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IMPROVING INITIAL MEDICATION ADHERENCE IN PRIMARY CARE: PRAGMATIC EVALUATION OF A COMPLEX BEHAVIOURAL INTERVENTION

CARMEN CORRAL PARTEARROYO

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CARMEN CORRAL PARTEARROYO

Thesis supervisors

Dr Maria Rubio Valera
Institut de Recerca Sant Joan de Déu

Dr Montserrat Gil Girbau
Institut de Recerca Sant Joan de Déu

Thesis tutor

Dr Mª José Martínez Zapata
Institut de Recerca Sant Pau

PhD Programme in Methodology of Biomedical Research and Public Health,
Department of Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine and Public Health,
Universitat Autònoma de Barcelona

UAB Universitat Autònoma de Barcelona

SJD Sant Joan de Déu Institut de Recerca

PhD Programme in Methodology of Biomedical Research and Public Health

UAB
Universitat Autònoma de Barcelona

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Carmen Corral Partearroyo

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Directed by

Dr Maria Rubio Valera and **Dr Montserrat Gil Girbau**

Thesis tutor

Dr Mª José Martínez Zapata

Barcelona, July 2025

CERTIFICATE OF THESIS SUPERVISION

Dr Maria Rubio Valera, PhD, researcher at the Institut de Recerca Sant Joan de Déu and Professor at the Facultat de Medicina i Ciències de la Salut at the Universitat de Barcelona with Identity Card number 46790030A, and

Dr Montserrat Gil Girbau, PhD, researcher at the Institut de Recerca Sant Joan de Déu with Identity Card number 33895741C.

CERTIFY THAT:

The thesis presented by **Carmen Corral Partearroyo** with the title "*Improving initial medication adherence in primary care: pragmatic evaluation of a complex behavioural intervention*" has been developed under our supervision and meets the necessary conditions for its presentation as a doctoral thesis.

Barcelona, 9 of July 2025.

Maria Rubio Valera, PhD
Thesis Supervisor

Montserrat Gil Girbau, PhD
Thesis Supervisor

A mi madre y a mis tías,
que me enseñaron el valor de la salud pública
e hicieron que en los hospitales me sintiera como en casa.

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PREFACE

The thesis entitled “Improving initial medication adherence in primary care: pragmatic evaluation of a complex behavioural intervention” is presented as a compendium of scientific publications. It comprises four peer-reviewed articles that collectively document the piloting, refinement, implementation, and evaluation of the Initial Medication Adherence (IMA) intervention—a complex, theory-informed, patient-centred intervention designed to improve adherence to newly prescribed treatments for cardiovascular disease and diabetes in primary care:

1) **Corral-Partearroyo C**, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Serrano-Blanco A, Carbonell-Duacastella C, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M. Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention. Front Public Health. 2022 Dec;10:1038138. doi: 10.3389/fpubh.2022.1038138. IF (2024): 3.4; Q1.
2) **Corral-Partearroyo C**, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M. Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol. BMJ Open. 2022 Oct;12:e067468. doi: 10.1136/bmjopen-2022-067468. IF (2024): 2.3; Q2.

3) **Corral-Partearroyo C**, Sánchez-Viñas A, Peñarrubia-María MT, Gil-Girbau M, Aznar-Lou I, Palma-Vasquez C, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M. Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation. BMJ Quality & Safety. 2025 Jun;0:1–14. doi: 10.1136/bmjqs-2024-018403. IF (2024): 6.5; Q1.
4) **Corral-Partearroyo C**, Sánchez-Viñas A, Aznar-Lou I, Peñarrubia-María MT, Gil-Girbau M, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M. Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using real-world data. BMJ Quality & Safety. 2025 Jul;0:1-15. doi: 10.1136/bmjqs-2024-018402. IF (2024): 6.5; Q1.

In addition, a fifth scientific article that is not part of the compendium of publications has been included as Appendix 1. The article describes the protocol of the pragmatic IMA-cRCT trial.

Sánchez-Viñas A, **Corral-Partearroyo C**, Gil-Girbau M, Peñarrubia-María MT, Gallardo-González C, Olmos-Palenzuela MC, Aznar-Lou I, Serrano-Blanco A, Rubio-Valera M. Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised

controlled trial and economic model (the IMA-cRCT study). BMC Prim Care. 2022 Jul;23(1):170. doi: 10.1186/s12875-022-01727-6.

The research presented in this thesis was funded by the College of Pharmacists of Barcelona (Col·legi de Farmacèutics de Barcelona) for the feasibility pilot study, and by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant Agreement No. 948973) for the subsequent phases of the project. It was conducted at the Institut de Recerca Sant Joan de Déu, Parc Sanitari Sant Joan de Déu and the Institut Català de la Salut (ICS). The authors of the publications included in this thesis are members of the Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP) and the Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS). Additionally, an international research stay at the Centre for Adherence Research & Education (CARE) at King's College London (KCL) enable the extension of the work with an emphasis on behavioural science and interventions to improve medication adherence.

ABSTRACT

Background: Medication non-adherence remains a major public health challenge, particularly in chronic conditions such as cardiovascular diseases and diabetes. The prescription of a new treatment is a critical moment when many patients decide whether to initiate the prescribed medication or not. Shared decision-making is proposed as a patient-centred approach with the potential to improve adherence, yet evidence on its impact remains limited, particularly in real-world settings.

Objectives: This doctoral thesis aims to develop, implement and evaluate the Initial Medication Adherence (IMA) intervention—a complex multidisciplinary intervention based on shared decision making—to improve adherence in primary care among patients newly prescribed pharmacological treatments for cardiovascular diseases and/or diabetes. The research is structured around four specific objectives: (1) to assess the feasibility and acceptability of an initial version of the intervention and of the pragmatic study design; (2) to refine the intervention and develop a logic model or theory of change, as well as refine the study design; (3) to conduct a process evaluation assessing the intervention's implementation, mechanisms of action, and contextual influences; and (4) to evaluate the effectiveness of the IMA intervention compared to usual care in improving initial and secondary medication adherence and clinical outcomes.

Methods: The research followed the United Kingdom's Medical Research Council framework for developing and evaluating complex

interventions. First, a pilot study—a cluster non-randomised controlled trial with an embedded process evaluation—was conducted in 5 primary care centres (November 2020 – January 2021) to assess the availability and quality of real-world data through analysis of electronic health records, and the feasibility and acceptability of the IMA intervention through professionals' and patients' experiences using qualitative methods. Second, based on these findings, the intervention and evaluation design were refined. Last, a hybrid type I effectiveness-implementation study was conducted through a pragmatic cluster-randomised controlled trial (cRCT) and a process evaluation involving 24 primary care centres (March 2022 – September 2022). The nested mixed-methods process evaluation combined quantitative methods—monitoring data and questionnaires descriptively analysed—, and qualitative methods—field diaries, individual semistructured interviews, and focus groups—analysed using framework analysis. Patients were identified from electronic health records for inclusion in the pragmatic cRCT. Effectiveness was assessed using data from prescription and dispensing (medication adherence) and clinical outcomes records analysed with multilevel regression models. Findings from effectiveness and implementation evaluations were integrated.

Results: The pilot trial included 67 healthcare professionals and 604 patients, while 25 professionals and 19 patients participated in the individual interviews and discussion groups of the process evaluation. The study confirmed the intervention's feasibility and acceptability but identified the need for refining professional training, shared decision-making support tools, and strategies to promote professional

engagement. Results of the pilot study also informed the design of the pragmatic hybrid study by highlighting the need for strategies to improve the quality of electronic health records and by helping to identify key logistical challenges. The hypothesised mechanisms through which the shared decision-making based intervention could improve adherence and ultimately impact health outcomes (logic model) included changes to healthcare professionals—such as increased shared decision-making knowledge and skills, greater self-efficacy, and improved interprofessional collaboration—and changes to patients and their interaction with professionals—such as improved health literacy, increased decision engagement through discussing options and aligning decisions with patient values, and stronger bond of trust. Regarding the hybrid type I effectiveness-implementation study, the process evaluation included quantitative methods involving 139 professionals and qualitative methods with 28 professionals and 19 patients. Fidelity to the IMA intervention and integration into clinical practice were adequate. Professionals reported increased knowledge and awareness, and both professionals and patients described positive experiences with shared decision-making. However, its application remained inconsistent, as some clinicians believed they were already implementing it, some patients preferred to delegate decisions to clinicians, and various contextual organisational factors were identified. The pragmatic cRCT of the hybrid study identified 3629 patients receiving 4910 new prescriptions for cardiovascular diseases and diabetes. No improvements in primary or secondary medication adherence compared to usual care were detected. A clinically meaningful reduction in blood pressure was observed among patients

prescribed antihypertensive medications. No differences were detected in other clinical outcomes.

Conclusions: This thesis demonstrates the viability of developing, implementing and evaluating a complex patient-centred intervention in primary care using a pragmatic hybrid effectiveness-implementation approach and real-world data. Although the IMA intervention impact on adherence was limited, the findings highlight the potential clinical relevance of shared decision-making and the intrinsic value of promoting patient-centred care models that enhance patient and professional experience and contribute to improving the overall quality of care.

Trial registrations: *ClinicalTrials.gov*; Pilot trial: NCT05094986 and cRCT: NCT05026775.

Keywords: complex intervention; behaviour change; shared decision-making; medication adherence; primary care; feasibility study; logic model; type I hybrid effectiveness-implementation study; process evaluation; effectiveness evaluation; pragmatic RCT; real-world data; electronic health records.

RESUM

Antecedents: La manca d'adherència a la medicació continua essent un repte important de salut pública, especialment en malalties cròniques com les cardiovasculars i la diabetis. La prescripció d'un nou tractament és un moment crític en què molts pacients decideixen iniciar o no el medicament prescrit. La presa de decisions compartides es planteja com un enfocament centrat en el pacient i potencial per millorar l'adherència; tanmateix, l'evidència sobre el seu impacte encara és limitada, especialment en entorns reals.

Objectius: Aquesta tesi doctoral té com a objectiu desenvolupar, implementar i avaluar la intervenció *Initial Medication Adherence* (IMA), una intervenció complexa i multidisciplinària basada en la presa de decisions compartides, per millorar l'adherència a l'atenció primària en pacients amb una prescripció farmacològica nova per a malalties cardiovasculars i/o diabetis. La recerca es va estructurar en quatre objectius específics: (1) avaluar la viabilitat i acceptabilitat d'una versió inicial de la intervenció i del disseny de l'estudi pragmàtic; (2) perfeccionar la intervenció i desenvolupar un model lògic o teoria del canvi, així com ajustar el disseny de l'estudi; (3) dur a terme una avaluació de procés que analitzés la implementació, els mecanismes d'acció i les influències contextuals; i (4) avaluar l'efectivitat de la intervenció IMA en comparació amb l'atenció habitual en la millora de l'adherència primària i secundària i dels resultats clínics.

Mètodes: La recerca va seguir el marc del *Medical Research Council* del Regne Unit per al desenvolupament i l'avaluació d'intervencions

complexes. En primer lloc, es va realitzar un estudi pilot—un assaig controlat no aleatoritzat per conglomerats amb una avaluació de procés integrada—en 5 centres d'atenció primària (novembre 2020 – gener 2021) per avaluar la disponibilitat i qualitat de les dades del món real mitjançant l'anàlisi de les històries clíniques electròniques, i la viabilitat i acceptabilitat de la intervenció IMA mitjançant les experiències de professionals i pacients amb mètodes qualitatius. En segon lloc, a partir d'aquests resultats, es va perfeccionar la intervenció i el disseny de l'avaluació. Finalment, es va dur a terme un estudi híbrid de tipus I d'efectivitat-implementació mitjançant un assaig controlat aleatoritzat per conglomerats pragmàtic i una avaluació de procés que va implicar a 24 centres d'atenció primària (març 2022 – setembre 2022). L'avaluació de procés, amb mètodes mixtos, va combinar mètodes quantitatius—dades de monitoratge i qüestionaris analitzats de manera descriptiva—i mètodes qualitatius—diaris de camp, entrevistes semiestructurades i grups focals—analitzats amb *framework analysis*. Els pacients es van identificar a partir de les històries clíniques electròniques per a la seva inclusió a l'assaig pragmàtic. L'efectivitat es va avaluar amb dades de prescripció i dispensació (adherència) i registres clínics analitzats amb models de regressió multinivell. Es van triangular els resultats de les avaluacions d'efectivitat i implementació.

Resultats: L'estudi pilot va incloure 67 professionals sanitaris i 604 pacients, mentre que 25 professionals i 19 pacients van participar en entrevistes individuals i grups de discussió de l'avaluació de procés. L'estudi va confirmar la viabilitat i acceptabilitat de la intervenció, però va identificar la necessitat de millorar la formació professional, les eines

de suport a la presa de decisions compartides i les estratègies per promoure la implicació dels professionals. Els resultats també van informar sobre el disseny de l'estudi híbrid en evidenciar la necessitat d'estratègies per millorar la qualitat del registre clínic i identificar reptes logístics clau. Els mecanismes hipotetitzats (model lògic) mitjançant els quals la intervenció basada en la presa de decisions compartides podria millorar l'adherència i impactar els resultats clínics van incloure: canvis en els professionals—més coneixements i habilitats, major autoeficàcia i millor col·laboració—i canvis en els pacients i la seva interacció amb els professionals—millor alfabetització en salut, més implicació en la presa de decisions i un vincle de confiança més sòlid. L'avaluació de procés de l'estudi híbrid va incloure mètodes quantitatius amb 139 professionals i qualitatius amb 28 professionals i 19 pacients. La fidelitat i integració a la pràctica clínica van ser adequades. Els professionals van informar més coneixement i consciència, i tant professionals com pacients van descriure experiències positives. Tanmateix, la seva aplicació va ser inconsistent: alguns professionals creien que ja estaven aplicant la presa de decisions compartides, alguns pacients preferien delegar decisions i es van identificar factors contextuals organitzatius. L'assaig pragmàtic va identificar 3629 pacients amb 4910 noves prescripcions per malalties cardiovasculars i diabetis. No es van observar millores en l'adherència respecte a l'atenció habitual. Es va detectar una reducció clínicament rellevant de la pressió arterial en pacients amb antihipertensius prescrits. No es van trobar diferències en altres resultats clínics.

Conclusions: Aquesta tesi demostra la viabilitat de desenvolupar, implementar i avaluar una intervenció complexa centrada en el pacient a l'atenció primària mitjançant un enfocament híbrid pragmàtic i dades del món real. Tot i l'impacte limitat en l'adherència, els resultats subratllen la potencial rellevància clínica de la presa de decisions compartides i el valor intrínsec de promoure models d'atenció centrats en el pacient que millorin l'experiència i la qualitat assistencial.

Registre d'assaigs: *ClinicalTrials.gov*; Estudi pilot: NCT05094986 i Assaig controlat aleatoritzat per conglomerats: NCT05026775.

Paraules clau: intervenció complexa; canvi de comportament; presa de decisions compartides; adherència a la medicació; atenció primària; estudi de viabilitat; model lògic; estudi híbrid d'efectivitat-implementació tipus I; avaluació de procés; assaig pragmàtic; dades del món real; històries clíniques electròniques.

RESUMEN

Antecedentes: La falta de adherencia a la medicación sigue siendo un importante desafío de salud pública, especialmente en patologías crónicas como las enfermedades cardiovasculares y la diabetes. La prescripción de un nuevo tratamiento es un momento crítico en el que muchos pacientes deciden iniciar o no la medicación prescrita. La toma de decisiones compartidas se plantea como un enfoque centrado en el paciente con potencial para mejorar la adherencia; sin embargo, la evidencia sobre su impacto sigue siendo limitada, particularmente en contextos reales.

Objetivos: Esta tesis doctoral tiene como objetivo desarrollar, implementar y evaluar la intervención *Initial Medication Adherence* (IMA), una intervención compleja y multidisciplinar basada en la toma de decisiones compartidas, para mejorar la adherencia en atención primaria en pacientes con una nueva prescripción de tratamientos farmacológicos para enfermedades cardiovasculares y/o diabetes. La investigación se estructuró en torno a cuatro objetivos específicos: (1) evaluar la viabilidad y aceptabilidad de una versión inicial de la intervención y del diseño de estudio pragmático; (2) perfeccionar la intervención y desarrollar un modelo lógico o teoría del cambio, así como ajustar el diseño del estudio; (3) realizar una evaluación de proceso para evaluar la implementación, los mecanismos de acción y las influencias contextuales; y (4) evaluar la efectividad de la intervención IMA frente a la práctica habitual en la mejora de la adherencia inicial y secundaria a la medicación y resultados clínicos.

Métodos: La investigación siguió el marco del *Medical Research Council* de Reino Unido para el desarrollo y evaluación de intervenciones complejas. En primer lugar, se realizó un estudio piloto—un ensayo controlado no aleatorizado por conglomerados con una evaluación de proceso integrada—en 5 centros de atención primaria (noviembre 2020 – enero 2021) para evaluar la disponibilidad y calidad de los datos del mundo real mediante el análisis de la historia clínica electrónica, y la viabilidad y aceptabilidad de la intervención IMA mediante experiencias de profesionales y pacientes usando métodos cualitativos. En segundo lugar, a partir de estos hallazgos, se optimizó la intervención y el diseño de la evaluación. Finalmente, se llevó a cabo un estudio híbrido de tipo I de efectividad-implementación mediante un ensayo controlado aleatorizado por conglomerados pragmático y una evaluación de proceso en 24 centros de atención primaria (marzo 2022 – septiembre 2022). La evaluación de proceso, de métodos mixtos, combinó métodos cuantitativos—datos de monitorización y cuestionarios analizados de manera descriptiva—y métodos cualitativos—diarios de campo, entrevistas individuales semiestructuradas y grupos focales—analizados mediante *framework analysis*. Los pacientes se identificaron a partir de la historia clínica electrónica para su inclusión en el ensayo pragmático. La efectividad se evaluó usando datos de prescripción y dispensación (adherencia) y registros de resultados clínicos, analizados mediante modelos de regresión multinivel. Los resultados de las evaluaciones de efectividad e implementación se triangularon.

Resultados: El estudio piloto incluyó a 67 profesionales sanitarios y 604 pacientes, mientras que 25 profesionales y 19 pacientes participaron en

entrevistas individuales y grupos de discusión de la evaluación de proceso. El estudio confirmó la viabilidad y aceptabilidad de la intervención, pero identificó la necesidad de mejorar la formación profesional, las herramientas de apoyo a la toma de decisiones compartidas y las estrategias para fomentar la implicación de los profesionales. Los resultados del estudio piloto también contribuyeron al diseño del estudio híbrido pragmático al evidenciar la necesidad de estrategias para mejorar la calidad del registro en la historia clínica electrónica y ayudar a identificar retos logísticos clave. Los mecanismos hipotetizados (modelo lógico) mediante los cuales la intervención basada en la toma de decisiones compartidas podría mejorar la adherencia e impactar en los resultados clínicos incluyeron: cambios en los profesionales—mayor conocimiento y habilidades en toma de decisiones compartidas, autoeficacia y colaboración interprofesional—y cambios en los pacientes y su interacción con los profesionales—como mejor alfabetización en salud, mayor implicación en las decisiones mediante la discusión de opciones y alineación con los valores del paciente, y un vínculo de confianza más sólido. En relación con el estudio híbrido de tipo I, la evaluación de proceso incluyó métodos cuantitativos con 139 profesionales y cualitativos con 28 profesionales y 19 pacientes. La fidelidad a la intervención y su integración en la práctica clínica fueron adecuadas. Los profesionales informaron de un aumento de conocimiento y concienciación, y tanto profesionales como pacientes describieron experiencias positivas con la toma de decisiones compartidas. Sin embargo, su aplicación fue inconsistente: algunos clínicos consideraban que ya la estaban aplicando, algunos pacientes preferían delegar las decisiones en los profesionales, y se identificaron

diversos factores contextuales organizativos. El ensayo pragmático identificó a 3629 pacientes que recibieron 4910 nuevas prescripciones para enfermedades cardiovasculares y diabetes. No se detectaron mejoras en la adherencia primaria o secundaria frente a la práctica habitual. Se observó una reducción clínicamente relevante de la presión arterial en pacientes con antihipertensivos prescritos. No se encontraron diferencias en otros resultados clínicos.

Conclusiones: Esta tesis demuestra la viabilidad de desarrollar, implementar y evaluar una intervención compleja centrada en el paciente en atención primaria, mediante un enfoque híbrido pragmático de efectividad-implementación y datos del mundo real. Aunque el impacto de la intervención IMA sobre la adherencia fue limitado, los hallazgos subrayan la relevancia clínica potencial de la toma de decisiones compartidas y el valor intrínseco de promover modelos de atención centrados en el paciente que mejoren la experiencia de pacientes y profesionales y contribuyan a incrementar la calidad asistencial global.

Registro de ensayos: *ClinicalTrials.gov;* Estudio piloto: NCT05094986 y Ensayo controlado aleatorizado por conglomerados: NCT05026775.

Palabras clave: intervención compleja; cambio de comportamiento; toma de decisiones compartidas; adherencia a la medicación; atención primaria; estudio de viabilidad; modelo lógico; estudio híbrido de efectividad-implementación tipo I; evaluación de proceso; evaluación de efectividad; ECA pragmático; datos del mundo real; historia clínica electrónica.

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ABBREVIATIONS

cRCT: cluster-Randomised Controlled Trial

CVD: Cardiovascular Disease

ESPACOMP: European Society for Patient Adherence, COMpliance, and Persistence

GP: General Practitioner

IMA: Initial Medication Adherence

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

MRC: Medical Research Council

PRECIS-2: PRagmatic Explanatory Consortium Indicator Summary

RCT: Randomised Controlled Trial

WHO: World Health Organization

1

Introduction

1 INTRODUCTION

1.1 Cardiovascular disease and diabetes

Global life expectancy is rising and people are living longer than ever before [1,2]. Between 2015 and 2050, the proportion of the population aged 60 and over is expected to increase from 12 to 20% [2]. Ageing is a well-known risk factor for chronic diseases, such as cardiovascular disease (CVD) and type II diabetes mellitus, driving the need for responsive healthcare systems capable of addressing the challenges of ageing populations [3].

CVDs encompass a broad range of conditions, including heart diseases and blood vessel disorders, which can lead to acute events such as heart attacks and strokes [4]. Similarly, type II diabetes mellitus develops when the body becomes resistant to insulin or when the pancreas fails to produce enough of it, resulting in elevated blood glucose levels [5]. Over time, this can cause serious damage to multiple body systems, particularly nerves and blood vessels, and increase the risk of heart attack, stroke and kidney failure [5]. Both conditions often progress silently, with no noticeable symptoms of the underlying disease. In the case of CVD, a fatal event may be the first sign of the disease, while diabetes symptoms may be mild or take years to become apparent [4,5].

Globally, more than 500 million people live with CVD and diabetes [6,7]. These conditions are among the leading causes of mortality worldwide [8], with CVD responsible for over 3 million deaths and diabetes for more than 1 million deaths per year in Europe alone [9,10]. The current rise in prevalence is driven by multiple factors, with lifestyle—such as diet, physical activity,

alcohol consumption or smoking—playing a significant role [11]. Understanding the risk factors associated with these conditions is key to predicting an individual's likelihood of developing them [12]. These factors are typically divided into two categories: modifiable and non-modifiable [13]. Modifiable risk factors are those that can be addressed through different measures—e.g., smoking and alcohol consumption, high intake of refined sugar and poor diet, sedentary lifestyle, obesity, stress and exposure to air pollution [13–15]. In contrast, non-modifiable risk factors are inherent to the individual—e.g., age, sex or family history [13].

Most CVD and diabetes cases can be prevented by tackling behavioural and environmental risk factors [4,5]. At the same time, early detection is crucial to initiate disease management as soon as possible and prevent disease progression [4,5]. In this context, both primary and secondary prevention are essential. Primary prevention targets individuals at risk and focuses mainly on lifestyle modifications to prevent disease onset, whereas secondary prevention is aimed at individuals with an established diagnosis and involves early detection, pharmacological treatment and lifestyle changes to prevent further complications [12].

As a result, an increasing number of patients rely on daily medications for the prevention and management of chronic conditions [16,17]. However, despite health promotion efforts, medication adherence remains low, limiting the effectiveness of these treatments in reducing the burden of CVD and diabetes [14].

1.2 Medication adherence

1.2.1 Definition

The term adherence is broadly used to describe an individual's medication-taking behaviour. In adherence research, *compliance* was introduced in the 1970s to refer to patients' use or misuse of prescribed medications. However, it implied a passive role for patients, describing them as merely following the prescriber's decision without active involvement [18]. In the 1990s, the term *concordance* emerged, emphasising the need for collaboration between patients and healthcare professionals, acknowledging the potentially differing views, and highlighting the importance of agreeing on the treatment plan [18]. Over the last decades, the term *adherence* has increasingly replaced these concepts, and various definitions have been proposed that reflect the evolving understanding of patient behaviour in relation to medication use. For instance, in 2003 the World Health Organization (WHO) Adherence to Long-term Therapies report defined it as “the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider”, taking into account non-pharmacological measures as well as medications and involving the patient agreement role in the definition [19]. Other authors have proposed simplified definitions. Vrijens *et al*. (2012) defined adherence as “the process by which patients take their medications as prescribed” [18]. Julius *et al*. (2009) described it as “the extent to which a patient's behaviour coincides with medical or prescribed health advice” [20] while Balkrishnan (2005) emphasised the patient's decision in their definition,

"the level of participation achieved in a medication regimen once an individual has agreed to the regimen" [21].

However, these definitions often fail to capture adherence as a broader concept, which goes beyond simply taking medication. It also encompasses the patient's involvement in managing their disease and treatment, while being influenced by interactions with healthcare professionals [22]. This thesis aims to explore adherence within this broader conceptual framework, focusing on its multidimensional nature, including patient involvement, commitment, and the influence of professionals.

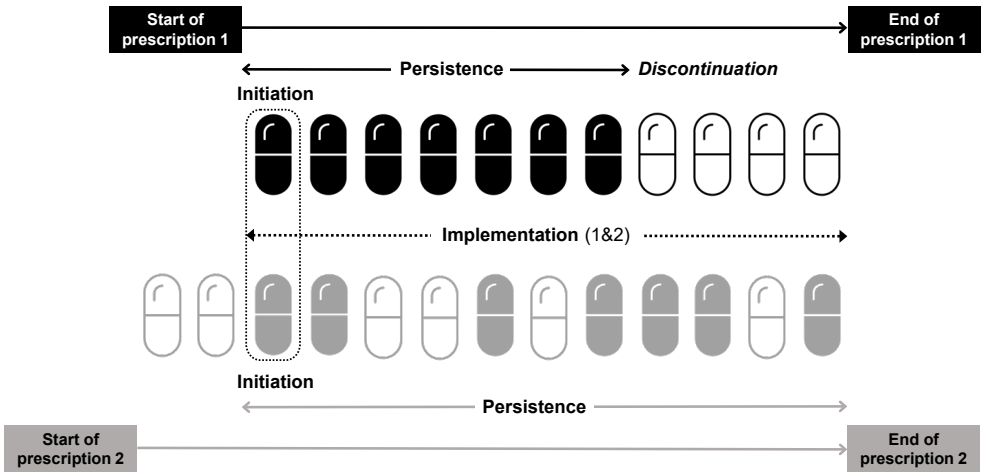
1.2.2 Key components of medication adherence

In 2012, Vrijens *et al*. developed a taxonomy for describing and defining adherence to medications and advocating consistency across research studies [18]. The taxonomy was published as part of the Ascertaining Barriers to Compliance (ABC) project, an international collaboration of European research groups within the European Society for Patient Adherence, COMpliance and Persistence (ESPACOMP) [18]. They defined the main behavioural components or interrelated phases of the adherence process to support the definition of research outcomes. The definitions presented here are those used in this thesis based on this taxonomy (illustrated in Figure 1): 1) *Initiation* of the treatment refers to the time when the patient takes the first dose of a prescribed medication; 2) *Implementation*[1]*,* or *ongoing adherence,* of the regimen considers the consistency between the prescribed

[1] To avoid confusion with terms used in implementation science, the term '*ongoing adherence'* will be used throughout this thesis to refer to *implementation* as defined by Vrijens *et al*. (2012) [18], except in this section where the original term *'implementation'* is used.

dosing regime and the patient's actual dosing intake from initiation until the end of the treatment; 3) *Discontinuation* indicate the cessation of the treatment when the next dose to be taken is omitted and no more doses are taken afterwards; and 4) *Persistence* which is the length of time between initiation and the last dose taken before discontinuation [18].

Figure 1. The process of adherence to medications interrelated phases illustrated in two prescriptions adapted from Vrijens *et al*. (2012) [18].



These terms not only acknowledge that adherence is a dynamic behaviour, describing it as a process that evolves over time, but also emphasise key moments that play a crucial role in the adherence process. The ABC taxonomy aligns with the framework proposed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), distinguishing between initial medication adherence and post-initiation medication adherence and highlighting initial medication adherence as a vital phase of medication adherence by considering the patient's intention and reasons to initiate a new treatment [23,24]. The initial medication adherence process represents a crucial period when behaviour change begins and habits and beliefs develop, potentially influencing long-term adherence and clinical

outcomes [25]. At this early point, patients typically have direct contact with a healthcare professional—sometimes the only such contact—presenting a valuable opportunity to identify and address known factors affecting adherence before the prescription is issued [25].

Consequently, understanding adherence as a dynamic process and exploring the factors that affect it at different time points of the patients' prescription process can help to tailor interventions to support short and long-term adherence [24,25].

1.2.3 Adherence as a health-related behaviour

Medication adherence can be explained through the decision-making process that shapes it. Adherence, or taking the medication as prescribed, has often been categorised as intentional or unintentional to understand the behaviour [26]. However, major issues have been reported regarding this theoretical analysis of adherence. For instance, it places patient-level factors at the core of the issue, overlooking broader influences. Also, intentional and unintentional reasons can overlap and lead to the same outcome; an individual may forget to take a medication due to memory issues or because of a perceived lack of treatment effectiveness [27].

The COM-B model for behaviour change, developed by Michie *et al*. (2011), has been used to describe medication adherence as a health-related behaviour [28,29]. It captures multiple mechanisms that influence the behaviour, providing more comprehensive explanations than the traditional intentional or unintentional model [27,29]. This framework illustrates how the components *Capability, Opportunity and Motivation* (COM) interplay to

determine whether a *Behaviour* (B) occurs. Likewise, it helps explain why individuals fail to engage in recommended health behaviours.

Building on the COM-B model [28,29], *Capability* refers to the individual's capacity to perform a behaviour or whether they have the knowledge, skills, and abilities to engage. It is divided into *psychological capability* (capacity to engage in the necessary thought processes such as comprehension or understanding of the disease and how the medication influences it, which could include cognitive impairment and memory issues) and *physical capability* (capacity to engage in necessary physical processes such as the ability to adapt to lifestyle changes). *Motivation* refers to internal processes that influence decision-making and drive behaviour. It is divided into *reflective motivation* (reflective processes of conscious evaluation and planning, such as perception of disease or beliefs about the treatment) and *automatic motivation* (automatic processes such as emotions, habits, and impulses, including action stimuli or changing mood states). Lastly, *Opportunity* represents external factors that enable or prompt behaviour. It is divided into *physical opportunity* (opportunities provided by the environment, such as access or medication availability) and *social opportunity* (cultural influences shaping thought and behaviour, such as religious or social beliefs and stigma associated with the disease).

Figure 2. Applying COM-B for behaviour change to adherence (adapted from Michie *et al*. (2011) and Jackson *et al*. (2014) [28,29]).

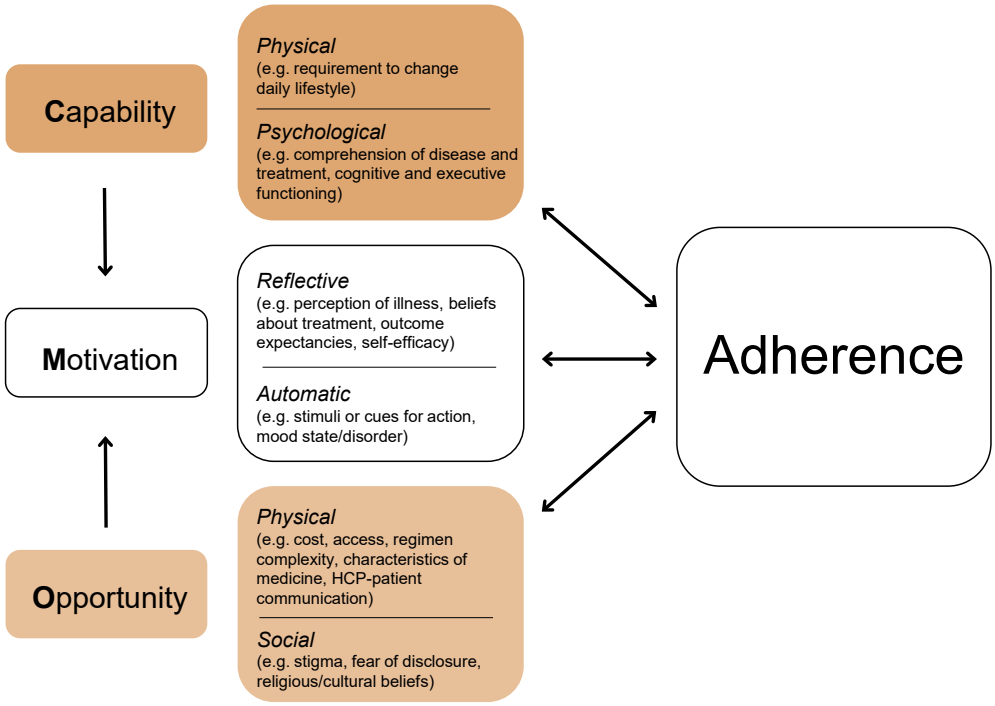


Figure 2, based on Michie *et al.* (2011) and Jackson *et al.* (2014) [28,29], illustrates the COM-B model applied to adherence and highlights key determinants of adherence identified in the literature. This dynamic framework shows how each component influences the Behaviour (adherence), but also how Capability and Opportunity shape Motivation, which affects the Behaviour, and equally how the performance of the Behaviour influences back each of the components. By explaining the underlying factors of adherence, the model provides insights into how to modify the behaviour and supports the design of effective interventions to improve it.

1.2.4 Non-adherence and explanatory factors

Non-adherence to pharmacological treatments is commonly defined as not taking the medications as prescribed [18]. It can vary depending on the timing of the prescription and/or the initiation of treatment, leading to different medication-taking patterns. Considering the timing, a wide range of non-adherence behaviours can be identified, including failing to initiate medication or initiating late, not taking the correct dose (underdosing or overdosing), or discontinuing the treatment or lacking persistence with the prescribed regimen [18].

Adherence is a complex health behaviour and it is well-known that there are multiple reasons why patients do not adhere to their medications [29]. A systematic review by Kardas *et al.* (2013) found more than 700 different factors of chronic medication non-adherence [30]. Any behaviour emerges from a complex ecological system of interacting influences [31]. Berben *et al*. (2012) used the Ecological Model to classify and identify modifiable factors that can be targeted for an intervention [32]. The ecological model illustrates the multiple levels of influence on health behaviours and outcomes and highlights the importance of addressing these factors at multiple levels simultaneously to design sustainable and effective public health interventions. This model is shaped by interactions between individuals and their environment and distinguishes different levels: individual-level (patient), micro-level (interpersonal relationships), meso-level (organisational) and macro-level (policy) [32–34].

Individual-level

Individual-level factors include all sociodemographic aspects, such as gender, age, income level, and educational background, among others. As well as it

involves aspects related to self-efficacy and attitudes, and beliefs about medication and disease, including perceptions of the treatment's effectiveness and safety and the perceived severity of the disease.

Micro-level

Micro-level factors are related to the interactions between individuals, particularly between the patient and healthcare professionals (doctors, nurses or pharmacists). For instance, providing patient-centred care vs paternalistic attitudes of professionals, but also communication skills or language barriers, as well as the patient's perception of the doctor's competencies and degree of trust. Additionally, it includes interactions and influences of the patient's closer environment and social circle, such as family, friends and the broader community.

Meso-level

Meso-level factors refer to the characteristics of the healthcare organisation where the patient receives care—such as access to the healthcare system, consultation time, availability of treatments, possibility of follow-up visits, or waiting times—as well as cultural influences and social norms.

