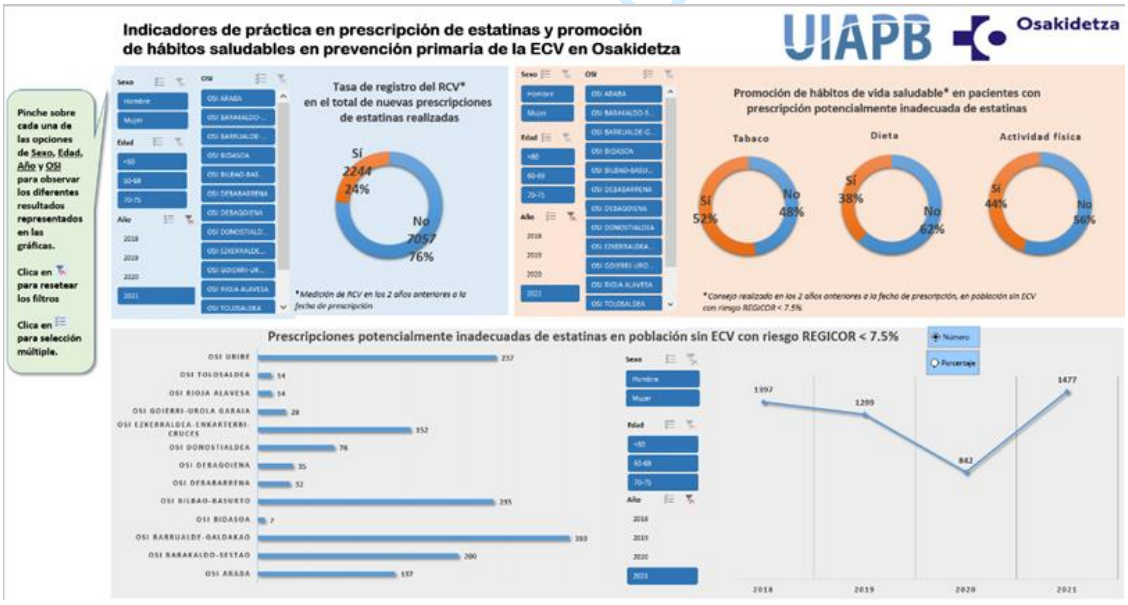


Figure 5. Draft of the Audit & Feedback report with practice- and organizational-level performance indicators of the family physicians regarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of cardiovascular disease in low-risk patients in the Basque Health Service

3.3. Objectives: Determinant - What needs to change

Knowledge:

- ✓ Increase awareness of the problem of the inappropriate prescribing of statins

Behavior regulation:

- ✓ Make data available on inappropriate prescribing of statins for the primary prevention of CVD
- ✓ Provide tools for the setting of clear specific goals, at personal and organizational levels, regarding the reduction of inappropriate prescribing of statins for the primary prevention of CVD

Active reflection on personal practice:

- ✓ Encourage further reflection on practice/performance in relation to inappropriate prescribing of statins for the primary prevention of CVD

Intentions:

- ✓ Reduce the intention to prescribe statins inappropriately and increase the intention to promote healthy lifestyles for the primary prevention of CVD

Goals:

- ✓ Encourage commitment to practice in the primary prevention of CVD that is in accordance with recommendations
- ✓ Increase the motivation to promote healthy lifestyles in the primary prevention of CVD

Beliefs about capabilities:

- ✓ Strengthen self-efficacy and enhance the skills required for promoting healthy lifestyles

Emotion:

- ✓ Strengthen self-confidence about not prescribing statins for the primary prevention of CVD
- ✓ Foster belief in the safety of and trust in the courses of action recommended in the guidelines
- ✓ Experience a negative emotion after inappropriate prescribing

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers
- ✓ Strengthen understanding that the role of FPs goes beyond prescribing drugs

Reinforcement:

- ✓ Generate positive/negative reinforcement related to good/poor performance in the primary prevention of CVD.

3.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., presenting prescription rate data in a simple, user-friendly way, namely, on a dashboard.

A2. Make information visible: make necessary information readily accessible.

Make own behavior visible: feedback.

Make external information visible: make decision-relevant information visible, e.g., showing the prescription rates of other FPs and other IHOs.

A3. Provide social reference point: influence decision-making through the behavior of others.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., showing other FPs' prescribing behavior.

B. Decision structure

B2. Change opinion-related effort: modify the physical or financial effort involved in the decision-making process.

Decrease physical effort: collect all prescribing data in one file, e.g., dashboard.

C. Decision assistance

C2. Facilitate commitment: overcome constrained self-control and bridge the intention-behavior gap.

Support self-commitment: arrange with the aim of helping fulfill a plan, e.g., self-commitment questionnaire

3.5. Exposure

By opening the A&F reports received by email.

Annex I. GLOSSARY OF TERMS

1. De-implementation: De-implementation is defined as the process of reducing or abandoning the use of guidelines practices, interventions or policies that are found to be ineffective, are not proven to be effective, do not have adecuated scientific support, are less effective or less cost-effective than an alternative one, are potentially harmful to patients, or that represent low-value care.

2. Implementation: Implementation (commonly defined as "to do"), in the context of Implementation Science refers to the actively designed process of putting into practice or integrating evidence-based interventions (e.g., practice, program, policy,...) within a specific real-world setting.

3. Theoretical Domains Framework (TDF): The Theoretical Domains Framework (TDF) is an integrative framework developed from a synthesis of psychological theories as a vehicle to help apply theoretical approaches to interventions aimed at behavior change. The TDF comprises of 14 domains and 84 constructs that allows synthesis of a multitude of coherent behavior change theories into a single framework that allows assessment and explanation of behavioral problems and associated barriers and enablers, and inform the design of appropriately targeted interventions.

References:

1. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155.
2. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci. 2012;7:37. doi:10.1186/1748-5908-7-37.
3. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77. doi: 10.1186/s13012-017-0605-9.

4. Behavior Change Wheel (BCW): The Behavior Change Wheel (BCW) is a theory- and evidence-based tool that provides a process for designing or refining behavior change interventions and policies. Its purpose is to promote a systematic and comprehensive analysis of behavior in its context to guide change. It can be used to identify the interventions and policies likely to be effective in changing behavior.

Reference:

1. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011 23;6:42. Published 2011 Apr 23. doi:10.1186/1748-5908-6-42.

5. Statin: Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications that are used to lower blood low-density lipoprotein (LDL) cholesterol levels.

6. Non-reflective: Non-reflective processes, such as habits and routines, are defined as those factors that bypass conscious deliberation and so generate actions fast, effortlessly, automatically and with little deliberation and awareness.

7. Reflective: Reflective processes involves conscious deliberation over situational demands, available options and/or outcome expectancies; and therefore generate slow and effortful actions or behaviors via reasoned intentions.

8. Decision assistance strategy. Decision information strategy. Decision structure strategy
According to the taxonomy suggested by Münscher et al., there are three broad categories of choice architecture intervention techniques: decision information, decision structure, and decision assistance (Münscher et al., 2016).

i) **Decision information** interventions aim to facilitate access to decision-relevant information without altering the options themselves by increasing its availability, comprehensibility, and/or personal relevance to the decision maker. There are several ways of achieving it, such as (re)arranging existing information or changing its presentation/format, providing social reference point, etc.
ii) **Decision structure** interventions target the way in which the choice options are organized and structured through the arrangement of choice alternatives and the format of decision making, which includes setting default options, rearranging their composition, and changing option-related efforts or consequences of selecting it.
iii) **Decision assistance** interventions aim to bridge the intention–behavior gap by reinforcing self-regulation by providing decision makers with further assistance to help them follow through with their intentions. To do so, examples of decision assistance interventions techniques include provision of reminders of the desirable behavioral option as well as facilitating deliberate commitment to beneficial actions.

References:
1. Münscher R, Vetter M, Scheuerle T. A review and taxonomy of choice architecture techniques. J Behav Decis Mak. 2016;29(5):511-24. doi.org/10.1002/bdm.1897.
2. Mertens S, Herberz M, Hahnel UJJ, Brosch T. The effectiveness of nudging: A meta-analysis of choice architecture interventions across behavioral domains. Proc Natl Acad Sci USA. 2022;119(1):e2107346118. doi: 10.1073/pnas.2107346118. Erratum in: Proc Natl Acad Sci USA. 2022;119(19):e2204059119.

9. Audit & feedback (A&F): Audit and feedback is a strategy that aims to encourage individuals to change their practice and improve their performance. In the audit process, an individual's professional practice or performance is assessed and monitored based on specific, pre-defined criteria or standards. Then, the results of the comparison is fed back to the individual in a structured manner.

Osakidetza

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unidad de investigación atención primaria bizkaia

Uiapb

Hoja de Información al Profesional de la salud y Consentimiento Informado

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Entidad financiadora: Instituto de salud Carlos III

Apreciado Sr./a,

Osakidetza-Servicio Vasco de Salud, con el propósito de mejorar la calidad en la prestación de servicios de salud hacia la ciudadanía, le invita a participar en el estudio "Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II".

Antes de decidir si desea participar, es importante que entienda los objetivos, la importancia de su participación y en qué consistirá, además de qué uso se dará a los datos recogidos y los posibles beneficios y riesgos.

Léalo atentamente y consulte cualquier duda con los miembros del equipo de investigación.

1. OBJETO DEL GRUPO DE DISCUSIÓN

El objetivo de los grupos de discusión del Proyecto De-ImFAR es generar conocimiento –a través de las percepciones de los/las profesionales de medicina de atención primaria- sobre la práctica clínica en prevención primaria de eventos cardiovasculares en pacientes de bajo riesgo. A través de una serie de preguntas abiertas se analizarán diferentes aspectos relacionados con el manejo del riesgo cardiovascular en estos pacientes, tratando de conocer la opinión de todos los integrantes del grupo sobre este tema.

No existen respuestas buenas o malas. Cualquier integrante del grupo está invitado a expresar libremente su opinión y a respetar la de los otros integrantes, aunque sea diferente de la suya.

2. PARTICIPACIÓN Y RETIRADA DEL ESTUDIO

Este estudio está aprobado por el Comité de Ética de la Investigación con Medicamentos de Euskadi (CEIm-E). Su participación en el mismo es voluntaria y en cualquier momento puede decidir abandonarlo, aunque haya proporcionado el consentimiento y el estudio esté en pleno desarrollo. Además, usted tiene derecho a solicitar al equipo investigador del estudio, en cualquier momento, y sin necesidad de especificar el motivo, la eliminación de sus datos.

3. DESARROLLO DEL ESTUDIO

Se realizará una sola entrevista llevada a cabo por dos investigadores con experiencia en métodos de investigación cualitativa, así como en el campo clínico y el proyecto. En dicha entrevista se le harán preguntas sobre su percepción y adaptación a las intervenciones implantadas. La discusión grupal será grabada (en formato audio) con el fin de transcribirla íntegramente. Esto permite a los miembros del equipo participar en la discusión sin necesidad de tomar notas, evitándose así el riesgo de no reflejar fidedignamente las opiniones expresadas por los miembros del grupo.

4. USO Y CONFIDENCIALIDAD DE LOS DATOS

Los datos que se obtengan en el grupo de discusión se utilizarán únicamente con fines de investigación y solamente por parte del equipo de investigación de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB). Todas las opiniones expresadas por los/las participantes serán tratadas de manera anónima y confidencial. Se le informa de que no se va a recoger ningún dato de carácter personal.

El estudio cumple lo establecido en el REGLAMENTO (UE) 2016/679 DEL PARLAMENTO EUROPEO Y DEL CONSEJO de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos. Se le solicita también su consentimiento para la realización de este proyecto de investigación conforme a las exigencias del Reglamento Europeo 2016/679 de Protección de Datos y a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales que deroga la Ley Orgánica 15/1999, de 5 de diciembre, de protección de datos personales. No se cederán datos a terceros, salvo obligación legal.

Para contactar con los responsables del estudio puede dirigirse a:

Nombre: Álvaro Sánchez Pérez

Teléfono: 946006673

e-mail: alvaro.sanchezperez@osakidetza.eus

Dirección: Edificio Biocruces 3, Plaza Cruces 12, 48903

Osakidetza

Iehen mailako atenzioa ikerketa unitatea unidad de investigación atención primaria bizkaia

Uiapb

5. DECLARACION DEL CONSENTIMIENTO INFORMADO

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Yo, Don/Doña....., Médico/a de Atención Primaria del Centro de Salud....., he leído este documento, he comprendido las explicaciones en él facilitadas acerca de la grabación del grupo de discusión y he podido resolver todas las preguntas que he planteado al respecto. Comprendo que mi participación en este ensayo es voluntaria y que puedo retirarme en cualquier momento.

También he sido informado/a de que mis datos personales serán protegidos y serán utilizados únicamente con fines de investigación por el equipo de investigadores de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB).

Tomando todo ello en consideración y en tales condiciones, CONSIENTO participar en el grupo de discusión, en la grabación del mismo y en que los datos que se deriven de mi participación sean utilizados para cubrir los objetivos especificados en el documento.

EN CONSECUENCIA, DOY MI CONSENTIMIENTO PARA PARTICIPAR EN ESTE PROYECTO DE INVESTIGACIÓN.

.....	.....
Firma del/la médico	Firma del/la responsable del proyecto
.....	.....
Nombre y apellidos	Nombre y apellidos
Fecha ...../...../20.....	Fecha ...../...../20.....

Hoja de Información al Paciente y Consentimiento Informado

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Antes de decidir si desea participar, es importante que entienda los objetivos, la importancia de su participación y en qué consistirá, además de qué uso se dará a los datos recogidos y los posibles beneficios y riesgos.

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3. DESARROLLO DEL ESTUDIO

Se realizará una sola entrevista llevada a cabo por dos investigadores con experiencia en métodos de investigación cualitativa, así como en el campo clínico y el proyecto. En dicha entrevista se le harán preguntas sobre su experiencia y satisfacción con el servicio recibido en prevención primaria de eventos cardiovasculares.

La discusión grupal será grabada (en formato audio) con el fin de transcribirla íntegramente. Esto permite a los miembros del equipo participar en la discusión sin necesidad de tomar notas, evitándose así el riesgo de no reflejar fidedignamente las opiniones expresada por los miembros del grupo.

4. USO Y CONFIDENCIALIDAD DE LOS DATOS

Los datos que se obtengan en el grupo de discusión se utilizarán únicamente con fines de investigación y solamente por parte del equipo de investigación de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB). Todas las opiniones expresadas por los/las participantes serán tratadas de manera anónima y confidencial. Se le informa de que no se va a recoger ningún dato de carácter personal.

El estudio cumple lo establecido en el REGLAMENTO (UE) 2016/679 DEL PARLAMENTO EUROPEO Y DEL CONSEJO de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos. Se le solicita también su consentimiento para la realización de este proyecto de investigación conforme a las exigencias del Reglamento Europeo 2016/679 de Protección de Datos y a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales que deroga la Ley Orgánica 15/1999, de 5 de diciembre, de protección de datos personales. No se cederán datos a terceros, salvo obligación legal.

Si usted tiene alguna duda o requiere cualquier tipo de información no dude en contactar con el/la médico que le informa, Dr./a _____, cuyo lugar de trabajo
es el Servicio de_____ del Hospital Universitario
_____; teléfono: _____ (extensión_____).

Usted también puede contactar con el Investigador Principal responsable:

Nombre: Álvaro Sánchez Pérez

Teléfono: 946006673

e-mail: alvaro.sanchezperez@osakidetza.eus

Dirección: Edificio Biocruces 3, Plaza Cruces 12, 48903

5. DECLARACION DEL CONSENTIMIENTO INFORMADO

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Investigador/a médico/a:……..

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Yo, Don/Doña…….(nombre y apellidos del paciente),

he leído este documento, he comprendido las explicaciones en él facilitadas acerca de la grabación del grupo de discusión y he podido resolver todas las preguntas que he planteado al respecto. Comprendo que mi participación en este ensayo es voluntaria y que puedo retirarme en cualquier momento.

También he sido informado/a de que mis datos personales serán protegidos y serán utilizados únicamente con fines de investigación por el equipo de investigadores de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB).

Tomando todo ello en consideración y en tales condiciones, CONSIENTO participar en el grupo de discusión, en la grabación del mismo y en que los datos que se deriven de mi participación sean utilizados para cubrir los objetivos especificados en el documento.

EN CONSECUENCIA, DOY MI CONSENTIMIENTO PARA PARTICIPAR EN ESTE PROYECTO DE INVESTIGACIÓN.

……..	……..
Firma del/la paciente	Firma del/la médico responsable
……..	……..
Nombre y apellidos	Nombre y apellidos
Fecha ……/……/20……	Fecha ……/……/20……

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9, 12-13

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15,18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			19-20

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28,29
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Reference: Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200-207. doi: 10.7326/0003-4819-158-3-201302050-00583.

BMJ Open

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.

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	General practice / Family practice, Health services research, Cardiovascular medicine, Research methods
Keywords:	Primary Care < Primary Health Care, Clinical Decision-Making, Clinical Trial, PREVENTIVE MEDICINE, Implementation Science, Cardiovascular Disease

TITLE PAGE

Title

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.

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ABSTRACT

Introduction

This study aims to reduce potentially inappropriate prescribing (PIP) of statins and foster healthy lifestyle promotion in cardiovascular disease (CVD) primary prevention in low-risk patients. To this end, we will compare the effectiveness and feasibility of several de-implementation strategies developed following the structured design process of the Behavior Change Wheel targeting key determinants of clinical decision-making process in CVD prevention.

Methods and analysis

A cluster randomized implementation trial, with an additional control group, will be launched, involving family physicians (FPs) from 13 Integrated Healthcare Organizations (IHOs) of Osakidetza-Basque Health Service with non-zero incidence rates of PIP of statins in 2021. All FPs will be exposed to a non-reflective decision assistance strategy based on reminders and decision support tools. Additionally, FPs from two of the IHOs will be randomly assigned to one of two increasingly intensive de-implementation strategies: adding a decision information strategy based on knowledge dissemination, and a reflective decision structure strategy through audit/feedback. The target population comprises 45- to 74-year-old women and 40- to 74-year-old men with moderately elevated cholesterol levels but no diagnosed CVD and low cardiovascular risk (REGICOR <7.5%), who attend at least one appointment with any of the participating FPs (May 2022-May 2023), and will be followed until May 2024. We use the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework to evaluate outcomes. The main outcome will be the change in the incidence rate of PIP of statins and healthy lifestyle counseling in the study population 12 and 24 months after

FPs' exposure to the strategies. Moreover, FPs' perception of their feasibility and acceptability, and patient experience regarding quality of care received will be evaluated.

Ethics and dissemination

The study was approved by the Basque Country Clinical Research Ethics Committee and was registered in ClinicalTrials.gov (NCT04022850). Results will be disseminated in scientific peer-reviewed journals.

Keywords: Inappropriate Prescribing, Cardiovascular Diseases / prevention & control, Hypercholesterolemia / drug therapy, Implementation Science, Research Design, Primary care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the DE-imFAR study is that it involves an efficient design that combines experimental and non-experimental comparisons through two randomly assigned intervention arms and one non-randomized control arm to test the comparative effectiveness on reducing potentially inappropriate prescribing (PIP) of statins and increasing healthy lifestyle promotion of several de-implementation strategies deployed in real-world settings.
- Counting with one non-randomized control arm is a strength because it allows capturing the effect of temporal trends, regression to the mean, and the learning curve due to the reference/background strategy to which all targeted family physicians (FPs) are exposed, when comparing this reference strategy with the two experimental de-implementation strategies.
- Another strength is the use of qualitative methods to better understand, from the perspective of the study participants, the reasons why (why not) the strategies work, to explain the variations in the results achieved and to identify the essential components of the strategy and those that will require to be optimized.

- To the best of our knowledge, the DE-imFAR study is one of the firsts of its kind that specifically uses the RE-AIM framework for the evaluation of the study results in terms of public health impacts.
- The main limitation lies in the planned comparisons of the randomized groups with respect to the control arm, likely to differ to some extent at baseline because of the non-random process of generation. To tackle this limitation, in addition to evaluating the change in PIP incidence in all eligible FPs, a matching strategy with the selection of one matched FP from this non-randomized group for each of the randomized FPs will be performed in order to increase comparability and reduce potential bias.

INTRODUCTION

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].