Macro-level

Macro-level factors encompass the characteristics of the healthcare system, including local and national health policies such as medication co-payment, insurance coverage, and community public health infrastructures, as well as broader social and economic policies.

1.2.5 The burden of non-adherence: prevalence and health impact

Non-adherence rates vary widely depending on the health condition, treatment, and phase of the adherence process being assessed [35]. The WHO report on adherence to long-term therapies estimated that 50% of patients with chronic conditions take less than 80% of their prescribed medications [19]. Similarly, a meta-analysis reviewing 50 years of adherence research across various conditions found an average implementation rate of 75% [36]. Non-initiation rates range from 2% up to 40%, with an estimated overall rate of 18% in Spain [37,38], and about half of the patients who initiate the medication discontinue it within the first 12 months [39–41]. In this line, most adherence studies have primarily focused on the implementation phase, often using a predefined threshold of 80% to classify patients as either adherent or non-adherent [42].

However, determining the optimal level of adherence required to achieve treatment goals varies between medications and individuals and remains a major challenge for researchers, as this binary approach may oversimplify the complexity of the behaviour [41–43]. Likewise, there is no current 'gold standard' to measure adherence; inconsistencies in adherence measurement across research further contribute to considerable variability in reported rates [41,43].

Non-adherence to pharmacological treatments prevents patients from getting the full therapeutic effect [44,45]. Although it highly depends on the disease and the treatment, it is often linked to worsening disease control and outcomes, such as higher morbidity and early mortality [19,41]. The

Organisation for Economic Co-operation and Development estimated, in a report published in 2018, that poor adherence contributes to 200,000 premature deaths each year in Europe [46]. Furthermore, in addition to missed opportunities for patient health gain, it is associated with more use of healthcare resources, resulting in increased costs for the healthcare system [41]. The mentioned report estimated that it costs European governments €125 billion annually in excess resources [46]. In addition to the costs of waste medications, non-adherent patients have higher odds of emergency and hospital admissions [41,47].

Therefore, medication non-adherence is not merely a patient-level issue from a lack of trust in medications; rather, it is a population-level health problem that demands a broader perspective [22]. However, it has not been historically prioritised on national or international health agendas, resulting in a lack of systematic monitoring and targeted interventions [22,46]. Consequently, the problem of non-adherence remains unresolved to this day.

1.2.6 Non-adherence to cardiovascular disease and diabetes medications

Adherence is particularly challenging in chronic asymptomatic diseases such as CVD and diabetes, where a lack of it compromises long-term outcomes [27]. For instance, in both primary and secondary prevention of CVD, adherence is low and often declines over time [48,49]. In developed countries, non-adherence to preventive medication for CVD is estimated at 50% for primary prevention and 30% for secondary prevention [49].

A significant proportion of prescribed treatments for CVD and diabetes, ranging from 2% to 40%, are never initiated [37,50], and over 30% of

individuals who start treatment for CVD or diabetes discontinue it within the first three years [51]. Non-adherence rates vary by medication, with approximately 46% for statins, 41% for antihypertensives, 31% for antidiabetic drugs, and 30% for aspirin [51].

The impact of non-adherence to CVD and diabetes medications increases as the burden of chronic diseases continues to grow worldwide [19], emphasising the importance of implementing effective interventions to enhance adherence.

1.3 Interventions to improve adherence

A Cochrane review published in 2002 and reviewed in 2014 examined interventions aimed at improving patient adherence to prescribed medications, focusing on both adherence and clinical outcomes [44,45]. The review included 182 randomised controlled trials (RCTs), with interventions varying in type, disease and treatments, patient population, adherence, and clinical outcome measures; most trials had a high risk of bias. Complex interventions involving multiple components, such as tailored support from healthcare professionals, education, counselling, and sometimes support from family or peers, were most commonly used [45]. Despite these efforts, only five RCTs reported improvements in adherence and clinical outcomes. However, these improvements were modest, and no consistent characteristics of effective interventions were identified [45].

Similarly, a more recent review on interventions to improve adherence identified various strategies such as patient education, regimen management, medication reminders, motivational interviewing and pharmacist-led consultations [52]. However, even though some of these

techniques show promising results in specific settings, evidence on the best strategies remains inconclusive. Previous research outlines that the methods to improve medication adherence for chronic conditions are complex and only moderately effective [45], which has led to a growing recognition of the need to shift towards patient-centred care by actively involving patients in decisions regarding their treatment plans to better manage adherence [22]. Moreover, it highlights the importance of developing and evaluating adherence interventions with a focus not only on effectiveness, but also on practical applicability—ensuring they can be effectively integrated and sustained in everyday clinical practice [53].

1.3.1 Patient-centred interventions

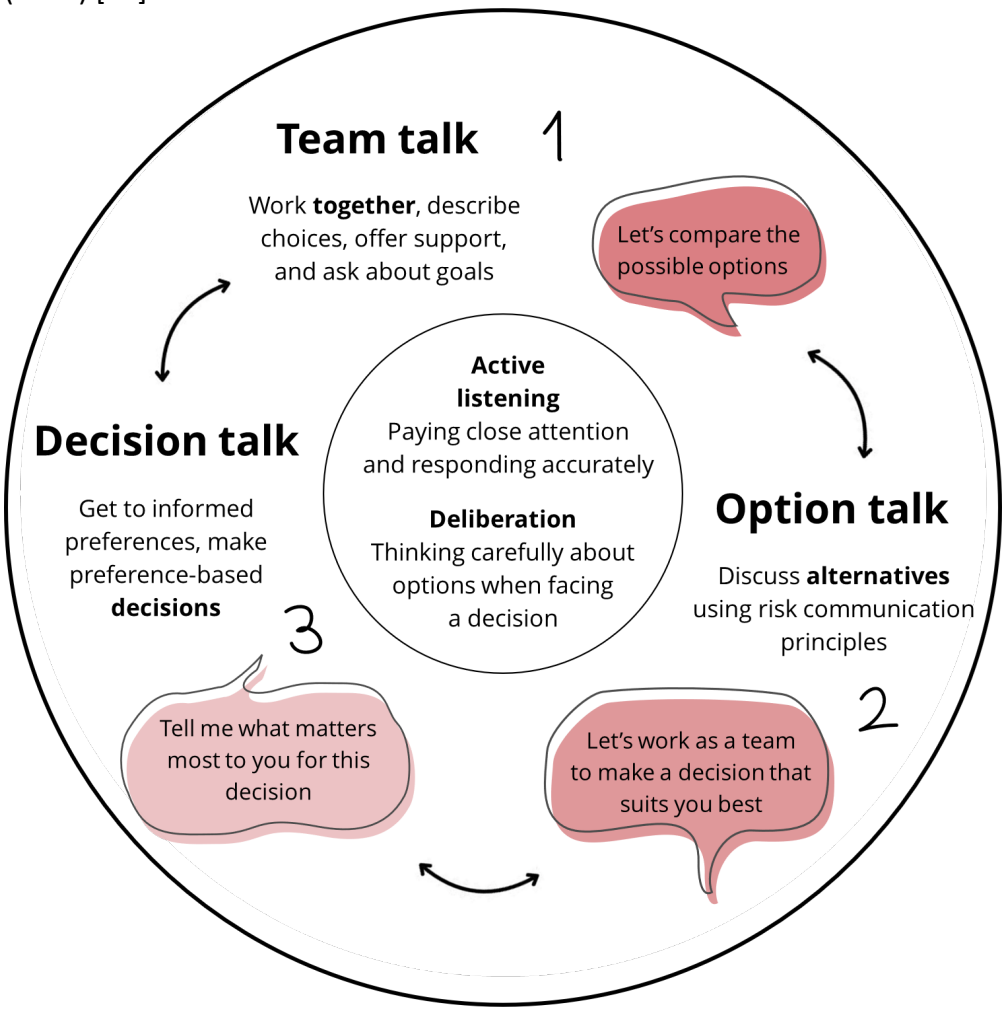
Traditional paternalistic approaches remain deeply ingrained in healthcare, limiting communication between healthcare professionals and patients and restricting discussions on chronic diseases and treatment [54]. These approaches overlook patient autonomy and the right to participate in decisions about their health, which is particularly important for those with chronic conditions facing ongoing health dilemmas over a long period of time [55,56]. It has been widely demonstrated that simply providing information is not sufficient to change a behaviour, and that informed decisions might not consider patients' opinions [29,57]. Patient-centred care emphasises patients' participation in health decisions, encouraging them to take a more proactive role in managing their disease and treatment by prioritising patients' preferences, needs, and perspectives [57].

Shared decision-making is recognised as a standard of high-quality care and has been advocated for inclusion in clinical guidelines [58,59]. By actively involving patients in health decisions, shared decision-making aims to

enhance patients' autonomy and self-efficacy, strengthen commitment to treatment, and improve disease control [58,60]. However, it involves a significant shift in professionals' attitudes, moving from acting as the sole experts on what is the best treatment for the patient towards adopting a more collaborative approach [61,62]. It moves from only providing information in a one-way conversation to two-way meaningful conversations between patients and healthcare professionals [63].

Elwyn *et al*. (2017) proposed the three-talk model for shared decision-making, developed in consultation with key stakeholders [64]. This model illustrates the core principles of shared decision-making by outlining a collaborative and deliberative process (Figure 3). It recommends three interrelated stages that incorporate active listening and deliberation throughout the process. First, *team talk* involves working together, describing choices and acknowledging that a decision needs to be made, supporting patients and identifying their goals; second, *option talk* focuses on discussing treatment alternatives, using risk communication strategies and addressing the trade-offs between potential benefits and risks; and third, *decision talk* emphasises guiding patients—drawing on professional experience and expertise—towards decisions that align with their preference, including exploring their willingness to participate in the decision and delaying the decision if needed [64].

Figure 3. Three-talk model of shared decision-making from Elwyn *et al*. (2017) [64].



Patient decision aids such as leaflets, booklets, websites or videos are commonly developed to support the shared decision-making process. These tools are designed to prepare patients to engage in health decisions by providing information about their condition, treatment options and associated risks and benefits [65]. They assist patients in aligning decisions with their values and preferences [65]. Decision aids should complement, rather than replace, the shared decision-making process and the

communication skills of healthcare professionals, which are crucial for engaging patients in decision-making [61,62,65].

Shared decision-making boosts patient knowledge, trust, and satisfaction with the healthcare system [66], while it enhances healthcare professionals' communication skills and the quality of information provided [67,68]. Beyond individual interactions, it fosters a collaborative culture where patients critically assess options, weigh benefits and risks, and share responsibility [69]. Nevertheless, despite being an ethical imperative, shared decision-making is difficult to implement in healthcare due to barriers like time constraints, heavy workloads, lack of training and entrenched medical cultures, and it remains uncommon in Spain and elsewhere [70–73].

Regarding medication adherence, shared decision-making during a consultation may foster discussions between the patient and healthcare professionals about key factors such as treatment options' effectiveness, side effects or expectations, which could differ based on the patient's situation and preferences [41]. However, the evidence regarding its effectiveness in enhancing medication adherence or clinical outcomes remains mixed. While some reviews suggest that patients who engage in decision-making show improved adherence [74–76], others have found little to no impact on either adherence or clinical outcomes, highlighting the need for further research [66,77–79].

1.4 Development and evaluation of complex behavioural interventions

1.4.1 Complex behavioural interventions

Behaviour change interventions—such as those targeting adherence—are a coordinated set of activities designed to influence behaviour through hypothesised mechanisms of action and are typically considered complex interventions [31]. Complex interventions are characterised by multiple interacting components, may target different behaviours, require specific knowledge and skills from both those delivering and receiving the intervention, involve various groups, organisational levels and/or settings, and are often flexible and can be tailored to different contexts [80].

This complexity presents significant challenges for developing and evaluating such interventions, and numerous frameworks have been designed to guide and inform this process [31]. Araujo-Soares *et al*. (2019) reviewed key frameworks and highlighted that although each adopts a distinct focus or approach, most agree on several essential steps in an intervention development process, which is iterative and cyclical rather than linear [31]:

Analysing the problem and developing an intervention objective

Analysing the problem and developing an intervention objective by first conducting a needs assessment of the target health problem and its behavioural, social, and environmental determinants. This stage also involves identifying which behaviours and who needs to change to ultimately impact the health outcome, by answering the questions “who needs to do what differently, when, where, and how?” [81].

Defining the scientific foundation

Defining the scientific foundation of the intervention by identifying the causal and contextual factors that influence behaviours, defining evidence-based mechanisms of action or techniques to address those factors, and developing a logic model or theory of change. This is a visual representation of the hypothesised causal pathways that illustrate how intervention components interact to produce change, anticipated intermediate and long-term outcomes, and the necessary resources and infrastructure for implementation [82].

Developing materials and interfaces

Developing materials and interfaces by ensuring the design of the intervention promotes sustained use and considering the delivery mode, the target population, and the behaviour context.

Empirical optimisation

Empirical optimisation by incorporating the perspectives of both those delivering and receiving the intervention to enhance acceptability and feasibility.

Effectiveness evaluation

Interventions should be designed to be evaluable. First, by conducting a pilot or feasibility study aiming to refine the intervention and optimise future evaluation design before proceeding to a full-scale evaluation of the intervention's effectiveness. The design of the effectiveness evaluation can vary depending on the objective, but it is generally recommended to consider randomisation when possible. In addition, a broad spectrum of effectiveness

outcomes should be considered, with health impact and economic outcomes being particularly important.

Process evaluation

Process evaluations are embedded within effectiveness evaluation studies in order to understand how, why, for whom, and under what circumstances an intervention works [82].

Implementation and real-world application

Implementation and real-world application should be considered from the outset. Demonstrating that an intervention is effective does not guarantee that it will be adopted or translated to real-world settings beyond a research project. Implementation Science focuses on developing and rigorously evaluating interventions that target the behaviours of those delivering and implementing them in real-world practice. For instance, as with patient behaviour change, simply providing information to healthcare professionals is insufficient; effective implementation requires theory-informed design, piloting, and robust evaluation of implementation strategies.

1.4.2 Development and evaluation framework

In 2000, the United Kingdom's Medical Research Council (MRC) published a framework to guide researchers and funders in the development and evaluation of complex interventions [83]. Since then, the MRC has produced additional guidance on specific research processes and has periodically updated this framework, with the most recent revision published in 2021 [80,84].

The framework aims to support researchers in collaborating with stakeholders to define key questions related to complex interventions and to

design and carry out research that incorporates diverse perspectives using appropriate methodological approaches [80]. It shifts the focus beyond determining whether an intervention is effective, towards understanding how it can be implemented, scaled, adapted, and sustained in real-world contexts, through early engagement with stakeholders and a broader systems perspective [80]. It identifies four perspectives that guide the design and conduct of complex interventions. Each perspective identifies different types of research questions that overlap and are not mutually exclusive [80]: 1) *Efficacy* or "to what extent does the intervention produce the intended outcomes in experimental or ideal settings?"; 2) *Effectiveness* or "to what extent does the intervention produce the intended outcomes in real-world settings?"; 3) *Theory-based* or "what works in which circumstances and how?"; and 4) *Systems* or "How do the system and intervention adapt to one another?".

Figure 4. MRC Framework for developing and evaluating complex interventions [80].

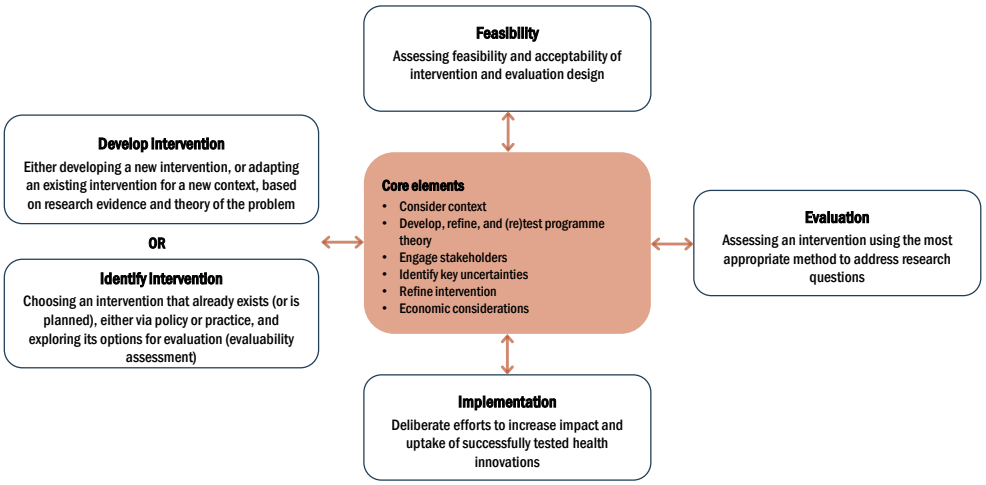


Figure 4 illustrates the framework divided into four phases that share core elements that should be identified early and revised throughout the whole process—considering context, developing and refining intervention theory, engaging stakeholders, identifying key uncertainties, refining the intervention, and economic considerations [80]. Research projects might start at any of the phases shown in Figure 4 based on the main uncertainties about the intervention [80]:

Developing or identifying complex interventions phase

This may involve developing a new intervention or adapting an existing one to a new context by drawing on research evidence and relevant theoretical models, or identifying an existing intervention and exploring options for its evaluation.

Feasibility phase

Assessing the feasibility and acceptability of both the intervention and its evaluation design by piloting them in order to inform decisions about progression to the next stage of evaluation.

Evaluation phase

This goes beyond effectiveness by encouraging the use of the most appropriate methods to address diverse research questions. While impact or effectiveness evaluations have often been conducted through RCTs, other study designs may also be appropriate depending on the research question and circumstances. In addition, process evaluations play a key role in understanding how interventions work by exploring three domains that influence their delivery: *implementation* ("What is implemented and how?"); *mechanisms of action* ("How does the implemented intervention produce

change?"); and *contextual factors* ("How does context affect its implementation and active mechanisms?"). Process evaluations ultimately provide critical insights into why an intervention may fail unexpectedly or produce unintended outcomes, or why it works and how it can be refined and optimised in the future.

Implementation phase

Considering implementation from the outset increases the likelihood of developing interventions that can be adopted and sustained in real-world contexts. This phase focuses on translating the intervention into routine practice through strategies that support its adoption, scalability, and sustainability across different contexts. Implementation is a dynamic process that may require ongoing adaptations or refinement as the intervention is implemented in different settings, while maintaining intervention key components and if adaptations are justified and understood. Conducting continuous monitoring and evaluation is essential, both to optimise the intervention over time and to maximise its impact in practice.

1.4.3 Effectiveness-implementation hybrid studies

In line with the MRC framework, *implementation science* focuses on understanding how evidence-based interventions can be successfully integrated into healthcare policy and routine practice, ensuring that they are not only effective but also feasible, acceptable, and sustainable in real-world settings [53]. Unlike traditional clinical research, which often tests whether an intervention works under controlled conditions, implementation science addresses how proven effective interventions can be implemented, adopted and sustained in complex healthcare environments [53]. A key principle of this approach is recognising and addressing complexity by early and

continuous involvement of stakeholders, in-depth contextual analyses of individuals, organisations, and systems, and the identification of factors that may enable or hinder successful implementation [53].

Effectiveness-implementation hybrid studies proposed by Curran *et al.* in 2012 and revised in 2022 aim to bridge the gap between traditional clinical research and real-world practice by combining effectiveness and implementation research questions within a single study [85,86]. Advocating for the integration of traditional RCTs and pragmatic designs, preserving the benefits of randomisation and providing real-world outcome data [87,88].

They proposed three types of hybrid studies, each with a dual focus but differing in emphasis: 1) *Type I hybrid study* primary focuses on assessing the effectiveness of an intervention on relevant outcomes, while collecting information on its implementation and exploring the context for future implementation; 2) *Type II Hybrid study* gives equal weight to both evaluating the intervention's effectiveness and assessing the implementation process and strategies; and 3) *Type III Hybrid study* primarily focuses on evaluating the impact of implementation strategies, while also gathering information on the intervention's effectiveness on relevant outcomes [85–87].

Selecting a specific type of study depends on several considerations, such as the strength of existing evidence regarding the effectiveness of the intervention, anticipated need for adaptation of the intervention, previous understanding of implementation determinants (e.g., implementation barriers or facilitators), and readiness of the implementation strategies to be evaluated [86]. Commonly, a type I is recommended when evidence of effectiveness is lacking or still emerging in real-world settings, type II when

there is moderate evidence of effectiveness, and both the intervention and its implementation strategy can be evaluated simultaneously, and type III when the intervention's effectiveness is well-established, and the main aim is to evaluate the implementation strategy itself [86].

Hybrid studies present several challenges due to their inherent complexity and the trade-offs they require [85–87]. For instance, researchers from clinical and implementation science backgrounds must collaborate effectively and align their understanding of conceptual frameworks, constructs, and terminology. These studies typically demand greater initial investment of time and resources, though they are ultimately more efficient than conducting multiple separate studies to achieve the same goals. Data collection might require using smaller patient subsamples or relying on administrative data or electronic health records, which can impact data quality. Moreover, aiming for dual objectives can lead to competing priorities, where the focus on achieving robust effectiveness outcomes may deprioritise the collection of implementation data. Nevertheless, despite these challenges, hybrid studies offer a valuable opportunity to accelerate the development and integration of evidence-based interventions in real-world clinical practice.

1.4.4 Pragmatic trials

Alongside hybrid studies, pragmatic trials are designed to evaluate the effectiveness of interventions under usual conditions of care, aiming to produce results that are directly applicable to routine practice [89]. Unlike explanatory trials, which test efficacy under tightly controlled conditions, pragmatic trials embrace the complexity of real-world settings by including typical patients, professionals, and healthcare environments [89]. The

PRagmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2) tool helps researchers design and assess how pragmatic a trial is across several domains—such as eligibility criteria, recruitment, setting, organisation, flexibility, follow-up and outcome relevance and analysis—ensuring alignment with the practical realities of healthcare [90]. This approach enhances the external validity and relevance of findings for healthcare system implementation.

1.5 Spanish national healthcare system

The Spanish national health system is based on the principles of universal coverage, free access and equity [91]. Since 2018, health systems reforms have focused on increasing population coverage, providing services, reducing co-payment and reinforcing primary care [91]. The Spanish national health system is mainly tax-funded and free of charge at the point of delivery, except for ortho-prosthetic devices and pharmaceutical prescriptions, which are co-paid by patients based on employment status and household income [91]. Co-payment is fixed, with a maximum monthly payment cap for pensioners and a reduced rate for a wide range of chronic conditions treatments, which also have a set maximum cost per prescription [91]. There are certain groups exempt from co-payment, including social benefits recipients. Since 2020, this exemption has been extended to individuals receiving the guaranteed minimum income, low-income pensioners, children with a recognised moderate or severe disability, and households receiving child benefits [91].

The Spanish national health system is decentralised and organised at a national and regional level; the Ministry of Health is responsible for the overall coordination, while health competencies are transferred to the

regions where the 17 Autonomous Communities hold full capacity in the provision of healthcare [91]. Each Autonomous Community has the capacity and responsibilities for planning, financing and provision of public health and healthcare services. The Spanish national health system provides a common benefits package to all regions, and each Autonomous Community has a complementary package for the inclusion of additional services [91].

Health services are provided at specialised hospitals and primary care levels. Primary care is at the centre of the Spanish national health system; it is the gatekeeper to the healthcare system and secondary care, and where most pharmacological prescriptions for chronic conditions are managed [91]. Primary care centre teams are composed of general practitioners (GPs), community nurses, and other healthcare professionals who attend to specific populations assigned by catchment area. Pharmaceutical care for chronic conditions such as CVD and diabetes is provided by: GPs, who act as prescribers and overall treatment supervisors; community nurses, who monitor adherence and clinical parameters and manage side effects; and ultimately by community pharmacists, who are responsible for dispensing medications providing patient counselling on their use, as well as supervising adherence and the early detection of side effects [91]. Pharmacological prescriptions can only be obtained at community pharmacies, which are private establishments of public interest, and patients are free to use any community pharmacy regardless of their assigned primary care centre [91].

2

Rationale

2 RATIONALE

Global life expectancy is increasing, and chronic conditions such as CVD and diabetes are becoming more prevalent, placing growing pressure on healthcare systems to support long-term disease management. Medication adherence is a critical challenge in chronic disease management, particularly for asymptomatic conditions such as CVD and diabetes, where patients are likely to face difficulties initiating and adhering to long-term pharmacological treatments. Despite extensive evidence showing the clinical and economic consequences of poor adherence, the issue remains largely unresolved, frequently treated as an individual patient problem rather than a broader public health challenge.

Adherence interventions often overlook its complex and multifactorial nature—influenced by patient, interpersonal, organisational and policy-related factors. Patient-centred care models, and particularly shared decision-making, have emerged as promising approaches to enhance communication, support informed treatment decisions, and strengthen patient engagement in healthcare. However, the implementation of shared decision-making in routine practice care remains limited, there is a lack of evidence of its effectiveness in improving adherence or clinical outcomes, and there is a limited understanding of the mechanisms of action through which these interventions can lead to behavioural change.

While developing theory-based interventions is essential, achieving real change requires thorough evaluation under real-world conditions. To date, few adherence interventions have been evaluated through pragmatic evaluations that reflect the complexity of clinical settings by not only focusing

on effectiveness but also on understanding the intervention implementation, how it works and the context influence.

This thesis addresses this gap by developing and evaluating a theory-based complex patient-centred intervention designed to improve initial medication adherence at the time of a new CVD and/or diabetes prescription in primary care. It is embedded within the non-initiation project following the principles of the MRC framework for developing and evaluating complex interventions.

3

Objectives

3 OBJECTIVES

3.1 General objective

To develop, implement and evaluate the Initial Medication Adherence (IMA) intervention to improve adherence to CVD and diabetes treatments in primary care.

3.2 Specific objectives

To address the overall aim, the thesis is structured around four specific objectives, each linked to a scientific publication:

OBJECTIVE 1: Feasibility study

To evaluate the feasibility and acceptability of the initial version of the IMA intervention and the feasibility of the evaluation study design—a pragmatic cluster-randomised controlled trial (cRCT)—to ultimately optimise the IMA intervention and its evaluation design prior to the definitive trial.

Scientific article 1: *"Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention".*

OBJECTIVE 2: Intervention and evaluation design refinement

To refine and describe the IMA intervention and develop a logic model that articulates the intervention theory by explaining its underlying mechanisms of action, as well as to refine the evaluation design of a mixed-methods process evaluation protocol embedded within the definitive cRCT.

Scientific article 2: *"Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol".*

OBJECTIVE 3: Process evaluation

To assess the implementation of the IMA intervention and understand how it becomes integrated into primary care practice, explain the intervention mechanisms of action and identify contextual factors that influence its implementation and active mechanisms, in order to inform its applicability and scalability for future implementation.

Scientific article 3: *"Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation".*

OBJECTIVE 4: Effectiveness evaluation

To evaluate the effectiveness of the IMA intervention in comparison to usual care in improving initial and secondary medication adherence and clinical parameters in patients with new pharmacological prescriptions for CVD and/or diabetes in primary care.

Scientific article 4: *"Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using real-world data".*

4

Methods and results

4 METHODS AND RESULTS

This thesis is presented as a compendium of publications derived from the non-initiation project. Accordingly, the methods and results section is structured around four peer-reviewed scientific articles. To contextualise the thesis within the broader scope of the non-initiation project, it begins with a comprehensive description of the development, piloting, evaluation, and implementation of the IMA intervention. Each scientific article is then presented in full accompanied by an overview of its main results. These overviews illustrate how each publication builds upon the previous one and how, together, they contribute to an integrated understanding of the research. The supplementary files for each article can be accessed through the respective journal in open access. In addition, Appendix 1 includes the protocol for the effectiveness evaluation of the IMA-cRCT study, offering further methodological detail on the design and conduct of the clinical trial that underpins part of this research.

Collectively, the publications and the accompanying protocol provide a comprehensive account of the methods and results that address the objectives of this thesis.

4.1 The non-initiation project

The non-initiation project represents a practical application of the MRC framework for developing and evaluating complex interventions [80]. While several other frameworks—such as Intervention Mapping, the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework, and the CFIR (Consolidated Framework for Implementation Research) [92–

94]—, are also relevant for guiding complex intervention research and facilitating their translation into practice [95], the MRC framework was selected for its emphasis on structuring the iterative process from development through to implementation. It offers clear guidance for rigorously addressing each phase of the intervention development and evaluation process, while also considering key elements that align with complex health system contexts [80].

The project emerged from observations made in the context of a previous study conducted in Catalonia (Spain), which found that a considerable proportion of patients never filled their new medications [96]. Therefore, it aimed to assess non-initiation as a public health problem and the need to develop and evaluate an intervention to increase initial medication adherence to new pharmacological prescriptions.

Figure 5. Non-initiation project within the MRC framework for developing and evaluating complex interventions.

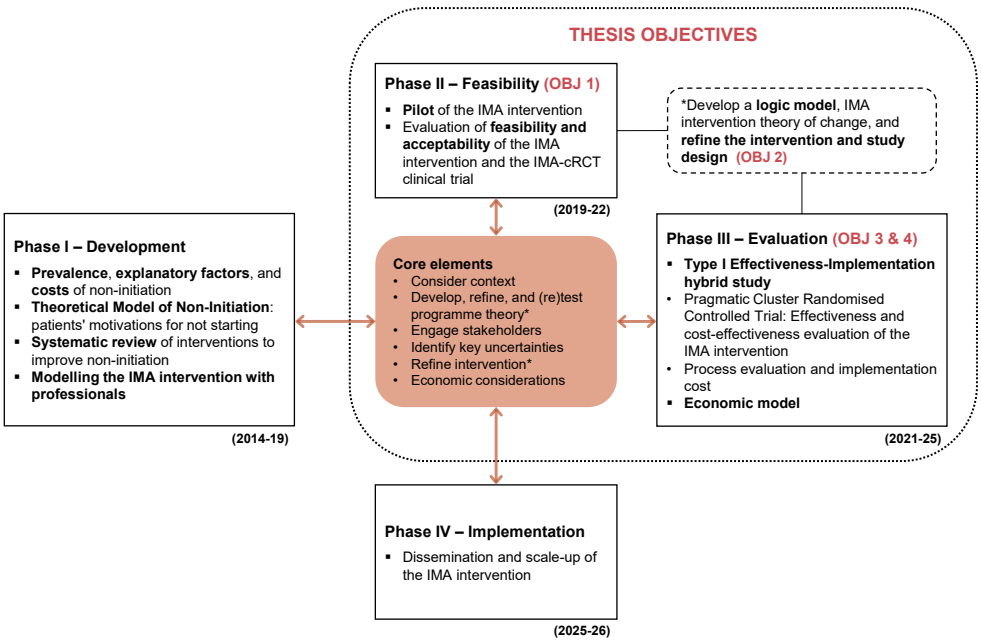


Figure 5 illustrates how the project progressed through several phases in line with the MRC framework [80]. This thesis focuses on the work conducted in Phases II and III.

In the initial *development phase (Phase I)*, the prevalence and explanatory factors of non-initiating the prescribed medication in primary care in Catalonia were explored. Real-world data from electronic health records covering the entire population registered in the public primary care system was analysed, and the overall non-initiation rate was found to be 18%, with rates between 6% and 9% for treatments targeting CVD and diabetes [38,50,97]. Factors associated with non-initiation included patient characteristics (such as younger age), treatment-related aspects (such as medication cost), and healthcare system factors (such as prescriptions issued by substitute or resident GPs). In addition, qualitative research with patients and healthcare professionals from the Catalan health system provided insights into patients' reasons and motivations to not initiate a new treatment [98,99]. The decision was multifactorial, patients conducted a risk-benefit assessment influenced by: disease and medication beliefs; their emotional reaction; previous health literacy; social and cultural factors; and the context and relationship with the healthcare system and healthcare professionals. Taking into account that initial medication adherence is a critical stage in the continuum of medication-taking behaviour, as a considerable proportion of patients failed to initiate the prescribed treatments [38], a systematic review of interventions targeting non-initiation was conducted.

Drawing on these findings, the IMA intervention was designed—a complex multidisciplinary intervention aiming to improve initiation and long-term adherence to CVD and diabetes treatments in primary care. Before piloting

the intervention and in order to enhance the intervention's acceptability and feasibility, discussion groups with various stakeholders—GPs, nurses, pharmacists, social workers, cardiologists, endocrinologists and internists—were held to refine the intervention, identify potential limitations, and anticipate implementation barriers.

The IMA intervention was developed to impact at two levels: individual-level—by improving patients' health literacy and self-efficacy—and micro-level—by standardising messages across GPs, nurses, and pharmacists to ensure consistency during patient–professional interactions. Rooted in the principles of shared decision-making, it is a patient-centred intervention that actively involves patients in treatment decisions at the time of a new prescription [58,64]. Recognising adherence as a multifactorial behaviour, the intervention addresses it through coordinated interprofessional support. Strengthening communication between patients and healthcare professionals promotes informed and shared decisions. Further details on the IMA intervention are provided in the overview of main results presented alongside scientific article 2 within this section.

A pilot study was subsequently conducted in five primary care centres in the Barcelona Metropolitan Area (Catalonia), as part of *the feasibility phase (Phase II)* (ClinicalTrials.gov, NCT05094986). The pilot incorporated elements of a hybrid study; the design was a cluster non-randomised controlled trial that included an embedded process evaluation and aimed to assess the feasibility and acceptability of both the initial version of the IMA intervention and the proposed evaluation study design (Thesis Objective 1) [100]. Specifically, the study aimed to test the availability and quality of data used to assess the effectiveness of the IMA intervention in terms of completion

rate and reliability, evaluate the feasibility and acceptability of the IMA intervention in primary care centres' routine practice, and review and redesign the intervention materials.

In addition to refining the IMA intervention, a logic model of change was developed to articulate the underlying mechanisms of the intervention and to guide both its implementation and evaluation [101]. Furthermore, the final design of the full-scale hybrid type I effectiveness-implementation study—including the pragmatic cRCT design (Appendix 1) and the nested mixed-methods process evaluation (Scientific article 2)—was informed by the lessons learned during the pilot study, with particular consideration given to the evolving context of the COVID-19 pandemic, which remained a significant factor at the time (Thesis Objective 2) [101,102].

The *evaluation phase (Phase III)*, or the IMA-cRCT study, was a type I hybrid effectiveness-implementation study (ClinicalTrials.gov, NCT05026775) which aimed to assess the effectiveness and cost-effectiveness of the IMA intervention through a pragmatic cRCT while understanding its implementation through a process evaluation. The pragmatic trial was conducted across 24 primary care centres from all regions of Catalonia, under real-world primary care conditions, to maximise the relevance and applicability of the findings to routine clinical practice. The pragmatic nature of the design was detailed using the PRECIS-2 tool [90,102]. Specifically, the process evaluation aimed to assess the implementation of the IMA intervention—implementation strategies, fidelity to intervention protocol and understanding how it becomes integrated into PC practice—explain the intervention mechanism of action and identify contextual factors that influenced its implementation and active mechanisms (Thesis objective 3)

[103]. The effectiveness evaluation aimed to evaluate the IMA intervention in comparison to usual care in improving initial and secondary medication adherence and clinical parameters in patients with new pharmacological prescriptions for CVD or diabetes in PC through a cRCT based on real-world data (Thesis Objective 4) [104].

The results of the effectiveness evaluation were triangulated with the findings from the process evaluation, helping to explain the cRCT outcomes. This triangulation, along with an economic evaluation, has informed the *implementation phase (Phase IV)* of the Non-Initiation project. The IMA intervention will be refined and scaled up to a larger number of primary care centres across Catalonia in order to establish shared decision-making as the standard of care.

In a cross-cutting manner throughout all phases of the project, economic considerations were taken into account as a core element. In particular, as part of Phase III, an implementation cost analysis of the IMA intervention was conducted to assess both material and human resources required for its implementation in real-world practice, accounting for fixed and variable costs. Additionally, a cost-effectiveness analysis was performed, evaluating outcomes in terms of medication adherence and cardiovascular risk reduction, adopting a societal perspective—which included healthcare costs and productivity losses—and a healthcare system perspective—focusing on direct costs to the Catalan public health system. However, these analyses are beyond the scope of this thesis and are therefore not further elaborated in this document.