Nonetheless, reducing or eliminating low-value practices is a complex matter, since drivers that foster or maintain them seem to operate at multiple levels and be context specific. Therefore, in order to design effective and efficient corrective measures, a careful process of formal analysis of the determinants of the clinical behavior in question is needed. In this context, behavior change theory has been extensively applied to understand the factors that may influence clinical behavior, identify and design possible techniques and interventions that could be used to change it, and explain the mechanisms through which such interventions operate [3,4].

The DE-imFAR study ("De-implementation of low-value pharmacological prescribing" in Spanish) is a two-phase project [5] that aims to apply behavioral science theory within a

structured process involving the main stakeholders (health professionals, patients, and researchers) in the design, deployment, and evaluation of targeted de-implementation strategies to reduce potentially inappropriate prescribing (PIP). Specifically, in the DE-imFAR study the target low-value practice 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, for patients with a 10-year cardiovascular risk (CVR) greater than 10% or in the secondary prevention [6-9]. Whereas, in the primary prevention for 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 about the benefits of lifestyle modification for the prevention of CVD, as well as other modifiable risk factors, before considering pharmacological treatment [7-9].

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 on lifestyle modification in the Basque Health Service-Osakidetza in 2018. The results showed that the prescription of statins had notably increased 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].

Secondly, we applied two of the most successfully used behavior change theories in the field of Implementation Science, the Theoretical Domains Framework (TDF) [3,11,12] and Behavior Change Wheel (BCW) [13], to a) understand and define the problem (low-value practice) in behavioral terms and select and specify the target behaviors; b) identify the factors that may influence it; and c) map targeted de-implementation and

implementation strategies conducive to reducing the low-value practice in question. Briefly, after having prioritized our specific target behavior (that is "clinician decision-making on intervention/treatment to be provided based on objective clinical information and subjective schemas and heuristics"), identified the determinants (facilitators of the non-desired behavior of PIP of statins and barriers to apply the recommended clinical practice behavior of promoting healthy lifestyles), and mapped specific behavior change techniques, three types of de-implementation strategies were selected based on being the most potentially effective, feasible, and acceptable to influence decision-making through different mechanisms [14]. Hence, the three strategies derived from the systematic theory- and evidence-based intervention design process were: a) a non-reflective decision assistance strategy based on providing family physicians (FP) with evidence-based information communication technology tools to help and guide decision-making; b) a decision information strategy based on the dissemination of CVD primary prevention evidence framed in a corporate campaign encouraging FPs to abandon PIP; and c) a reflective decision structure strategy encouraging reflection on actual performance based on an audit/feedback system [14].

According to the literature review performed within the Phase I of the DE-imFAR project [14] regarding the evaluation of effective intervention strategies for the reduction of low-value prescribing [15-24], multicomponent interventions—combining passive dissemination interventions, based on training in or dissemination of clinical practice guidelines (CPGs), with more proactive interventions incorporating decision-making aids or sending audit/feedback—achieve the most positive results. Specifically, in the context of PIP of statins, a positive impact was observed on recording of CVR and prescription adequacy using a) multicomponent dissemination strategies including informational websites and implementation of electronic CPGs compared to routine practice and training activities, and b) interventions based on sending clinical scenarios/cases and audit/feedback to professionals as well as decision support tools [19-23]. All these

strategies can be conceived and theoretically differentiated in terms of how they may affect clinicians' decision-making [25]. There is plenty of evidence to support de-implementation of inappropriate medical practices through the lens of clinician cognition using audit/feedback, decision support tools, etc. [26-28]. In this context, the growing field of choice architecture aims to explore how the structure and framing of decision situations influence the choice of certain behaviors over alternative ones. On the one hand, FPs' decision-making ability can be influenced by unconscious processes that occur in response to environmental or emotive cues, that is, through Type 1 (or automatic) cognition. On the other, clinicians' conscious intention to change can be promoted by engaging their reflective cognition to consciously evaluate and correct their inappropriate behavior, that is, using Type 2 (or reflective) cognition [29]. However, further research is needed to determine whether these evidence-based and barrier-specific de-implementation strategies identified in the DE-imFAR Phase I are also effective in our context.

Thus, the goal of the present Phase II of the DE-imFAR study is to assess the potential effectiveness and feasibility of this set of de-implementation strategies to reduce the PIP of statins in the primary prevention of CVD (low-risk patients, REGICOR [30] CVR score <7.5%, with moderately elevated cholesterol levels, low-density lipoprotein (LDL) cholesterol levels between 70 and 189 mg/dL and/or total cholesterol (TC) between 200 and 289 mg/dL, but without ischemic heart disease/CVD).

Specifically, we aim to answer the following research questions:

1. Observational comparison questions:

Compared to a reference non-reflective decision assistance strategy based on reminders and decision support tools integrated into the electronic health record (EHR) to help clinical decision-making, what is the effect on the incidence of PIP of statins and of delivery of healthy lifestyle counseling in CVD primary prevention of a) a decision

information strategy comprising a corporate “Stopping Low-Value Prescribing” campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD; b) a reflective decision structure strategy based on an audit/feedback system; and c) any intervention based on a reflective de-implementation strategy (a or b)?

2. Experimental comparison question:

Compared to a decision information strategy comprising a corporate “Stopping Low-Value Prescribing” campaign and the dissemination of evidence-based CPGs for the primary prevention of CVD, together with the non-reflective decision assistance intervention based on reminders and decision support tools integrated into the EHR to help clinical decision-making, what is the effect on the incidence of PIP of statins and of delivery of healthy lifestyle counseling in CVD primary prevention of adding a reflective decision structure strategy based on an audit/feedback system?

METHODS AND ANALYSIS

Design

A cluster randomized implementation trial with an additional control group will be conducted to evaluate the potential effectiveness and feasibility of three de-implementation strategies (Figure 1). A mixed methods evaluation will be undertaken: quantitative in order to assess the implementation results at professional level (effectiveness outcomes regarding changes in the incidence rates of PIP of statins and provision of healthy lifestyle counseling) and qualitative to assess the feasibility and perceived impact of the de-implementation strategies from the FPs’ perspective and patients’ experience and satisfaction with the clinical care received. The unit of randomization and intervention will be the primary care FP, while observation and analysis will be performed at professional and patient levels. The DE-imFAR research protocol was reviewed and approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered

in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 5 February 2024).

Osakidetza-Basque Health Service provides universal coverage and services are free at the point of use, aside from drug copayment, funded through regional general taxation. Primary, specialized, and social health-related service provision is organized around 13 Integrated Healthcare Organizations (IHOs) that cover the 3 provinces of the region of the Basque Country: Araba, Bizkaia, and Gipuzkoa. Each resident is on the list of one FP or pediatrician who provides comprehensive primary care and refers patients to hospital and specialized services. Primary care professionals work in full-time teams, which include FPs, pediatricians, nurses and administrative staff, based at local centers that provide users with access to healthcare in a defined geographical area.

We used the SPIRIT reporting guidelines and the SPIRIT checklist when writing the present study [31].

Participants

Eligibility criteria for the study will be:

1. Professionals: FPs belonging to any of the 13 IHOs of Osakidetza with a non-zero annual incidence rate of PIP of statins at baseline (2021) with a minimum cluster size of n ≥10 patients

2. Patients: All 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL but without ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% who attend at least one appointment with any of the participating FP during the study period (from May 2022 to May 2023).

Clinical interventions

The DE-imFAR study, with regard to the prescription of statins in the 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 the 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.

De-implementation strategies evaluated

Within the present Phase II of the DE-imFAR study, the three types of strategies that were derived from the Phase I systematic theory- and evidence-based intervention design process will be set up (see Supplemental file 1 for a more detailed description):

1) *A non-reflective decision assistance strategy* that targets Type 1 cognitive processes through decision support systems that prompt and remind FPs about the recommended practice in a simplified way, thereby reducing the cognitive burden. In short, pop-up reminders and alerts with associated messages will be integrated into OSABIDE's (Osakidetza's EHR system) REGICOR CVR calculator and PRESBIDE (the electronic drug prescribing component). The tools devised include an interactive media-based algorithm with the recommended practice for the primary prevention of CVD in low-risk patients developed by an expert panel, and a patient information sheet that depicts and promotes evidence-based practice to address cholesterol in the primary prevention of CVD in low-risk patients.

2) *A both reflective and non-reflective decision information strategy* that targets both Type 1 and 2 cognitive processes, based on the principle of knowledge dissemination and consisting of a "Stopping Low-Value Prescribing" campaign run by the organization (Osakidetza- Basque Health Service) that also eases access (decreasing the physical effort required) to the evidence-based CPGs for the primary prevention of CVD in low-risk patients.

3) *A reflective decision structure strategy* that targets Type 2 cognition through an audit/feedback system that reports data about individual's and organizational performance indicators with regard to PIP of statins and healthy lifestyle promotion to prompt reflection on their own clinical practice, provided along with intention formation and goal-setting-focused messages.

Allocation of intervention units to compared groups

The DE-imFAR study is a cluster randomized implementation trial conducted under real world conditions in the 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 under routine conditions of healthcare service provision in

Osakidetza to reduce the low-value practice and increase the recommended practice by PC healthcare professionals. Specifically, the decision support tools integrated into 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 the exposure to either the second (provision of decision information strategy) or the second and third (provision of decision information and reflective decision structure strategies). The allocation sequence within these two groups will be generated using a specific restricted randomization scheme by one member of the research team. The sequence will be concealed at the coordinating center. In all cases, FPs will be only allocated to the study groups after they have agreed to participate through an opt-out strategy. The data analyst and the staff in charge of measurements will be blind to FP allocation to study arms. Given that the audit/feedback strategy will involve regular reports privately sent to individuals, the participants in the experimental arms are also expected to be blind to group allocation.

Outcome measures

To evaluate the implementation of the de-implementation strategies in terms of public health impact, we will use the following dimensions of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [33]:

Reach

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

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 healthy lifestyle advice in

patients in the target population eligible for CVD primary prevention, from baseline to 12 months after exposure of target FPs to the de-implementation strategies.

As a secondary outcome, we will compare the change in the incidence of CVR (REGICOR) recording in the EHR, from baseline to 12 months after exposure of FPs to the de-implementation strategies compared, in 40- to 74-year-old men and 45- to 74-year-old women without ischemic heart disease/CVD.

Adoption

Degree to which the recommended CVD primary prevention clinical intervention is adopted by the FPs 12 months after their exposure to the de-implementation strategies, that will be measured by the percentage of FPs who reduce PIP of statins and/or increase health promotion activities in the target population; and their representativeness.

Implementation

The fidelity of the delivery of each de-implementation strategy under study (i.e., the degree to which they were 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].

Maintenance

Change in the incidence of PIP of statins and provision of healthy lifestyle counseling in eligible patients, 24 months after exposure of FPs to the de-implementation strategies compared to the levels observed at the 12-month assessment.

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 incidence rate of PIP of statins; and b) patient level: sociodemographic variables (age, sex, socioeconomic status) and clinical variables (baseline cholesterol level, presence of hypertension, prescribed antihypertensives, tobacco use).

Feasibility Evaluation

Professionals' perception of the feasibility and acceptability of the de-implementation strategies to enhance the provision of the recommended CVD primary prevention clinical practice will be assessed through key informant semi-structured individual interviews. The 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 of statins and at least six who did not, as informed by the quantitative results. 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.

Patients' experience and perception of the quality of CVD prevention care received will be also assessed through key informant semi-structured interviews. The interviews will be carried out with at least ten patients until data saturation is reached: at least five patients who were clinically managed according to the recommended practice and five who did not. The interview script will contain open-ended questions that will focus on the perceived care received.

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 verbatim transcribed. Regarding the analysis of the qualitative study, the responses will be extracted from the interview transcripts. 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. Deductive and inductive approaches will be combined. For the deductive approach, the discourse of each professional and patient interviewed will be associated with constructs derived from the behavior change 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.

Analysis

Frequencies and proportions along with the corresponding 95% confidence intervals (CIs) will be used to describe the prevalence and cumulative incidence of PIP of statins and healthy lifestyle counseling in the primary prevention of CVD by FPs. The primary effectiveness outcomes will be the changes in the cumulative incidence of PIP of statins and healthy lifestyle counseling in patients from the target population (individuals with no history of statin use, LDL cholesterol levels between 70 and 189 mg/dL and/or TC between 200 and 289 mg/dL, without past or current ischemic heart disease/CVD, and an estimated CVR REGICOR <7.5% who attend at least one medical appointment with their FP during the study period), from baseline to 12 months after exposure of FPs to the de-implementation strategies. Therefore, to evaluate the impact of the three de-implementation strategies, we will estimate the relative risk reduction of receiving PIP of statins in patients from the target population whose FPs were assigned to the experimental strategies over that in patients from the non-randomized group (non-reflective decision assistance strategy group). With respect to this group and in order to increase comparability and reduce potential bias, in addition to evaluating the change in the incidence rate of PIP of statins in patients from all eligible FPs, we will select two matched FPs from this non-randomized group for each of the randomized FP taking into

account both FP' characteristics (e.g., baseline incidence rate of PIP of statins, etc.) and characteristics of the patients assigned to the FP (e.g., average socioeconomic status, etc.). Change in the incidence rates of PIP of statins from baseline to 12 and 24 months after FPs' exposure to the de-implementation strategies and the relative risk reduction will be estimated with the corresponding 95% CIs. To adjust for potential confounding factors, stratified statistical analyses and logistic models will be used. These models will be extended to generalized mixed effects models to take into account the hierarchical structure of data (patients nested within FPs and FPs within primary care teams), with fixed effects (comparison group, effect of time on outcome indicators, and time-group interactions) and random effects on the intercept and the time slope (for each patient, FP, center, etc.). These models will be adjusted for potential confounders, following a backward strategy, guided by the stratified analyses. A similar approach will be taken to analyze the secondary outcomes. The analysis will be carried out using SAS (v. 9.2, SAS Institute, Cary, NC, USA) and R (R Development Core Team, 2014).

Calculation of the required sample size in the worst-case scenario, i.e. the comparison between the two randomized de-implementation strategies, was based on: i) a baseline incidence rate of statin PIP of 7.4% estimated among the patients from the target population seen in 2021 by FPs with an incidence rate of statin PIP > 0% with a minimum cluster size n ≥10 patients, ii) an intra-class correlation coefficient of 0.01, iii) an average cluster size of 39 patients with a coefficient of variation of 0.63, iv) $\alpha = 0.05$ and statistical power of 80%, and v) hypothetical decreases in annual PIP incidence rates of 20% in the decision information strategy group and 50% in the decision structure strategy group. With these assumptions, it was estimated that at least 58 FPs were required for each experimental arm.

Management, quality, and safety in data processing

This study will be carried out in accordance with international standards for the conduct of epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies [36]. This is a prospective intervention study mainly focused on the collection of information from data recorded by health professionals in the Osakidetza EHR (OSABIDE) under routine clinical practice conditions. The process indicators related to the professionals' clinical practice (prescription of statins and record in the EHR of provision of personalized healthy lifestyle advice on the need to increase physical activity, follow a healthy diet and smoking cessation), patients' sociodemographic and clinical characteristics (age, sex, CVR, active health problems recorded in the EHR, socioeconomic status, etc.) and clinical outcomes will be extracted from OSABIDE through the corporate Oracle Business Intelligence platform. In particular, for the provision of healthy lifestyle advice, OSABIDE includes a specific electronic form to check that each single piece of advice (diet, exercise, tobacco quitting) was or was not provided. The Primary Care Research Unit of Bizkaia is formally authorized to extract and use data from the EHR for research purposes by the Healthcare Directorate of Osakidetza. On the other hand, it will be necessary to inform participants (professionals and patients) about the study and obtain their written informed consent concerning the information directly collected from them through the key informant semi-structured interviews (Supplemental File 2 and 3). All the information regarding the study subjects, either expressly extracted for this research from EHRs or collected from the participants, will be protected and treated confidentially for all purposes, in accordance with the provisions of the Spanish Organic Law 3/2018, of 5 December, on Personal Data Protection and digital rights guarantee (LOPD-GDD) and the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, RGPD). Specifically, all data will be anonymously documented and de-identified, linked to a unique code that is meaningless without the context of the system. The final resulting database will be

exported to a formatted plain text file that then will be compressed and encrypted using a secure algorithm and subsequently will be processed and included in a robust and secure database server.

Patient and public involvement

Patients were involved in the DE-imFAR Phase I project as one of the main stakeholders (health professionals, patients, and researchers) in the formative process conducted to map and design de-implementation strategies to reduce PIP, which will be evaluated in the DE-imFAR Phase II project. Specifically, during the Phase I project, a focus group with six patients was conducted to ascertain patients' experience with the clinical practice of statin prescription and triangulate physicians discourse [14].

During the Phase II project, semi-structured interviews will be conducted with patients to assess their experience and perception of the clinical care received as a result of their healthcare professionals´ exposure to the different de-implementation strategies. These interviews will help to better understand from the perspective of the study participants the reasons why the strategies work (or do not), to explain the variations in the outcomes and to identify the key strategy components and those that need to be optimized as well as triangulating the analysis.

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.

ETHICS AND DISSEMINATION

The research protocol (version 1; 170221) was approved by the Basque Country Clinical Research Ethics Committee (Reference: EOM2022018, approved on 30 March 2022) and was registered in the U.S. NLM ClinicalTrials.gov database (ClinicalTrials.gov Identifier NCT04022850, Registered 17 July 2019; Last update 5 February 2024).The Primary Care Research Unit of Bizkaia is explicitly authorized by the Healthcare Directorate of Osakidetza - Basque Health Service to extract and use data from EHRs for research purposes. Since data supporting the present study will mostly concern routine data retrieved from the EHR of the Basque Health Service-Osakidetza, it will be only shared upon justified request to the study guarantors. The results of this study will be disseminated via publication in scientific peer-reviewed journals.

LIST OF ABBREVIATIONS

EHR: Electronic health record

BCW: Behavior Change Wheel

CI: Confidence interval

CVD: Cardiovascular disease

CVR: Cardiovascular risk

CPG: Clinical practice guideline

FP: Family physician

IHO: Integrated Healthcare Organization

LDL: Low-density lipoprotein

PIP: Potentially inappropriate prescribing

PC: Primary care

RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

TC: Total cholesterol

TDF: Theoretical Domains Framework

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AUTHORS' CONTRIBUTIONS

AS, JIP, and GG conceived the idea and are the study guarantors. They are primarily responsible for the study design and planning, obtained funding, will be responsible for project coordination and supervision, analysis and interpretation of results, and were responsible for manuscript preparation. RSR, IL, RSV, JAQ, RR, AE, CM, MMC, MM, CGR, RS, MOL, SC, NMI, ML, MGST, and AGA are co-investigators of the projects and collaborated in the study design and/or manuscript preparation; and they will be responsible for study coordination and interpretation of results. AS, JIP, and AGA will be responsible for the analysis of results. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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WORD COUNT

4515 words excluding title page, abstract, strengths and limitations of this study, list of abbreviations, full references, authors' contributions, funding statement, competing interests statement and acknowledgements.

FIGURES

Figure 1. Study design diagram. (PDF format)

Note: FP: Family Physician; IHO: Integrated Healthcare Organization; R: Randomization.