4.2 Scientific article 1

OBJECTIVE 1: Feasibility study

Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention

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Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Serrano-Blanco A, Carbonell-Duacastella C, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M

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EDITED BY
Ana Clavería,
Instituto de Investigación Sanitaria Galicia Sur (IISGS), Spain

REVIEWED BY
Patrick Okwen,
Effective Basic Services (eBASE) Africa, Cameroon
Martin Schulz,
Freie Universität Berlin, Germany

*CORRESPONDENCE
Maria Rubio-Valera
maria.rubio@sjd.es

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Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention

Carmen Corral-Partearroyo[1,2,3], Alba Sánchez-Viñas[1,3,4], Montserrat Gil-Girbau[1,5,6], María Teresa Peñarrubia-María[1,3,7,8], Ignacio Aznar-Lou[1,3], Antoni Serrano-Blanco[1,3,4,5], Cristina Carbonell-Duacastella[1,3,9], Carmen Gallardo-González[1,6,7,8], Maria del Carmen Olmos-Palenzuela[6,7] and Maria Rubio-Valera[1,3,5]*

[1]Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain, [2]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Univ Autonoma de Barcelona, Bellaterra, Spain, [3]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública), Madrid, Spain, [4]Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain, [5]Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain, [6]Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Barcelona, Spain, [7]Primary Care Centre Bartomeu Fabrés Anglada, Direcció D'Atenció Primària Regió Metropolitana Sud, Institut Català de la Salut, Barcelona, Spain, [8]Unitat de Suport a la Recerca Regió Metropolitana Sud, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain, [9]Facultat de Farmàcia, Universitat de Barcelona, Barcelona, Spain

Introduction: The Initial Medication Adherence (IMA) intervention is a multidisciplinary and shared decision-making intervention to improve initial medication adherence addressed to patients in need of new treatments for cardiovascular diseases and diabetes in primary care (PC). This pilot study aims to evaluate the feasibility and acceptability of the IMA intervention and the feasibility of a cluster-RCT to assess the effectiveness and cost-effectiveness of the intervention.

Methods: A 3-month pilot trial with an embedded process evaluation was conducted in five PC centers in Catalonia (Spain). Electronic health data were descriptively analyzed to test the availability and quality of records of the trial outcomes (initiation, implementation, clinical parameters and use of services). Recruitment and retention rates of professionals were analyzed. Twenty-nine semi-structured interviews with professionals (general practitioners, nurses, and community pharmacists) and patients were conducted to assess the feasibility and acceptability of the intervention. Three discussion groups with a total of fifteen patients were performed to review and redesign the intervention decision aids. Qualitative data were thematically analyzed.

Results: A total of 901 new treatments were prescribed to 604 patients. The proportion of missing data in the electronic health records was up

to 30% for use of services and around 70% for clinical parameters 5 months before and after a new prescription. Primary and secondary outcomes were within plausible ranges and outliers were barely detected. The IMA intervention and its implementation strategy were considered feasible and acceptable by pilot-study participants. Low recruitment and retention rates, understanding of shared decision-making by professionals, and format and content of decision aids were the main barriers to the feasibility of the IMA intervention.

Discussion: Involving patients in the decision-making process is crucial to achieving better clinical outcomes. The IMA intervention is feasible and showed good acceptability among professionals and patients. However, we identified barriers and facilitators to implementing the intervention and adapting it to a context affected by the COVID-19 pandemic that should be considered before launching a cluster-RCT. This pilot study identified opportunities for refining the intervention and improving the design of the definitive cluster-RCT to evaluate its effectiveness and cost-effectiveness.

Clinical trial registration: ClinicalTrials.gov, identifier NCT05094986.

KEYWORDS

primary care, complex intervention, shared decision-making (SDM), medication adherence, pilot, feasibility study

Introduction

The prevalence of non-initiated pharmacological treatments ranges from 2 to 40%, varying between medications and contexts and depending on patient characteristics and motivations (1–3). Non-initiation of chronic treatments, such as those for cardiovascular disease (CVD) and diabetes, generates a high burden on the healthcare system, which is aggravated by poor adherence (2, 4–8). Reducing non-initiation and improving long-term adherence is, therefore, a priority (9). Previous studies have evaluated interventions to reduce non-initiation but none of these interventions were theory-based and most of the studies showed a high risk of bias (10–15). To date, few interventions have focused on shared decision-making (SDM) strategies to improve adherence, which present promising results regarding improved health outcomes (16–19).

Carefully designing and piloting an intervention improves the likelihood of its effectiveness, transferability and sustainability (20, 21), especially in the case of complex interventions such as those aiming to change patients' and healthcare professionals' behavior. The Non-Initiation project followed the Medical Research Council (MRC) framework for complex interventions to gain an in-depth understanding of this behavior and contribute to the appropriate use of medications in primary care (PC) (20). Between 2014 and 2019, phase I, or the development phase, was carried out and epidemiological studies and qualitative research with patients and healthcare professionals were conducted to understand initiation behavior and design the Initial Medication Adherence (IMA) intervention (22–27). It is a complex, multidisciplinary, SDM intervention to improve initiation, secondary adherence, and clinical parameters in patients who receive a new prescription for CVDs or diabetes in PC. As per the non-initiation model (25, 26), the intervention works on two levels: the patient's intrapersonal level, based on the empowerment of the patient by increasing health literacy and SDM (28–30); and the patient's interpersonal level, based on the interaction between the patient and healthcare professionals, and their support (31–33). The intervention includes decision aids that target patients >18 years old with a risk of CVD and diabetes and were designed in collaboration with healthcare professionals.

This paper describes the results of phase II, or feasibility phase, which aimed to evaluate the feasibility and acceptability of the IMA intervention, the feasibility of the evaluation study, a pragmatic cluster-Randomized Controlled Trial (34, 35), and to ultimately optimize the IMA intervention and its evaluation design. The specific aims were to (1) test the availability and quality of data used to assess the effectiveness and cost-effectiveness of the IMA intervention, (2) evaluate the feasibility

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; COVID-19, Coronavirus Disease; cRCT, cluster-Randomized Controlled Trial; CVD, Cardiovascular Disease; GP, General Practitioner; MRC, Medical Research Council; IMA, Initial Medication Adherence; PC, Primary Care; RWD, Real-World Data; SDM, Shared Decision Making; SIDIAP, System for the development of Research in Primary Care.

and acceptability of the IMA intervention in PC, and (3) revise and redesign the intervention decision aids.

Materials and methods

Study design

This pilot study was a cluster non-randomized controlled trial with an embedded process evaluation. The availability and quality (completion rate and reliability) of Real-World Data (RWD) records of the pilot trial were explored (aim 1), recruitment and retention rates were estimated and intervention group participants were interviewed (aim 2) and discussion groups with PC patients were conducted to review and redesign the decision aids (aim 3).

The results of this study are reported according to the Consolidated Standards of Reporting Trials (CONSORT) extension to pilot and feasibility trials (36).

Figure 1 shows the timeline of the pilot study, which was affected by the Coronavirus Disease (COVID-19) pandemic and the need to adapt it to this context. The intention was to carry out the intervention from March 2020 to May 2020, but adaptations were applied and it was finally launched in November 2020 and continued until January 2021.

Setting

Healthcare in Spain is based on universal coverage for all citizens with free access at the point of use (with some exceptions) and is mostly funded by taxes (37). PC is the gatekeeper of the healthcare system, providing healthcare, health education, prevention activities, and community services. It consists essentially of a team of general practitioners (GP), nurses, and social workers, who are based in PC centers. Patients have an assigned GP and nurse. Prescription medicines are dispensed in community pharmacies by pharmacists who have access to the electronic prescription system (37). Patients can fill a prescription at any community pharmacy. The e-prescription system includes a warning that alerts the pharmacist to first prescriptions of inhalers, platelet aggregation inhibitors, anticoagulation, and insulin treatments.

Pilot study

Participants and group assignment

A convenience sample of five PC centers in Catalonia (Spain) participated in the study. GPs and nurses at the selected PC centers, together with pharmacists from community pharmacies in the reference area of the PC centers, were invited to participate. Professionals that agreed to participate provided signed informed consent. No other inclusion criteria were applied.

The study targeted patients (>18 years old) who received a new prescription of antihypertensive, lipid-lowering, antiplatelet, and/or antidiabetic (oral and/or insulin) medications. A prescription was considered new in the absence of prescriptions for medications of the same pharmacotherapeutic group during the previous 6 months. Patients' informed consent was obtained by simplified means (see "Ethics statement") (38). No other inclusion criteria were applied.

Using convenience criteria, two PC centers were assigned to the control group and three to the intervention group. Healthcare professionals and patients were classified into intervention and control groups according to the reference PC centers and due to the nature of the intervention; professionals and patients were not blind to it.

Sample size calculation was not estimated prior to the pilot trial, although the sample was designed to be representative of the target cRCT population and was based on the same inclusion/exclusion criteria (39).

Description of intervention

The IMA intervention standardizes care and provides knowledge, skills, and tools to GPs to promote SDM when prescribing a new treatment for CVDs or diabetes, and to nurses and pharmacists to explore patients' doubts and offer supplementary information, promoting consistency and coordination of care. By applying the principles of SDM the patient is encouraged to express their concerns and preferences and actively participate in the decision process at their preferred level (29, 30). The implementation strategy has two main inputs: *training for professionals* on the motives underlying non-initiation, communication skills, health literacy, SDM, and the use of the decision aids; and *decision aids* (leaflets and a website) with information on the disease and treatment options to increase patients' health literacy and support SDM. The GP delivers the intervention at least once during the prescription process. Nurses and pharmacists deliver intervention on patients' demand during follow-up consultations and medication dispensing.

No training or decision aids were provided to professionals in the control group, who were asked to provide care as usual.

The IMA intervention was designed to be applied during face-to-face consultations, yet it was adapted to the COVID-19 context during the pilot study. When the new treatment was prescribed by phone, the GP emailed the leaflet contents to patients, and/or they were invited to collect it at the pharmacy. Additionally, the GP or nurse phoned the patient a week after the prescription to check whether questions had arisen.

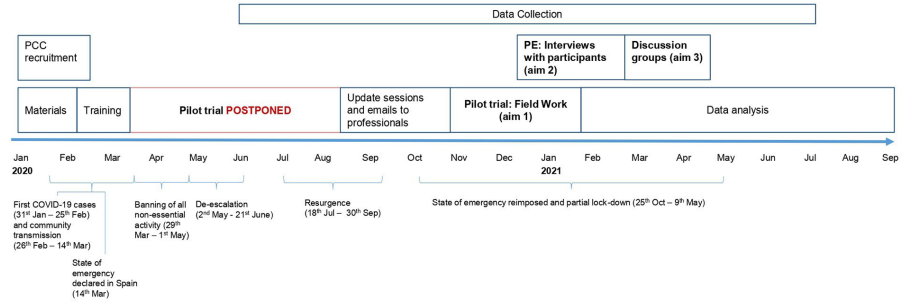

FIGURE 1
Timeline of the pilot study and COVID-19 periods in Spain. PCC, primary care center; PE, process evaluation. Aim 1: To test the availability and quality of data used to assess the effectiveness and cost-effectiveness of the IMA intervention. Aim 2: To evaluate the feasibility and acceptability of the IMA intervention in PC. Aim 3: To review the intervention decision aids to ultimately redesign them.

Availability and quality of RWD for the trial (aim 1)

Trial outcomes and data collection

The primary trial outcome was initiation, defined as having a dispensing record following a new prescription (the index prescription) (40). A single prescription filled was considered an alternative outcome for initiation in sensitivity analysis. Secondary outcomes included implementation, clinical parameters [systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, blood glucose, glycated hemoglobin, estimated glomerular filtration rate, and cardiovascular risk (41)] and costs (use of healthcare services and days of sick leave).

Other variables included patient characteristics (sex, age, and diagnosis) and PC center characteristics according to non-initiation predictors (22): reference population, type of center (resident-training center or not), and socioeconomic status of the area divided into four urban categories based on quartiles, from low (urban 4) to high (urban 1), and a rural category.

All data were obtained from electronic health records registered at the public primary healthcare system database in Catalonia (Institut Català de Salut; ICS): System for the development of Research in Primary Care (SIDIAP) (42). Data were extracted for the follow-up period from June 2020 to June 2021.

Analysis

Descriptive analysis (counts, proportions, and means) was conducted using Stata 17 to explore all available variables and identify missing data and outliers.

First, the sociodemographic profile of the PC centers and participants at a prescription level (a patient can have more than one new prescription) was described.

Secondly, initiation was assessed by considering the time of prescription at the PC center and the dispensing month at the community pharmacy. Non-initiation was defined as not having collected the treatment prescribed (i.e., absence of dispensing records) within 3 months after the index prescription. A single prescription filled was defined as one dispensation only during the follow-up period. Costs were measured by taking into account the use of healthcare services, which included visits to PC professionals (GP or nurse), secondary care referrals, diagnostic tests, and days of sick leave. We assessed the reliability of recorded visits to PC professionals by calculating the proportion of new prescriptions and clinical parameters with a visit record on the same day.

Thirdly, the quality of clinical parameter records in the electronic health records was assessed. We calculated clinical parameter values and the proportion of prescribed treatments that had a clinical parameter registered during the follow-up period following care quality standards based on clinical practice guidelines (43–46).

Feasibility and acceptability of the IMA intervention (aim 2)

A process evaluation was integrated into the pilot study, collecting quantitative and qualitative data to measure professional recruitment and retention rates, assess the context and implementation of the IMA intervention in terms of fidelity to study protocol and the COVID-19 pandemic, and describe professionals' and patients' experiences and perceptions of the intervention in terms of feasibility and acceptability.

Quantitative data collection and analysis

Professional recruitment rates were registered in study forms before the pilot trial (March 2020) and after the trial was stopped

and restarted (November 2020). Those professionals recruited in November were interviewed to estimate retention rates.

We used descriptive statistics (frequency and proportion) to estimate professionals' recruitment and retention rates.

Qualitative data collection and analysis

Following purposive sampling criteria, all the professionals and a selection of patients from the intervention group were invited to participate in the process evaluation. The research team contacted nineteen GPs, three nurses, and sixteen pharmacists by phone and email. GPs from the intervention group contacted five patients and invited them to participate in the study and to be interviewed by a researcher. All the participants signed informed consent prior to the interview.

Semi-structured telephone interviews with professionals were performed during and after the study was completed using a topic guide based on the intervention and the health theories and models it is based on (range 15–25 min). Field notes were made during and after the call. To increase the validity of the results, answers were summarized at the end of the interview and participants were asked to validate them.

Semi-structured face-to-face and telephone interviews with patients followed a topic guide based on the intervention and their intention to initiate the new medication after the intervention (range 20–40 min). These were recorded, anonymized, and transcribed by the research team.

Field notes and transcripts from semi-structured interviews were included as narrative data and analyzed following the principles of thematic content analysis (47) by two qualitative researchers. Data were organized and grouped by professionals and patients. Firstly, the researchers familiarized themselves with the data by re-reading notes and listening to recordings. Each researcher created a coding framework following a deductive and inductive approach. Open coding was applied to the data and codes were then organized into themes as per the research questions, based on pre-existing categories of the intervention, and new categories extracted about the mechanisms of action and context of the intervention and the attitude of patients regarding their pathology and treatment. Coding frameworks were triangulated, and themes were reviewed and refined by the two researchers before applying them to all the data.

Redesign of the IMA intervention tools (aim 3)

Patients from the PC system in Catalonia were recruited following a maximum variation sampling strategy based on some of the predictors of non-initiation: nationality, age, educational level, and presence of CVD and diabetes risk (22). Twenty-four patients were contacted. Patients that agreed to participate provided signed informed consent.

Data collection and analysis

Three discussion groups (duration 90–120 min) were conducted with four to six participants using a topic guide based on the protocol and IMA intervention decision aids, focusing particularly on health literacy and SDM. Discussion groups were recorded, anonymized, and transcribed by the research team.

Discussion groups were analyzed following a thematic analysis approach (47) by four researchers. Firstly, the researchers familiarized themselves with the data by listening to the recordings. Comments of the discussion groups were transcribed and rearranged to follow the intervention protocol, pre-existing categories of the decision aids, and new categories involving these tools that arose in the discussion groups. For each category, the main ideas were coded and reviewed to determine themes and identify patterns and, finally, the findings were triangulated between the researchers. No new themes emerged after coding the second discussion group.

Results

Participants

During the pilot trial, 901 new treatments of antihypertensive, lipid-lowering, antiplatelet, and/or antidiabetic (oral and/or insulin) medications were prescribed to 604 patients, 314 in the intervention group (see Figure 2 for details on recruitment and follow-up).

Tables 1, 2 show the characteristics of the participant PC centers and patients. PC centers were located in urban areas with different socioeconomic status, size and proportion of immigrant population and most were training centers (Table 1). Half of the medications were prescribed to women (50.83%), with the mean age of patients being 62.6 years old. Most of the prescriptions had a diagnosis record (89.7%); with the highest frequency being hypertensive disease (59.6%). There were almost no differences between women and men in terms of age and diagnoses, except for diabetes (Table 2).

The process evaluation involved 12 GPs, three nurses, 10 pharmacists, and four patients. Two GPs declined the invitation to participate due to time restrictions, and the rest failed to reply. One patient declined to participate in the study. Over half of the professionals were women, ranging between 41 and 52 years old and with more than 10 years of experience in PC. Half of the patients were women, ranging between 50 and 68 years old, and they were prescribed different medications and had different work and educational levels. Finally, 15 patients from the PC system in Catalonia agreed to participate in the discussion groups, varying by sex, age, cardiovascular risk, and educational level. Characteristics of the participants are shown in Supplementary Tables 1–3.

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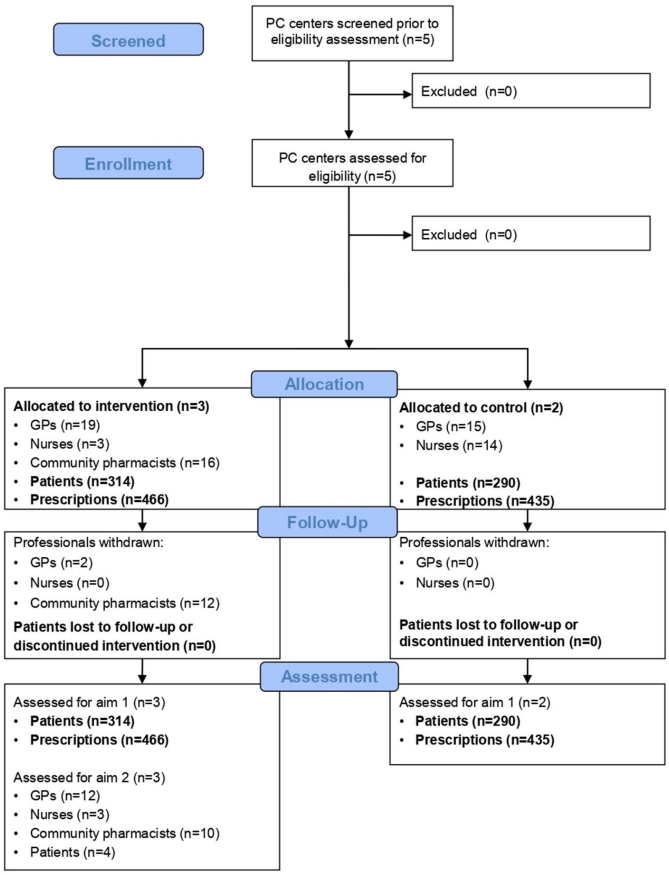

FIGURE 2
CONSORT Flow diagram (36). GP, general practitioner; PC, primary care. Aim 1: To test the availability and quality of data used to assess the effectiveness and cost-effectiveness of the IMA intervention. Aim 2: To evaluate the feasibility and acceptability of the IMA intervention in PC.

Availability and quality of RWD for the trial (aim 1)

Initiation and implementation

These variables have no missing data. In total, 10.7% of prescriptions were not initiated 3 months after the index prescription, and 18.4% were single prescriptions filled.

Table 3 summarizes indicators of data availability and quality for clinical parameters. Missing records in patient electronic health records were >50% in all cases before the index prescription, and between 39.7% (systolic and diastolic blood pressure) and 85.2% (cardiovascular risk) after the index prescription, with the lowest being cardiovascular risk in both cases. All parameter values were within plausible ranges except one estimated glomerular filtration rate CKD-EPI value which was recorded manually.

Tables 4, 5 summarize indicators of data availability and quality for use of services and productivity losses. A 33.3% of prescriptions didn't have a visit registered on the day of a new prescription, while there were 13.8–27% of clinical parameter measures without any visit records on the same day (Table 4). After the index prescription all values for healthcare services and productivity losses were within plausible ranges, and no outliers were detected (Table 5).

TABLE 1 Characteristics of the PC centers.

	Training center	Area socioeconomic status[a]	Reference population[b] (N)	Immigrant population (%)
Intervention group				
PCC1	No	Urban 4	10,174	7.15%
PCC2	Yes	Urban 4	20,299	37.33%
PCC3	Yes	Urban 4	26,782	33.41%
Control group				
PCC4	Yes	Urban 3	26,094	11.07%
PCC5	Yes	Urban 2	14,092	13.41%

PCC, primary care center.
[a]Socioeconomic status: four urban categories based on quartiles from low (urban 4) to high (urban 1) socioeconomic level and a rural category.
[b]Number of people assigned to the Primary Care Center (48).

TABLE 2 Characteristics of the patients*.

Prescriptions	Women (N = 458)	Men (N = 443)	Total (N = 901)
Age (mean, SD)	64.15 (16.22)	61.01 (15.21)	62.60 (15.80)
Diagnosis records (ICD-10)	404 (88.21%)	406 (91.24%)	808 (89.68%)
Diabetes mellitus type 2 (E10–E14)	151 (32.97%)	212 (47.86%)	363 (40.29%)
Dyslipidemia (E70–E90)	220 (48.03%)	197 (44.47%)	417 (46.28%)
Hypertensive diseases (I10–I15)	275 (60.04%)	262 (59.14%)	537 (59.60%)
Ischemic heart diseases (I20–I25)	30 (6.55%)	58 (13.09%)	88 (9.77%)
Other heart diseases (I30–I52)	29 (6.33%)	33 (7.45%)	62 (6.88%)
Cerebrovascular diseases (I60–I69)	68 (14.85%)	46 (10.38%)	114 (12.65%)
Arterial diseases (I79–I79)	15 (3.28%)	29 (6.55%)	44 (4.88%)
Glomerular diseases (N00–N08)	4 (0.87%)	3 (0.68%)	7 (0.78%)
Acute and chronic kidney failure (N17–N19)	52 (11.35%)	58 (13.09%)	110 (12.21%)
No diagnosis records[a]	54 (11.79%)	39 (8.80%)	93 (10.32%)

SD, standard deviation; ICD, International classification of diseases (49).
*Patients characteristics are described using prescription level as a unit of analysis.
[a]Absence of intervention-related diagnosis records in the electronic health records.

Feasibility and acceptability of the IMA intervention (aim 2)

Professional recruitment and retention rates

Table 6 shows the professional recruitment and retention rates. Overall, recruitment was lower for nurses than for GPs and pharmacists. Retention was the highest for GPs and nurses. Only two GPs were lost due to sick leave. Low retention rates of pharmacists were attributed to the study being postponed and the COVID-19 distance measures in place.

Context and implementation of the IMA intervention

The COVID-19 pandemic influenced the implementation of the IMA intervention and fidelity to the study protocol. Training was completed long before the pilot was finally carried out, and professionals described more consultations for acute health problems, fewer follow-up and preventive consultations and therefore fewer chronic medication prescriptions. All along with an increased workload at both PC centers and pharmacies. All professionals described an increase in telephone consultations and, as a result, an increase in the duration of face-to-face consultations (reporting ~15 min per patient). Nevertheless, different practices within different organizations were reported. One of the PC centers in the intervention group had returned to face-to-face consultations by November 2020, whereas the other two were doing mainly telephone consultations. In the case of community pharmacies, most had increased the physical distance from patients due to the pandemic.

The implementation strategy and processes of the IMA intervention, contextual factors, and the grade of fidelity to the study protocol and grade of adaptability to the intervention are described below and summarized in Figure 3.

Training for professionals

The training was generally valued positively in terms of content and hours dedicated. Professionals understood non-initiation as a public health problem, GPs recognized situations in which the patient accepted a new prescription during

TABLE 3 Data availability and quality for clinical parameters for baseline (pre-prescription) and follow-up (post-prescription) assessment.

Medication prescribed and clinical parameter	Prescriptions	Missing records pre-prescription	Missing records post-prescription	Records	Clinical parameter values	Clinical parameter values
	N	N (%)	N (%)	N	Mean (SD)	Range
Antihypertensive[a]	406	277 (68.23%)	161 (39.66%)			
Systolic blood pressure (mmHg)		277 (68.23%)	161 (39.66%)	797	138.17 (20.25)	85; 230
Diastolic blood pressure (mmHg)		277 (68.23%)	161 (39.66%)	798	81.55 (12.65)	45;129
Lipid-lowering[b]	199	118 (59.30%)	147 (73.87%)			
High-density lipoprotein (mg/dl)		118 (59.30%)	147 (73.87%)	433	55.89 (15.17)	21; 106
Low-density lipoprotein (mg/dl)		118 (59.30%)	147 (73.87%)	432	114.61 (40.86)	31; 244
Total cholesterol (mg/dl)		59 (29.65%)	123 (61.81%)	681	200.21 (52.30)	70; 489
Antidiabetic[c]	191	95 (49.74%)	108 (56.54%)			
Blood glucose (mg/dl)		71 (36.79%)	78 (40.41%)	847	119.84 (48.21)	62; 486
Glycated hemoglobin (%)		84 (43.52%)	89 (46.11%)	368	7.10 (1.61)	4.3; 15.3
Estimated glomerular filtration rate		84 (43.52%)	100 (51.81%)	1,629		
MDRD (mL/min/1.73 m^2)				161*	46.79 (11.78)	12.9; 59.9
CKD-EPI (mL/min/1.73 m^2)				512*	68.38 (18.06)	0.4; 89.9
All prescriptions[d]	901	842 (93.45%)	768 (85.24%)			
Cardiovascular Risk (REGICOR %)						

[a]Pharmacotherapeutic groups: C02 Antihypertensives, C03 Diuretics, C07 Beta blocking agents, C08 Calcium channel blockers, and C09 Agents acting on the renin-angiotensin system.
[b]Pharmacotherapeutic groups: C10 Lipid modifying agents.
[c]Pharmacotherapeutic groups: A10 Drugs used in diabetes.
[d]Pharmacotherapeutic groups: A10 Drugs used in diabetes, B01 Antithrombotic agents, C02 Antihypertensives, C03 Diuretics, C07 Beta blocking agents, C08 Calcium channel blockers, C09 Agents acting on the renin-angiotensin system, and C10 Lipid modifying agents.
*Estimated Glomerular Filtration Rate MDRD and CKD-EPI appear as >60.1 and >90.1, respectively, in the electronic health records for normal values. We have considered only those values below 60.1 and 90.1 to assess the quality of the records. For more details, please refer to Supplementary material.

a consultation but never initiated it, and appreciated the tools provided during training to approach new prescriptions. Nevertheless, due to the delay of the pilot study, some GPs and nurses and most pharmacists, mentioned that they had forgotten about it.

Decision aids

PC professionals agreed that the leaflet was helpful in organizing the information given to patients. However, some found it challenging and questioned its utility when used with older patients and people who did not speak Spanish or Catalan. Most of the pharmacists reported not using the leaflets, and none of the professionals reported using the website or recommending it to patients.

GPs considered it was easier to implement the intervention face-to-face using the leaflets than by telephone consultations. Those that implemented it by telephone used the leaflet to guide themselves through the explanation and sent it online only to those patients that had email. Three out of four patients stated that GPs used a leaflet during the explanation of the new prescription, one of them through telephone consultation. In the last case, the leaflet was sent by email and the GP phoned the patient some days later to ensure the information was understood.

Shared decision-making

At the time of a new prescription, GPs considered that the intervention was easy to apply and adapted their clinical practice accordingly. They mainly reported applying the intervention during face-to-face consultations and having enough time to do so. Providing information to the patient about the disease and treatment options was considered part of the standard practice of the GP, and all of them reported doing so. Nonetheless, only two GPs reported following the principles of SDM when recommending a new medication. The majority stated that the patient agreed with the prescription, and only two mentioned that the patient decided with them to issue the prescription.

Of the patients that stated that the GP provided information using the leaflet, only one reported SDM during the prescribing process. In the other cases, the GP did not ask their opinion or preferences and prescribed the medication only after they explained the disease and the treatment. When patients were asked about participating in the decision process, some of them considered it was not a decision for them to make. Some considered they need not be involved because of a lack of knowledge in the field but also because they trusted the GP's decision.

TABLE 4 Data availability of visits the day prescriptions were issued and clinical parameters were measured.

Medication prescribed	Prescriptions	Missing visits on the day of prescription
	N	N (%)
Antihypertensive[a]	406	125 (30.79%)
Lipid-lowering[b]	199	65 (32.66%)
Antidiabetics[c]	191	60 (31.41%)
All prescriptions[d]	901	300 (33.30%)
Clinical parameter	**Records**	**Missing visits on the day of measure**
	N	N (%)
Systolic blood pressure	797	113 (14.18%)
Diastolic blood pressure	798	114 (14.29%)
High-density lipoprotein	433	67 (15.47%)
Low-density lipoprotein	432	66 (15.28%)
Total cholesterol	681	119 (17.47%)
Blood glucose	847	229 (27.04%)
Glycated hemoglobin	368	54 (14.67%)
Estimated glomerular filtration rate	1,629	439 (26.95%)
Cardiovascular risk (REGICOR %)	159	22 (13.84%)

[a] Pharmacotherapeutic groups: C02 Antihypertensives, C03 Diuretics, C07 Beta blocking agents, C08 Calcium channel blockers, and C09 Agents acting on the renin-angiotensin system.
[b] Pharmacotherapeutic groups: C10 Lipid modifying agents.
[c] Pharmacotherapeutic groups: A10 Drugs used in diabetes.
[d] Pharmacotherapeutic groups: A10 Drugs used in diabetes, B01 Antithrombotic agents, C02 Antihypertensives, C03 Diuretics, C07 Beta blocking agents, C08 Calcium channel blockers, C09 Agents acting on the renin-angiotensin system, and C10 Lipid modifying agents.

TABLE 5 Data quality for use of services (number of services used) and productivity losses (number of days of sick leave) (*N* prescriptions = 901).

	Mean (SD)	Range
Use of services		
GP visits	6.45 (4.77)	0; 34
Nurse visits	4.54 (5.97)	0; 59
Secondary care referrals	0.14 (0.41)	0; 3
Diagnostic tests	0.21 (0.52)	0; 4
Productivity losses		
Days of sick leave	5.61 (24.83)	0; 152

GP, general practitioner; SD, standard deviation.

Other professional information support

Both GPs and nurses considered the fact that few nurses participated in the study to be a barrier to the intervention. Nurses were believed to have an important role in the follow-up and identification of patients with CVDs or diabetes. Additionally, professionals at the PC centers and pharmacists cited a lack of communication between one another. Pharmacists were often not considered as part of the multidisciplinary PC team, which was seen as a barrier to implementing the intervention at all levels; GPs as prescribers, and nurses and pharmacists as central supporters.

Most nurses and pharmacists participating reported implementing the intervention on very few occasions, and none of the patients interviewed confirmed that the nurse or the pharmacist implemented the intervention with them. Some visited the nurse after the prescription for a follow-up on the chronic disease and all mentioned that the pharmacist dispensed the medication without any explanation.

Broadly, the main barrier to implementing the intervention was forgetfulness. Professionals tended to overlook it before they had internalized it as their standard practice. In addition, pharmacists found it difficult to recognize a new prescription at the time of dispensation, especially if the alert on the e-prescription system was not available.

Professionals' and patients' experiences and perceptions in terms of feasibility and acceptability: Key themes

Summarized below are the key themes regarding feasibility and acceptability, such as the experiences and perceptions of the GPs as prescribers, nurses, and pharmacists as key supporters, and patients as recipients of the IMA intervention.

Perceived effect of the IMA intervention by professionals

Professionals believed that, even though the information was very similar to that of usual care, patients understood it better when the leaflet was used to structure the information and considered this could have a direct impact on adherence. A negative effect in terms of initiation was related to giving more information about medication adverse effects to patients with chronic conditions with no symptoms. Some professionals believed patients may be more afraid of adverse effects than future complications associated with the disease.

Relationship and trust between the professional and patient

Trust in professional recommendations was perceived to be affected by the relationship between the professional and the patient, which was considered to be mainly influenced by the length of time the patient had visited the same professional. Trust was described as the main facilitator. From the professional's point of view, it makes it easier to maintain a conversation with the patient and explore their perceptions, while from the patient's perspective, it makes it easier to ask questions and express their opinion.

TABLE 6 Professional recruitment and retention rates.

	Professionals N	Recruitment N (%)	Retention[a] N (%)	
		February 2020	November 2020	
Intervention group				
PCC1	GPs (8)	5 (62.50%)	5 (62.50%)	5 (100%)
	Nurses (7)	7 (100%)	3 (42.86%)	3 (100%)
	Community pharmacies (8)	8 (100%)	8 (100%)	3 (37.50%)
PCC2	GPs (15)	10 (66.67%)	10 (66.67%)	9 (90%)
	Nurses (12)	3 (25%)	0 (0%)	N/A
	Community pharmacies (5)	4 (80%)	4 (80%)	1 (25%)
PCC3	GPs (15)	4 (26.67%)	4 (26.67%)	3 (75%)
	Nurses (12)	0 (0%)	0 (0%)	N/A
	Community pharmacies (6)	4 (66.67%)	4 (66.67%)	0 (0%)
Control group				
PCC4	GPs (14)	7 (50%)	7 (50%)	7 (100%)
	Nurses (13)	8 (61.54%)	7 (53.85%)	7 (100%)
PCC5	GPs (10)	8 (80%)	8 (80%)	8 (100%)
	Nurses (9)	7 (77.78%)	7 (77.78%)	7 (100%)

GP, general practitioner; N/A, not applicable; PCC, primary care center.
[a]Retention rate based on the professionals recruited in November 2020.

Motivation for professionals to adapt their clinical practice

Even though most professionals described the COVID-19 pandemic as a difficult situation, some GPs emphasized they were more willing to make changes as they considered the IMA intervention as reinforcement of the importance of SDM in their routine practice. Similarly, pharmacists saw it as an opportunity to provide health education in the community pharmacy, especially to those patients that were not able to visit the PC center during the pandemic.

Redesign of the IMA intervention tools (aim 3)

PC patients highlighted the advantages and disadvantages of the pilot leaflets according to their needs. As for disadvantages, they emphasized a lack of topic titles to introduce the content, the medical jargon, and the large amount of information provided. As advantages, they highlighted the structure of the leaflet and specific contents such as the epidemiological data on the disease, data on the consequences of the decision not to treat, and the encouragement to express their doubts and opinions and participate in the decision process.

Moreover, patients recommended that the new leaflets should clarify whether the non-pharmacological measures are an alternative to the medication or an addition to it, so the patient is encouraged to adopt non-pharmacological measures in the case of a pharmacological prescription. Additionally, patients suggested that only the most common adverse effects of the medication should be mentioned so that the risk-benefit assessment of the medication is balanced.

Patients acknowledged they looked on the internet when they had questions about their disease or treatment after consultation with clinicians. However, they found it very difficult to find a website that was reliable and supported by official organizations, and with easy-to-understand content. With respect to the website that was being designed for the definitive trial, they considered it should have links to other patients' associations, as well as to the Catalan Electronic Health System, so they had the option to contact a PC professional directly if they had any queries.

Discussion

The results of this pilot study suggest that implementing an intervention based on SDM to improve adherence to medications for CVDs and diabetes in PC is feasible and that the intervention is well-accepted. Carrying out a pragmatic cRCT to evaluate the effectiveness and cost-effectiveness of such an intervention is also feasible but weaknesses in the study design and the implementation of the intervention were identified and the knowledge gained should be used to refine the intervention and the study (50).