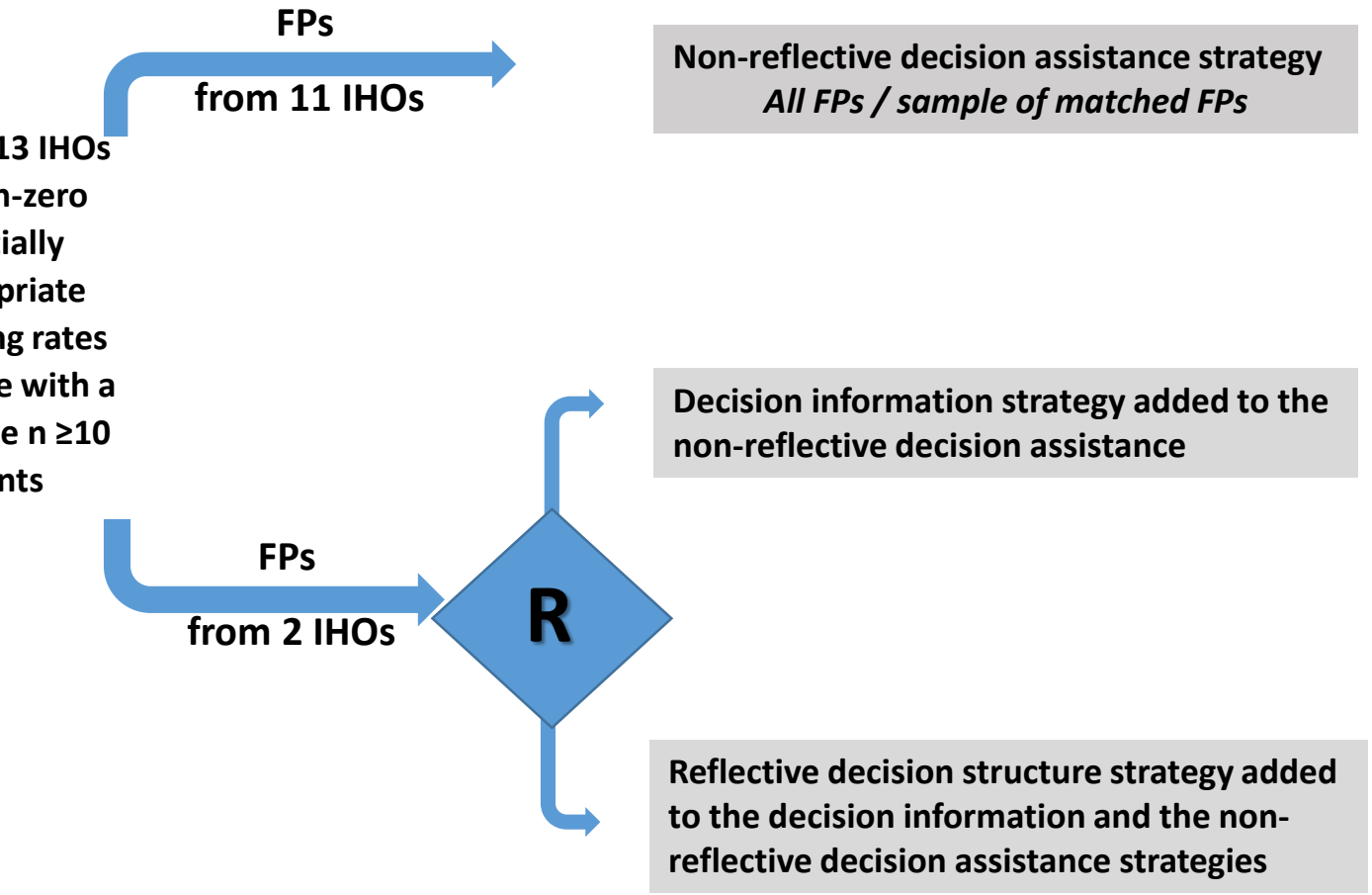
SUPPLEMENTAL FILES

Supplemental File 1 [DE-imFAR de-implementation strategies] (PDF format)

Supplemental File 2 [DE-imFAR Phase II - Informed Consent Form for Family Physicians (Spanish)] (PDF format)

Supplemental File 3 [DE-imFAR Phase II - Informed Consent Form for Patients (Spanish)] (PDF format)

Experimental implementation trial with an additional control group



Change in the incidence of potentially inappropriate prescriptions and provision of lifestyle advice from baseline to 12 months after exposure of physicians to the compared strategies, in 40- to 74-year-old men and 45- to 74-year-old women with no history of statin use, with LDL-cholesterol levels between 70 and 189 mg/dl and/or Total Cholesterol between 200 and 289 mg/dl but without ischemic heart/cardiovascular disease and with an estimated cardiovascular risk <7.5% attending during the field-work period

Outcome

The DE-imFAR de-implementation strategies

1. Strategy - *Non-reflective decision assistance strategy*

Support for clinical decision-making on the primary prevention of cardiovascular disease (CVD) in low cardiovascular risk (CVR) patients integrated into the electronic health record (EHR) of the Basque Health Service (Osakidetza), based on pop-up reminders and alerts, together with an interactive media-based algorithm stating the recommended practice and a patient information sheet.

1.1. Target audience

This strategy targets all family phyisicians (FPs) from all 13 Integrated Healthcare Organizations (IHOs) of the Basque Health Service (Osakidetza), both in primary and specialist or hospital care.

1.2. Active components (actions) of the intervention

- "Lighthouse" guiding alert in the REGICOR CVR calculator. Reminders of recommended clinical practice in the primary prevention of CVD that pop-up in the REGICOR CVR calculator when the CVR is estimated in patients aged between 35 and 74 years old. The alert varies depending on the CVR score (<10% or ≥10%).

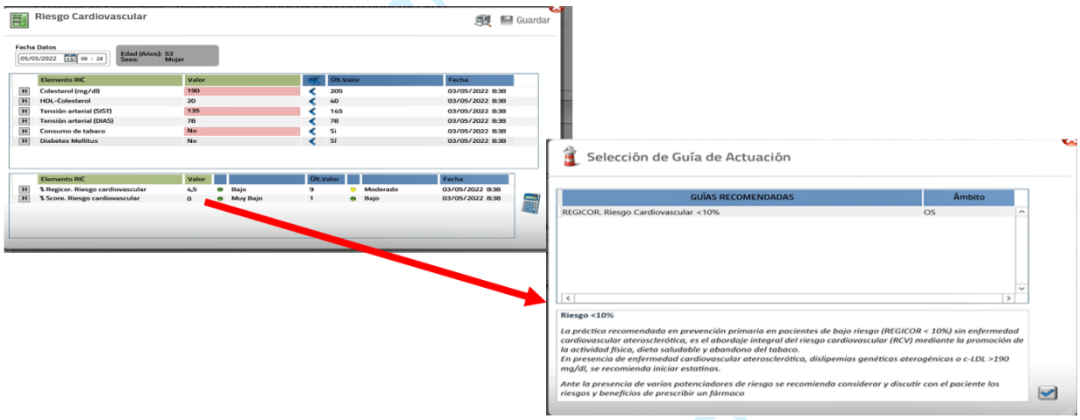


Figure 1. Pop-up reminder ("Lighthouse" guiding alert) in the REGICOR cardiovascular risk calculator when estimated cardiovascular risk score is <10%.

- Alerts in PRESBIDE. Pop-up reminders that appear when the PRESBIDE software is used to prescribe statins. There are three types of alerts depending on the patient's age group (<35, 35-74, and ≥75 years old). Further, links are providedto a decision-making algorithm and a patient information sheet (i-botika).
- Decision-making algorithm: "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease". Clinical decision tree presenting potential courses of action based on clinical practice guidelines (CPGs), specifically for reducing cholesterol for the primary prevention of CVD in patients of different age groups and levels of CVR. Interactive decision-making support tool, developed by researchers collaborating in the DE-imFAR project, that also includes links for downloading two further documents: one providing information on CVD risk factors and the other on the 5As "Ask, Assess, Advise, Assist, Arrange" clinical intervention, recommended for promoting healthy lifestyles.

- Patient information sheet on cholesterol levels (i-botika: "Cholesterol levels are not the only thing", developed in the framework of this project, providing information on high cholesterol levels and their role together with other risk factors associated with CVD)

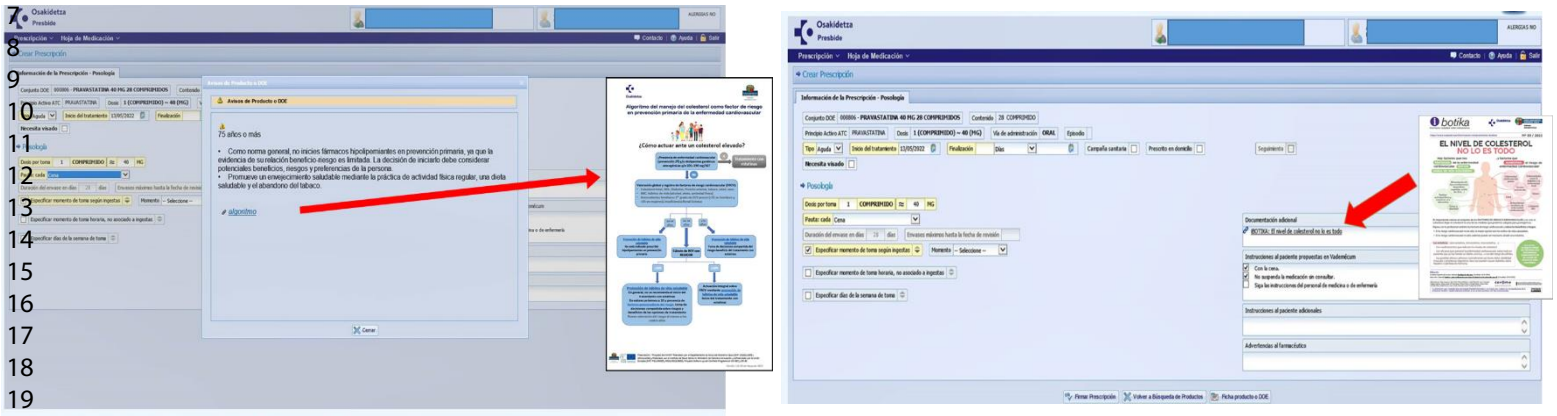


Figure 2. a). Pop-up reminder in the PRESBIDE software with recommendations on the prescribing of statins in people ≥75 years old that includes a link to the "Management of cholesterol as a risk factor in primary prevention of cardiovascular disease" algorithm, b) PRESBIDE form for prescribing statins, with a link to the patient information sheet (i-botika).

1.3. Objectives: *Determinant - What needs to change*

Pop-up alerts, reminders, and an algorithm

Cognitive and interpersonal skills:

✓ Enhance skills to enable appropriate prescribing of statins based on clinical practice recommendations

Attention, memory, and decision-making processes:

✓ Promote recall of recommended clinical practice in the primary prevention of CVD, reducing the impact of therapeutic inertia

Context and resources:

✓ Develop support systems in the EHR as reminders of and to promote the practices recommended in CPGs for the primary prevention of CVD (avoiding statins and encouraging healthy lifestyles)

✓ Restrict or impede inappropriate prescribing of statins due to clinical prescribing behavior driven by simplicity and speed

Emotion/Reinforcement:

✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended practice and this is made evident by alerts

Patient information sheet

Social influence (patient involvement):

✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits

✓ Increase patient knowledge of the criteria and courses of action recommended in CPGs (concerning cholesterol, CVD, and CVR)

1.4. Choice architecture techniques

A. Decision Information

A1. Translate information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., Presenting the contents of CPGs in several different ways (i.e., text within alerts, in the form of an algorithm, etc.).

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.

A2. Make information visible: make necessary information readily accessible.

Make external information visible: make decision-relevant information visible, e.g., text within alerts recalling the CPGs.

B. Decision structure

B1. Change choice defaults

Prompted choice: avoid the status quo bias or default effects because of inertia or assumed recommendations, e.g., pop-up alerts.

B2. Change option-related effort: change physical effort.

Increase physical effort: e.g., pop-up alerts.

C. Decision assistance

C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., Pop-up alerts with the recommendation to not prescribe statins.

1.5. Exposure

- "Lighthouse" guiding alert in the REGICOR CVR calculator: by clicking to "save" the result after estimating CVR
- Alerts in PRESBIDE: by starting to prescribe statins or clicking on the links to the algorithm or the patient information sheet

2. Strategy - *Reflective/non-reflective decision information strategy*

Corporate campaign entitled "Stopping low-value prescribing" (in Spanish: "*Abandono de prescripciones farmacológicas de escaso valor*"), promoted through a knowledge dissemination strategy based on circulars and notifications (e.g., mass mailing and internal newsletters) concerning content, informative material and documents on recommended clinical practice and improving the appropriateness and/or optimization in prescribing drug treatments, including that of statins for the primary prevention of CVD, made available to FPs on the corporate intranets of the Ezkerraldea-Enkarterri-Cruces (EEC) and Barakaldo-Sestao (BS) IHOs, part of the Basque Health Service (Osakidetza).

2.1. Target audience

This strategy targets all FPs from the EEC and BS IHOs, who will also be exposed to the first strategy, namely, non-reflective decision assistance.

2.2. Active components (actions) of the intervention

- Adherence to and implementation of best practice pages on the EEC and BS IHO intranets which have dedicated sections focused on improving the appropriateness of the use of statins providing easy access to the CPGs and recommended practice for the primary prevention of CVD.

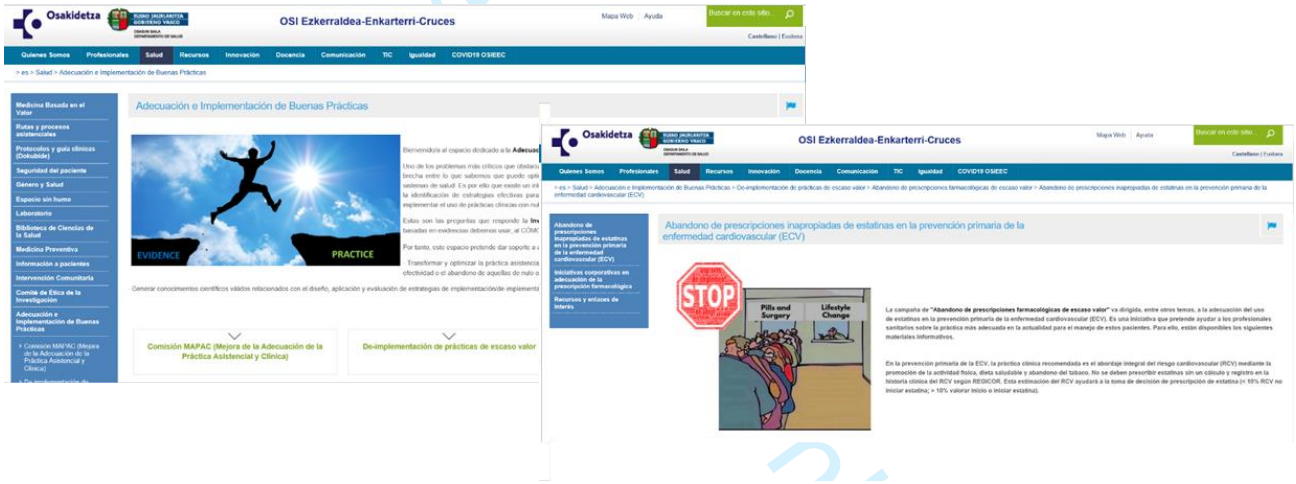


Figure 3. Main page of the adherence to and implementation of best practice ("A*decuación e Implementación de Buenas Prácticas*") section on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet and main page of the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section. Equivalent pages were also created on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Corporate dissemination campaign: activities aimed at attracting FPs to the pages created on the EEC and BS IHO intranets, in order that they access the information and documents available
  - News story on the launch of the campaign with links to the pages on the corporate intranets, e.g.,

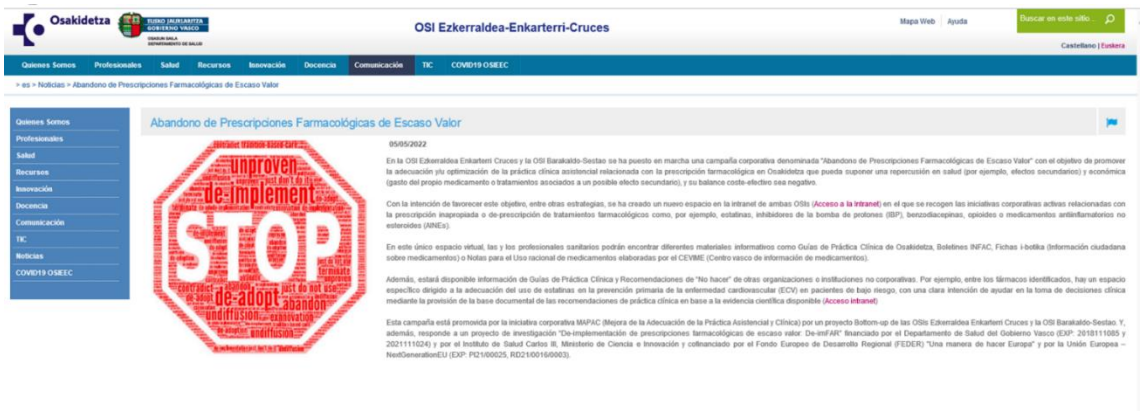


Figure 4. News story published on the Ezkerraldea-Enkarterri-Cruces Integrated Healthcare Organization intranet to announce the launch of the corporate "Stopping low-value prescribing" campaign and the development of pages on its intranet and that of the Barakaldo-Sestao Integrated Healthcare Organization, on May 5, 2022. The story was also published on the Barakaldo-Sestao Integrated Healthcare Organization intranet.

- Monthly newsletter: reporting of the launch of the campaign in the monthly newsletter circulated by the BS IHO to all its employees
- Mass mailing on the launch of the campaign with links to the pages on the corporate intranets
- Revitalization of the corporate campaign: periodic publication of news stories on the EEC and BS IHO intranets with content related to the campaign informing FPsof the updating of content/informative materials (for example, any changes in the recommendations in CPGs and INFAC [pharmacotherapy information] newsletters) on the dedicated pages on the intranets of both IHOs, aimed at improving the appropriateness of the use of statins in primary prevention of CVD, including links to these pages.

- Justification email from the Healthcare Management of the Basque Health Service, telling all FPs about the initiatives being put in place to improve the approach to the prevention of CVD, improving the appropriateness of statin prescribing, and encouraging the provision of healthy lifestyle advice, among other components.

2.3. Objectives: Determinant - *What needs to change*

Knowledge:

- ✓ Increase awareness of the problem of the inappropriate prescribing of statins
- ✓ Increase knowledge of the CPGs on the primary prevention of CVD, in particular, the appropriate or recommended care as a function of the estimated CVR
- ✓ Provide evidence-based standardized and up-to-date clinical guidelines

Behavior regulation:

- ✓ Encourage reflection on practice/performance in relation to inappropriate prescribing of statins in the primary prevention of CVD

Beliefs about capabilities:

- ✓ Strengthen the belief that the prescribing of statins is not as straightforward and safe as might be thought
- ✓ Strengthen the belief that statin treatment is not easy for patients (dosage)

Beliefs about consequences:

- ✓ Strengthen the belief that not prescribing statins for the primary prevention of CVD is not the same as "not treating".
- ✓ Strengthen the belief that statins are not more effective in reducing cardiovascular events than healthy lifestyle promotion in the primary prevention of CVD
- ✓ Strengthen the belief that statins, in the primary prevention of CVD, may have adverse effects and are not risk-free.

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers.
- ✓ Strengthen understanding that the role of FPs goes beyond that of prescribing drugs.

Social influence:

- ✓ Increase awareness of the organizational goals for reducing inappropriate prescribing of statins in the primary prevention of CVD.
- ✓ Increase patient awareness of the problems associated with the inappropriate prescribing of statins: risks vs benefits
- ✓ Increase patient knowledge of the criteria and recommended courses of action (concerning cholesterol, CVD, and CVR)

Emotion/reinforcement:

- ✓ Reduce the likelihood of inappropriate prescribing due to habit, routine, or inertia (to "treat" cholesterol), through the experiencing of negative emotions when going against the recommended clinical practice and this is made evident by alerts.

Cognitive and interpersonal skills:

- ✓ Enhance skills to enable the appropriate prescribing of statins based on CPGs.

2.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Reframe: present the (same) information in several ways, e.g., clinical guidelines, algorithm, patient information leaflet.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., algorithm.

A2. Make information visible: make necessary information readily accessible.

Make external information visible: make decision-relevant information visible, e.g., Links about inappropriate statin prescription in the Basque Health Service (Osakidetza), adverse effects of statins and cholesterol treatment, and promotion of the campaign through emails and news.

A3. Provide social reference point: influence decision-making through other's behavior.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., links about inappropriate statin prescription in the Basque Health Service (Osakidetza).

Refer to opinion leader: use them as information disseminators to improve the impact of the campaign, e.g., Setting of goals in an email sent by an opinion leader, using the source as much as the content of the message to improve the impact of the campaign.

B. Decision structure

B2. Change option-related effort: modify the physical or financial effort involved in the decision-making process.

Change physical effort, e.g., decreasing physical effort by making all theme-related information accessible on the same website and including links to the website in the text of emails and news stories.

C. <u>Decision assistance</u>

C1. Provide reminders: provide positive reminders that heighten the salience of a desired option and/or diminish the salience of an undesired option, e.g., links to clinical guidelines with recommended practice about CVD primary prevention, and information about adverse effects of statins.