A non-initiation rate of 11% is in line with previous studies that were used to calculate the sample size of the cRCT (22,

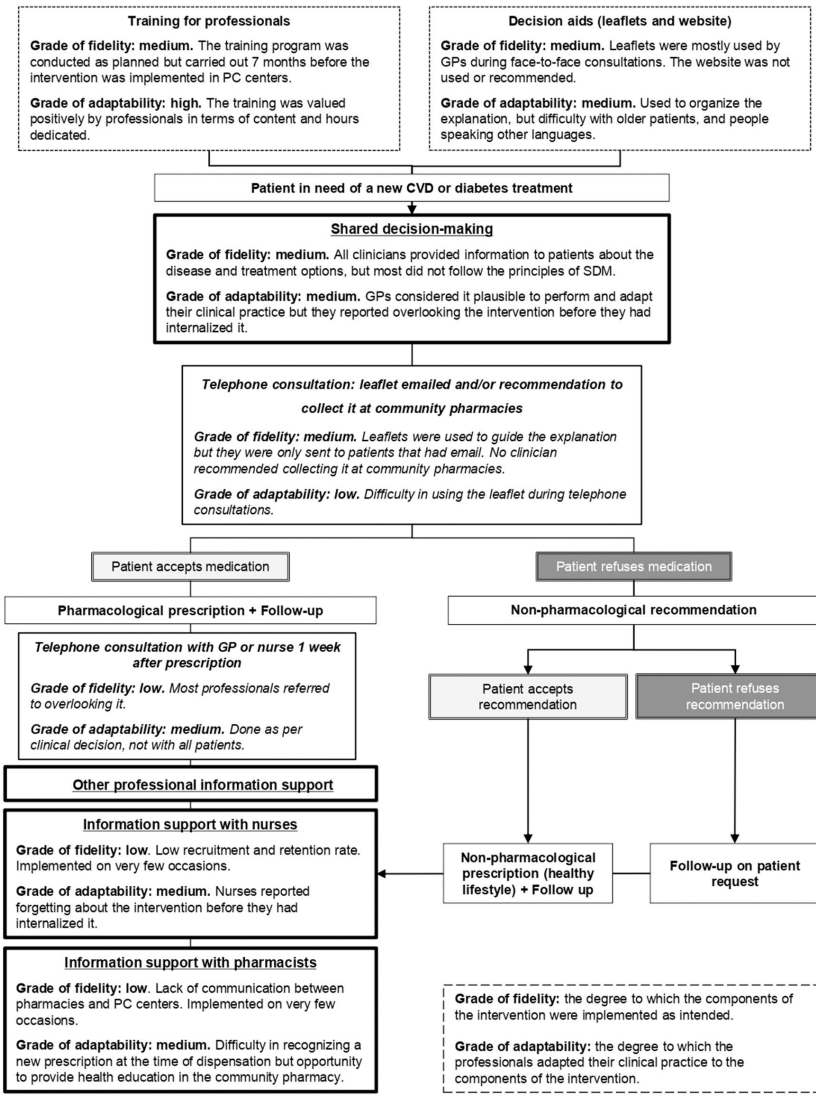

FIGURE 3
Grade of fidelity and adaptability to the implementation strategy and processes of the IMA intervention. CVD, cardiovascular disease; GP, general practitioner; PC, primary care. Text in italics describes the intervention adaptations made due to the COVID-19 pandemic.

27). The study identified weaknesses in the electronic health records by recognizing a high prevalence of missing registered visits. This could be explained, in the context of the COVID-19 pandemic, and by an increased number of telephone and emergency consultations (51). At the time of the pilot study the workload in PC centers was high, which could partly explain flaws in data records. This is not expected to happen during the cRCT, but if missing visit records are identified, and taking into account that all prescriptions would be issued in PC centers in the public health system, every prescription would be imputed as one visit to the GP so costs are not underestimated. Additionally, there was a high proportion of missing clinical parameter records that could be explained by the COVID-19 situation, when face-to-face visits were kept to the minimum, and by the short follow-up period (5 months). Care quality standards based on clinical practice guidelines from the Catalan Health System recommend taking measurements at least every 12 months for all parameters except cholesterol, which is recommended every 18 months (43–46). During the training stage for professionals, the importance of registering clinical parameters according to clinical practice guidelines will be reinforced to reduce the percentage of missing data obtained through RWD during the trial. However, values of the parameters were mainly within the expected range. Special attention will be paid to records entered manually that are expected to increase during the cRCT. The sample size of the trial exceeded the estimates determined in previous feasibility study research (39, 52, 53).

The COVID-19 pandemic impacted the recruitment of nurses and the retention of pharmacists, as professionals reported, although recruitment rates of PC professionals were already low in some centers in February 2020, especially in the case of nurses. Other studies have also identified difficulties in recruitment and retention rates of healthcare professionals in PC, particularly due to lack of time, high workload, and low engagement with the research topic (54, 55). To improve professional recruitment rates and promote participation, before contacting PC professionals, we will inform stakeholders of PC and pharmacy organizations in Catalonia, as well as managers and directors of PC centers. Furthermore, the IMA-cRCT will be presented in a short session to professionals at each selected PC center and pharmacy, and they will be given time to ask the research team questions and deliberate participation in the study. Additionally, the research team will contact professionals participating in the trial regularly to troubleshoot, provide support, and therefore improve retention.

In general, professionals failed to apply the principles of SDM and both professionals and patients perceived some of the barriers and facilitators that have previously been cited in the literature (56, 57). For instance, professionals reported overlooking the intervention and both professionals and patients questioned patients' willingness to get involved in the decision process. However, patient preferences for SDM are influenced by the perception of professionals regarding SDM and its approach when inviting the patient to take part in the process (29, 56). Professionals recognized that SDM could increase patients' knowledge and improve adherence to medications, and even though time has been reported as a barrier before (56), none considered time to be a restriction to applying the intervention in this study. SDM is the foundation of the IMA intervention, involving patients in the decision process empowers them and increases self-efficacy by increasing health literacy and awareness of their pathologies and treatment options, and therefore the potential to increase adherence to treatment plans (17, 30). Patients are invited to express their opinions and if they decide not to start the medication the prescription is not issued. Likewise, they are actively involved in the treatment follow-up, information on medication effects and adverse events is given so patients can take them into account in the decision-making process as well as identify them and act accordingly if the treatment is initiated. To increase professionals' understanding and engagement with SDM, the training will be extended to 6 h, with 3 h dedicated to SDM. To balance professionals' schedules, it will be divided into two sessions. Session one would cover non-initiation as a public health problem and the development of the IMA intervention, as well as its practical aspects, such as records and ethical requirements. Session two will focus on communication skills and SDM and this preparation has been designed by an expert in the field. All professionals will be trained together to increase cohesion between GPs, nurses, and pharmacists, and reinforce the role of the latter two in providing information and supporting the patient in the decision process when a new chronic pharmacological treatment is prescribed.

The main advantages and disadvantages of the decision aids were identified and will be used to redesign and respect the preferred information format for patients as recommended by SDM models (29). The leaflets will contain essential information written in plain language, with a clear distinction between non-pharmacological measures and pharmacological treatments, and a section encouraging patients to express their opinion and professionals to write recommendations to patients. Additionally, they will be translated into the most widely-spoken languages in Catalonia. The content of the website will be appraised by healthcare organizations in Catalonia and the layout will be designed to make it more user-friendly. It will be divided into pathologies and pharmacological treatments and the leaflets will be easier to acquire as patients and professionals will be able to download them from the website.

The COVID-19 pandemic has inevitably impacted the implementation of the intervention during the pilot study. However, not all the consequences were negative. As described by professionals, the pandemic encouraged them to adapt their clinical practice to new situations and reinforced the role of pharmacists in providing health education. Additionally, the duration of face-to-face consultations was increased, which might have favored the implementation of the IMA intervention.

Organizational changes during the COVID-19 pandemic and the reintroduction of usual practices in PC centers and pharmacies would need to be considered carefully during the implementation of the IMA intervention in a pragmatic PC setting during the upcoming cRCT.

Some limitations need to be acknowledged. First, the duration proposed for this pilot study was 3 months of fieldwork and 6 months of follow-up before and after the index prescription. However, due to the COVID-19 pandemic, the duration of the follow-up period dropped to 5 months, which might have impacted the access to parameter data in the electronic health records. Second, the study was only carried out in one region of Catalonia in the context of a pilot study, and even though PC centers had dissimilar socioeconomic characteristics, the results obtained might have been different if various regions of Catalonia had been included. Third, the low recruitment rate of nurses, especially after the COVID-19 pandemic, might have limited the assessment of the role of nurses in the IMA intervention. Lastly, not all the professionals who participated in the trial were interviewed and we might have missed some important insights. Nevertheless, the percentage of participation among professionals was high, all were invited to participate and had the opportunity to be interviewed at their preferred date and time.

Involving patients in the decision-making process is fundamental in achieving better clinical outcomes, although patient-centered care requires modifications to clinical practice in PC. We identified barriers and facilitators to implementing the intervention as well as adapting it to a context affected by the COVID-19 pandemic. This pilot study contributes information regarding the feasibility and acceptability of the IMA intervention and its evaluation design in a pragmatic setting. It has helped to identify strengths and weaknesses and refine the IMA intervention and its evaluation design accordingly before the definitive cRCT to evaluate the effectiveness and cost-effectiveness of the IMA intervention.

Data availability statement

The datasets presented in this article are not readily available because the research team is not the quantitative data owner as it only analyzes information that is property of public health institutions. The data that support the findings of this study are available from SIDIAP but restrictions apply to the availability of these data, which were used under license for the current study, and thus are not publicly available. However, data are available from the authors upon reasonable request and with the permission of SIDIAP. Qualitative data and the study protocol are available from the authors upon reasonable request. Requests to access the datasets should be directed to maria.rubio@sjd.es.

Ethics statement

This study was reviewed and approved by the Drug Research Committee (CEIm) at the IDIAP Jordi Gol, codeCEIm 19/198-P. The pilot study is a low-intensity intervention clinical trial where groups of subjects are allocated to the control and the intervention group. Informed consent was obtained by simplified means which requires that the same information stated under Article 30 of Regulation (EU) No 536/2014 is provided before anyone is enrolled in the trial, and after being informed, the patient does not object to participating (38). All conditions described in Regulation (EU) No 536/2014 and the Real Decreto 1090/2015 were fulfilled (38, 58). Informed consent in the present study was obtained by displaying posters in prominent locations of the participating PC centers notifying people that a clinical trial was being conducted in the center and that patients could be part of this comparative study. Posters contained information on how and why the trial was being conducted and what the implications of participating in the study were. Furthermore, professionals in the intervention and control groups were trained to deal with patients' queries regarding the study. If patients declined to participate in the study, this information was documented by clinicians in the electronic health records and data from those patients was not used for the study. Finally, patients could withdraw at any time from the study without any detriment.

Participation in this study was entirely voluntary. Professionals that agreed to participate signed informed consent at the training session and agreed to be interviewed as part of the process evaluation. Patients who participated in the process evaluation and discussion groups signed informed consent after recruitment and prior to the beginning of data collection. All participants had the right to refuse to participate and to withdraw from the study at any time.

Author contributions

MR-V led the design of the study and obtained funding for the study. IA-L, MG-G, and MP-M advised and contributed to the study design. MR-V, IA-L, MG-G, MP-M, and CC-D designed the decision aids. MR-V, IA-L, MG-G, and MP-M recruited and trained professionals. CC-P, AS-V, IA-L, and MR-V developed the statistical analysis plan and analyzed quantitative data. CC-P, MG-G, MP-M, and AS-V collected and analyzed qualitative data. CC-P wrote the first draft of the manuscript. All authors added to and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1038138/full#supplementary-material

References

1. Menckeberg TT, Bouvy ML, Bracke M, Hugtenburg JG, Lammers JW, Raaijmakers JAM. Patients' understanding of the reasons for starting and discontinuing inhaled corticosteroids. *Br J Clin Pharmacol.* (2008) 66:255–60. doi: 10.1111/j.1365-2125.2008.03168.x

2. Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Prefer Adherence.* (2018) 12:721–31. doi: 10.2147/PPA.S161151

3. Zeber JE, Manias E, Williams AF, Hutchins D, Udezi WA, Roberts CS, et al. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR medication adherence & persistence special interest group. *Value Heal.* (2013) 16:891–900. doi: 10.1016/j.jval.2013.04.014

4. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. *Am J Med.* (2013) 126:357.e7–e27. doi: 10.1016/j.amjmed.2012.09.004

5. Xu T, Yu X, Ou S, Liu X, Yuan J, Tan X, et al. Adherence to antihypertensive medications and stroke risk: a dose-response meta-analysis. *J Am Heart Assoc.* (2017) 6:e006371. doi: 10.1161/JAHA.117.006371

6. Bouchard MH, Dragomir A, Blais L, Bérard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary prevention. *Br J Clin Pharmacol.* (2007) 63:698–708. doi: 10.1111/j.1365-2125.2006.02828.x

7. Kim Y-Y, Lee J-S, Kang H-J, Park SM. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. *Sci Rep.* (2018) 8:12190. doi: 10.1038/s41598-018-30740-y

8. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open.* (2018) 8:e016982. doi: 10.1136/bmjopen-2017-016982

9. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva: World Health Organization (2003). Available from: https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf?sequence$=$1&isAllowed$=$y (accessed September 05, 2022).

10. Derose SF, Green K, Marrett E, Tunceli K, Cheetham TC, Chiu VY, et al. Automated outreach to increase primary adherence to cholesterol-lowering medications. *JAMA Intern Med.* (2013) 173:38–43. doi: 10.1001/2013.jamainternmed.717

11. Fischer MA, Choudhry NK, Bykov K, Brill G, Bopp G, Wurst AM, et al. Pharmacy-based interventions to reduce primary medication nonadherence to cardiovascular medications. *Med Care.* (2014) 52:1050–4. doi: 10.1097/MLR.0000000000000247

12. Fischer MA, Jones JB, Wright E, Van Loan RP, Xie J, Gallagher L, et al. A randomized telephone intervention trial to reduce primary medication nonadherence. *J Manag care Spec Pharm.* (2015) 21:124–31. doi: 10.18553/jmcp.2015.21.2.124

13. O'Connor PJ, Schmittdiel JA, Pathak RD, Harris RI, Newton KM, Ohnsorg KA, et al. Randomized trial of telephone outreach to improve medication adherence and metabolic control in adults with diabetes. *Diabetes Care*. (2014) 37:3317–24. doi: 10.2337/dc14-0596

14. Kerner DE, Knezevich EL. Use of communication tool within electronic medical record to improve primary nonadherence. *J Am Pharm Assoc*. (2017) 57:S270–3.e2. doi: 10.1016/j.japh.2017.03.009

15. McCarthy ML, Ding R, Roderer NK, Steinwachs DM, Ortmann MJ, Pham JC, et al. Does providing prescription information or services improve medication adherence among patients discharged from the emergency department? A randomized controlled trial. *Ann Emerg Med*. (2013) 62:212–23.e1. doi: 10.1016/j.annemergmed.2013.02.002

16. Saheb Kashaf M, McGill ET, Berger ZD. Shared decision-making and outcomes in type 2 diabetes: a systematic review and meta-analysis. *Patient Educ Couns*. (2017) 100:2159–71. doi: 10.1016/j.pec.2017.06.030

17. Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, Popa CD, Vriezekolk JE. Interventions to support shared decision making for medication therapy in long term conditions: a systematic review. *Patient Educ Couns*. (2019) 103:254–65. doi: 10.1016/j.pec.2019.08.034

18. Coronado-Vázquez V, Canet-Fajas C, Delgado-Marroquín MT, Magallón-Botaya R, Romero-Martín M, Gómez-Salgado J. Interventions to facilitate shared decision-making using decision aids with patients in Primary Health Care: a systematic review. *Medicine*. (2020) 99:e21389. doi: 10.1097/MD.0000000000021389

19. Milky G, Thomas J. Shared decision making, satisfaction with care and medication adherence among patients with diabetes. *Patient Educ Couns*. (2020) 103:661–9. doi: 10.1016/j.pec.2019.10.008

20. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. (2008) 337:a1655. doi: 10.1136/bmj.a1655

21. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS ONE*. (2016) 11:e0150205. doi: 10.1371/journal.pone.0150205

22. Aznar-Lou I, Fernández A, Gil-Girbau M, Fajó-Pascual M, Moreno-Peral P, Peñarrubia-María MT, et al. Initial medication non-adherence: prevalence and predictive factors in a cohort of 16 million primary care patients. *Br J Clin Pharmacol*. (2017) 83:1328–40. doi: 10.1111/bcp.13215

23. Aznar-Lou I, Iglesias-González M, Gil-Girbau M, Serrano-Blanco A, Fernández A, Peñarrubia-María MT, et al. Impact of initial medication non-adherence to SSRIs on medical visits and sick leaves. *J Affect Disord*. (2018) 226:282–6. doi: 10.1016/j.jad.2017.09.057

24. Aznar-Lou I, Pottegård A, Fernández A, Peñarrubia-María MT, Serrano-Blanco A, Sabés-Figuera R, et al. Effect of copayment policies on initial medication non-adherence according to income: a population-based study. *BMJ Qual Saf*. (2018) 27:878–91. doi: 10.1136/bmjqs-2017-007416

25. Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, Moreno-Peral P, Fernández A, Bellón J, et al. Reasons for medication non-initiation: a qualitative exploration of the patients' perspective. *Res Soc Adm Pharm*. (2020) 16:663–72. doi: 10.1016/j.sapharm.2019.08.002

26. Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, Aznar-Lou I, Serrano-Blanco A, Mendive Arbeloa JM, et al. Non-initiation of prescribed medication from a Spanish health professionals' perspective: a qualitative exploration based on Grounded Theory. *Health Soc Care Community*. (2022) 30:e213–21. doi: 10.1111/hsc.13431

27. Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, Serrano-Blanco A, Fernández-Vergel R, Petitbò-Antúnez D, et al. Initiation and single dispensing in cardiovascular and insulin medications: Prevalence and explanatory factors. *Int J Environ Res Public Health*. (2020) 17:3358. doi: 10.3390/ijerph17103358

28. Edwards M, Wood F, Davies M, Edwards A. The development of health literacy in patients with a long-term health condition: the health literacy pathway model. *BMC Public Health*. (2012) 12:130. doi: 10.1186/1471-2458-12-130

29. Elwyn GJ, Edwards A, Kinnersley P, Grol R. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. *Br J Gen Pract*. (2000) 50:892–9. Available online at: https://bjgp.org/content/bjgp/50/460/892.full.pdf

30. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med*. (2012) 27:1361–7. doi: 10.1007/s11606-012-2077-6

31. Rimer B, Glanz K. *Theory at a Glance: A guide For Health Promotion Practice*. 2nd ed. Bethesda, MD: National Cancer Institute (2005).

32. Cragg L, Davies M, McDowall W. Using theory to guide change at the individual level. In: McGraw-Hill, editor. *Health Promotion Theory*. 2nd ed. London: Open University Press (2013).

33. Gil-Girbau M, Pons-Vigués M, Rubio-Valera M, Murrugarra G, Masluk B, Rodríguez-Martín B, et al. Theoretical models of health promotion in primary healthcare everyday practice. *Gac Sanit*. (2021) 35:48–59. doi: 10.1016/j.gaceta.2019.06.011

34. Sánchez-Viñas A, Corral-Partearroyo C, Gil-Girbau M, Peñarrubia-María MT, Gallardo-González C, Olmos-Palenzuela MC, et al. Effectiveness and cost-effectiveness of an intervention to improve initial medication adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study). *BMC Prim Care*. (2022) 23:170. doi: 10.1186/s12875-022-01727-6

35. Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María M, Aznar-Lou I, Gallardo-González C, et al. Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): Mixed methods process evaluation protocol. *BMJ Open*. (2022) 12:e067468. doi: 10.1136/bmjopen-2022-067468

36. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Br Med J*. (2016) 355:i5239. doi: 10.1136/bmj.i5239

37. Bernal E, Sandra D, Juan G-A, Fernando O, Sánchez Martínez I, Ramón J, et al. Spain: health system review. *Health Syst Transit*. (2018) 20:1–179. Available online at: https://www.euro.who.int/_data/assets/pdf_file/0008/378620/hit-spain-eng.pdf

38. European Union. *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC Text With EEA Relevance*. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri$=$celex%3A32014R0536 (accessed September 05, 2022).

39. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. (2010) 10:1. doi: 10.1186/1471-2288-10-1

40. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. (2012) 73:691–705. doi: 10.1111/j.1365-2125.2012.04167.x

41. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordón F, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. *Rev Esp Cardiol*. (2003) 56:253–61. doi: 10.1016/S0300-8932(03)76861-4

42. SIDIAP. *Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària*. Available from: https://www.sidiap.org/ (accessed September 05, 2022).

43. Coll de Tuero G, Dalfó i Baqué A, de la Figuera Von Wichmann M, Gibert i Llorach E, Isnard Blanchar M, Martínez Alonso V, et al. *Guies de pràctica clínica*. Barcelona: Hipertensió Arterial Institut Català de la Salut (2012).

44. Baena Díez J, Barcelo Colomer E, Ciurana Misol R, Franzi Sisó A, García Cerdán M, Ríos Rodríguez M, et al. *Guies de pràctica clínica. Colesterol i risc coronari*. Vol 1. Barcelona: Institut Català de Salut (2009).

45. Mata M, Cos FX, Morros R, Diego L, Barrot J, Berengué M, et al. Guies de pràctica clínica. *Abordatge de la diabetes mellitus tipus 2*. Barcelona: Institut Català de la Salut (2013).

46. Verdú Rotellar J, Pacheco Huergo V, Amado Guirado E, Esgueva de Haro N, López Pareja N, Alemany Vilches L, et al. *Guies de pràctica clínica. Insuficiència cardíaca*. Barcelona: Institut Català de la Salut (2008). Available online at: https://scientiasalut.gencat.cat/bitstream/handle/11351/4516/insuficiencia_cardiaca_guies_practica_clinica_2007_versio_extensa.pdf?sequence$=$1&isAllowed$=$y (accessed September 05, 2022).

47. Green J, Thorogood N. *Qualitative Methods for Health Research*. 4th ed. London: SAGE (2018). 440 p.

48. Servei Català de la Salut. *Població de referència del Servei Català de la Salut per a l'any 2020 - Dades per ABS i UP assignada*. (2020). Available from: https://catsalut.gencat.cat/web/.content/minisite/catsalut/proveidors_professionals/registres_catalegs/documents/poblacio-referencia.pdf (accessed September 05, 2022).

49. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. Available from: https://icd.who.int/browse10/2019/en (accessed September 05, 2022).

50. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. *Health Technol Assess*. (2021) 25:1–132. doi: 10.3310/hta25570

51. Feldman J, Szerencsy A, Mann D, Austrian J, Kothari U, Heo H, et al. Giving your electronic health record a checkup after COVID-19: a practical framework for reviewing clinical decision support in light of the telemedicine expansion. *JMIR Med Informat.* (2021) 9:e21712. doi: 10.2196/21712

52. Teare D, Dimairo M, Hayman A, Shephard N, Whitehead A, Walters S. Sample size requirements for pilot randomised controlled trials with binary outcomes: a simulation study aims. *Trials*. (2013) 14:O21. doi: 10.1186/1745-6215-14-S1-O21

53. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res.* (2016) 25:1057–73. doi: 10.1177/0962280215588241

54. Johnston S, Liddy C, Hogg W, Donskov M, Russell G, Gyorfi-Dyke E. Barriers and facilitators to recruitment of physicians and practices for primary care health services research at one centre. *BMC Med Res Methodol*. (2010) 10:109. doi: 10.1186/1471-2288-10-109

55. Krebs F, Lorenz L, Nawabi F, Lück I, Bau AM, Alayli A, et al. Recruitment in health services research-A study on facilitators and barriers for the recruitment of community-based healthcare providers. *Int J Environ Res Public Health*. (2021) 18:10521. doi: 10.3390/ijerph181910521

56. Gravel K, Légaré F, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health professionals' perceptions. *Implement Sci.* (2006) 1:16. doi: 10.1186/1748-5908-1-16

57. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. *Patient Educ Couns*. (2008) 73:526–35. doi: 10.1016/j.pec.2008.07.018

58. Gobierno de España. *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos*. Madrid: Bol Of Del Estado. (2015). p. 121 923–64.

4.2.1 Main results overview – Scientific article 1

Over three months, a cluster non-randomised controlled trial was conducted. The IMA intervention was implemented in three primary care centres (19 GPs, 3 nurses and 16 community pharmacists), while two centres provided usual care (15 GPs and 14 nurses). During this pilot trial, 604 patients received 901 new prescriptions for antihypertensive, lipid-lowering, antiplatelet, and/or oral/injectable antidiabetic medications.

The *availability and quality of real-world data from electronic health records* were evaluated. Data on the primary outcome (medication initiation) and secondary adherence (ongoing adherence and persistence) were available for all patients. Overall, 10.7% of prescriptions were not initiated within three months, a rate used to calculate the sample size for the definitive trial. Data for secondary clinical outcomes had a high proportion of missingness (40-85%) according to care quality standards based on clinical guidelines. Nonetheless, recorded values fell within plausible ranges, with few outliers. This analysis allowed a pre-planned strategy for missing data management in the definitive trial.

Feasibility and acceptability of the IMA intervention were confirmed through qualitative individual semistructured interviews with 25 professionals (12 GPs, 3 nurses and 10 community pharmacists) and 4 patients. Professionals valued the training and decision aids, noting improved patient health literacy when leaflets were used. GPs highlighted the importance of shared decision-making, the role of nurses in chronic disease management was acknowledged, and pharmacists viewed the intervention as an opportunity for community pharmacy-based health education. Reported barriers included limited nurse engagement, pharmacist retention issues, forgetting the

intervention in daily practice, and high workload—exacerbated by the COVID-19 pandemic at the time. Shared decision-making principles were not always applied; while decision aids were used to provide information, few GPs actually involved patients in the decision-making process. To address these challenges, a new professional engagement strategy was designed, and the training programme was revised. Its duration was extended to six hours, three hours were dedicated specifically to shared decision-making to deepen professionals' understanding and commitment. Training sessions were planned to be delivered jointly to GPs, nurses, and pharmacists to foster team cohesion and reinforce the collaborative roles of all healthcare professionals in supporting patients with new prescriptions.

Three discussion groups with 15 patients informed the *refinement of the IMA intervention decision aids*. Patients endorsed the leaflets as written materials but requested simpler language, clearer layout, separation of lifestyle and medication information, and translations into additional languages. This feedback informed the revised leaflets and the design of a website with reliable, easy-to-understand content supported by official organisations.

These findings guided the refinement of the IMA intervention and the final design of the pragmatic type I hybrid effectiveness-implementation study. Additionally, logistical challenges identified during the pilot (e.g., training scheduling, data extraction procedures, and contingency plans for COVID-19 restrictions) were addressed in advance, allowing the definitive trial to proceed with minimal disruptions and largely within the projected timelines.

4.3 Scientific article 2

OBJECTIVE 2: Intervention and evaluation design refinement

Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol

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Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M

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Open access Protocol

BMJ Open

Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol

Carmen Corral-Partearroyo,[1,2] Alba Sánchez-Viñas,[1,3] Montserrat Gil-Girbau ,[1,4] Maria Teresa Peñarrubia-María,[1,5] Ignacio Aznar-Lou,[1,6] Carmen Gallardo-González,[1,5] María del Carmen Olmos-Palenzuela,[7] Maria Rubio-Valera[1,6]

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For numbered affiliations see end of article.

Correspondence to
Dr Montserrat Gil-Girbau; mariamontserrat.gil@sjd.es

ABSTRACT

Introduction Medication non-initiation, or primary non-adherence, is a persistent public health problem that increases the risk of adverse clinical outcomes. The initial medication adherence (IMA) intervention is a complex multidisciplinary intervention to improve adherence to cardiovascular and diabetes treatments in primary care by empowering the patient and promoting informed prescriptions based on shared decision-making. This paper presents the development and implementation strategy of the IMA intervention and the process evaluation protocol embedded in a cluster randomised controlled trial (the IMA-cRCT) to understand and interpret the outcomes of the trial and comprehend the extent of implementation and fidelity, the active mechanisms of the IMA intervention and in what context the intervention is implemented and works.

Methods and analysis We present the protocol for a mixed-methods process evaluation including quantitative and qualitative methods to measure implementation and fidelity and to explore the active mechanisms and the interactions between the intervention, participants and its context. The process evaluation will be conducted in primary care centres and community pharmacies from the IMA-cRCT, and participants include healthcare professionals (general practitioners, nurses and community pharmacists) as well as patients. Quantitative data collection methods include data extraction from the intervention operative records, patient clinical records and participant feedback questionnaires, whereas qualitative data collection involves semistructured interviews, focus groups and field diaries. Quantitative and qualitative data will be analysed separately and triangulated to produce deeper insights and robust results.

Ethics and dissemination Ethical approval has been obtained from the Research Ethics Comittee (CEIm) at IDIAP Jordi Gol (codeCEIm 21/051 P). Findings will be disseminated through publications and conferences, as well as presentations to healthcare professionals and stakeholders from healthcare organisations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This process evaluation will explain how the intervention was implemented, how different components interact and work and how they influence outcomes.
⇒ This study includes a wide range of quantitative and qualitative research methods; it is logistically challenging and time consuming. A multidisciplinary research team has been involved.
⇒ The flexible and pragmatic design will be crucial to react to changes and adapt the intervention to emerging contextual factors.
⇒ Data collection methods have been designed to adapt to the participants in what we anticipate might be an overloaded and difficult time due to the persisting COVID-19 pandemic.
⇒ There is a risk of response bias among professionals that answer questionnaires and agree to participate in the qualitative evaluation as they may have engaged more with the intervention. Additionally, patients will be recruited by professionals and this might bias their responses and the decision of the patient towards filling the prescription.

Trial registration number NCT05026775.

INTRODUCTION

Medication non-initiation, or primary non-adherence, is defined as not initiating the prescribed pharmacological treatment.[1] In recent years, there has been an increase in evidence regarding non-initiation.[2–5] It is subject to patients' characteristics and motivations, the pharmacological treatment prescribed and the context,[4 6 7] and for some treatments, it reaches a prevalence of 40%.[3]

Adherence to long-term medications has been shown to be crucial to the prevention of further complications.[8] Low adherence to cardiovascular disease (CVD) and diabetes treatments worsens patients' clinical outcomes[9–12] and increases direct and indirect costs to healthcare systems,[10 13 14] highlighting the need for interventions to prevent it.

In the past, some studies evaluated the effectiveness of interventions to improve non-initiation, focused mainly on CVD medications.[15–20] The majority were based on patients' reminders: two on automated messages,[15 19] two on phone calls performed by professionals[17 18] and one on both automated and professional's phone calls.[16] Only two of these studies reported a significant decrease in non-initiation,[15 19] and most showed a high overall risk of bias. Hawthorne effect and desirability bias was high overall due to lack of blinding of participants and the characteristics of the outcome under study[15–18 20]; most studies used medicine acquisition as a proxy for initiation with no further follow-up, and false-positive initiation could occur when patients know they are being observed.[21 22] None of the interventions tested was described as being founded on a health behaviour change theory.

In the last decade, there has been growing interest in behavioural interventions based on shared decision-making (SDM) to improve adherence.[23–26] SDM is a process whereby the professional and the patient jointly decide on a treatment or healthcare choice.[27] Both share their knowledge, and the patient is invited to express their preferences and consider all options to achieve a mutual agreement.[27 28] This respects patient autonomy yet offers guidance to the patient by involving them in the decision at their preferred level.[27] By involving the patient in the decision process, SDM increases patients' health literacy and satisfaction.[23–26 29] However, there is not sufficient evidence for an effect of SDM-based interventions on medication adherence, and there is a lack of standardised outcomes in studies evaluating the impact of SDM interventions on adherence to pharmacological treatments.[23–26 29]

The non-initiation project

The non-initiation project is based on the framework for developing and evaluating complex interventions proposed by the Medical Research Council (MRC)[30 31] and aims to develop and evaluate an intervention to decrease non-initiation. Figure 1 summarises the project phases.

In phase I, or the development phase, the prevalence and explanatory factors of non-initiation were explored. Overall prevalence of non-initiation in primary care (PC) in Catalonia (Spain) was found to be 18% and between 6% and 9% for treatments for CVD and diabetes.[5 32] Predictors of non-initiation included patient characteristics (such as being younger), the treatment (such as cost) and the system (such as receiving the prescription from a substitute or resident general practitioner (GP)).[5 32] The patients' reasons for non-initiation were explored by carrying out qualitative research with patients and professionals.[7 33] Based on the results of these studies, the Initial Medication Adherence (IMA) intervention, a complex, multidisciplinary intervention to improve initiation and adherence to CVD and diabetes treatments, was modelled. To increase the acceptability of the intervention, discussion groups were conducted with GPs, nurses, pharmacists, social workers, cardiologists, endocrinologists and internists, who made suggestions for refinement, described its limitations and anticipated barriers to its implementation.

To assess the feasibility of the IMA intervention and the evaluation design, a pilot trial with an embedded process evaluation was conducted as part of phase II, or feasibility phase (ClinicalTrials.gov, NCT05094986). Detailed methods and results of the pilot study are presented elsewhere.[34] The intervention components and implementation strategies were considered feasible and acceptable. However, barriers to the engagement of professionals, training for professionals and intervention decision aids

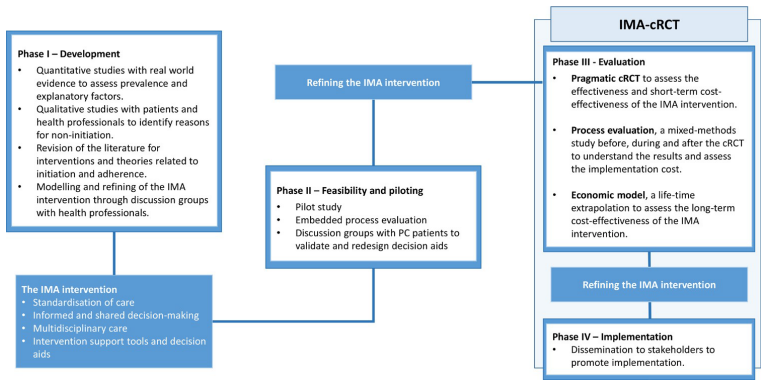

Figure 1 IMA intervention phases: development, feasibility, evaluation and implementation. cRCT, cluster randomised controlled trial; IMA, initial medication adherence; PC, primary care.

were identified. These results were used to refine the IMA intervention prior to the definitive cluster-randomised controlled trial (cRCT).

The process evaluation outlined in this paper is integrated into the IMA-cRCT, phase III or evaluation phase: a pragmatic cRCT with two parallel groups that aims to evaluate the effectiveness, cost-effectiveness and understand the impact of the IMA intervention. Detailed cRCT methods (ClinicalTrials.gov, NCT05026775) are described elsewhere.[35] The trial is being conducted in 24 PC centres in Catalonia (May 2022–September 2023), randomised to the control (usual care) or the intervention group (the IMA intervention), as well as community pharmacies in the area covered by PC centres of the intervention group. Professionals in the intervention group were trained on the IMA intervention and will apply it to all patients receiving a new prescription for lipid-lowering medication, antihypertensive medication, antiplatelet medication and/or antidiabetic medication during the study period (7 months).[35] The primary outcome of the trial is the rate of initiation. Secondary outcomes include other measures of adherence (implementation and persistence), clinical outcomes and cost-effectiveness.

The IMA intervention

The IMA intervention is founded on the theoretical model for non-initiation.[7 33] According to this model, the decision to initiate pharmacological treatments is multifactorial, and it is influenced by the patients' beliefs about the disease and treatment options, the existence of non-pharmacological measures, the interaction with healthcare professionals (GPs, nurses and pharmacists) and the context, cultural factors and health literacy of the patient.[7 33] The model suggests that an intervention that improves health literacy, helping the patient to understand the risks of the disease and the benefits and risks of treatment options and involves the patient in the decision-making process could improve initiation and long-term adherence.[7 33] The model also highlights the influence of healthcare professionals and the importance of multidisciplinary recommendations when a new pharmacological treatment is prescribed.

As illustrated by the non-initiation model, the IMA intervention is expected to work at the intrapersonal level by increasing patients' health literacy and empowerment and the interpersonal level by promoting SDM through the interaction between the patient and healthcare professionals and supporting the standardisation of clinical practice among all the PC professionals that interact with the patient (GPs, nurses and pharmacists).

During a consultation, the GP applies the principles of SDM.[27 28] They define the problem and decision at hand by providing information about the disease and treatment options and exploring the patient's perspectives, concerns and expectations supported by decision aids. Both the GP and patient have coresponsibility to negotiate a decision before the prescription of a new CVD or diabetes pharmacological treatment is issued. When necessary, the decision is delayed to offer the patient the opportunity to reflect on it, obtain complementary information (reliable decision aids are recommended as sources of information) and/or discuss the decision with others (including nurses and pharmacists). When consulted by patients, nurses and pharmacists explore patients' queries regarding new CVD or diabetes medication prescriptions, or those of patients considering the use of medication, and use decision aids to provide information support, standardising the message from all healthcare professionals and improving interdisciplinary collaboration. In the case that the patient changes their mind about the use of medication, nurses and pharmacists refer them back to the GP. The IMA intervention is a one-shot intervention at the time of a new prescription. The dosage, or times the intervention has been applied to the same patient, varies on the healthcare professionals (GPs, nurses and pharmacists) consulted during and after a new prescription and whether they are participating in the trial, with the minimum dose being one time (when the prescription is issued).

The logic model illustrated in figure 2 shows how the intervention would primarily influence the adequate use of treatment (primary and secondary adherence) and ultimately impact the health outcomes of the population under study, as well as influence the interdisciplinary collaboration between professionals and patient–healthcare professional interaction. The IMA intervention has three main inputs as part of the implementation strategy (figure 2). First, *professional engagement* increases professionals' interest and promotes participation. PC and pharmacy stakeholders, including scientific organisations, healthcare quality agencies, official colleges, and managers and directors of PC centres were first contacted and informed. Thereafter, professionals were informed at PC centres, community pharmacies and official colleges. Second, the IMA intervention *training* was provided to professionals (GPs, nurses and pharmacists) in two sessions of 3 hours each. Professionals were trained together to promote standardisation and mutual understanding of each other's role and to generate bonds. The first session covers the basics of the intervention: the evidence on non-initiation, the practical aspects of the intervention, the role of each professional and the intervention decision aids. The second session was designed by an SDM expert and focuses on SDM and communication skills. Third, the IMA intervention *decision aids* promote discussion of all relevant topics with the patient and SDM (increasing adherence to the intervention and standardisation of practice). *Leaflets* (one for each pharmacotherapeutic group) contain information on the risks of the disease, the risks and benefits of pharmacological and non-pharmacological treatments and key messages to encourage the patients to express their opinions and share their uncertainties with the professional, as well as other reliable sources of information (including other healthcare professionals and a website). The *website* www.iniciadores.es is divided into pathologies and

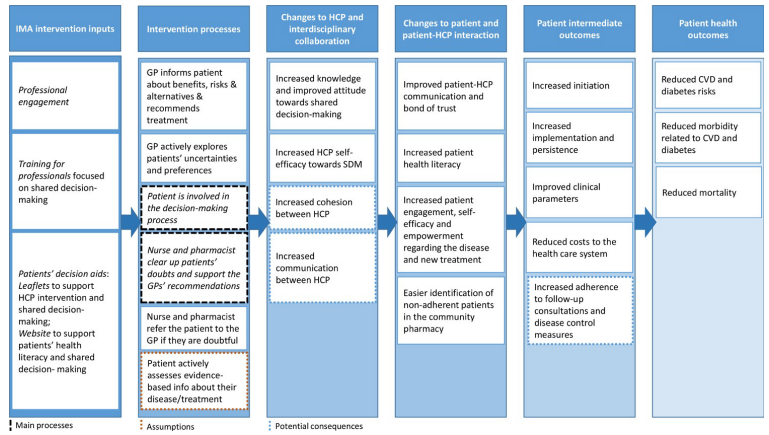

Figure 2 IMA intervention logic model. CVD, cardiovascular disease; GP, general practitioner; HCP, healthcare professional; IMA, Initial Medication Adherence.

pharmacological treatments, with extended information on the disease, treatments and additional links to other reliable websites (such as those run by the national health system). The content of the leaflets and website are reliable and are endorsed by public healthcare organisations.

The IMA intervention in the context of the COVID-19

In the case of a COVID-19 outbreak, when a new treatment is recommended during a telephone consultation, the doctor sends the leaflet through email and refers the patient to the website (where leaflets are also available). Additionally, the patient can collect the leaflet from participating pharmacies when collecting the medication. In this case, a follow-up telephone consultation (GP or nurse) is recommended a week after the prescription is issued to explore patients' queries and concerns.

Process evaluation

Randomised controlled trials (RCTs) have been presented as the gold standard for evaluating effectiveness and efficiency of complex interventions.[36] Complex interventions combine multiple components that interact with each other, involve several stakeholders and generally require a behavioural change by those that implement and receive the intervention.[30 31 36] However, RCTs typically have rigid designs, tend to focus mainly on outcome effect and fail to explain how the intervention was implemented and in what context, what the active components were and for whom it worked.[30 31] Process evaluations embedded in pragmatic RCTs are needed to understand how the intervention was delivered, how different components interact and work, how they influence the intervention's primary and secondary outcomes and its effectiveness.[37]

Ultimately, some very efficient interventions can be difficult to translate into routine practice, especially when the intervention cost is high because it requires organisational and behavioural changes. Assessing the cost of implementation, costs of the strategies to put in practice and sustain an intervention, provides decision makers with relevant information when evaluating the translation of the intervention into routine clinical practice.[38]

Aims and objectives

This process evaluation aims to understand the implementation and mechanism of action of the IMA intervention and how the context affects them and therefore understand and explain the results of the cRCT in terms of effectiveness and cost-effectiveness, refine the IMA intervention and provide information on replicability and generalisability to other contexts.

The objectives of the study are to:

1. Assess the extent to which the IMA intervention was implemented as intended (fidelity) and understand how the IMA intervention becomes integrated into routine healthcare practice (implementation).
2. Identify and understand the active mechanisms of the IMA intervention (mechanisms of impact).
3. Understand the context where the IMA intervention is implemented and identify factors that can influence the IMA intervention's active mechanisms (context).
4. Assess the cost of implementing the IMA intervention.

METHODS AND ANALYSIS

Study design and framework of the process evaluation

A mixed-methods process evaluation study will be undertaken, involving analysis of real-world practice evidence, data collection forms, field diaries and interviews with professionals and patients. The MRC guideline for process evaluations of complex interventions was used to guide the design of this evaluation.[37] It focuses on three domains that interact with each other: (1) the implementation of the intervention; (2) the mechanisms of the intervention that affect the outcomes; and (3) the characteristics of the contexts that can influence the previous domains in the intervention group and control group

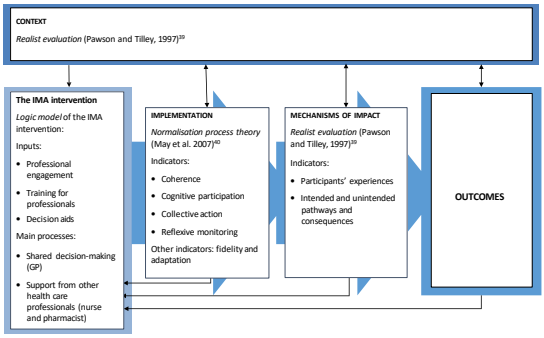

Figure 3 Domains and theoretical framework of the IMA-cRCT process evaluation (adapted from Moore *et al*[37]). GP, generalpractitioner; IMA, Initial Medication Adherence.

contextual factors that could influence the outcomes of the cRCT.

Figure 3 shows the interaction between the three domains and the theoretical frameworks used to evaluate them.[39 40] Implementation will be assessed through the normalisation process theory,[41 42] which explains how an intervention becomes routinely integrated into everyday healthcare practice by assessing four indicators: coherence, cognitive participation, collective action and reflexive monitoring.[42] The evaluation of the mechanisms of impact and the context of the intervention will be assessed following the recommendations of realist evaluation[39] to explain how active mechanisms of the intervention generate an effect, for whom and under what circumstances.[37 39] It takes into account the expected and unexpected consequences that may result from the activation of different hypothesised mechanisms in different contexts and end up generating different effects.[37 39]

Additionally, the Stages of Implementation Completion framework will be used, and the Cost of Implementing New Strategies tool will be adapted to the IMA intervention[43] to assess the costs of implementation when translating the IMA intervention into other settings.

The process evaluation will be conducted by the IMA-cRCT research team. This is a multidisciplinary team formed by researchers with expertise in quantitative and qualitative research and PC professionals. The main components of the intervention are not expected to be adapted during the trial, although the dynamic approach of this pragmatic evaluation gives the design the flexibility to react to changes if needed.

Setting and participants

The IMA intervention will be implemented in PC centres and community pharmacies in Catalonia (Spain). PC is the gateway to the healthcare system and where the vast majority of the prescriptions for long-term treatments are issued.[44] Patients have an assigned GP and nurse. GPs monitor and prescribe treatments and nurses follow-up the patient. Medications are electronically prescribed, and patients can fill them only at community pharmacies where the pharmacist can check the prescription directly through the electronic prescription system.[44] A warning appears when a new platelet aggregation inhibitors excluding heparin and insulin is going to be dispensed. Full details on the cRCT setting are provided elsewhere.[35]

The IMA-cRCT will recruit 24 PC centres, around 300 professionals and 4000 patients.[35] The sampling strategy of the process evaluation is conditioned by the cluster sampling design of the cRCT and is detailed below.

Intervention group

Professionals

GPs, nurses and pharmacists from all PC centres will have feedback questionnaires sent to them, but only professionals from six to eight PC centres will be recruited to participate in the qualitative research due to time restrictions. The recruitment will be based on a theoretical sampling strategy according to the type of PC centre (size and location) and taking into account predictors of non-initiation (socioeconomic level of the area, rurality and the proportion of immigrant population). Professionals from the recruited PC centres will be invited to participate in the interviews by phone calls following maximum variation sampling according to role and type of contract, years of experience in PC, sex and age, nationality and owner or not of the pharmacy.

Each PC centre will have a study coordinator, a GP or nurse. The coordinator will be the link with the research team, promoting the implementation of the intervention, coordinating the distribution of intervention materials and informing the research team of external events that may influence the correct implementation of the intervention and development of the trial.

Patients

The coordinator of the PC centres will identify patients that were prescribed a new treatment for CVD or diabetes during the study period and invite them to participate in an interview. They will be asked to follow a variation sampling strategy based on medication prescribed and treatment being initiated or not. In addition, we will follow a maximum variation criterion based on the previous aspects, educational and socioeconomic level, sex and age. Once patients agree to participate, the research team will contact them by phone calls to provide further information about the study.

Control group

The coordinator from the control group PC centres will be contacted and interviewed by phone calls to explore any external events and contextual factors that could have influenced outcomes on the usual care groups and, therefore, the results of the cRCT.

Data collection

The specific objectives and research questions, as well as the data collection method used to assess the first three domains are presented in table 1 (implementation), table 2 (mechanisms of impact) and table 3 (context). Specific quantitative and qualitative methods used to meet the process evaluation aims and objectives are described for each domain.

Implementation

Data will be collected on intervention fidelity to identify how consistent the implementation of the intervention was with the initial plan and if it required any adaptations during the trial, as well as assess the implementation into routine practice (table 1). Fidelity will be assessed through quantitative data on professional interaction and the intervention implementation plan (PC centres and professional engagement, training attendance, use of intervention tools and follow-up consultations). Adaptations will be assessed using quantitative data from professionals' feedback questionnaires and qualitative data from the coordinator's field diary.

Additionally, qualitative methods will be used to evaluate the implementation of the IMA intervention into routine PC centre practice. Interviews with professionals will assess the perceived need and adequacy of the IMA intervention as well as measures used to appraise it. Professionals' feedback questionnaires will collect data on professionals' attitudes towards the IMA intervention before and after the trial and how it is operationalised and integrated into routine practice.

Mechanisms of impact

Qualitative methods will be used to identify and understand the active mechanisms of the IMA intervention that bring about any effects and explains the intervention's logic (table 2). Interviews with professionals and patients will explore their perspectives and experiences with the intervention, potential changes to professionals' attitudes and interdisciplinary collaboration, changes to patients' knowledge, behaviour and interaction with professionals and any expected or unexpected consequences.

Context

Data on the context of both the intervention and control groups will be collected (table 3). Demographic data from the PC centres will be extracted from Catalan health system records. Interviews will be carry out with professionals and patients to explore the context of the PC centre and examine in which circumstances mechanisms of impact work and therefore influence the study outcomes.

Cost of implementation

To assess the cost of implementing the intervention, all human and material resources used in each stage of the implementation process to put the IMA intervention into practice will be collected and taken into account.

Data collection methods

Quantitative methods

Monitoring data

Data will be collected from the operative records, website records and clinical records from real-world databases in the public PC system in Catalonia (System for the Development of Research in Primary Care).[45] Data will be structured and descriptively summarised to assess fidelity, context and cost of implementation through:

- Professional engagement: number of PC centres and professionals that decline to participate after the information session.
- Training attendance rate.
- Intervention tools usage rate: website indicators (number of views, percentage of rebound, mean view time and depth) and number of times the leaflet was downloaded.
- Follow-up consultation rate at the PC centre after a new prescription.
- Demographic records: PC centre size and location, number of professionals, socioeconomic level of the area, rurality, average age of the population and the proportion of the immigrant population.
- Implementation costs: human resources based on time invested and professional category, and consumable materials based on units used.

Professionals' questionnaires

Professionals will be asked to complete post-training questionnaires to evaluate the quality of the training and professionals' understanding of SDM. Furthermore, questionnaires will be sent by email to professionals during and after the cRCT. These will provide measures about adaptation and implementation, as well as professionals' attitudes towards the intervention and its usefulness in clinical practice.

Table 1 Implementation domain: specific objectives, research questions and data sources and collection methods

Implementation	Specific objectives	Research questions	Data source	Data collection
Fidelity and adaptation	Understand the extent to which the IMA intervention was implemented as intended. 1. How is the IMA intervention implemented?	1.1. How consistent is the intervention implementation plan?	Operative records, website records and real-world databases (patients' clinical records).	Monitoring data extraction and questionnaires.
		1.2. Did the IMA intervention require any adaptations during the cRCT?	Professionals.	Questionnaires and field diaries.
Coherence	Understand how professionals make sense of the IMA intervention. 2. What is the IMA intervention for professionals?	2.1. How is the IMA intervention conceptualised by professionals?	Professionals.	Interviews.
		2.2. What are the professionals' perspectives and attitudes towards the use and usefulness of the IMA intervention?	Professionals.	Questionnaires and interviews.
Cognitive participation	Understand how professionals engage and commit with the IMA intervention. 3. Who implements the IMA intervention?	3.1. How do professionals engage and commit with the IMA intervention?	Professionals.	Questionnaires and interviews.
		3.2. What factors promote or inhibit professionals' participation and commitment?	Professionals.	Interviews.
Collective action	Understand how professionals make use and execute the intervention as part of their clinical practice. 4. How is the IMA intervention operationalised?	4.1. How are the resources of the IMA intervention structured and used?	Professionals.	Questionnaires and interviews.
		4.2. To what extend and why have professionals integrated the intervention into their clinical practice?	Professionals.	Questionnaires and interviews.
		4.3. To what extent and why do participants enact the IMA intervention?	Professionals.	Questionnaires and interviews.
Reflexive monitoring	Understand how professionals assess and comprehend the effect of the intervention on their clinical practice. 5. How is the IMA intervention understood?	5.1. How the professionals appraise the IMA intervention and its effects?	Professionals.	Interviews and questionnaires.
		5.2. How the professionals value the IMA intervention in comparison with standard practice?	Professionals.	Interviews and questionnaires.

Professionals: GPs, nurses and pharmacists.
cRCT, cluster-randomised controlled trial; GPs, general practitioners; IMA, Initial Medication Adherence.

Qualitative methods

Field diary

A field diary will be completed by a member of the research team. It will contain field notes from periodic calls (every 2 weeks the first month, and monthly until the study finishes) to the PC centre coordinators. Additionally, field diaries will be completed by each PC centre coordinator. These will include data on any barriers, facilitators or thoughts concerning the organisation and operation of the PC centre or pharmacy and the intervention.

Interviews

Individual semistructured interviews will be conducted during and after the cRCT with professionals to explore their perspectives and experiences after implementing the IMA intervention and with patients to determine their experience with the IMA intervention and SDM and its impact on their behaviour in relation to the treatment. Approximately 30–40 interviews will be carried out with professionals and 20–30 with patients to ensure representativeness. Focus groups will be conducted with

Table 2 Mechanisms of impact domain: specific objectives, research questions and data sources and collection methods

Mechanisms of impact	Specific objectives	Research questions	Data sources	Data collection
Participants' experiences	Understanding the mechanism of the IMA intervention that influences the outcomes and explains its logic.	1. What are the experiences of the participants (professionals and patients) with the intervention?	Professionals and patients.	Interviews.
		2. What attitude and behaviour changes have occurred because of the intervention?	Professionals and patients.	Interviews.
Intended and unintended consequences	Understanding anticipated and unanticipated consequences of the IMA intervention and its effects on the outcomes.	3. Did the intervention lead to anticipated pathways or consequences? 4. Did the intervention lead to any unanticipated pathways or consequences?	Professionals and patients.	Interviews and field diary.

Professionals: GPs, nurses and pharmacists.
GPs, general practitioners; IMA, Initial Medication Adherence.

professionals after the cRCT to understand the intervention's impact mechanisms and explore professionals' opinions of the IMA intervention and its integration into the PC centre and pharmacy practice. Moreover, we will explore the perceived barriers and facilitators to implementation and continuity of the intervention in PC and in particular those related to COVID-19 outbreaks. About three to four focus groups will be conducted with professionals from varying PC centres. Interviews and focus groups will be recorded, anonymised and transcribed by the research team before analysis.

Different types of data will be collected at different time points: before, during, and after the trial to account for the intervention dynamics and to comprehend how the context and the intervention adapt to one another (figure 4).

Analysis

The analysis of process evaluation data will be performed throughout the study and at the end. Quantitative data will be analysed using descriptive statistics (ie, counts, proportions and means) and regression models using Stata V.17 to describe how the intervention was implemented overall and explore variations between PC centres and pharmacies.

Qualitative data will be analysed using the principles of framework analysis by qualitative researchers.[46 47] This will help researchers to organise large amounts of data systematically and focus the analysis as a group (PC centres) and as individuals (professional and patient). Field notes (from diaries) and transcripts from the interviews will be included as narrative data. After a process of familiarisation with the data (listening to recordings and reading

Table 3 Context domain: specific objectives, research questions and data sources and collection methods

Context	Specific objectives	Research questions	Data sources	Data collection
Intervention group	Understanding the conditions in which the intervention is implemented that can be relevant to the process of the intervention mechanisms.	1. What is the context of the PC centres?	Professionals, patients, demographic records.	Questionnaires and monitoring data extraction.
		2. What mechanisms of the IMA intervention and consequences change depending on the context, and what can explain these differences?	Professionals and patients.	Interviews and field diary.
		3. Was there any contextual factor related to the community, PC centre, professional or patient that could have influenced the outcomes of the cRCT?	Professionals.	Interviews.
Control group	Evaluate contextual and organisational changes, and understand the factors that could influence the process.	4. Was there any contextual factor related to the community, PC centre, professional or patient that could have influenced the outcomes of the cRCT?	Professionals.	Interviews.

Professionals: GPs, nurses and pharmacists.
cRCT, cluster-randomised controlled trial; GPs, general practitioners; IMA, Initial Medication Adherence; PC, primary care.

	STUDY PERIOD		
	Pre-trial*	Trial*	Post-trial*
IMA-cRCT			
Healthcare professionals: training	X		
Healthcare professionals: implementation		X	
Real-World Data (patients' clinical records): Effectiveness and Cost-Effectiveness Evaluation			X
PROCESS EVALUATION			
Monitoring data	→	→	→
Healthcare professionals' questionnaires	X	X	X
Field diary		→	
Healthcare professionals' interviews		X	X
Patients' interviews		X	X

Figure 4 Process evaluation timeline. *Pretrial: September 2021 until February 2022; trial: March 2022 until September 2022; Post-trial: September 2022 until December 2022. cRCT, cluster randomised controlled trial.

field notes), the researchers will use thematic content analysis[48] to generate a coding framework following a mixed-method approach: deductive and inductive. The coding frameworks generated by the researchers will be put in common until a final one is created and applied to all the data. Data will be organised by cases and categories and will be compared within cases (PC centres) and between cases (professionals and patients) while mapping and interpreting it. NVivo software will be used to manage the data.

Triangulation of results

Quantitative and qualitative data from the process evaluation will be analysed separately and then interpreted in combination.[49 50] First, two researchers will combine and compare the results of both, quantitative and qualitative, analyses independently. Then, a final summary of key findings will be produced jointly by the two researchers, and if there are any unresolved disagreements, another researcher will be involved. The final summary of key findings will be presented to the rest of the research team for review and clarification. The combined interpretation of results will allow us to generate deeper insights than use of either of the methods alone.

Additionally, process and effectiveness evaluation results will be integrated. Analyses will be performed separately, and once both analyses are done, the results will be combined. Combining process and effectiveness results will facilitate better understanding and interpretation of the IMA-cRCT outcomes.

Patient and public involvement

Patient and public were not involved in setting the research questions and outcomes of the no-initiation project, yet they have been closely involved in the development and design of the IMA intervention and its support tools and will be informed of the results through the project website suitable for a non-specialist audience.

ETHICS AND DISSEMINATION

The IMA-cRCT and its integrated process evaluation were approved by the Research Ethics Comittee (Comitè Ètic d'Investigació amb medicaments (CEIm)) at IDIAP Jordi Gol, code CEIm 21/051 P. The IMA-cRCT is a low-intensity intervention clinical trial where groups of subjects are allocated to the intervention and control groups. Informed consent from patients participating in the clinical trial will be obtained by simplified means, and it fulfils the conditions described in Regulation (EU) No 536/2014[51] and the Real Decreto 1090/2015.[52] Details of how informed consent will be obtained by simplified means are described somewhere else.[35] Participation in the process evaluation is entirely voluntary. As approved by the CEIm, all healthcare professionals participating in the process evaluation will have signed an informed consent prior to the trial commencement agreeing to have feedback questionnaires sent by mail and to take part in an interview if invited to do so towards the end of the trial. Patients participating in the process evaluation will sign an informed consent after the recruitment and prior to the beginning of interviews. All participants have the right to refuse to participate and to withdraw from the study at any time.

Findings will be disseminated through publications and conferences, as well as presentations to healthcare professionals and stakeholders from healthcare organisations in Catalonia. Full details of the dissemination strategy are outlined in the main trial protocol.[35]

Author affiliations
[1]Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Parc Sanitari Sant Joan de Deu, Institut de Recerca Sant Joan de Deu, St Boi de Llobregat, Catalunya, Spain
[2]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Universitat Autonoma de Barcelona, Bellaterra, Catalunya, Spain
[3]Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Catalunya, Spain
[4]Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Barcelona, Spain
[5]Unitat de Suport a la Recerca Regió Metropolitana Sud, Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Catalunya, Spain
[6]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Comunidad de Madrid, Spain
[7]Primary Care Centre Bartomeu Fabrés Anglada, Institut Català de la Salut Gerència Territorial Metropolitana Sud, Barcelona, Catalunya, Spain

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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ORCID iD

Montserrat Gil-Girbau http://orcid.org/0000-0002-4396-6492

REFERENCES

1 Vrijens B, De Geest S, Hughes DA, *et al*. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
2 Hutchins DS, Zeber JE, Roberts CS, *et al*. Initial medication Adherence-Review and recommendations for good practices in outcomes research: an ISPOR medication adherence and persistence special interest group report. *Value Health* 2015;18:690–9.
3 Lemstra M, Nwankwo C, Bird Y, *et al*. Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Prefer Adherence* 2018;12:721–31.
4 Zeber JE, Manias E, Williams AF, *et al*. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR medication adherence & persistence special interest group. *Value Health* 2013;16:891–900.
5 Aznar-Lou I, Fernández A, Gil-Girbau M, *et al*. Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. *Br J Clin Pharmacol* 2017;83:1328–40.
6 Menckeberg TT, Bouvy ML, Bracke M, *et al*. Patients' understanding of the reasons for starting and discontinuing inhaled corticosteroids. *Br J Clin Pharmacol* 2008;66:255–60.
7 Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, *et al*. Reasons for medication non-initiation: a qualitative exploration of the patients' perspective. *Res Social Adm Pharm* 2020;16:663–72.
8 World Health Organization. *Adherence to long-term therapies: evidence for action [Internet]*. Geneva: World Health Organization, 2003. https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf?sequence=1&isAllowed=y
9 Bouchard M-H, Dragomir A, Blais L, *et al*. Impact of adherence to statins on coronary artery disease in primary prevention. *Br J Clin Pharmacol* 2007;63:698–708.
10 Bitton A, Choudhry NK, Matlin OS, *et al*. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. *Am J Med* 2013;126:357.e7–357.e27.
11 Xu T, Yu X, Ou S, *et al*. Adherence to antihypertensive medications and stroke risk: a dose-response meta-analysis. *J Am Heart Assoc* 2017;6:e006371.
12 Kim Y-Y, Lee J-S, Kang H-J, *et al*. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. *Sci Rep* 2018;8:12190.
13 Aznar-Lou I, Fernández A, Gil-Girbau M, *et al*. Impact of initial medication non-adherence on use of healthcare services and sick leave: a longitudinal study in a large primary care cohort in Spain. *Br J Gen Pract* 2017;67:e614–22.
14 Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e016982.
15 Derose SF, Green K, Marrett E, *et al*. Automated outreach to increase primary adherence to cholesterol-lowering medications. *JAMA Intern Med* 2013;173:38–43.
16 Fischer MA, Choudhry NK, Bykov K, *et al*. Pharmacy-based interventions to reduce primary medication nonadherence to cardiovascular medications. *Med Care* 2014;52:1050–4.
17 Fischer MA, Jones JB, Wright E, *et al*. A randomized telephone intervention trial to reduce primary medication nonadherence. *J Manag Care Spec Pharm* 2015;21:124–31.
18 O'Connor PJ, Schmittdiel JA, Pathak RD, *et al*. Randomized trial of telephone outreach to improve medication adherence and metabolic control in adults with diabetes. *Diabetes Care* 2014;37:3317–24.
19 Kerner DE, Knezevich EL. Use of communication tool within electronic medical record to improve primary nonadherence. *J Am Pharm Assoc* 2017;57:S270–3.
20 McCarthy ML, Ding R, Roderer NK, *et al*. Does providing prescription information or services improve medication adherence among patients discharged from the emergency department? A randomized controlled trial. *Ann Emerg Med* 2013;62:212–23.
21 Tedla YG, Bautista LE. Factors associated with false-positive self-reported adherence to antihypertensive drugs. *J Hum Hypertens* 2017;31:320–6.
22 Stirratt MJ, Dunbar-Jacob J, Crane HM, *et al*. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med* 2015;5:470–82.
23 Saheb Kashaf M, McGill ET, Berger ZD. Shared decision-making and outcomes in type 2 diabetes: a systematic review and meta-analysis. *Patient Educ Couns* 2017;100:2159–71.
24 Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, *et al*. Interventions to support shared decision making for medication therapy in long term conditions: a systematic review. *Patient Educ Couns* 2020;103:254–65.
25 Coronado-Vázquez V, Canet-Fajas C, Delgado-Marroquín MT, *et al*. Interventions to facilitate shared decision-making using decision AIDS with patients in primary health care: a systematic review. *Medicine* 2020;99:e21389.
26 Milky G, Thomas J. Shared decision making, satisfaction with care and medication adherence among patients with diabetes. *Patient Educ Couns* 2020;103:661–9.
27 Elwyn G, Edwards A, Kinnersley P, *et al*. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. *Br J Gen Pract* 2000;50:892–9.
28 Elwyn G, Frosch D, Thomson R, *et al*. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012;27:1361–7.
29 Légaré F, Adekpedjou R, Stacey D, *et al*. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev* 2018;7:CD006732.
30 Craig P, Dieppe P, Macintyre S, *et al*. Developing and evaluating complex interventions: the new medical Research Council guidance. *BMJ* 2008;337:a1655.
31 Skivington K, Matthews L, Simpson SA, *et al*. Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. *Health Technol Assess* 2021;25:1–132.
32 Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, *et al*. Initiation and single dispensing in cardiovascular and insulin medications: prevalence and explanatory factors. *Int J Environ Res Public Health* 2020;17:3358.
33 Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, *et al*. Non-initiation of prescribed medication from a Spanish health professionals' perspective: a qualitative exploration based on Grounded theory. *Health Soc Care Community* 2022;30:e213–21.
34 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, *et al*. Improving initial medication adherence to cardiovascular diseases and diabetes treatments in primary care: pilot trial of a complex intervention 2022.
35 Sánchez-Viñas A, Corral-Partearroyo C, Gil-Girbau M, *et al*. Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study). *BMC Prim Care* 2022;23:170.
36 Oakley A, Strange V, Bonell C, *et al*. Process evaluation in randomised controlled trials of complex interventions. *BMJ* 2006;332:413–6.
37 Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: medical Research Council guidance. *BMJ* 2015;350:h1258.
38 Eisman AB, Kilbourne AM, Dopp AR, *et al*. Economic evaluation in implementation science: making the business case for implementation strategies. *Psychiatry Res* 2020;283:112433.
39 Pawson R, Tilley N. *Realist evaluation*. London: SAGE, 1997: 256.
40 May C, Finch T, Mair F, *et al*. Understanding the implementation of complex interventions in health care: the normalization process model. *BMC Health Serv Res* 2007;7:148.
41 Elwyn G, Légaré F, van der Weijden T, *et al*. Arduous implementation: does the normalisation process model explain why it's so difficult to

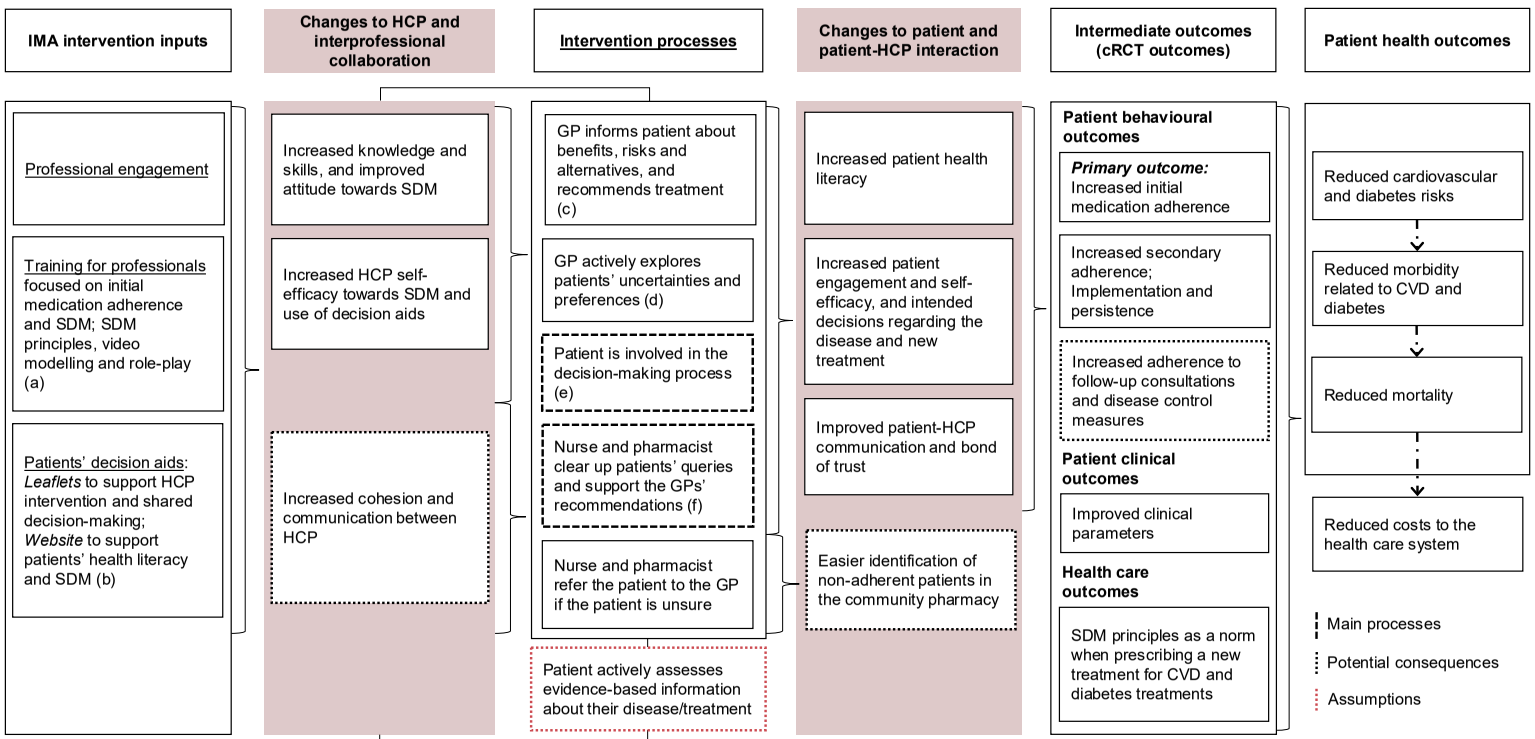
embed decision support technologies for patients in routine clinical practice. *Implement Sci* 2008;3:57.
42 May C, Finch T. Implementing, embedding, and integrating practices: an outline of normalization process theory. *Sociology* 2009;43:535–54.
43 Saldana L, Chamberlain P, Bradford WD, *et al*. The cost of implementing new strategies (coins): a method for mapping implementation resources using the stages of implementation completion. *Child Youth Serv Rev* 2014;39:177–82.
44 Bernal-Delgado E, Garcia-Armesto S, Oliva J, *et al*. Spain: health system review. *Health Syst Transit* 2018;20:1–179.
45 SIDIAP. Sistema d'Informació per al desenvolupament de la Investigació en Atenció Prim ria [Internet]. Available: https://www.sidiap.org/
46 Russell J, Berney L, Stansfeld S, *et al*. The role of qualitative research in adding value to a randomised controlled trial: lessons from a pilot study of a guided e-learning intervention for managers to improve employee wellbeing and reduce sickness absence. *Trials* 2016;17:396.
47 Gale NK, Heath G, Cameron E, *et al*. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013;13:117.
48 Green J, Thorogood N. *Qualitative methods for health research*. London: SAGE, 2018: 440.
49 O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. *BMJ* 2010;341:c4587.
50 Tonkin-Crine S, Anthierens S, Hood K, *et al*. Discrepancies between qualitative and quantitative evaluation of randomised controlled trial results: achieving clarity through mixed methods triangulation. *Implement Sci* 2016;11:66.
51 European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. [Internet]. Available: https://eur-lex.europa.eu/legal content/EN/TXT/?uri=celex%3A32014R0536
52 Gobierno de España. Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos. [Internet]. Available: https://www.boe.es/diario_boe/txt.php?id=BOE-A-2015-14082

4.3.1 Main results overview – Scientific article 2

Following the pilot, the IMA intervention and its implementation strategies were refined, and a logic model was developed to explain its theory of change. Figure 6 illustrates how the intervention was expected to produce effects, progressing from inputs and processes linked to Behaviour Change Techniques (BCTs) [105,106] to long-term outcomes. Three main implementation strategies: early *professional engagement*, *shared decision-making training*, and *patient decision aids (leaflets and website)* supported the core processes: GPs discussing treatment options, benefits and risks while actively exploring patients' concerns and preferences; patients being invited to participate in the decisions; and nurses and pharmacists reinforcing the information and resolving doubts. Combined, these actions aimed to standardise information and embed shared decision-making throughout the prescribing pathway.

Two mechanisms of action were hypothesised. First, *changes to professionals*—greater knowledge and skills in shared decision-making, increased self-efficacy, and interprofessional collaboration. Second, *changes to patients and their interaction with professionals*—improved health literacy, increased decision engagement by explicitly discussing options and aligning decisions with patient values, and a stronger bond of trust. Together, these mechanisms were expected to improve intermediate outcomes: medication initiation, secondary adherence, and adherence to disease control measures. Over time, these behavioural changes were anticipated to lead to better clinical outcomes and ultimately reduce cardiovascular and diabetes risk, while normalising shared decision-making as the standard approach to new prescriptions for CVD and diabetes in primary care.

Figure 6. The IMA intervention logic model.



Intervention Behaviour Change Techniques (BCTs) [105]: (a) 4.1 Instruction of how to perform a behaviour, 6.1. Demonstration of the behaviour and 8.1. Behavioural practice/rehearsal; (b) 12.5. Adding objects to the environment; (c) 5.1. Information about health consequences and 9.1. Credible source; (d) 1.2. Problem solving; (e) 1.9. Commitment; (f) 3.1. Social support (unspecified).