2.5. Exposure

- By accessing the pages of the EEC and BS IHO corporate intranet and clicking on the links to the CPGs, INFAC newsletters, i-botika patient information sheets, recommendations, etc. available in the dedicated "Stopping inappropriate prescribing of statins for the primary prevention of cardiovascular disease" section
- By accessing the news section on the dedicated pages on the intranets of EEC and BS IHOs

3. Strategy - *Reflective decision structure strategy*

Sending of regular personalized *Audit & Feedback (A&F)* reports with practice- and organizational-level performance indicators of the FPsregarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of CVD in low-risk patients in the Basque Health Service

3.1. Target audience

This strategy targets a randomly selected set of FPs from the EEC and BS IHOs, who will also be exposed to the previously described interventions, namely, *non-reflective decision assistance and decision information*.

3.2. Active components (actions) of the intervention

- Informative email concerning the sending of A&F reports, including the possibility to opt out: email with information for primary care FPs of the EEC and BS IHOs on the sending of regular personalized A&F reports, in the framework of the corporate campaign, with the goal of encouraging adherence to recommendations and stopping inappropriate prescribing of statins

- A&F reports mailing: periodic A&F reports with indicators describing global performance across the Basque Health Service: a) rate of new potentially inappropriate prescribing of statins to people without CVD and with REGICOR CVR scores <7.5% and practice in the promotion of healthy habits in these patients; b) rate of documentation of CVR (in the 2 years before the prescription date) in all 40- to 75-year-olds with no clinical history of CVR who are newly prescribed statins. Future A&F reports are expected to contain a link to a short voluntary exercise on goal setting for improving the appropriateness of statin prescribing for the primary prevention of CVD

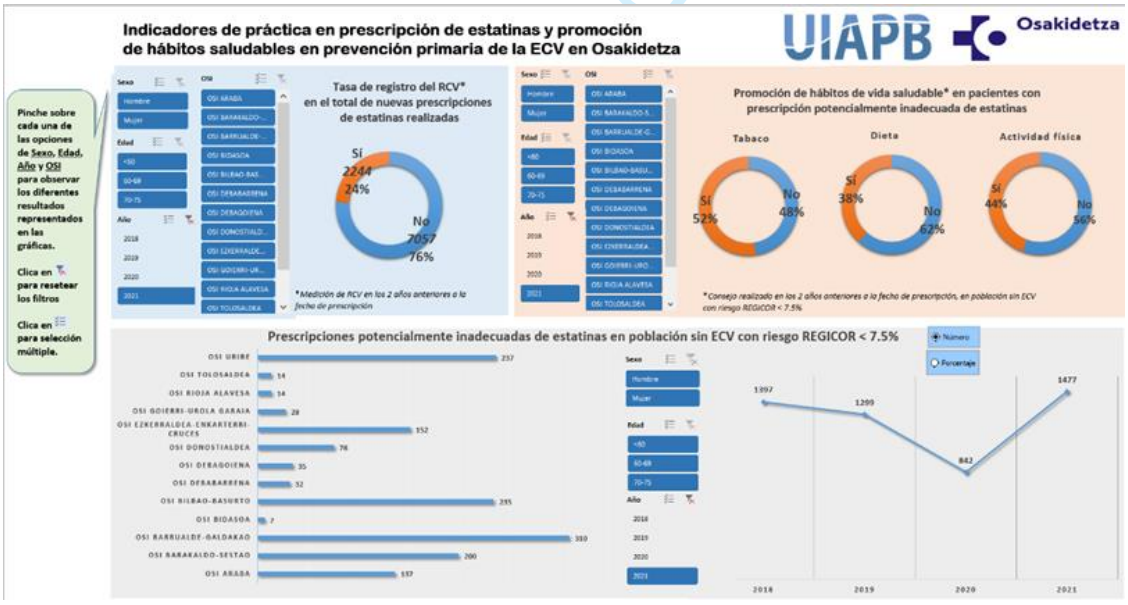


Figure 5. Draft of the Audit & Feedback report with practice- and organizational-level performance indicators of the family physicians regarding inappropriate prescribing of statins and healthy lifestyle promotion in the primary prevention of cardiovascular disease in low-risk patients in the Basque Health Service

3.3. Objectives: Determinant - What needs to change

Knowledge:

- ✓ Increase awareness of the problem of the inappropriate prescribing of statins

Behavior regulation:

- ✓ Make data available on inappropriate prescribing of statins for the primary prevention of CVD
- ✓ Provide tools for the setting of clear specific goals, at personal and organizational levels, regarding the reduction of inappropriate prescribing of statins for the primary prevention of CVD

Active reflection on personal practice:

- ✓ Encourage further reflection on practice/performance in relation to inappropriate prescribing of statins for the primary prevention of CVD

Intentions:

- ✓ Reduce the intention to prescribe statins inappropriately and increase the intention to promote healthy lifestyles for the primary prevention of CVD

Goals:

- ✓ Encourage commitment to practice in the primary prevention of CVD that is in accordance with recommendations
- ✓ Increase the motivation to promote healthy lifestyles in the primary prevention of CVD

Beliefs about capabilities:

- ✓ Strengthen self-efficacy and enhance the skills required for promoting healthy lifestyles

Emotion:

- ✓ Strengthen self-confidence about not prescribing statins for the primary prevention of CVD
- ✓ Foster belief in the safety of and trust in the courses of action recommended in the guidelines
- ✓ Experience a negative emotion after inappropriate prescribing

Professional/social role and identity:

- ✓ Foster the belief that appropriate primary prevention of CVD is considered important at the organizational level and among peers
- ✓ Strengthen understanding that the role of FPs goes beyond prescribing drugs

Reinforcement:

- ✓ Generate positive/negative reinforcement related to good/poor performance in the primary prevention of CVD.

3.4. Choice architecture techniques

A. Decision Information

A1. Translate Information: change the format or presentation of information but not the content.

Simplify: reduce the burden of cognitive effort necessary to process the information available and increase its usefulness in the decision-making process, e.g., presenting prescription rate data in a simple, user-friendly way, namely, on a dashboard.

A2. Make information visible: make necessary information readily accessible.

Make own behavior visible: feedback.

Make external information visible: make decision-relevant information visible, e.g., showing the prescription rates of other FPs and other IHOs.

A3. Provide social reference point: influence decision-making through the behavior of others.

Refer to descriptive norm: depict the observable behavior of other people to impact on the decision-making process, e.g., showing other FPs' prescribing behavior.

B. Decision structure

B2. Change opinion-related effort: modify the physical or financial effort involved in the decision-making process.

Decrease physical effort: collect all prescribing data in one file, e.g., dashboard.

C. Decision assistance

C2. Facilitate commitment: overcome constrained self-control and bridge the intention-behavior gap.

Support self-commitment: arrange with the aim of helping fulfill a plan, e.g., self-commitment questionnaire

3.5. Exposure

By opening the A&F reports received by email.

Annex I. GLOSSARY OF TERMS

1. De-implementation: De-implementation is defined as the process of reducing or abandoning the use of guidelines practices, interventions or policies that are found to be ineffective, are not proven to be effective, do not have adecuated scientific support, are less effective or less cost-effective than an alternative one, are potentially harmful to patients, or that represent low-value care.

2. Implementation: Implementation (commonly defined as "to do"), in the context of Implementation Science refers to the actively designed process of putting into practice or integrating evidence-based interventions (e.g., practice, program, policy,...) within a specific real-world setting.

3. Theoretical Domains Framework (TDF): The Theoretical Domains Framework (TDF) is an integrative framework developed from a synthesis of psychological theories as a vehicle to help apply theoretical approaches to interventions aimed at behavior change. The TDF comprises of 14 domains and 84 constructs that allows synthesis of a multitude of coherent behavior change theories into a single framework that allows assessment and explanation of behavioral problems and associated barriers and enablers, and inform the design of appropriately targeted interventions.

References:

1. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155.
2. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci. 2012;7:37. doi:10.1186/1748-5908-7-37.
3. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77. doi: 10.1186/s13012-017-0605-9.

4. Behavior Change Wheel (BCW): The Behavior Change Wheel (BCW) is a theory- and evidence-based tool that provides a process for designing or refining behavior change interventions and policies. Its purpose is to promote a systematic and comprehensive analysis of behavior in its context to guide change. It can be used to identify the interventions and policies likely to be effective in changing behavior.

Reference:

1. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011 23;6:42. Published 2011 Apr 23. doi:10.1186/1748-5908-6-42.

5. Statin: Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications that are used to lower blood low-density lipoprotein (LDL) cholesterol levels.

6. Non-reflective: Non-reflective processes, such as habits and routines, are defined as those factors that bypass conscious deliberation and so generate actions fast, effortlessly, automatically and with little deliberation and awareness.

7. Reflective: Reflective processes involves conscious deliberation over situational demands, available options and/or outcome expectancies; and therefore generate slow and effortful actions or behaviors via reasoned intentions.

8. Decision assistance strategy. Decision information strategy. Decision structure strategy
According to the taxonomy suggested by Münscher et al., there are three broad categories of choice architecture intervention techniques: decision information, decision structure, and decision assistance (Münscher et al., 2016).

i) **Decision information** interventions aim to facilitate access to decision-relevant information without altering the options themselves by increasing its availability, comprehensibility, and/or personal relevance to the decision maker. There are several ways of achieving it, such as (re)arranging existing information or changing its presentation/format, providing social reference point, etc.
ii) **Decision structure** interventions target the way in which the choice options are organized and structured through the arrangement of choice alternatives and the format of decision making, which includes setting default options, rearranging their composition, and changing option-related efforts or consequences of selecting it.
iii) **Decision assistance** interventions aim to bridge the intention–behavior gap by reinforcing self-regulation by providing decision makers with further assistance to help them follow through with their intentions. To do so, examples of decision assistance interventions techniques include provision of reminders of the desirable behavioral option as well as facilitating deliberate commitment to beneficial actions.

References:
1. Münscher R, Vetter M, Scheuerle T. A review and taxonomy of choice architecture techniques. J Behav Decis Mak. 2016;29(5):511-24. doi.org/10.1002/bdm.1897.
2. Mertens S, Herberz M, Hahnel UJJ, Brosch T. The effectiveness of nudging: A meta-analysis of choice architecture interventions across behavioral domains. Proc Natl Acad Sci USA. 2022;119(1):e2107346118. doi: 10.1073/pnas.2107346118. Erratum in: Proc Natl Acad Sci USA. 2022;119(19):e2204059119.