The logic model was revised and evolved throughout the project while maintaining the IMA intervention's core elements; the version shown here is the model evaluated in phase III.

cRCT: cluster-Randomised Controlled Trial; CVD: Cardiovascular Diseases; GP: General Practitioner; HCP: Healthcare Professionals; SDM: Shared Decision-Maki

To assess the intervention implementation and the underlying theory of change under real-world conditions, a mixed-methods process evaluation embedded within the pragmatic cRCT was designed. The integration of implementation and effectiveness outcomes was intended to enhance the understanding and interpretation of the trial results by understanding how the intervention was implemented, how different components interacted and worked and how they influenced the intervention's primary and secondary outcomes, to finally support the translation of the IMA intervention into routine healthcare practice [85].

4.4 Scientific article 3

OBJECTIVE 3: Process evaluation

Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation

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Corral-Partearroyo C, Sánchez-Viñas A, Peñarrubia-María MT, Gil-Girbau M, Aznar-Lou I, Palma-Vasquez C, Gallardo-González C, Olmos-Palenzuela MC, Rubio-Valera M

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ORIGINAL RESEARCH

OPEN ACCESS

Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation

Carmen Corral-Partearroyo ,[1,2,3] Alba Sánchez-Viñas ,[1,3,4] María Teresa Peñarrubia-María,[1,3,5] Montserrat Gil-Girbau ,[1,6] Ignacio Aznar-Lou,[1,3] Claudia Palma-Vasquez ,[1,6] Carmen Gallardo-González ,[1,5,6] María del Carmen Olmos-Palenzuela ,[1,5,6] Maria Rubio-Valera [1,3,4]

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For numbered affiliations see end of article.

Correspondence to
Dr Maria Rubio-Valera;
maria.rubio@sjd.es

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ABSTRACT

Introduction The initial medication adherence (IMA) intervention aims to improve adherence to cardiovascular disease (CVD) and diabetes treatments in primary care (PC) through standardised shared decision-making (SDM) and healthcare professional (HCP) collaboration (general practitioners (GPs), nurses and pharmacists). This study assessed the intervention's implementation (strategies, fidelity and integration into routine practice—based on the Normalisation Process Theory), mechanisms of action and the role of context.

Methods The IMA-cRCT was an effectiveness-implementation cluster-Randomised Controlled Trial involving 24 Spanish PC centres (>300 HCP; >3000 patients) based on real-world evidence. This nested process evaluation used quantitative (monitoring data; HCP questionnaires) and qualitative methods (field diaries; 36 semistructured individual interviews and two focus groups (19 patients, 28 HCPs)). Quantitative data explored implementation and context and were analysed descriptively, while qualitative data examined implementation, mechanisms of action and context and were analysed using framework analysis. Both analyses were integrated for interpretation.

Results Intervention implementation fidelity (6.5/10) and normalisation into clinical practice (7.6/10) were adequate, particularly regarding SDM and use of decision aids. HCPs recognised the importance of SDM, although some assumed it was already part of routine practice. The anticipated mechanisms of action were moderately supported. HCPs' knowledge and attitudes towards SDM improved as they acknowledged its relevance to practice. Some patients reported participation in decision-making, while others preferred the GP to decide on their behalf. Patients found leaflets helpful for understanding information. Contextual factors influencing the intervention were mainly organisational, such as lack of time and familiarity with SDM.

Conclusions The interprofessional SDM-based IMA intervention was considered beneficial for patients and HCPs, with adequate implementation fidelity and normalisation into practice. The intervention was important for HCPs, and patients accepted it. However, greater effort is needed to extend SDM throughout healthcare, moving towards patient-centred care. These results have enhanced understanding of SDM interventions and support their refinement for future implementation.

Trial registration number ClinicalTrials.gov, NCT05026775.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Challenges with medication initiation and long-term adherence to chronic treatments can impact disease management and patients' clinical outcomes.

⇒ Patient-centred care interventions are increasingly in the spotlight and show promising results in increasing patient health literacy, satisfaction and autonomy in decision-making for chronic treatments. Yet, evidence on how these interventions are implemented and work remains limited.

Original research

WHAT THIS STUDY ADDS

⇒ This study evaluates the implementation of a shared decision-making (SDM) intervention alongside a cluster-randomised controlled trial (cRCT). These findings promote an in-depth understanding of how the initial medication adherence (IMA) intervention was implemented and worked, and they support the development of evidence-based interventions in healthcare.

⇒ This paper outlines an approach to the design and development of process evaluations of complex interventions and offers a guide to other researchers developing process evaluations for cRCTs based on real-world evidence in primary care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patient-centred care and SDM are viewed positively by both professionals and patients; however, changes to traditional practices and healthcare system structures are needed to facilitate their wider adoption as a care model.

INTRODUCTION

Initial medication adherence (IMA) refers to the starting point 'when the patient takes the first dose of a prescribed medication'.[1] The prevalence of non-initiation varies by medication and context (2–40%)[2–4] and is influenced by prescriber and patient characteristics, their context and disease and treatment perceptions.[2 4–6] Effective patient-centred interventions are needed to support adherence, as it can impact disease management,[7–10] while increasing costs of care.[11] To date, most interventions addressing initiation have been based on patient reminders, none were theory based and all showed a high risk of bias in their evaluation.[12–16]

The IMA intervention was developed to improve initiation and secondary adherence to cardiovascular disease (CVD) and diabetes treatments in primary care (PC).[6 17–22] It is a complex, multidisciplinary, patient-centred intervention that promotes shared decision-making (SDM) when a new prescription is issued. SDM is a healthcare quality standard and shows promise in increasing patient self-efficacy regarding health decisions.[23 24] However, evidence on the effect of SDM on patient health literacy, satisfaction with care and medication adherence is inconclusive.[25–27]

Randomised controlled trials (RCTs) focus on effectiveness evaluations and generally do not describe the intervention implementation process, its mechanisms of action and for whom and in which contexts it works.[28] Process evaluations are essential in determining how intervention components interact to impact outcomes and guiding optimisation of the intervention for future implementation, scalability and generalisation to other contexts.[28] This study presents a process evaluation embedded in the IMA-cluster-RCT (cRCT) which aimed to: (1) assess the implementation of the IMA intervention, implementation strategies, fidelity to intervention protocol and understand how it becomes integrated into PC practice, (2) explain the intervention mechanism of action and (3) identify contextual factors that can influence its implementation and active mechanisms. The results of this process evaluation served to explain the cRCT results and refine the IMA intervention for future implementation. These results are presented and discussed in the effectiveness evaluation paper.[29]

METHODS

Study design

The IMA-cRCT was a type I hybrid effectiveness-implementation trial conducted in 24 PC centres and 37 community pharmacies within the catchment area of the 12 intervention group (IG) centres between March and September 2022, with a 1-year patient follow-up.[21 22 29 30]

The embedded mixed-methods process evaluation was designed following Medical Research Council guidelines for the development and evaluation of complex interventions.[28 31] Therefore, it explored three interactive domains that could influence trial outcomes: (1) *implementation* of the intervention was explored by assessing *implementation strategies* or methods used to adopt the intervention, *fidelity* or the degree to which the intervention was implemented as intended in the original protocol and *normalisation* or processes through which the intervention was integrated into routine practice using quantitative and qualitative methods. Normalisation was assessed using Normalisation Process Theory (NPT) and evaluated four constructs: *coherence* (how professionals define and understand it), *cognitive participation* (how professionals engage and commit to sustaining it), *collective action* (how professionals put it into practice) and *reflexive monitoring* (how professionals assess and monitor it)[32]; (2) the intervention *mechanisms of action* that bring about any effects and explain the intervention logic using qualitative methods; and (3) the *context* that could influence implementation and its active mechanisms using quantitative and qualitative methods.

This study is reported according to the Standards of Reporting Implementation Studies (StaRI) checklist[33] and the Good Reporting of A Mixed Methods Study (GRAMMS) checklist for mixed-methods research.[34]

Intervention

The IMA intervention is a complex multidisciplinary intervention that aims to improve medication adherence and clinical outcomes and reduce cardiovascular risk, based on the non-initiation model[6 19] and the principles of SDM.[23 24] It promotes health literacy and

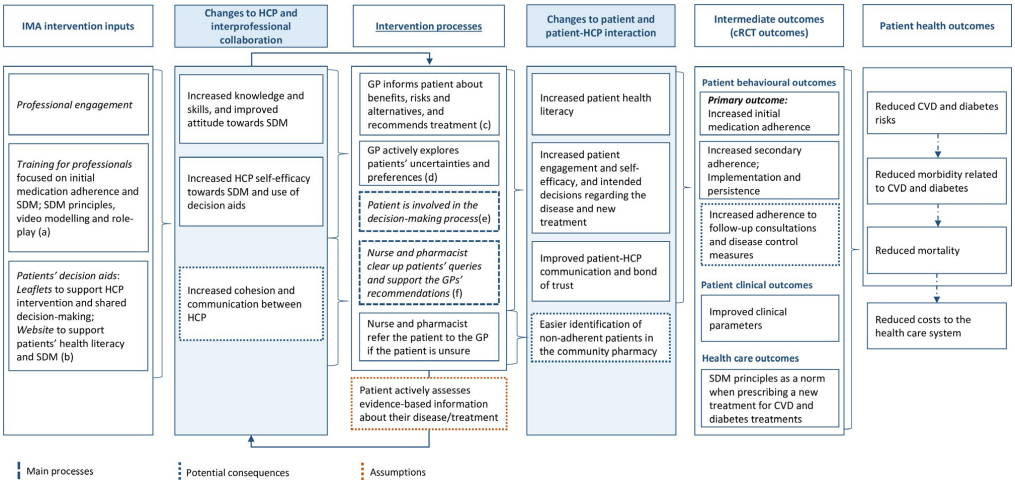

Figure 1 IMA intervention logic model. Intervention Behaviour Change Techniques (BCTs)[35]: (a) 4.1 Instruction of how to perform a behaviour, 6.1. Demonstration of the behaviour and 8.1. Behavioural practice/rehearsal. (b) 12.5. Adding objects to the environment. (c) 5.1. Information about health consequences and 9.1. Credible source. (d) 1.2. Problem-solving (e) 1.9. Commitment. (f) 3.1. Social support (unspecified). CVD, cardiovascular disease; GP, general practitioner; HCP, healthcare professional; IMA, initial medication adherence; SDM, shared decision-making.

SDM when the general practitioner (GP) prescribes a new lipid-lowering, antihypertensive, antiplatelet and/or glucose-lowering treatment. Nurses and pharmacists support the information provided by the GP, thus standardising the message and promoting collaboration between the professionals involved in the process. Patients could have a pre-existing therapeutic relationship with the professionals.

The intervention logic model (figure 1) illustrates the intervention implementation strategies (inputs) and intervention processes linked to Behaviour Change Techniques (BCTs)[35] and the hypothesised mechanisms of action (changes to healthcare professionals (HCPs) and interprofessional collaboration and changes to patient and patient-HCP interactions) to influence adherence (intermediate outcome) and ultimately patient health outcomes. Details on intervention development are described elsewhere.[21] The implementation strategies consisted of *professional engagement* to promote the intervention and improve attitudes towards it by holding information sessions with managers and professionals; *training for professionals* focused on IMA and SDM to increase knowledge and professionals' self-efficacy, including role-playing; and *intervention decision aids* (leaflets and website[36] translated into the most spoken languages) to support the intervention implementation and standardise practice. GPs, nurses and pharmacists were trained together to increase cohesion.

Usual care

HCPs in the control group were asked to provide usual care. In this, GPs generally decide how to provide information, nurses monitor chronic treatments, and community pharmacists explore patients' queries about the medication.

Setting and participants

The IMA-cRCT was carried out in public PC centres and private community pharmacies in Catalonia, Spain. The Spanish National Health system provides universal coverage and is primarily tax-funded, with free access to care except for pharmaceutical prescriptions, which require co-payment.[37] PC is the gateway to the public healthcare system and where most long-term CVD and diabetes treatments are prescribed. PC funding is mainly dependent on regional budgets, with generally fewer resources allocated to PC compared with hospital care. PC centres are organised into teams comprised of physicians, community nurses, other HCPs and administrative staff. Community pharmacies are private healthcare establishments of public interest.[37] Their public funding derives exclusively from the dispensing of medicines and medical products. Patients are assigned to one GP and one nurse. GPs prescribe treatments using an electronic prescription system, which can only be dispensed at free-of-choice community pharmacies.[22 37] The physical distance between PC centres and community pharmacies, along with poor communication among professionals and a lack of established collaborative practices, has traditionally limited direct interaction and interprofessional collaboration.[38]

The IMA-cRCT included over 300 professionals and 3000 patients overall. Professionals from the IG (83 GPs, 69 nurses and 58 pharmacists) completed

the training and implemented the intervention over 7 months. Each PC centre had a coordinator, either a GP or nurse participating in the study, who was contacted regularly during the study period. The process evaluation sampling strategy was conditioned by the trial cluster design.

Professionals

All IG professionals were asked to complete questionnaires, and professionals from eight centres were invited to participate in qualitative interviews. Maximum sample variability was ensured for both PC centres (location, rurality, area socioeconomic status, population size and nationality, and professionals' workload perceptions and motivation at pre-implementation) and professionals (professional category, age, sex and years of experience).

Patients

Patients in the IG were identified by PC coordinators, who may or may not have been the patient's treating GP or nurse, and invited to participate in an interview. PC coordinators contacted patients who had been prescribed a new medication during the study period, 15 days to 1 month after the consultation, inviting them to participate while avoiding mention of adherence or the IMA intervention. After acceptance, the research team contacted them to provide further information and schedule interviews. Recruitment followed maximum variation criteria based on age, sex, nationality, medication prescribed, education and employment status.

Data collection and analysis

Quantitative methods

1. *Monitoring data* were collected from trial operative sheets (professional engagement, training attendance rate and intervention tools usage) and PC centre demographic records (area socioeconomic status, population size and nationality, and training centre) to assess implementation strategies, fidelity and understand the context.
2. *Pre-implementation professionals' questionnaires* were completed to assess training quality and professionals' workload and motivation perceptions. 3-month and 7-month *post-implementation questionnaires* were emailed to professionals to assess implementation fidelity and normalisation into routine practice. Five items assessed fidelity based on the intervention protocol recommendations: apply SDM principles when prescribing a new medication (GP) or encountering a patient with a new prescription (nurses and pharmacists); use of decision aids (leaflets and a website); and, in case of a first telephone consultation, follow-up with a second telephone consultation to address any queries or concerns regarding the prescription. 22 items assessed normalisation divided into NPT constructs based on the Normalisation Measure Development (NoMAD) questionnaire[39] and adapted for this specific use. All items were rated from 1 (strongly disagree) to 10 (strongly agree). Evidence on questionnaire instrument validity was collected based on content, response process and internal structure that supports its use (online supplemental file 1).

Descriptive analyses and linear regression models were used to assess differences between professionals (category, sex and experience) and PC centres and pharmacies (location, population size and nationality) using Stata V.17.

Qualitative methods

1. *Field diaries* were completed by both the research team and the IG PC centre coordinators with data on implementation barriers and facilitators and the organisation of PC centres and pharmacies as reported by participating professionals.
2. *Individual semistructured interviews* with professionals and patients were conducted throughout the trial's 7-month fieldwork to explore implementation strategies, fidelity and normalisation into routine practice; participants' perceptions and experiences to assess the mechanisms of action, perceived impact on patients' and professionals' behaviours; and contextual factors. The interviews were conducted by telephone with professionals and face to face or by telephone (n=4) with patients. Interviews lasted 30–70 min and patients were reimbursed for their time. Two *focus groups* with professionals explored conflicting themes that arose during

Table 1 Sociodemographic information on quantitative and qualitative professionalsamples

	Quantitative professional sample			Qualitative professional sample		
	GPs (n=59)	Nurses (n=41)	Pharmacists (n=39)	GPs (n=11)	Nurses (n=7)	Pharmacists (n=10)
Mean age (SD)	47.64 (8.32)	45.11 (9.27)	46.67 (9.54)	50.32 (8.97)	46.90 (5.66)	47.77 (9.01)
Sex: female, n (%)	45 (76.27)	39 (95.12)	28 (71.79)	7 (63.64)	6 (85.71)	8 (80.00)
Nationality: Spanish, n (%)	53 (89.83)	40 (97.56)	31 (79.49)	11 (100)	6 (85.71)	9 (90.00)
Mean years of experience (SD)	18.45 (8.32)	13.73 (8.97)	19.06 (10.69)	22.45 (7.84)	20.17 (4.45)	18.30 (9.84)
Student supervisor, n (%)	33 (55.93)	22 (53.66)	n/a	7 (63.64)	4 (57.14)	n/a
Type of PCC/pharmacy: urban, n (%)	44 (74.58)	33 (80.49)	31 (79.49)	9 (81.82)	3 (42.86)	7 (70.00)

Sex: female, male; Nationality: Spanish, other; Student supervisor: yes, no; Type of PCC/pharmacy: urban, rural.
GPs, general practitioners; PCC, primary care centre; SD, standard deviation.

individual interviews and shared opinions regarding the IMA intervention. Predefined themes were explored deductively, such as the main intervention processes and normalisation into routine practice, and open questions were used to explore participants' experiences and perceptions inductively (online supplemental file 2 tables 1–3). Focus groups (three and eight professionals) were conducted by videoconference and lasted 45 min each. After each interview, researchers circulated a summary for participants' review. Interviews were audio recorded, anonymised and transcribed.

Qualitative data were analysed following framework analysis.[40] Field notes and transcripts were included and organised by group (PC centres) and cases (professionals and patients). NVivo software was used for data management. Three researchers familiarised themselves with the data and analysed the transcripts separately by interpreting the results and mapping them onto intervention processes, NPT constructs and the ecological model to understand the contextual factors (deductively),[32 41] while remaining open to new themes that emerged from the data on participants' experiences and perceptions (inductively) to generate coding frameworks. The researchers triangulated coding frameworks until a final version was generated and applied to all data. Data were compared by group and between cases while charting into the framework matrix for interpretation.

Triangulation of results

Quantitative and qualitative results were combined into a framework matrix and interpreted together.[42] A final summary of findings was produced and presented to all coauthors for review, clarification and final interpretation.

Deviations from study protocol

There were protocol[21] deviations in line with the dynamic nature of the study. Intervention protocol fidelity was to be explored through questionnaires and field diaries, but interviews were conducted to provide richer information. See online supplemental file 2 table 4 and online supplemental file 2 figure 1 for data sources and collection techniques per domain evaluated and study timeline deviations.

RESULTS

Tables 1 and 2 present participant sociodemographic characteristics. Online supplemental file 3 tables 1–3 show further characteristics of participants and PC centres. The quantitative methods involved 139 professionals (66% response rate). The qualitative methods included 28 professionals (34 declined to participate due to time restrictions). 38 patients were contacted, of whom 19 declined to participate due to time restrictions and personal reasons, leaving 19 patients who participated.

Table 2 Sociodemographic information on the qualitative patient sample

Qualitative patient sample	Patients (n=19)
Mean age (SD)	53.38 (12.19)
Sex: female, n (%)	8 (42.11)
Nationality: Spanish, n (%)	15 (78.95)
Type of PCC/pharmacy: urban, n (%)	12 (63.16)
Medication prescribed, n (%)*	
Antihypertensive	10 (52.36)
Lipid-lowering	4 (21.05)
Antiplatelet	2 (10.53)
Oral glucose-lowering	8 (42.11)
Injectable glucose-lowering	3 (15.79)
>1 CVD or diabetes diagnosis, n (%)	11 (57.89)
Educational status, n (%)	
No formal education	1 (5.26)
Primary education	4 (21.05)
Secondary education	9 (47.37)
University education	4 (21.05)
Not reported	1 (5.26)
Employment status, n (%)	
Unemployed	1 (5.26)
Employed	13 (68.42)
Retired/pensioner	4 (21.05)
Not reported	1 (5.26)
Income (€, monthly), n (%)	
<500	2 (10.53)
500 to <1000	5 (26.32)
1000 to <2000	5 (26.32)
2000 to <3000	2 (10.53)
3000 to <4000	3 (15.79)
4000 to <6000	1 (5.26)
Not reported	1 (5.26)

Sex: female, male; Nationality: Spanish, other; Type of PCC/pharmacy: urban, rural; >1 CVD or diabetes diagnosis: yes, no.
*Each patient may have had more than one new medication prescribed.
CVD, cardiovascular disease; PCC, primary care centre; SD, standard deviation.

Quantitative and qualitative results are reported together for each domain to offer deeper insights and highlight their complementarity. Professionals' fidelity and normalisation questionnaire results correspond to the 7-month post-implementation responses. Online supplemental file 3 table 4 compares 3-month and 7-month post-implementation results.

Implementation

Implementation strategies

See online supplemental file 3 table 5 for *professional engagement* details. Professional recruitment rate was higher among GPs (63.3%) than nurses (45.1%) and community pharmacies (37.6%). Training attendance was high across all professional categories (89% to 96.8%).

Professionals rated all aspects of the quality of the *training for professionals* highly, including organisation, materials, objectives, methodology and applicability to clinical practice. Two highly valued aspects were combined training of GPs, nurses and pharmacists to encourage collaboration and role-play; *"You have heard about SDM, you have read... But you need a little practice, if you do not practice it in a course before, even briefly, if you start directly without practicing, you think: "How the hell do I do it?" (Nurse-1)"*. Negative aspects included training duration, scheduling difficulties and lack of training continuity.

Leaflets were described by GPs and nurses as facilitators to implementation, who highlighted their value in supporting SDM at the consultation; *"Because you create the best possible environment for the SDM to take place. (GP-2)"*, adding; *"We assume that the moment you explain it, they have understood it all and will remember it and in most cases it's not like that. It's about being able to take it with you and review it later, and to have the chance to take notes. (GP-7)"*. They valued their format, content, plain language and the language translations. Patients highlighted their value in understanding the information; *"It was like a summary, a little summary of what he had explained to me. Let's say like language that was easier to understand, not so medical. (Patient-5)"*, although few reported subsequently consulting it.

Fidelity

Professionals scored higher on fidelity when implementing SDM principles than when using decision aids for support. Nonetheless, leaflets were used more frequently than the website (table 3). Some professionals reported not using the leaflets at all times, either because they forgot about them or did not have them to hand, although they provided the same information; *"I maybe didn't always give them the leaflet but I explained its contents to them. (Nurse-4)"*. Others reported selecting information based on their professional opinion or not applying SDM when urgent treatment was required; *"I may have adapted some things based on the drugs they are taking. Or I may not be completely neutral when explaining the options available, as I also have preferences. (GP-1)"*.

Overall, nurses scored highest on fidelity (mean=7.4; $p<0.05$ compared with GPs and pharmacists). GPs acknowledged adapting the intervention according to the patient's needs, and pharmacists frequently reported overlooking it and generally providing information to patients facing adherence challenges or with queries about the treatment; *"I usually did it [the intervention] if they already had questions. (Pharmacist-2)"*.

Fidelity was also assessed through patient experiences. Patients reported that the first consultation was with the GP (as per intervention protocol) or nurse, depending on the PC centre, and highlighted the role of nursing regarding new medications for chronic pathologies; *"The doctor is the one who makes the diagnosis but the nurse is the one who monitors you. So, I practically trust the nurse more in chronic treatments... (Patient-3)"*. Most patients mentioned the professional giving health information at the time of prescription, yet leaflets were not always used. Two patients mentioned the website being recommended, but none consulted it. Half of the patients recalled SDM, based mainly on how the professional presented the medication as a choice or as the only option; *"She gave me the information, she told me that the pill helped to improve blood pressure, and so I decided that it was perfect. (Patient-17)"*. Overall, they reported a lack of information support at community pharmacies; "*No, she [the pharmacist] didn't ask me anything, she just looked at the prescriptions and gave it to me. (Patient-18)"*.

Normalisation

Normalisation of the IMA intervention into clinical practice was assessed through questionnaires (table 3 and figure 2) and qualitative responses (see online supplemental file 3 table 6 for details on main themes identified).

1. *Coherence*. Professionals defined SDM as the core of the intervention independently of decision aids; *"I suppose the aim is to do all the explaining, make them understand and let them decide what options they have and what they want to do... But whether to give it to them in writing or not, that depends on the patient. (GP-5)"*. However, differentiation from usual care had the lowest coherence score (mean=6.3) and was particularly low in the case of pharmacists (mean=5.9). This was consistent with the qualitative results, where some considered the intervention was already in line with their existing practice; *"We haven't done much more than what we normally do. (Pharmacist-2)"*. Depending on the PC centre, professionals understood their roles and tasks differently. In some PC centres, nurses mainly monitored chronic conditions and thus implemented SDM at the time of prescription. Pharmacists understood their role but considered it secondary to other professionals; *"Our work doesn't make much sense unless previous work has been done. As for SDM, that's what this is all about. (Pharmacist-1)"*.
2. *Cognitive participation*. Professionals scored low on encouraging other professionals to implement the IMA intervention (mean=4.4). Nonetheless, they believed the IMA intervention to be a legitimate part of their role (mean=8.0). GPs and nurses were willing to continue implementing it once the trial ended as they saw the benefits for patients; *"It really structures a way of modifying or introducing a new drug in agreement with the patient, with the tools that, in some way, can improve therapeutic adherence. (GP-4)"*. Pharmacists were less motivated due to a perceived lack of interest from patients. Broadly, professionals suggested ideas to sustain it, such as electronic system alerts when issuing new prescriptions and

Table 3 Fidelity and normalisation questionnaire scores for professionals 7 months post implementation

	Overall (n=139) Mean (SD)	GPs (n=59) Mean (SD)	Nurses (n=41) Mean (SD)	Pharmacists (n=39) Mean (SD)
Fidelity	6.53 (1.97)	**6.17 (1.94)**	7.37 (1.46)	**6.21 (2.26)**
I implement the IMA intervention based on the principles of SDM	7.71 (1.79)	7.61 (1.80)	8.14 (1.24)	**7.41 (2.20)**
I use leaflets to support SDM	6.99 (2.37)	**6.63 (2.36)**	8.07 (1.79)	**6.41 (2.60)**
I give the leaflet to the patients so that they can evaluate it outside the consultation	6.89 (2.53)	**6.49 (2.45)**	8.00 (1.84)	**6.33 (2.94)**
I recommend patients to consult the website (www.iniciadores.es)	5.52 (2.50)	**5.27 (2.47)**	6.68 (2.03)	**4.67 (2.61)**
In the case of prescriptions made through telephone consultation, I call the patient a week later to resolve queries about the prescription	5.29 (2.69)*	**4.85 (2.89)**	5.93 (2.26)	n/a
Normalisation				
General experience				
I am familiar with the IMA intervention based on SDM	8.02 (1.70)	8.07 (1.71)	8.32 (1.08)	7.64 (2.13)
I think the intervention has become a normal part of my clinical practice	7.43 (1.95)	7.34 (1.99)	7.93 (1.13)	**7.05 (2.44)**
Coherence	7.08 (1.58)	**6.94 (1.46)**	7.70 (1.10)	**6.63 (1.98)**
There are differences between the IMA intervention based on SDM and my previous clinical practice (Differentiation)	6.34 (2.06)	6.20 (2.07)	6.98 (1.62)	**5.87 (2.31)**
I consider that PCC/pharmacy professionals have a shared understanding of the purpose of the IMA intervention (Communal specification)	7.33 (1.95)	7.27 (1.82)	7.49 (1.63)	7.26 (2.44)
I understand how the IMA intervention impacts my clinical practice (Individual specification)	6.97 (1.97)	**6.76 (1.84)**	7.90 (1.50)	**6.31 (2.27)**
I can see the added value of the IMA intervention for my clinical practice (Internalisation)	7.66 (1.92)	**7.53 (1.77)**	8.41 (1.26)	**7.08 (2.42)**
Cognitive participation	7.15 (1.60)	6.97 (1.59)	7.58 (1.13)	6.99 (1.94)
I have encouraged other professionals to implement the IMA intervention (Initiation)	4.44 (2.77)	4.39 (2.79)	4.83 (2.71)	4.10 (2.83)
I believe that participating in the IMA intervention is part of my professional role (Legitimation)	8.02 (1.79)	**7.73 (1.76)**	8.46 (1.31)	8.00 (2.18)
I am open to working with my colleagues in new ways to implement the IMA intervention (Enrolment)	7.94 (1.80)	7.71 (1.86)	8.41 (1.26)	7.79 (2.10)
I will continue to support the IMA intervention and implement the principles of SDM (Activation)	8.22 (1.61)	8.05 (1.61)	8.61 (1.02)	8.05 (2.01)
Collective action	8.10 (1.43)	8.02 (1.57)	8.41 (0.92)	7.90 (1.63)
I consider the IMA intervention can be easily integrated into my clinical practice (Interactional workability)	7.73 (1.89)	7.66 (1.85)	8.27 (1.32)	**7.26 (2.30)**
The IMA intervention improves the relationship between professionals (GPs, nurses and pharmacists) (Relational integration)	7.75 (2.05)	7.78 (2.03)	7.98 (1.62)	7.46 (2.46)
I have confidence in other professionals' ability to implement the IMA intervention (Relational integration)	8.05 (1.71)	7.88 (1.84)	8.29 (1.27)	8.05 (1.90)
The role of each professional in the IMA intervention is appropriate to each professional category (medicine, nursing and pharmacy) (Skill set Workability)	8.19 (1.63)	8.03 (1.64)	8.46 (1.23)	8.13 (1.95)
Sufficient training is provided to enable professionals to implement the IMA intervention (Skill set Workability)	8.08 (1.85)	7.95 (2.07)	8.44 (1.32)	7.90 (1.94)
The resources of the IMA intervention are sufficient to support SDM (Contextual integration)	8.24 (1.63)	8.19 (1.75)	8.71 (1.03)	**7.82 (1.85)**
The PCC/pharmacy management team adequately supports the IMA intervention (Contextual integration)	8.70 (1.68)	8.66 (1.83)	8.73 (1.32)	8.72 (1.83)
Reflexive monitoring	7.95 (1.49)	7.87 (1.34)	8.26 (1.12)	7.74 (1.94)
I am aware of evidence that supports the effects of SDM on which the IMA intervention is based (Systematisation)	7.39 (1.90)	7.51 (1.48)	7.20 (2.02)	7.41 (2.33)
PCC/pharmacy professionals agree that implementing the IMA intervention is worthwhile (Communal appraisal)	8.09 (1.63)	7.97 (1.53)	8.34 (1.33)	8.00 (2.01)
I value the effects that the IMA intervention has had on my clinical practice (Individual appraisal)	8.04 (1.77)	**7.80 (1.81)**	8.56 (1.10)	7.85 (2.16)
Professional opinions about the intervention can be used to improve the IMA intervention in the future (Reconfiguration)	8.18 (1.60)	8.03 (1.53)	8.56 (1.12)	8.00 (2.05)
I can improve how I work with the IMA intervention (Reconfiguration)	8.07 (1.77)	8.07 (1.64)	8.68 (1.15)	**7.44 (2.26)**

Values marked in bold indicate significant differences between nurses (ref) and other professional categories.
*GPs and nurses (n=100).
GPs, general practitioners; IMA, initial medication adherence; SD, standard deviation; SDM, shared decision-making.

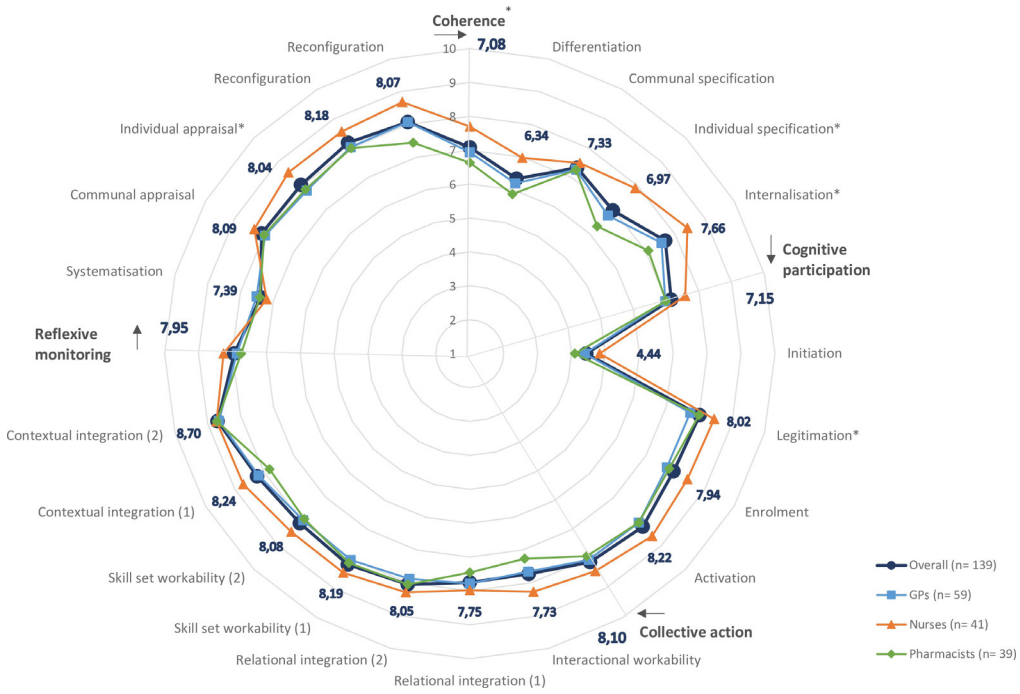

Figure 2 Mean scores for Normalisation Process Theory constructs and subconstructs[39] across all professionals and professional categories. *Statistically significant differences among professionals. GP, general practitioner.

continued SDM training, although these rely on the wider system.

3. *Collective action* had the highest mean score (mean=8.1). PC centre professionals considered integration easier than pharmacists. Professionals trusted their skills and those of their colleagues and highlighted the role of each professional in the care of chronic patients; *"Medicine is more about making decisions together with the patient (…) But both nursing and pharmacy have a role in monitoring and follow-up (…) I think we are all in the same team. (GP-3)"*.
4. *Reflexive monitoring*. Professionals valued the intervention effect on their clinical practice (mean=7.9), with nurses having the highest score (mean=8.3). Even though professionals did not directly monitor intervention effects, they showed interest in its impact, trial results and influence on adherence. GPs and nurses reported improvements in SDM awareness and their role as educators and promotors of patient autonomy; *"Because you adopt the role of professional more… More of an educator, more of a motivator. Especially the aspect of educating the patient and giving them autonomy. (GP-1)"*. Pharmacists generally considered it difficult to detect non-initiation but acknowledged being more attentive to patients facing adherence issues. Generally, there was a sense of increased time invested, accompanied by a feeling that this could lead to timesaving in subsequent encounters; *"You spend more time over the consultation, but I believe that in the long run, when you invest more time in a patient one day, you save it on others. (GP-1)"*.

On the whole, nurses reported the highest fidelity and normalisation into routine practice. Statistically significant differences between nurses, GPs and pharmacists are observed in table 3. There were no significant differences between other professionals or PC centres and pharmacy characteristics.

Mechanisms of action

Qualitative results detailed the intervention mechanisms that influence participants' behaviours (see online supplemental file 3 table 7 for details on main themes identified). *Changes to HCPs and interprofessional collaboration* were assessed through professionals' experiences. Professionals' attitudes towards SDM largely improved as they understood the importance of increasing patients' health literacy and decision-making autonomy; *"I think, in general, it should always be used. In this case, we have applied it to new treatments, but I think it always has to be there. Whatever you ask them [patients], ordering tests or anything to do with them, they have to be well informed and accept it, of course. (Nurse-2)"*. Nevertheless, some professionals thought SDM could not be implemented with all patients, depending on,

for instance, their bond of trust or differing patient profiles; *"My experience is that for some patients it does work, but it is not for everyone. It depends on each patient's profile. But, of course, you are deciding something about another person and I believe that the fact that the other person also decides if they want to do it, how they want to do it and so on, is very important. (GP-7)"*. Individuals from all professional categories agreed that cohesion and communication did not change because of the intervention. GPs and nurses generally had favourable relationships with each other and reported it as an implementation facilitator, whereas none reported interprofessional collaboration between PC centres and pharmacies.

Changes to patient and patient–HCP interactions were assessed through professionals' and patients' experiences. Professionals perceived that the IMA intervention helped patients understand their disease and treatment and therefore increased health literacy; *"It helps the patient a lot to position themselves, about what the disease is and what therapeutic options they have. Knowing where you are is always important. (GP-2)"*. As perceived by professionals, patients asked more questions and reflected more on their preferences, which could increase patients' confidence regarding the medication. Patients with previous personal or familial pathology experiences reported no new knowledge gained after the intervention. Those who reported knowledge gained emphasised learning new information about the pharmacological treatment, adverse effects and disease complications. Nevertheless, a few patients reported that detailed information could increase their concerns; *"I'm a bit of a hypochondriac and too much information is counterproductive for me. I tend to get stressed, to worry about everything, to be very emotional. (Patient-19)"*. Professionals believed patients appreciated being involved in the decision, which increased patient autonomy and adherence; *"Any person you let choose and decide on any aspect, you raise their self-esteem and improve compliance and improve involvement. (GP-1)"*, as well as humanisation of clinical care; *"Feeling that they are included and that you are treating them as people, not as numbers or diseases. (GP-11)"*. However, professionals perceived not all patients wanted to be involved in the decision, and some patients expressed discomfort; *"Look, I haven't studied medicine, I have to go to medical school, study for five years, so that we could talk face to face and they could explain everything to me, it is impossible! (Patient-10)"*. Patients who participated in the decision valued being involved, although some recognised that not being involved would not have altered the outcome; *"If I hadn't been part of it [the decision], if she hadn't asked me about it, it wouldn't have made any difference. But when she mentioned it to me, I said: "Well yes, if my opinion is useful, then sure. (Patient-18)"*. At last, even though professionals believed the IMA intervention could improve patient–professional trust and reduce power imbalances, no participant reported relationship changes.

Context

Contextual factors that influenced implementation and intervention active mechanisms are presented in line with the ecological model and distinguish among microlevel (patient), mesolevel (organisation and culture) and macrolevel (wider environment)[41 43] (see online supplemental file 3 table 8 for details on main themes identified).

As microlevel factors, professionals defined patient profiles as facilitators or barriers to implementing SDM. They emphasised low education, financial difficulties and cultural and language differences as barriers to providing health education and involving patients in decisions. Additionally, they considered age to be an important aspect. They perceived that the younger the patient, the more willing they were to be involved in the decision; *"They are usually middle-aged people, not very old, who like to participate, because they are worried. They want to participate. (GP-6)"*.

As mesolevel factors, PC centre professionals highlighted longitudinality as a facilitator to SDM, enabling patients to visit the same professional regularly so decisions do not need to be made at the first consultation; *"The advantage of primary care is longitudinality. If they do not want to start today, I explain it, and after two or three months, they might think about it and accept it. (GP-8)"*. In addition, the fact that GPs and nurses generally work as a team and visit the same patients facilitated implementation by ensuring alignment and continuity of care. However, time restrictions and heavy workloads were cited as some of the main barriers by professionals and patients across all organisations; *"I knew time was limited, it is very limited and yes, I would have liked to know a lot more. (Patient-10)"*. Additionally, organisational, cultural and work-environment factors were mentioned. Some professionals recognised being accustomed to a model without patient involvement and sometimes overlooked their inclusion. Moreover, most patients interviewed did not expect the pharmacist to provide health education when dispensing a medication; *"I mean, if the nurse and the doctor do their job, the pharmacist does their job by giving me the pills. (Patient-14)"*.

Finally, at the macrolevel, we anticipated the COVID-19 pandemic would have been an implementation barrier. However, even though professionals reported low motivation after the pandemic, this was not the case.

DISCUSSION

This process evaluation contributes to understanding how the components of the IMA intervention were implemented, the factors that affected its implementation, its mechanisms of action and its impact on patients' and professionals' behaviours. Improving

adherence through SDM and interprofessional collaboration was considered important to both professionals and patients. The intervention was implemented with adequate fidelity and was generally integrated into clinical practice. However, professionals and patients are not yet fully prepared for this new paradigm of care. Some professionals perceived little distinction between the intervention and usual practice, and some patients preferred the professional to make the final decision.

Effective intervention implementation strategies are crucial for reaching the target population.[44] Training for professionals was considered key in enhancing SDM and learning about the roles of other professionals engaged in patient care. Formal training has been identified as a facilitator in providing professionals with the skills and knowledge needed to engage in and conduct SDM.[45 46] However, consistent with previous research, our findings highlight that a single training intervention may be insufficient, as professionals emphasised the need for continuous training.[45] Furthermore, the literature suggests that insufficient humanistic training may result in professionals lacking essential communication skills, potentially leading them to view SDM merely as a technique, rather than recognising its foundation for effective communication.[46 47]

Fidelity was adequate overall, except for use of the website. The use of decision aids to support SDM has been extensively explored.[48] Leaflets mainly supported understanding of the information rather than encouraging the patient to take part in the decision.[49] Professionals acknowledged applying SDM without the use of decision aids. However, decision aids are known to support patient health literacy and play an active role in risk–benefit discussions, even where patients prefer professional-led decisions.[50] Other web-based studies have revealed that an important implementation barrier is difficulty accessing the tool during the consultation. In our study, this hindered familiarisation with the website and limited its recommendations.[51 52]

Interprofessional collaboration and care standardisation are central to the IMA intervention, especially as the prevalence of chronic diseases increases, necessitating the involvement of the entire multidisciplinary team in making a single decision.[53 54] Although the intervention protocol aligned with professional roles as outlined in healthcare guidelines,[37 55–58] the results showed that roles can be interchangeable in real-life practice. Nurses play a fundamental role in chronic disease care.[59–61] In some PC centres, nurses served as the main patient contact, with interprofessional collaboration acting as a key facilitator. The role of pharmacists in healthcare systems has been widely explored.[62] In the IMA intervention, their role was influenced by the Spanish context, where pharmacies are private establishments of public interest.[37] Although pharmacists recognised their influence on patient behaviour, none reported communication with GPs or nurses, and their role was frequently unclear to other professionals and patients. The role of pharmacists in the IMA intervention requires redefinition. Although community pharmacists are considered health community agents in Spain, they primarily focus on dispensing medications and providing counselling on their use, rather than playing an active role in chronic disease management and health screening.[37] As noted in the previous literature, they are not adequately integrated into the PC model and are often perceived merely as 'vendors'.[38 63–65]

The intervention was considered important and integrated into routine practice, although some professionals perceived no difference between the intervention and usual care, which could indicate low motivation to change practice.[66 67] Although attitudes improved, SDM was sometimes misunderstood as informed decisions rather than an exchange of opinions and decision-making.[68 69] While professionals have expressed a preference for SDM, paternalistic approaches remain deeply ingrained, often limiting conversations about treatment options.[70] Professionals were generally committed to the intervention, as they perceived benefits to the patient and their practice, but organisational integration was hampered by a failure to promote implementation among other professionals. The full integration of SDM into routine practice requires more awareness of patient-centred care models and a broader understanding of the aims and benefits of patient involvement.[66 71]

Patients accepted the intervention and found the leaflets useful for understanding the information provided. Willingness to participate in decision-making varies among patients and should be explored beforehand.[24] However, their views, preferences and context should always be considered when providing treatment recommendations.[24 68 69 72] Some patients appreciated being involved in the decision, while others felt uncomfortable and preferred the GP to make the decision, often not recognising the value of their own experiences and knowledge.[46 73] As highlighted by other authors, adapting SDM to the patient's level of health literacy is crucial for ensuring high-quality care.[74] Moreover, SDM has been recognised for its potential to strengthen patient–professional relationships by viewing the patient as an active agent.[75] This not only reinforces treatment adherence but also fosters a supportive environment that facilitates SDM implementation.[76]

Overall, the adoption of SDM remains limited in clinical practice,[69] and contextual barriers and facilitators need to be considered. As previously described, we identified mainly organisational factors, such as time restrictions and heavy workloads, and patient characteristics, as hindering implementation.[45 71 77] Some of these represent more structural aspects, which require a deeper understanding of the context in order

to enhance the effectiveness of the intervention.[43] Without structural support, SDM risks remaining more of an aspiration than a routine practice in PC. Much progress in SDM has been driven by academia, which often lacks sustainable programmes to integrate it into the system.[78] In addition to increasing professional awareness of patient-centred models, advancing SDM requires the engagement of healthcare managers, inclusion in professional training, and public awareness campaigns.[79] Going forward, prior to implementing an SDM intervention in a new context, it is crucial to assess the local context by engaging stakeholders, understanding organisational structures and evaluating available resources to anticipate potential challenges and guide the development of tailored implementation strategies.

The IMA intervention did not improve adherence[29]; however, SDM remains crucial for enhancing care quality and patient engagement within value-based healthcare. Moreover, SDM is grounded in ethical principles, reinforcing patients' right to make informed choices as a fundamental aspect of professional practice.[80] We believe this alone justifies further discussion on the need for its continued expansion, despite the intervention's limited effectiveness.

Strengths and limitations

This study provided valuable insights into the implementation of the IMA intervention. It illustrated how different components and contexts interacted and potentially influenced the trial outcomes, using a combination of quantitative and qualitative methods to generate deeper insights. The standardised fidelity and NPT questionnaire used showed adequate validity.

Despite this, there were some limitations. These include potential memory bias from participants, the possible over-representation of responses from professionals who were more actively engaged with the intervention, and patient recruitment being conducted by professionals, which may have led to more positive responses. Furthermore, positively skewed answers might have resulted from interviewers being members of the IMA-cRCT research team themselves. Qualitative interviews were limited to eight PC centres due to logistical constraints, which may have reduced the broader representativeness of all centres. However, the sampling strategy was theoretical and ensured variability based on the centre characteristics and the results of the pre-implementation questionnaire. At last, this study did not capture the experiences of the control group receiving usual care, which hinders the possibility to contrast these with those of the IG.

CONCLUSIONS

The IMA intervention proved beneficial for both professionals and patients, with adequate fidelity of implementation, and an overall high normalisation into practice. However, additional efforts are needed to embed SDM within PC, as part of the broader shift towards patient-centred care models and continuous improvement of quality of care. This evaluation provided valuable information for the future refinement and expansion of SDM and other complex interventions and for understanding factors influencing SDM in PC.

Author affiliations
[1]Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, St Boi de Llobregat, Catalonia, Spain
[2]Department of Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine and Public Health, Universitat Autònoma de Barcelona, Bellaterra, Catalonia, Spain
[3]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Madrid, Spain
[4]Department of Medicine, Universitat de Barcelona, Barcelona, Catalonia, Spain
[5]Primary Care Centre Bartomeu Fabrés Anglada, Primary Care Research Institute (IDIAP Jordi Gol), Catalan Institute of Health South Metropolitan Territory Management, Barcelona, Catalonia, Spain
[6]Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Barcelona, Catalonia, Spain

X Ignacio Aznar-Lou @Ignaznar and Claudia Palma-Vasquez @https://x.com/cpalmavasquez

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The IMA-cRCT and its integrated process evaluation were approved by the drug research committee (CEIm) at IDIAP Jordi Gol, codeCEIm 21/051-P. Informed consent from the patients was obtained by simplified means in the cRCT. The IMA-cRCT is a low-intervention clinical trial where groups

of subjects are allocated to the intervention groups and which satisfies all the conditions described in paragraphs 2 and 3 of Article 30 of EU regulation number 536/2014. The electronic database used meets all current legal requirements and is encrypted and pseudonymised so that researchers do not have access to data that identifies the patients or professionals. Professionals signed informed consent prior to trial commencement and consented to taking part in the process evaluation. Patients signed informed consent after recruitment and prior to the beginning of interviews. Participants were compensated for their time and travel expenses incurred in participating.

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Data availability statement Data are available upon reasonable request. Quantitative and qualitative data and evaluation materials are available from the authors upon reasonable request. Requests to access the datasets should be directed to the corresponding author.

ORCID iDs

Carmen Corral-Partearroyo http://orcid.org/0000-0001-9517-4916
Alba Sánchez-Viñas http://orcid.org/0000-0001-5020-7534
Montserrat Gil-Girbau http://orcid.org/0000-0002-4396-6492
Claudia Palma-Vasquez http://orcid.org/0000-0001-8830-1884
Carmen Gallardo-González http://orcid.org/0000-0003-0688-1366
María del Carmen Olmos-Palenzuela http://orcid.org/0000-0003-4078-6717
Maria Rubio-Valera http://orcid.org/0000-0003-2856-1697

REFERENCES

1 Vrijens B, De Geest S, Hughes DA, *et al*. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
2 Zeber JE, Manias E, Williams AF, *et al*. A Systematic Literature Review of Psychosocial and Behavioral Factors Associated with Initial Medication Adherence: A Report of the ISPOR Medication Adherence & Persistence Special Interest Group. *Value Health* 2013;16:891–900.
3 Lemstra M, Nwankwo C, Bird Y, *et al*. Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Prefer Adherence* 2018;12:721–31.
4 Cheen MHH, Tan YZ, Oh LF, *et al*. Prevalence of and factors associated with primary medication non-adherence in chronic disease: A systematic review and meta-analysis. *Int J Clin Pract* 2019;73:e13350.
5 Tarn DM, Barrientos M, Pletcher MJ, *et al*. Perceptions of Patients with Primary Nonadherence to Statin Medications. *J Am Board Fam Med* 2021;34:123–31.
6 Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, *et al*. Reasons for medication non-initiation: A qualitative exploration of the patients' perspective. *Res Social Adm Pharm* 2020;16:663–72.
7 World Health Organization. Adherence to long-term therapies. Evidence for action. Geneva, 2003. Available: https://iris.who.int/handle/10665/42682
8 Ettehad D, Emdin CA, Kiran A, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–67.
9 Xu T, Yu X, Ou S, *et al*. Adherence to Antihypertensive Medications and Stroke Risk: A Dose-Response Meta-Analysis. *J Am Heart Assoc* 2017;6:e006371.
10 Bouchard MH, Dragomir A, Blais L, *et al*. Impact of adherence to statins on coronary artery disease in primary prevention. *Br J Clin Pharmacol* 2007;63:698–708.
11 Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e016982.
12 Derose SF, Green K, Marrett E, *et al*. Automated outreach to increase primary adherence to cholesterol-lowering medications. *JAMA Intern Med* 2013;173:38–43.
13 Fischer MA, Choudhry NK, Bykov K, *et al*. Pharmacy-based interventions to reduce primary medication nonadherence to cardiovascular medications. *Med Care* 2014;52:1050–4.
14 Fischer MA, Jones JB, Wright E, *et al*. A Randomized Telephone Intervention Trial to Reduce Primary Medication Nonadherence. *JMCP* 2015;21:124–31.
15 O'Connor PJ, Schmittdiel JA, Pathak RD, *et al*. Randomized Trial of Telephone Outreach to Improve Medication Adherence and Metabolic Control in Adults With Diabetes. *Diabetes Care* 2014;37:3317–24.
16 Kerner DE, Knezevich EL. Use of communication tool within electronic medical record to improve primary nonadherence. *J Am Pharm Assoc (2003)* 2017;57:S270–3.
17 Aznar-Lou I, Fernández A, Gil-Girbau M, *et al*. Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. *Br J Clin Pharmacol* 2017;83:1328–40.
18 Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, *et al*. Initiation and Single Dispensing in Cardiovascular and Insulin Medications: Prevalence and Explanatory Factors. *Int J Environ Res Public Health* 2020;17:3358.
19 Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, *et al*. Non-initiation of prescribed medication from a Spanish health professionals' perspective: A qualitative exploration based on Grounded Theory. *Health Soc Care Community* 2022;30:e213–21.
20 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, *et al*. Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention. *Front Public Health* 2022;10.
21 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, *et al*. Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol. *BMJ Open* 2022;12:e067468.
22 Sánchez-Viñas A, Corral-Partearroyo C, Gil-Girbau M, *et al*. Effectiveness and cost-effectiveness of an intervention to

improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study). *BMC Prim Care* 2022;23:170.
23 Elwyn G, Edwards A, Kinnersley P, *et al*. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. *Br J Gen Pract* 2000;50:892–9.
24 Elwyn G, Frosch D, Thomson R, *et al*. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012;27:1361–7.
25 Légaré F, Adekpedjou R, Stacey D, *et al*. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev* 2018;7:CD006732.
26 Saheb Kashaf M, McGill ET, Berger ZD. Shared decision-making and outcomes in type 2 diabetes: A systematic review and meta-analysis. *Patient Educ Couns* 2017;100:2159–71.
27 Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, *et al*. Interventions to support shared decision making for medication therapy in long term conditions: A systematic review. *Patient Educ Couns* 2020;103:254–65.
28 Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;350:h1258.
29 Corral-Partearroyo C, Sánchez-Viñas A, Aznar-Lou I, *et al*. Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using Real World Data [Submitted]. 2025.
30 Curran GM, Bauer M, Mittman B, *et al*. Effectiveness-implementation Hybrid Designs: Combining Elements of Clinical Effectiveness and Implementation Research to Enhance Public Health Impact. *Med Care* 2012;50:217–26.
31 Skivington K, Matthews L, Simpson SA, *et al*. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;374:n2061.
32 May CR, Mair F, Finch T, *et al*. Development of a theory of implementation and integration: Normalization Process Theory. *Implement Sci* 2009;4:29.
33 Pinnock H, Barwick M, Carpenter CR, *et al*. Standards for Reporting Implementation Studies (StaRI) Statement. *BMJ* 2017;356:i6795.
34 O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. *J Health Serv Res Policy* 2008;13:92–8.
35 Michie S, Richardson M, Johnston M, *et al*. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;46:81–95.
36 Iniciadores. IMA-cRCT. n.d. Available: https://www.iniciadores.es/
37 Bernal-Delgado E, Angulo-Pueyo E, Ridao-López M, *et al*. Spain: health system review. Health systems in transition. Copenhagen WHO Regional Office for Europe; 2024. Available: https://eurohealthobservatory.who.int/publications/i/spain-health-system-review-2024
38 Rubio-Valera M, Jové AM, Hughes CM, *et al*. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. *BMC Health Serv Res* 2012;12:188.
39 May C, Rapley T, Mair F, *et al*. Normalization process theory on-line users' manual, toolkit and nomad instrument. 2015. Available: http://www.normalizationprocess.org
40 Gale NK, Heath G, Cameron E, *et al*. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013;13:117.
41 McLaren L, Hawe P. Ecological perspectives in health research. *J Epidemiol Community Health* 2005;59:6–14.
42 O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. *BMJ* 2010;341:c4587.
43 Nilsen P, Bernhardsson S. Context matters in implementation science: a scoping review of determinant frameworks that describe contextual determinants for implementation outcomes. *BMC Health Serv Res* 2019;19:189.
44 Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. *Implement Sci* 2013;8:139.
45 Waddell A, Lennox A, Spassova G, *et al*. Barriers and facilitators to shared decision-making in hospitals from policy to practice: a systematic review. *Implement Sci* 2021;16:74.
46 Tang C, Wang A, Yan J. Exploring motivations and resistances for implementing shared decision-making in clinical practice: A systematic review based on a structure–process–outcome model. *Health Expect* 2022;25:1254–68.
47 Kunneman M, Gionfriddo MR, Toloza FJK, *et al*. Humanistic communication in the evaluation of shared decision making: A systematic review. *Patient Educ Couns* 2019;102:452–66.
48 Stacey D, Légaré F, Lewis K, *et al*. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2017;4:CD001431.
49 Wieringa TH, Rodriguez-Gutierrez R, Spencer-Bonilla G, *et al*. Decision aids that facilitate elements of shared decision making in chronic illnesses: a systematic review. *Syst Rev* 2019;8:121.
50 Coronado-Vázquez V, Canet-Fajas C, Delgado-Marroquín MT, *et al*. Interventions to facilitate shared decision-making using decision aids with patients in Primary Health Care: A systematic review. *Medicine (Baltimore)* 2020;99:e21389.
51 Peters LJ, Torres-Castaño A, van Etten-Jamaludin FS, *et al*. What helps the successful implementation of digital decision aids supporting shared decision-making in cardiovascular diseases? A systematic review. *Eur Heart J Digit Health* 2023;4:53–62.
52 Jimbo M, Shultz CG, Nease DE, *et al*. Perceived barriers and facilitators of using a Web-based interactive decision aid for colorectal cancer screening in community practice settings: findings from focus groups with primary care clinicians and medical office staff. *J Med Internet Res* 2013;15:e286.
53 Hsiao C-Y, Wu J-C, Lin P-C, *et al*. Effectiveness of interprofessional shared decision-making training: A mixed-method study. *Patient Educ Couns* 2022;105:3287–97.
54 Diouf NT, Menear M, Robitaille H, *et al*. Training health professionals in shared decision making: Update of an international environmental scan. *Patient Educ Couns* 2016;99:1753–8.
55 Coll de Tuero G, Dalfó i Baqué A, de la Figuera Von Wichmann M, *et al*. Guies de pràctica clínica. Hipertensió Arterial. Institut Català de la Salut. Guies pràctica clínica i Material docent. 2012. Available: https://scientiasalut.gencat.cat/handle/11351/4540.2

56 Mata M, Xavier Cos F, Morros R, *et al*. Guies de pràctica clínica. Abordatge de la diabetis mellitus tipus 2. Institut Català de la Salut. Guies pràctica clínica i Material docent. Barcelona, 2013. Available: https://scientiasalut.gencat.cat/handle/11351/4514

57 Verdú Rotellar J, Pacheco Huergo V, Amado Guirado E, *et al*. Guies de pràctica clínica. Insuficiència cardíaca. Institut Català de la Salut. Guies pràctica clínica i Material docent. Barcelona; 2008. Available: https://scientiasalut.gencat.cat/handle/11351/4516

58 Franzi Sisó A, Armengol Alegre J, Baena Díez J, *et al*. Guia de lípids i risc cardiovascular. Institut Català de la Salut. Guies pràctica clínica i Material docent. Barcelona, 2021. Available: https://scientiasalut.gencat.cat/handle/11351/5955.2

59 Gorina M, Limonero JT, Álvarez M. Effectiveness of primary healthcare educational interventions undertaken by nurses to improve chronic disease management in patients with diabetes mellitus, hypertension and hypercholesterolemia: A systematic review. *Int J Nurs Stud* 2018;86:139–50.

60 Martínez-González NA, Rosemann T, Tandjung R, *et al*. The effect of physician-nurse substitution in primary care in chronic diseases: a systematic review. *Swiss Med Wkly* 2015;145:w14031.

61 Hämel K, Röhnsch G, Heumann M, *et al*. How do nurses support chronically ill clients' participation and self-management in primary care? A cross-country qualitative study. *BMC Prim Care* 2022;23:85.

62 WHO Consultative Group on the Role of the Pharmacist in the Health Care System (f1988: New Delhi, India)f, World Health Organization. Pharmaceuticals unit & WHO meeting on the role of the pharmacist: quality pharmaceutical services - benefits for governments and the public (2nd: 1993: Tokyo, Japan). The role of the pharmacist in the health care system: report of a WHO consultative group, New Delhi, India, 13-16 December 1988; report of a WHO meeting, Tokyo, Japan, 31 August - 3 September 1993. 1994. Available: https://iris.who.int/handle/10665/59169

63 Mossialos E, Courtin E, Naci H, *et al*. From "retailers" to health care providers: Transforming the role of community pharmacists in chronic disease management. *Health Policy* 2015;119:628–39.

64 Brewster S, Holt R, Portlock J, *et al*. The role of community pharmacists and their position in the delivery of diabetes care: an update for medical professionals. *Postgrad Med J* 2020;96:473–9.

65 Zardaín E, del Valle MO, Loza MI, *et al*. Psychosocial and behavioural determinants of the implementation of Pharmaceutical Care in Spain. *Pharm World Sci* 2009;31:174–82.

66 Lloyd A, Joseph-Williams N, Edwards A, *et al*. Patchy "coherence": using normalization process theory to evaluate a multi-faceted shared decision making implementation program (MAGIC). *Implement Sci* 2013;8:102.

67 Joseph-Williams N, Lloyd A, Edwards A, *et al*. Implementing shared decision making in the NHS: lessons from the MAGIC programme. *BMJ* 2017;357:j1744.

68 Serrano V, Rodriguez-Gutierrez R, Hargraves I, *et al*. Shared decision-making in the care of individuals with diabetes. *Diabet Med* 2016;33:742–51.

69 Elwyn G. Shared decision making: What is the work? *Patient Educ Couns* 2021;104:1591–5.

70 Driever EM, Stiggelbout AM, Brand PLP. Shared decision making: Physicians' preferred role, usual role and their perception of its key components. *Patient Educ Couns* 2020;103:77–82.

71 Légaré F, Ratté S, Gravel K, *et al*. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. *Patient Educ Couns* 2008;73:526–35.

72 Inkeroinen S, Virtanen H, Stolt M, *et al*. Patients' right to know: A scoping review. *J Clin Nurs* 2023;32:4311–24.

73 Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. *Patient Educ Couns* 2014;94:291–309.

74 Pel-Littel RE, Buurman BM, Minkman MM, *et al*. The influence of health literacy, anxiety and education on shared decision making and decisional conflict in older adults, and the mediating role of patient participation: A video observational study. *Patient Educ Couns* 2024;124:108274.

75 Elwyn G, Lloyd A, May C, *et al*. Collaborative deliberation: a model for patient care. *Patient Educ Couns* 2014;97:158–64.

76 Deniz S, Akbolat M, Çimen M, *et al*. The Mediating Role of Shared Decision-Making in the Effect of the Patient-Physician Relationship on Compliance With Treatment. *J Patient Exp* 2021;8:23743735211018066.

77 Veenendaal H van, Chernova G, Bouman CM, *et al*. Shared decision-making and the duration of medical consultations: A systematic review and meta-analysis. *Patient Educ Couns* 2023;107:107561.

78 Härter M, Moumjid N, Cornuz J, *et al*. Shared decision making in 2017: International accomplishments in policy, research and implementation. *Z Evid Fortbild Qual Gesundhwes* 2017;123–124:1–5.

79 Coulter A. National strategies for implementing shared decision making (Engl.). Gütersloh Ger Bertelsmann Stift; 2018. Available: https://www.bertelsmann-stiftung.de/en/publications/publication/did/national-strategies-for-implementing-shared-decision-making-engl

80 Elwyn G, Tilburt J, Montori VM. The ethical imperative for shared decision-making. *EJPCH* 2013;1:129.

4.4.1 Main results overview – Scientific article 3

The process evaluation provided valuable insights into the real-world implementation of the IMA intervention in primary care, clarifying its mechanisms of action and identifying key contextual factors influencing it. Quantitative data were collected through monitoring data and questionnaires (139 professionals, 66% response rate), while qualitative data included field diaries, individual semistructured interviews, and focus groups (19 patients, 28 professionals).

Implementation strategies assessed involved professional engagement and training, and decision aids (leaflets and website). Engagement was highest among GPs, followed by nurses and pharmacists, though nurse participation improved considerably versus the pilot. Professionals highly valued the training and the leaflets for supporting patient decisions. Despite expanding the training to incorporate additional time and content dedicated to shared decision-making, some professionals felt a single training was insufficient, highlighting the need for ongoing reinforcement to sustain shared decision-making in routine practice over time.

Overall, *implementation fidelity* was adequate (mean score 6.5 out of 10), with nurses showing the highest scores, emphasising their role in chronic disease management. *Normalisation of the IMA intervention into clinical practice* was found to be well integrated into routine care (mean score 7.6 out of 10). GPs and nurses viewed shared decision-making as the core of the intervention, expressed willingness to continue its use, and appreciated the positive impact on their clinical practice. They reported increased awareness of their educational role advocating for patient autonomy. Pharmacists were less engaged, reporting overlooking the intervention and citing perceived

patient disinterest. Across all professional groups, shared decision-making was inconsistently applied; some clinicians adapted the information according to their opinion, and did not clearly distinguish shared decision-making from their usual practice, assuming they were already applying its principles.

The hypothesised *mechanisms of action* were partially supported. Positive changes among professionals were evident in increased knowledge, improved attitudes towards shared decision-making, and greater awareness of the importance of actively involving patients in treatment decisions. However, interprofessional cohesion and communication showed little change. Some patients felt actively engaged and appreciated the clear information and invitation to participate, whereas others felt uncomfortable and preferred clinician-led decisions.

Contextual factors shaped both the implementation process and the intervention's active mechanisms. At the individual level, younger patients were more open to shared decision-making. At the interaction level, continuity of care in primary care facilitated implementation, GPs and nurses typically work as a team and follow the same patients over time, which helped deliver aligned and consistent messages. Conversely, several organisational level barriers hindered implementation; limited consultation time and heavy workloads, lack of prior experience with shared decision-making among both professionals and patients, and—within the Spanish healthcare context [107,108]—persistent difficulties in fully integrating community pharmacists in healthcare interventions.

4.5 Scientific article 4

OBJECTIVE 4: Effectiveness evaluation

Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using real-world data

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ORIGINAL RESEARCH

OPEN ACCESS

Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using real-world data

Carmen Corral-Parteearroyo ,[1,2,3] Alba Sánchez-Viñas ,[1,3,4] Ignacio Aznar-Lou,[1,3] María Teresa Peñarrubia-María,[1,3,5] Montserrat Gil-Girbau ,[1,6] Carmen Gallardo-González ,[1,5,6] María del Carmen Olmos-Palenzuela ,[1,5,6] Maria Rubio-Valera [1,3,4]

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For numbered affiliations see end of article.

Correspondence to
Dr Ignacio Aznar-Lou; ignacio.aznar@sjd.es

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ABSTRACT

Introduction Non-adherence to cardiovascular disease and diabetes treatments contributes to suboptimal clinical outcomes and higher cost. The initial medication adherence (IMA) intervention is a multidisciplinary primary care (PC) intervention based on shared decision-making (SDM). The IMA-cluster-randomised controlled trial (cRCT) study evaluated the impact of the IMA intervention on medication initiation, secondary adherence and clinical outcomes compared with usual care (UC).

Methods This was a pragmatic cRCT with a hybrid effectiveness-implementation design which randomised 24 PC centres in Spain to intervention or UC. Patients receiving a new prescription of antihypertensive, lipid-lowering, antiplatelet and/or oral/injectable antidiabetic medication at the intervention centres (March 2022–September 2022) were attended by general practitioners (GPs), nurses and community pharmacists who had been trained in SDM and given decision aids (leaflets and website). Real-world data from prescription and dispensing records—used to assess medication initiation and secondary adherence (correct dosing and continued use)—and clinical outcome data from electronic health records were collected up to 18 months after initial prescription and analysed using multilevel regression models.

Results Overall, 4910 prescriptions were issued to 3629 patients (Intervention=2148; UC=1481) by 150 GPs (Intervention=91; UC=59). No differences were detected between groups in medication initiation or secondary adherence. Among clinical outcomes, only blood pressure outcomes favoured the IMA intervention, reflecting a small but clinically meaningful improvement.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Evidence on the impact of shared decision-making (SDM) on adherence and clinical outcomes for cardiovascular disease and diabetes pharmacological treatments remains limited and mixed, coming mostly from the USA and often associated with a high risk of bias.

WHAT THIS STUDY ADDS

⇒ The IMA-cRCT represents a large, pragmatic trial based on real-world data (RWD) that provides robust evidence on the effectiveness of SDM with high internal and external validity.

⇒ This study contributes to SDM research by focusing on medication adherence as a primary outcome—a rarely prioritised behavioural outcome in SDM trials—and by using RWD rather than self-reported measures to assess impact, while highlighting the inherent complexity of working with routinely collected data.

Original research

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further evidence is needed to understand for which patients and in which contexts SDM can positively affect health outcomes.

⇒ This study promotes a debate on the intrinsic value of SDM (improving patient and professional experience) irrespective of direct patient health outcomes.

Conclusions The IMA intervention had limited overall impact, with no effect on adherence, but showed potential benefits in blood pressure. However, SDM, as an ethically grounded approach, may enhance patients and professional experiences, supporting its consideration for broader implementation. Future efforts should prioritise these benefits by investing in professional training and patient support, addressing implementation challenges and deepening understanding of SDM effects, which would warrant further evaluation.

Trial registration number NCT05026775.

INTRODUCTION

Cardiovascular diseases (CVDs) and diabetes are major contributors to non-communicable disease morbidity and mortality.[1] Adherence to pharmacological treatments to control these conditions remains low; between 2% and 40% of prescribed medications are never initiated, and poor secondary adherence and discontinuation are common.[2–4] This results in worse disease control, higher morbidity and mortality and increased healthcare costs,[5–10] highlighting the need for effective interventions to improve adherence.

Patient-centred care interventions are increasingly being implemented across healthcare systems to enhance quality of care[11–13] and are particularly important for individuals with chronic conditions who face a succession of health-related decisions.[14 15] Shared decision-making (SDM) is a benchmark for quality care, and its inclusion in clinical prescribing guidelines has been advocated.[16 17] However, evidence regarding its effectiveness in improving medication adherence or clinical outcomes remains inconclusive.[18–22] The initial medication adherence (IMA) intervention is a theory-based[23 24] multidisciplinary patient-centred intervention designed to improve primary (medication initiation) and secondary adherence (correct dosing–medication implementation–and continued use over time–persistence) to CVD and diabetes pharmacological treatments prescribed in primary care (PC). It promotes health literacy and SDM at the time of a new prescription. Care is standardised among general practitioners (GPs), nurses and community pharmacists.

The IMA intervention was developed within the Medical Research Council Framework for complex interventions as part of the non-initiation project.[3 23–28] This paper presents Phase III, or the evaluation phase, a pragmatic effectiveness-implementation type I hybrid trial based on real-world data (RWD). Hybrid trials are essential for evaluating interventions in real-world contexts and facilitating the translation of research, not only by assessing effectiveness but also by understanding its implementation, how it works and the interaction of context with trial outcomes.[29 30] RWD has considerable potential for pragmatic trials, provides real-world outcomes, facilitates monitoring and follow-up, reduces costs and enables larger-scale trials with less involvement from researchers, eliminating the Hawthorne effect.[31 32] However, RWD presents challenges as it is not intended for research, leading to potential variability in data quality and consistency.[31 32]

This study aims to evaluate the effectiveness of a quality care-enhancing intervention, the IMA intervention, in comparison to usual care (UC) in improving initial and secondary medication adherence and clinical outcomes in patients with new pharmacological prescriptions for CVD or diabetes in PC using a cluster-randomised controlled trial (cRCT) based on RWD.

METHODS

Trial design

The IMA-cRCT is an effectiveness-implementation type I hybrid trial; a 7-month pragmatic cRCT (March 2022–September 2022) with an embedded process evaluation and economic modelling.[27 28] Patient follow-up was between 12 and 18 months depending on the specific outcome (online supplemental file 1). 24 PC teams were assigned to two parallel arms; 12 to UC and 12 to the IMA intervention group. See study protocol for further details on design and trial methods[27] (ClinicalTrials.gov trial registration n° NCT05026775).

This study is reported according to the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement: extension to cRCTs.[33]

Setting

The trial was conducted in urban and rural PC centres and community pharmacies in Catalonia, Spain. The Spanish National Healthcare System provides universal coverage, is tax-funded and services are free of charge, although pharmaceutical prescriptions are co-paid by patients based on employment and household income status.[34 35] PC is the access point to the healthcare system where most pharmacological prescriptions are managed. Generally, GPs carry out early detection, diagnosis and treatment of the most prevalent CVD and diabetes, and nurses monitor adherence and assess treatment results.[34] Medications can only be obtained at community pharmacies, which are considered private establishments of public interest. Pharmacists serve as dispensers and health agents by providing information and early detection of side effects.[34 36] Patients are free to choose any community pharmacy within or without their PC centre catchment area.

Study population

PC centre based teams are groups of GPs, nurses and other healthcare professionals that attend specific populations by area. All Catalan Health Institute PC centres were assessed for eligibility (n=287), randomly selected and paired according to location and non-initiation predictors.[25 27] The selected PC centres and healthcare professionals were invited to participate if inclusion criteria were fulfilled; (1) the manager agreed to participate and guarantee ethical standards; (2) at least five GPs in urban or two GPs in rural PC centres agreed to participate; and (3) GPs and nurses signed informed consent, were willing to attend intervention training and did not anticipate employment termination or interruption during the study period.

All community pharmacies located within the intervention PC centres catchment areas were invited to participate if inclusion criteria were fulfilled; (1) the manager agreed to guarantee ethical standards; (2) at least one pharmacist agreed to participate in the trial; and (3) pharmacists signed informed consent and were willing to attend intervention training. Pharmacies located within the catchment areas of the UC PC centres were neither contacted nor involved. In the intervention areas, the proportion of pharmacies that agreed to participate ranged from 10% to 100%.