9. Audit & feedback (A&F): Audit and feedback is a strategy that aims to encourage individuals to change their practice and improve their performance. In the audit process, an individual's professional practice or performance is assessed and monitored based on specific, pre-defined criteria or standards. Then, the results of the comparison is fed back to the individual in a structured manner.

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Hoja de Información al Profesional de la salud y Consentimiento Informado

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Entidad financiadora: Instituto de salud Carlos III

Apreciado Sr./a,

Osakidetza-Servicio Vasco de Salud, con el propósito de mejorar la calidad en la prestación de servicios de salud hacia la ciudadanía, le invita a participar en el estudio "Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II".

Antes de decidir si desea participar, es importante que entienda los objetivos, la importancia de su participación y en qué consistirá, además de qué uso se dará a los datos recogidos y los posibles beneficios y riesgos.

Léalo atentamente y consulte cualquier duda con los miembros del equipo de investigación.

1. OBJETO DEL GRUPO DE DISCUSIÓN

El objetivo de los grupos de discusión del Proyecto De-ImFAR es generar conocimiento –a través de las percepciones de los/las profesionales de medicina de atención primaria- sobre la práctica clínica en prevención primaria de eventos cardiovasculares en pacientes de bajo riesgo. A través de una serie de preguntas abiertas se analizarán diferentes aspectos relacionados con el manejo del riesgo cardiovascular en estos pacientes, tratando de conocer la opinión de todos los integrantes del grupo sobre este tema.

No existen respuestas buenas o malas. Cualquier integrante del grupo está invitado a expresar libremente su opinión y a respetar la de los otros integrantes, aunque sea diferente de la suya.

2. PARTICIPACIÓN Y RETIRADA DEL ESTUDIO

Este estudio está aprobado por el Comité de Ética de la Investigación con Medicamentos de Euskadi (CEIm-E). Su participación en el mismo es voluntaria y en cualquier momento puede decidir abandonarlo, aunque haya proporcionado el consentimiento y el estudio esté en pleno desarrollo. Además, usted tiene derecho a solicitar al equipo investigador del estudio, en cualquier momento, y sin necesidad de especificar el motivo, la eliminación de sus datos.

3. DESARROLLO DEL ESTUDIO

Se realizará una sola entrevista llevada a cabo por dos investigadores con experiencia en métodos de investigación cualitativa, así como en el campo clínico y el proyecto. En dicha entrevista se le harán preguntas sobre su percepción y adaptación a las intervenciones implantadas. La discusión grupal será grabada (en formato audio) con el fin de transcribirla íntegramente. Esto permite a los miembros del equipo participar en la discusión sin necesidad de tomar notas, evitándose así el riesgo de no reflejar fidedignamente las opiniones expresadas por los miembros del grupo.

4. USO Y CONFIDENCIALIDAD DE LOS DATOS

Los datos que se obtengan en el grupo de discusión se utilizarán únicamente con fines de investigación y solamente por parte del equipo de investigación de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB). Todas las opiniones expresadas por los/las participantes serán tratadas de manera anónima y confidencial. Se le informa de que no se va a recoger ningún dato de carácter personal.

El estudio cumple lo establecido en el REGLAMENTO (UE) 2016/679 DEL PARLAMENTO EUROPEO Y DEL CONSEJO de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos. Se le solicita también su consentimiento para la realización de este proyecto de investigación conforme a las exigencias del Reglamento Europeo 2016/679 de Protección de Datos y a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales que deroga la Ley Orgánica 15/1999, de 5 de diciembre, de protección de datos personales. No se cederán datos a terceros, salvo obligación legal.

Para contactar con los responsables del estudio puede dirigirse a:

Nombre: Álvaro Sánchez Pérez

Teléfono: 946006673

e-mail: alvaro.sanchezperez@osakidetza.eus

Dirección: Edificio Biocruces 3, Plaza Cruces 12, 48903

Osakidetza

Iehen mailako atenzioa ikerketa unitatea unidad de investigación atención primaria bizkaia

Uiapb

5. DECLARACION DEL CONSENTIMIENTO INFORMADO

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Yo, Don/Doña....., Médico/a de Atención Primaria del Centro de Salud....., he leído este documento, he comprendido las explicaciones en él facilitadas acerca de la grabación del grupo de discusión y he podido resolver todas las preguntas que he planteado al respecto. Comprendo que mi participación en este ensayo es voluntaria y que puedo retirarme en cualquier momento.

También he sido informado/a de que mis datos personales serán protegidos y serán utilizados únicamente con fines de investigación por el equipo de investigadores de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB).

Tomando todo ello en consideración y en tales condiciones, CONSIENTO participar en el grupo de discusión, en la grabación del mismo y en que los datos que se deriven de mi participación sean utilizados para cubrir los objetivos especificados en el documento.

EN CONSECUENCIA, DOY MI CONSENTIMIENTO PARA PARTICIPAR EN ESTE PROYECTO DE INVESTIGACIÓN.

.....	.....
Firma del/la médico	Firma del/la responsable del proyecto
.....	.....
Nombre y apellidos	Nombre y apellidos
Fecha ...../...../20.....	Fecha ...../...../20.....

Hoja de Información al Paciente y Consentimiento Informado

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

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Antes de decidir si desea participar, es importante que entienda los objetivos, la importancia de su participación y en qué consistirá, además de qué uso se dará a los datos recogidos y los posibles beneficios y riesgos.

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1. OBJETO DEL GRUPO DE DISCUSIÓN

El objetivo de los grupos de discusión del Proyecto De-ImFAR es generar conocimiento –a través de las percepciones de los/las pacientes de atención primaria- sobre la práctica clínica en prevención primaria de eventos cardiovasculares en pacientes de bajo riesgo. A través de una serie de preguntas abiertas se analizarán diferentes aspectos relacionados con la experiencia percibida por los/las pacientes con la atención recibida, tratando de conocer la opinión de todos los integrantes del grupo sobre este tema.

No existen respuestas buenas o malas. Cualquier integrante del grupo está invitado a expresar libremente su opinión y a respetar la de los otros integrantes, aunque sea diferente de la suya.

2. PARTICIPACIÓN Y RETIRADA DEL ESTUDIO

Este estudio está aprobado por el Comité de Ética de la Investigación con Medicamentos de Euskadi (CEIm-E). Su participación en el mismo es voluntaria y en cualquier momento puede decidir abandonarlo, aunque haya proporcionado el consentimiento y el estudio esté en pleno desarrollo. Su decisión no afectará la atención sanitaria que reciba posteriormente. Además, usted tiene derecho a solicitar al equipo investigador del estudio, en cualquier momento, y sin necesidad de especificar el motivo, la eliminación de sus datos. Su participación en este estudio no supondrá para usted ningún coste económico, así como tampoco será recompensado económicamente por ello.

3. DESARROLLO DEL ESTUDIO

Se realizará una sola entrevista llevada a cabo por dos investigadores con experiencia en métodos de investigación cualitativa, así como en el campo clínico y el proyecto. En dicha entrevista se le harán preguntas sobre su experiencia y satisfacción con el servicio recibido en prevención primaria de eventos cardiovasculares.

La discusión grupal será grabada (en formato audio) con el fin de transcribirla íntegramente. Esto permite a los miembros del equipo participar en la discusión sin necesidad de tomar notas, evitándose así el riesgo de no reflejar fidedignamente las opiniones expresada por los miembros del grupo.

4. USO Y CONFIDENCIALIDAD DE LOS DATOS

Los datos que se obtengan en el grupo de discusión se utilizarán únicamente con fines de investigación y solamente por parte del equipo de investigación de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB). Todas las opiniones expresadas por los/las participantes serán tratadas de manera anónima y confidencial. Se le informa de que no se va a recoger ningún dato de carácter personal.

El estudio cumple lo establecido en el REGLAMENTO (UE) 2016/679 DEL PARLAMENTO EUROPEO Y DEL CONSEJO de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos. Se le solicita también su consentimiento para la realización de este proyecto de investigación conforme a las exigencias del Reglamento Europeo 2016/679 de Protección de Datos y a la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales que deroga la Ley Orgánica 15/1999, de 5 de diciembre, de protección de datos personales. No se cederán datos a terceros, salvo obligación legal.

Si usted tiene alguna duda o requiere cualquier tipo de información no dude en contactar con el/la médico que le informa, Dr./a _____, cuyo lugar de trabajo
es el Servicio de_____ del Hospital Universitario
_____; teléfono: _____ (extensión_____).

Usted también puede contactar con el Investigador Principal responsable:

Nombre: Álvaro Sánchez Pérez

Teléfono: 946006673

e-mail: alvaro.sanchezperez@osakidetza.eus

Dirección: Edificio Biocruces 3, Plaza Cruces 12, 48903

5. DECLARACION DEL CONSENTIMIENTO INFORMADO

Título: Efectividad de estrategias de de-implementación para favorecer el abandono de prescripciones farmacológicas de bajo valor en prevención primaria de la ECV: proyecto De-imFAR Fase II

Investigador Principal: Álvaro Sánchez Pérez

Investigador/a médico/a:……..

Servicio/Centro: Subdirección para la coordinación de atención primaria/Unidad de investigación atención primaria-IIS Biocruces Bizkaia

Yo, Don/Doña…….(nombre y apellidos del paciente),

he leído este documento, he comprendido las explicaciones en él facilitadas acerca de la grabación del grupo de discusión y he podido resolver todas las preguntas que he planteado al respecto. Comprendo que mi participación en este ensayo es voluntaria y que puedo retirarme en cualquier momento.

También he sido informado/a de que mis datos personales serán protegidos y serán utilizados únicamente con fines de investigación por el equipo de investigadores de la Unidad de Investigación de Atención Primaria de Bizkaia (UIAPB).

Tomando todo ello en consideración y en tales condiciones, CONSIENTO participar en el grupo de discusión, en la grabación del mismo y en que los datos que se deriven de mi participación sean utilizados para cubrir los objetivos especificados en el documento.

EN CONSECUENCIA, DOY MI CONSENTIMIENTO PARA PARTICIPAR EN ESTE PROYECTO DE INVESTIGACIÓN.

……..	……..
Firma del/la paciente	Firma del/la médico responsable
……..	……..
Nombre y apellidos	Nombre y apellidos
Fecha ……/……/20……	Fecha ……/……/20……

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9, 12-13

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15,18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28,29
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Reference: Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200-207. doi: 10.7326/0003-4819-158-3-201302050-00583.