To avoid contamination between both PC centres and community pharmacies, a maximum of one PC centre was selected per municipality if ≤100 000 inhabitants, or per neighbourhood (if municipality >100 000 inhabitants). At least 3 km between PC centres was ensured to prevent contamination.

All patients over 18 years old, who received a new lipid-lowering, antihypertensive, antiplatelet and antidiabetic medication prescription from a participating GP between March 2022 and September 2022, were identified from electronic health records (EHR) and included in the study. Patients' informed consent was obtained through simplified means.[27 37]

A prescription was considered new if a patient had no prescription/dispensation record of the same pharmacotherapeutic group in the previous 6 months. Each new prescription was considered the index prescription and patients were included as often as pharmacotherapeutic groups were prescribed. Pharmacotherapeutic groups were aggregated by pharmacological treatment; lipid-lowering medication, antihypertensive medication, antiplatelet medication and antidiabetic medication (online supplemental file 2). For this study, we refer to prescription as individual index prescriptions and to treatment as the aggregation of index prescriptions by pharmacological treatments.

Intervention

The IMA intervention is a patient-centred intervention aiming to improve medication initiation, secondary adherence and ultimately patient clinical outcomes by promoting SDM and standardising clinical practice among healthcare professionals (GPs, nurses and community pharmacists). Training was provided to all professionals on medication adherence, the principles of SDM and use of decision aids. GPs were trained to apply SDM during the consultation by informing the patient about their disease and available treatment options using decision aids (leaflets and a website[38]), and by exploring patient's perspective and questions before prescribing new pharmacological treatments for CVD or diabetes.[16 39] Nurses and pharmacists were encouraged to reinforce the information provided by GPs by addressing patients' questions and using decision aids. A full description of the intervention, its logic model and implementation strategy is described elsewhere.[28 40]

Usual care

Healthcare professionals in UC centres received no training or access to study decision aids. The prescription process is not standardised in Spain, nor is patient involvement in the decision-making process guaranteed when being prescribed a new treatment. Each GP decides how to provide disease and treatment-option information, and in some situations, it is the nurse who gives this information to the patient during a follow-up consultation. Nurses usually promote adherence by exploring any potential side-effects of prescribed treatments and monitoring clinical parameter results. Community pharmacists are expected to explore patients' information and queries about the medication during drug dispensing; however, this is not standardised.

Sample size

A proportion of 10% non-initiation for CVD and diabetes medications in Catalonia was assumed for sample size calculations.[3] To detect a 3% reduction in non-initiation with 80% power and 5% significance, given an intracluster correlation coefficient of 0.01, assuming that on average each GP issues 30 new prescriptions every 6 months, and estimating losses of 10% (incomplete EHR), 3878 prescriptions and 130 GPs were required. Therefore, 24 PC centres were contacted to reach the sample needed for both groups.

Randomisation

First, PC centres were matched in pairs (1:1) based on key characteristics of the PC teams—rurality/urbanity, area socioeconomic status, size of the population served, proportion of immigrant population and number of GPs in the team. For each pair, an ordered list of replacement centres with the same characteristics was randomly generated, to account for non-participation or ineligibility. Second, consent for participation was obtained. Finally, paired centres were randomised into UC or intervention groups using a computerised random number generator, ensuring allocation concealment at the cluster level.

Concealment of allocation for patients was unfeasible due to intrinsic cluster-design characteristics.

Blinding

Owing to the nature of the intervention, healthcare professionals and patients could not be blinded.

Data collection

All data were collected from the EHR (SIDIAP (Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària) database[41]), including patients' sociodemographic and clinical data, and information on dispensed medications at any Catalan community pharmacy (March 2021–December 2023). This database was encrypted, anonymised and provided RWD for research purposes under a legal and regulatory framework, following ethical principles and maintaining transparency.[41]

Outcomes

Baseline sociodemographic characteristics

Sociodemographic characteristics were collected at baseline (first index prescription): patient (sex, age, nationality, socioeconomic[42] and pharmacy copayment status, tobacco use and diagnoses (based on International Classification of Diseases-10 code)); prescribing GP (sex, age, population assigned and covered and care quality standards[43 44]); and PC centre (rurality and area socioeconomic status, size of the population served, proportion of immigrant population, number of GPs in the team and training centre).

Impact on adherence

Prescription and dispensation data from EHRs were compared to assess prescription adherence. The absence of data implies a non-existent prescription or dispensation. Data on the prescribed dose were unavailable. Most studied treatments involve a single daily dose, and medicine boxes generally contain 28 pills, therefore assumed to last 28 days.

Primary adherence or initiation (primary outcome measure): Prescriptions were considered initiated if obtained at any community pharmacy in Catalonia within 3 months after index prescription.[45] 1-month initiation, late initiation or initiation at any time after index prescription, and single prescription dispensation (only for initiated prescriptions with an active period >45 days) were also estimated.

Secondary adherence: For initiated treatments lasting ≥6 months, 6-month and 12-month secondary adherence was estimated. The level of adherence in terms of medication implementation, or correct dosing, was based on the *proportion of days covered (PDC)*; the number of days for which the prescription was available divided by the number of days from initiation to end of active prescription period.[45] Treatment PDC was estimated as a continuous measure and dichotomised as implemented if PDC ≥80%. *Persistence* was based on the time from initiation to discontinuation of treatment,[45] accepting a maximum gap of 2 months and classified as persistent if ≥1 prescriptions were not discontinued within each treatment. Finally, *total adherence* was estimated by combining the dichotomised PDC and persistence variables.

Impact on clinical outcomes

Clinical parameter observations from EHR were dated and could have been repeatedly registered for one patient at different time points during follow-up, from 12 months before the index prescription by treatment up to 18 months afterwards.

The impact on clinical outcomes was assessed per treatment as per clinical guidelines[46–48]; Antihypertensive: systolic and diastolic blood pressure; Antidiabetic: glycated haemoglobin and impaired fasting blood glucose; Lipid-lowering: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides. Cardiovascular risk (CVR) was assessed using the Framingham Risk Score, calculated per patient based on clinical outcomes (diabetes diagnosis, total cholesterol, HDL, systolic and diastolic blood pressure) and sociodemographic variables (age, sex and tobacco use). It was only calculated for patients aged 35–74 years, free of CVD or event, diabetes mellitus type I and familial hypercholesterolaemia as per the score authors and clinical guidelines.[48 49]

Statistical methods

Main analyses followed the intention-to-treat (ITT) principle (all patients treated by GPs who fulfilled inclusion criteria—signed an informed consent, were willing to attend intervention training and did not anticipate employment termination or interruption during the study period) and the per protocol (PP) principle (only patients who received a prescription by GPs who completed the training in the intervention group and visited a participating GP or nurse at least 7 days before or after the index prescription in both groups). The basic units of analysis were either prescriptions, patients or GPs based on the outcome (online supplemental file 3), and were performed using multilevel techniques clustered by PC centre and GP.

A descriptive analysis of baseline sociodemographic characteristics was performed at all levels to summarise differences between groups. Continuous variables were described using means and standard deviations (SD), and categorical variables using counts and percentages. Multiple imputation using chained equations (MICE) was applied to handle missing values for nationality and pharmacy copayment, which were required for covariate adjustment.

Impact on adherence

Intervention impact on adherence was assessed for prescriptions overall and for each aggregated treatment, estimated using multilevel logistic regression

models (linear regression when considering mean PDC) in which the dependent variable was adherence and the independent variable the group. Models were adjusted for randomisation matching variables and adherence predictors (age, nationality, teaching centre status and pharmacy copayment as a proxy for socioeconomic status[3 25]).[50 51] To account for missing data in nationality and pharmacy copayment, the models were run across imputed data sets and the results were combined following Rubin's rules.

Impact on clinical outcomes

The range and completion of clinical parameters on EHRs were assessed by summarising the data and identifying missing values. All values were within feasible ranges and completion rates ranged from 65% to 90% (online supplemental file 4). The differences between groups in the proportion of missing data were explored using logistic regression models. A missing at random pattern was assumed.

Multilevel linear repeated measures models gauged the impact of the intervention on clinical outcomes.[52] These allowed us to include varying numbers of observations and time points, account for within-patient correlation over time, consider the interaction between group and time and avoid excluding patients with partial measurements.

CVR was the clinical outcome with the highest proportion of missing data required for its calculation. Therefore, two imputation strategies were tested: multilevel repeated measure models and MICE (online supplemental file 5). CVR calculations estimated from the two strategies were very similar and the results presented are based on the more restrictive one: MICE.

Intervention impact was estimated per treatment on all clinical outcomes but CVR, which was estimated per patient using multilevel linear repeated measure models adjusted for randomisation matching variables and baseline covariates known to influence clinical outcomes (age, sex, nationality, tobacco use and pharmacy copayment as a proxy for socioeconomic status).[50 51] CVR and triglycerides were transformed to logarithmic scale to achieve a normal distribution. These observations were considered several times at diverse time points during follow-up, and the interaction 'time x group' as the independent variable. Time was measured in days, with index prescription time=0. All models were run across imputed databases to account for missing data, and Rubin's rules were used to combine the results.

Taking into account the maximum fraction of missing information, a total of 90 imputed data sets were generated for all the analyses.

Sensitivity analysis

Complete case analyses (patients attended by GPs who completed the 7-month study period and had 12-month follow-up) and model outputs without controlling for baseline characteristics to assess uncertainty were performed. A secondary analysis was performed by stratifying all the outcomes by sex (online supplemental file 9).

To assess the potential impact of the small number of clusters (n=24), we conducted additional sensitivity analyses applying small-sample corrections to those outcomes that showed statistically significant effects by applying Satterthwaite degrees-of-freedom corrections.[53]

Deviations from study protocol

There were deviations from the study protocol:[27] (1) Visits with participating GPs or nurses at least 7 days before or after the index prescription were included as PP cohort criteria; (2) Secondary adherence was calculated only for initiated treatments from initiation and not from the moment of prescription; (3) CVR was only calculated for 35–74 year-old patients, free of CVD, diabetes mellitus type I and familial hypercholesterolaemia as per the score authors and clinical guideline recommendations[48 49]; (4) Intervention impact on cardiovascular events was not explored due to follow-up duration constraints; (5) A secondary analysis limited to lipid-lowering prescriptions for secondary prevention was conducted, as these treatments are primarily recommended for such cases[48] (online supplemental file 10); (6) Following the recommendations of an external expert reviewer, two key adjustments were made: (a) statistical models were adjusted for prespecified randomisation matching variables and outcome baseline predictors identified in the literature,[50 51] rather than variables showing baseline significant differences, as originally outlined in the study protocol, and (b) small-cluster sample corrections were applied as sensitivity analyses for outcomes with statistically significant effects; (7) Based on the preliminary results, a post hoc exploratory hypothesis was formulated to explore whether the IMA intervention could have influenced *professionals' prescribing behaviour*—whether GPs in the intervention group issued fewer prescriptions following SDM implementation. The prescription monthly ratio (new IMA pharmacological treatments or otherwise) per 30 visits (mean visits per shift) made by participating GPs was compared between groups 12 months prior to and during the 7-month trial. The impact was estimated through multilevel repeated measure models which considered the ratio as the dependent variable and the interaction 'time x group' as the independent variable (online supplemental file 11); (8) Trial effectiveness results were shared in a focus group with professionals (online supplemental file 12) and, together with the process evaluation findings,[40] the opinions gathered on clinical implications and the intervention logic model were integrated to facilitate interpretation of trial outcomes and inform the discussion.

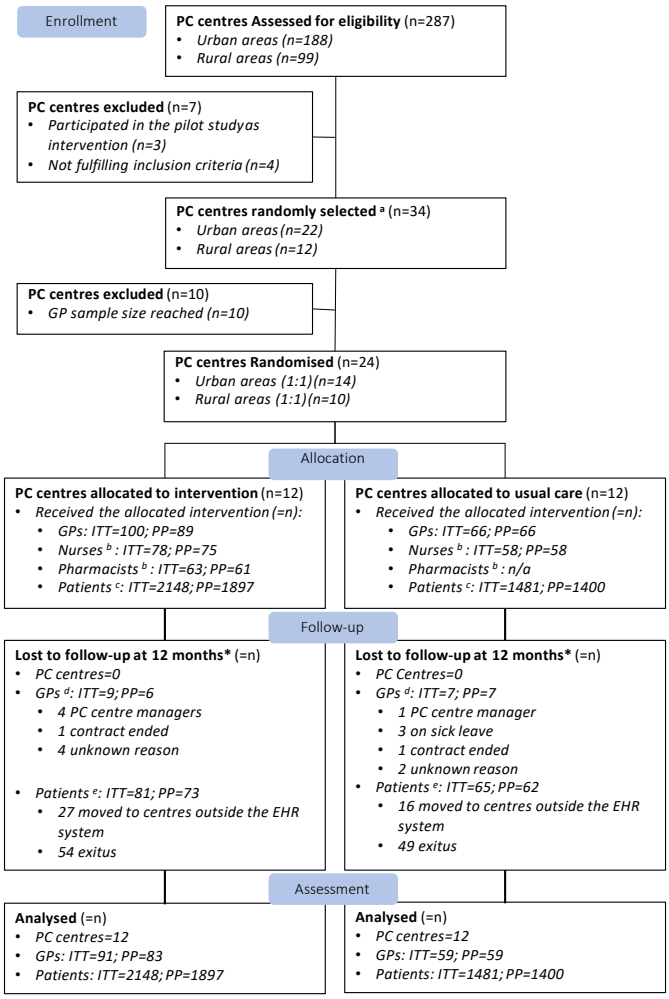

Figure 1 CONSORT flow diagram of participants. (a) Three centres declined to participate and their replacements were selected instead. (b) Nurses and pharmacists from the enrolled PC centres were allocated, they supported GPs but did not include patients in the trial. Data on these professionals were not available in the EHR and they were not included in the analysis. (c) Each patient can have >1 pharmacological treatment prescribed and/or >1 prescription per pharmacological treatment. (d) GPs were lost to follow-up when they were not identified in the EHR database. (e) Patients lost to follow-up were included in the analysis until their discharge date in the EHR. *42% of patients with antihypertensive treatments, 58% of patients with antidiabetic treatments and 42% of patients with lipid-lowering treatments were followed up >12 months (data used only for clinical parameters and cardiovascular risk impact evaluation). CONSORT, Consolidated Standards of Reporting Trials; GPs, general practitioners; ITT, intention-to-treat; PC, primary care.

RESULTS

Figure 1 shows the study flowchart. 24 PC centres, 150 GPs and 3629 patients (receiving 4910 prescriptions) were included and analysed. 16 included GPs (Intervention=9; UC=7) had no follow-up data in the EHR: 5 were managers with no prescription history, 3 were on sick leave, 2 had contract termination and 6 had no records for unknown reasons. Given the intrinsic RWD study characteristics, all patients were included in the analysis until their EHR discharge date; 103 patients died and 43 moved to centres outside the EHR system before follow-up completion. Nurses and pharmacists did not include patients in the study and were not identified in the EHR; therefore, no data on

these professionals were available, and they were not included in the statistical analyses.

Almost 95% of GPs and 91% of patients were included in the PP analyses. There were no relevant differences between ITT and PP analyses (online supplemental file 6) nor in any sensitivity analysis, including when small-cluster sample corrections were applied (analysis available on request), therefore only ITT main analysis results are reported and discussed in the main text.

Baseline characteristics of patients, GPs and PC centres are presented in table 1.

Impact on adherence

No differences were detected between groups in medication initiation (at 1 or 3 months), late initiation or single prescription dispensation or in PDC, persistence or total adherence at 6–12 months (table 2; by aggregated treatment see online supplemental file 7). Although persistence at 6 months reached statistical significance (p=0.043), the absolute difference was small. Similarly, in the stratified sex analysis, some statistically significant differences at 6 months were found in the male subgroup against the intervention, but these were also minor in magnitude (online supplemental file 9).

Impact on clinical outcomes

Tables 3 and 4 present the results of the multilevel repeated measures model and the model-based mean values for each group at baseline and 12 months postintervention (online supplemental file 8 shows raw clinical data). Statistically significant group and 'time x group' interaction in favour of the IMA intervention was observed for blood pressure. Based on model-based estimates, the mean extra 12-month reduction in the intervention group was 9.0 mm Hg for systolic and 3.7 mm Hg for diastolic blood pressure. When stratified by sex, this difference was observed only among females (online supplemental file 9). Statistically significant 'time x group' interactions were also observed for total cholesterol, LDL, HDL and triglycerides. However, these interactions favoured UC, and the overall 12-month differences between groups were small.

Impact on professionals' prescription behaviour (post hoc exploratory hypothesis)

No differences were detected between groups in GP new prescriptions/visits ratio for all prescriptions, although intervention GPs issued 0.3 more IMA study prescriptions per one shift (30 visits) 6 months postintervention (online supplemental file 11).

DISCUSSION

This study evaluated a patient-centred SDM intervention in PC to improve adherence to CVD and diabetes treatments, presenting a methodology for evaluating complex behavioural interventions in real-world settings using RWD. The IMA intervention had no impact on medication initiation or secondary adherence, with only a slight effect on blood pressure.

Our large-scale pragmatic trial used adherence (medication initiation) as the primary outcome, measured using robust RWD rather than self-reported methods. Most studies evaluating SDM interventions primarily focus on psychosocial or clinical outcomes, while behavioural outcomes like adherence are often treated as secondary, with small samples and methodological limitations leading to low-to-moderate evidence quality.[20 21 54–56] SDM research is primarily conducted in the USA or northern Europe, with few studies conducted in Spain and none targeting adherence as a primary outcome.[57–59] Few of these trials integrated process evaluations, limiting understanding on outcome mechanisms.

Consistent with prior studies on SDM's effects on adherence to diabetes or CVD treatments, the IMA intervention had no impact on adherence.[20 58 60–63] Overall, both groups improved clinical outcomes at 12 months, although clinically relevant between-group differences were observed in blood pressure, with a reduction shifting classification from hypertension to normal.[46] Total cholesterol, HDL, LDL and triglycerides showed clinically insignificant 12-month differences.[48] The impact of SDM interventions on clinical outcomes reported in the literature is inconclusive, with most studies showing no effect.[60 61 63] Previous SDM interventions failed to improve blood pressure[56 63] but showed positive effects on glycaemic control.[56 64] Notably, one study supported SDM's potential to improve the reach of treatment goals for blood pressure and glycated control.[62] These differences reflect SDM's contradictory evidence, with stronger effects on knowledge, trust, decisional conflict or satisfaction (typically primary outcomes) compared with adherence and clinical outcomes (often secondary) for which the evidence remains limited and generally of low-to-moderate quality.

The impact observed on clinical outcomes was not mediated by improved adherence. Therefore, we tested an exploratory hypothesis that SDM training might have led to fewer new treatments being indicated and accepted (ie, prescribed). However, analysis showed no change in overall prescription trends. In fact, GPs in the intervention group issued slightly more IMA prescriptions 6 months postintervention.

Adherence, as a dynamic behaviour, requires more than a single intervention to sustain long-term change, despite the importance of the moment of the initial prescription.[65] Although SDM can positively impact satisfaction, knowledge, communication and decision involvement,[21] it did not impact adherence, and its slight effect on blood pressure and mechanisms driving this change remain uncertain. Focus group feedback on clinical implications and intervention logic model

Table 1 Sample baseline characteristics: patient, professional and PC centre level

	Intervention	Usual care
Patient level	**n=2148**	**n=1481**
Sex % (N)		
Female	51.7 (1110)	48.5 (718)
Male	48.3 (1038)	51.5 (763)
Age mean (SD)	61.2 (13.9)	62.7 (13.8)
Nationality % (N)		
Spain	75.1 (1612)	61.6 (912)
Other	16.5 (355)	17.1 (254)
Missing	*8.4 (181)*	*21.3 (315)*
Postal code area % (N)		
Urban	77.2 (1659)	64.5 (955)
Rural	11.9 (255)	19.8 (294)
Missing	*10.9 (234)*	*15.7 (232)*
Socioeconomic deprivation* % (N)		
Low	14.5 (311)	11.4 (169)
Low intermediate	27.5 (590)	21.9 (324)
Intermediate	27.9 (600)	29.2 (433)
High intermediate	16.5 (355)	21.7 (322)
High	4.6 (99)	1.7 (25)
Missing	*9.0 (193)*	*14.0 (208)*
Pharmacy copayment % (N)		
Low-income population (0%)	17.0 (365)	17.6 (260)
Low–middle-income pensioners (10%)	32.2 (692)	32.3 (479)
Low-income non-pensioners (40%)	28.0 (602)	28.4 (421)
Middle–high-income non-pensioners (>50%)	21.1 (454)	19.5 (288)
Missing	*1.6 (35)*	*2.2 (33)*
Tobacco % (N)		
Non-smoker	64.3 (1382)	65.5 (970)
Smoker	29.1 (625)	27.2 (403)
Missing	*6.6 (141)*	*7.3 (108)*
Diagnosis records % (N)		
Lack of record	10.9 (234)	10.0 (148)
Record	89.1 (1914)	90.0 (1333)
Diabetes mellitus type 2 (E10–E14)	28.0 (602)	29.9 (443)
Dyslipidaemia (E70–E90)	47.9 (1029)	50.5 (748)
Hypertensive diseases (I10–I15)	60.0 (1288)	57.4 (850)
Coronary heart diseases (I20–I25)	4.8 (103)	5.7 (85)
Other heart diseases (I50–I52)	3.4 (72)	4.9 (72)
Cerebrovascular diseases (I60–I69)	5.4 (115)	5.1 (75)
Arterial diseases (I79–I79)	5.4 (115)	5.3 (78)
Acute and chronic kidney failure (N17–N19)	6.8 (145)	5.9 (88)
General Practitioner level	**n=91**	**n=59**
Sex % (N)		
Female	72.5 (66)	72.9 (43)
Male	27.5 (25)	27.1 (16)
Age % (N)		
18–45	36.3 (33)	37.3 (22)
45–55	42.9 (39)	40.7 (24)
≥55	20.9 (19)	22.0 (13)
Population assigned mean (SD)	1338.4 (346.7)	1333.7 (329.7)
Proportion of population covered mean (SD)	67.7 (10.8)	67.3 (10.1)
Healthcare quality standard in 2022 % (N)		
Low/intermediate	8.8 (8)	17.0 (10)
High	82.4 (75)	78.0 (46)

Continued

Table 1 Continued

	Intervention	Usual care
Missing	*8.8 (8)*	*5.0 (3)*
Pharmacological prescription quality standard in 2022% (N)		
Low	13.2 (12)	16.9 (10)
Intermediate	34.1 (31)	32.2 (19)
High	48.3 (44)	42.4 (25)
Missing	*4.4 (4)*	*8.5 (5)*
Primary care centre level	**n=12**	**n=12**
Area socioeconomic deprivation † % (N)		
Rural	41.7 (5)	41.7 (5)
Urban 1	16.7 (2)	8.3 (1)
Urban 2	8.3 (1)	16.7 (2)
Urban 3	16.7 (2)	8.3 (1)
Urban 4	16.7 (2)	25.0 (3)
Size of the population mean (SD)	18 640.5 (10 336.5)	18 195.9 (9598.0)
Proportion of immigrant population mean (SD)	16.6 (12.9)	13.7 (4.1)
Number of GPs mean (SD)	13.6 (5.5)	11.9 (6.1)
Training centre‡ % (N)	66.7 (8)	25.0 (3)

*Deprivation Index 2011 of the Spanish Society of Epidemiology (IP2011).[42]
†Area socioeconomic deprivation: four urban categories based on quartiles from low (urban 4) to high (urban 1) socioeconomic deprivation and a rural category.
‡Training centre: PC centres that host university students and clinical residents and have trained professionals as student supervisors.
GPs, general practitioners; N, number; PC, primary care; SD, standard deviation.

revealed professionals were surprised by the lack of adherence impact but improved blood pressure. They attributed this to increased awareness leading to better adherence to non-pharmacological measures, despite acknowledging these are usually harder for patients to follow (further details in online supplemental file 12). A complementary process evaluation study similarly found increased patient awareness, although it could

Table 2 Intervention impact on adherence: prescription level

	Intervention	Usual care	
Primary adherence	**n=2856**	**n=2054**	**P value**
Initiation % (N)			
1-month initiation	86.6 (2473)	85.8 (1762)	0.646
3-month initiation	91.3 (2607)	91.3 (1876)	0.708
Late initiation	94.2 (2689)	95.0 (1951)	0.857
Single prescription dispensation*	7.0 (182)	7.5 (141)	0.315
Secondary adherence by treatment†			
6-month secondary adherence	**n=2003**	**n=1415**	**P value**
Proportion of days covered (PDC)			
PDC ≥80% % (N)	49.4 (990)	48.2 (682)	0.121
PDC mean (SD)	73.8 (26.5)	72.6 (27.1)	0.082
Persistence % (N)	73.7 (1477)	72.2 (1022)	0.043
Total adherence % (N)	49.3 (988)	48.1 (681)	0.112
12-month secondary adherence	**n=2038**	**n=1432**	**P value**
Proportion of days covered (PDC)			
PDC ≥80% % (N)	48.8 (994)	47.2 (676)	0.341
PDC mean (SD)	70.9 (28.9)	69.5 (29.3)	0.205
Persistence % (N)	62.5 (1273)	60.2 (862)	0.186
Total adherence % (N)	47.0 (958)	45.5 (651)	0.304

All intraclass correlation coefficients (ICCs) indicate minimal variability across GPs and PC centres.
P values estimated by multilevel logistic regression models in all but PDC-mean (multilevel linear regression model).
*Single prescription dispensation in 3-month initiators sample (Intervention=2607; UC=1876).
†Secondary adherence was calculated by aggregating prescriptions by pharmacological treatment and considering 3-month initiators with an active prescription period of ≥6 months from the first pharmacy refill at 6 and 12 months.
GPs, general practitioners; N, number; PC, primary care; SD, standard deviation; UC, usual care.

Table 3 Multilevel model b-coefficients (95% CI) and p values of clinical outcomes impact models: prescriptions aggregated by pharmacological treatment

	b-coefficients (95% CI)	P value
Antihypertensive*		
Systolic blood pressure (mm Hg)		
Constant	139.81 (134.36 to 145.25)	0.000
Group		
Usual care	Ref	
Intervention	−6.09 (−7.13 to −5.06)	0.000
Time (days)	−0.01 (−0.01 to −0.008)	0.000
Time (days) × group interaction	−0.008 (−0.01 to −0.004)	0.000
Diastolic blood pressure (mm Hg)		
Constant	101.48 (97.65 to 105.31)	0.000
Group		
Usual care	Ref	
Intervention	−2.22 (−2.85 to −1.58)	0.000
Time (days)	−0.006 (−0.008 to −0.005)	0.000
Time (days) × group interaction	−0.004 (−0.006 to −0.002)	0.001
Antidiabetic*		
Blood glucose (mg/dL)		
Constant	158.91 (131.89 to 185.93)	0.000
Group		
Usual care	Ref	
Intervention	−21.76 (−28.56 to −14.97)	0.000
Time (days)	−0.02 (−0.03 to −0.007)	0.001
Time (days) × group interaction	0.004 (−0.02 to 0.03)	0.663
Glycated haemoglobin (%)		
Constant	8.15 (7.31 to 8.98)	0.000
Group		
Usual care	Ref	
Intervention	−0.32 (−0.55 to −0.09)	0.006
Time (days)	−0.0009 (−0.001 to −0.0005)	0.000
Time (days) × group interaction	−0.0004 (−0.001 to 0.0003)	0.250
Lipid–lowering*		
Total cholesterol (mg/dL)		
Constant	248.21 (224.83 to 271.58)	0.000
Group		
Usual care	Ref	
Intervention	−46.89 (−52.84 to −40.94)	0.000
Time (days)	−0.06 (−0.07 to −0.05)	0.000
Time (days) × group interaction	0.07 (0.05 to 0.09)	0.000
High-density lipoprotein (mg/dL)		
Constant	42.16 (34.52 to 49.81)	0.000
Group		
Usual care	Ref	
Intervention	−2.71 (−3.94 to −1.48)	0.000
Time (days)	0.0007 (−0.001 to 0.003)	0.490
Time (days) × group interaction	0.005 (0.001 to 0.009)	0.011
Low-density lipoprotein (mg/dL)		
Constant	142.68 (121.69 to 163.67)	0.000
Group		
Usual care	Ref	
Intervention	−44.55 (−49.82 to −39.28)	0.000
Time (days)	−0.05 (−0.06 to −0.04)	0.000
Time (days) × group interaction	0.06 (0.05 to 0.08)	0.000
Triglycerides (mg/dL)		
Constant	140.77 (124.42 to 159.26)	0.000
Group		
Usual care	Ref	
Intervention	0.82 (0.78 to 0.87)	0.000
Time (days)	0.9998 (0.9997 to 0.9999)	0.000
Time (days) × group interaction	1.0002 (1.00006 to 1.0004)	0.007
Cardiovascular risk†		
Constant	3.65 (3.45 to 3.87)	0.000
Group		
Usual care	Ref	
Intervention	0.94 (0.92 to 0.97)	0.000
Time (days)	0.9998 (0.9997 to 0.9998)	0.000
Time (days) × group interaction	0.99990 (0.9998 to 1.00003)	0.137

All intraclass correlation coefficients (ICCs) indicate minimal variability across GPs and PC centres.
P values estimated by multilevel repeated measures models.
Coefficients are presented as mean differences in the dependent variable (beta).
*Prescription level by pharmacological treatment:(1) Antihypertensive: Intervention=1135; UC=784; (2) Antidiabetic: Intervention=414; UC=303; (3) Lipid-lowering: Intervention=765; UC=521.
†Patient level from 35 to 74 years old and free of CVD, DM1 and familial hypercholesterolaemia: Intervention=1490; UC=987.
CVD, cardiovascular disease; DM1, diabetes mellitus type 1; GPs, general practitioners; PC, primary care; UC, usual care.

not confirm an influence on non-pharmacological measures.[40] Adherence behaviour includes pharmacological and non-pharmacological treatment components, and the former, along with refilling medication, includes correct dosing and regularity.[66] While the method used to measure adherence in this study is consistent and widely used, and medication collection was similar across groups, we cannot determine if more precise adherence in the intervention group contributed to clinical changes.

When exploring sex differences, the blood pressure decrease was only observed in females. While no direct evidence links SDM interventions to gender-specific effects, research suggests that female physician–female patient interactions can enhance patient-centred care and health outcomes.[67–69] Since most GPs in this study were women, this finding might align with previous research but requires further investigation.

In the context of a type I effectiveness-implementation hybrid trial, a process evaluation was conducted to help interpret the trial findings.[40] Triangulating results from the effectiveness and process evaluations provided insights into the observed lack of effect. Findings from the process evaluation showed that although professionals valued the training, many felt it was insufficient, highlighting the need for ongoing training.[40] Although patients reported feeling engaged and most

Table 4 Multilevel model-based clinical outcomes mean (SE) at baseline and 12 months follow-up: prescriptions aggregated by pharmacological treatment

	Intervention	Usual care	
Antihypertensive*	**n=1135**	**n=784**	**P value**
Systolic blood pressure (mm Hg)			
Baseline	133.7 (2.8)	139.8 (2.8)	0.000
12 months	127.1 (2.8)	136.1 (2.8)	0.000
Diastolic blood pressure (mm Hg)			
Baseline	99.3 (1.9)	101.5 (1.9)	0.000
12 months	95.5 (1.9)	99.1 (1.9)	0.000
Antidiabetic*	**n=414**	**n=303**	**P value**
Blood glucose (mg/dL)			
Baseline	137.1 (14.1)	158.9 (13.8)	0.000
12 months	132.5 (13.9)	152.5 (13.9)	0.000
Glycated haemoglobin (%)			
Baseline	7.8 (0.4)	8.1 (0.4)	0.006
12 months	7.4 (0.4)	7.8 (0.4)	0.000
Lipid-lowering*	**n=765**	**n=521**	**P value**
Total cholesterol (mg/dL)			
Baseline	201.3 (12.3)	248.2 (11.9)	0.000
12 months	206.1 (12.1)	226.3 (12.3)	0.000
High-density lipoprotein (mg/dL)			
Baseline	39.5 (3.9)	42.2 (3.9)	0.000
12 months	41.6 (3.9)	42.4 (3.9)	0.214
Low-density lipoprotein (mg/dL)			
Baseline	98.1 (11.0)	142.7 (10.7)	0.000
12 months	102.8 (10.8)	124.5 (10.8)	0.000
Triglycerides (mg/dL)			
Baseline	115.8 (7.8)	140.8 (8.9)	0.000
12 months	117.0 (7.5)	130.6 (8.5)	0.000
Cardiovascular risk†	**n=1490**	**n=987**	**P value**
Baseline	3.5 (0.1)	3.7 (0.1)	0.000
12 months	3.0 (0.1)	3.3 (0.1)	0.000

P values estimated from linear combination of estimates following multilevel repeated measures models.
*Prescription level by pharmacological treatment.
†Patient level from 35 to 74 years old and free of CVD, DM1 and familial hypercholesterolaemia.
CVD, cardiovascular disease; DM1, diabetes mellitus type 1.

professionals indicated that they had integrated SDM into routine practice, some perceived no difference between the intervention and UC.[40] This highlights the challenge of promoting behavioural change when professionals believe they are already implementing SDM. While attitudes towards SDM and its perceived benefits improved, implementation was inconsistent due to time constraints and ingrained habits that often exclude patients from decision-making.[40] Furthermore, patients appreciated involvement but noted it did not always influence their decision to start medication.[40] Despite these challenges, both professionals and patients reported an overall positive experience with the intervention, suggesting it might add value beyond clinical outcomes.

While the impact on adherence or clinical outcomes may be limited, SDM enhances the experiences of patients and healthcare professionals.[40] Within value-based healthcare, its ability to endorse quality of care and patient engagement warrants discussion on its broader implementation. Rooted in ethical principles, SDM respects patients' right to informed choices as the foundation of professional practice.[70] It promotes autonomy and active participation, while repeated SDM practice enhances professionals' communication skills and the quality of health information provided.[70 71] Beyond individual interactions, SDM can foster a culture of collaboration, encouraging patients to critically evaluate decisions, weigh benefits and harms and ultimately share responsibility in healthcare.[13]

Nevertheless, implementing SDM is complex and requires sustained efforts to achieve and maintain its adoption. It involves behavioural changes among professionals, patients and the healthcare system. While rooted habits in healthcare and organisational

constraints pose challenges, addressing these barriers and promoting SDM offers the opportunity to build a more inclusive, patient-centred healthcare system.

Strengths and limitations

The IMA-cRCT is a large, methodologically robust study designed to ensure reliable and reproducible results. Its cRCT design minimised bias, achieved statistical power, employed rigorous analysis for accurate finding interpretation and ensured representativeness through random sampling of the centres. By using a hybrid effectiveness-implementation approach, the trial enhanced pragmatism, addressing both dimensions and providing comprehensive insights for clinical decision-making and research translation.

The use of RWD as part of the pragmatic trial enabled a large sample size, reduced researcher involvement and improved transferability, but presented challenges. These were addressed through tailored analytical strategies, but assumptions and imputation methods were necessary.[72] For instance, measuring adherence through pharmacy dispensation may have overestimated adherence, as refilling medication does not guarantee it was taken. Clinical parameter observations, based on guideline recommendations, were not always followed in practice, and variations in measurement time points and missing data were observed.

The pragmatic nature of the study hampered identification of which professionals actually delivered the intervention in the PP analysis. Additionally, while RWD offered valuable insights into adherence and clinical outcomes unattainable with traditional trials, it may not capture specific behaviours potentially influenced by SDM affecting clinical outcomes, indicating a need for further research. Notably, no direct, proximal measures of SDM uptake or professional behaviour were included, limiting the understanding of the intervention mechanisms. This was a deliberate trade-off to maintain the trial's pragmatism, while exploring insights into the intervention mechanisms through the complementary process evaluation.[40] A further contextual limitation relates to the pharmacy component as patients are free to use any pharmacy, and dispensing data are not linked to specific establishments. As a result, actual exposure to this component of the intervention could not be assessed through RWD.

CONCLUSIONS

This study indicates that the IMA intervention, based on SDM models, does not improve medication adherence in the current context. While a modest positive effect in blood pressure was observed, the mechanisms of action underlying this effect remain unclear. Future efforts should balance the benefits of enhanced patient and professional experiences with the resource implications of SDM implementation and additional care costs. Continued investment in professional training, patient support and research to address implementation challenges is essential to fully understand and enhance the benefits of SDM, which would warrant further evaluation.

Author affiliations
[1]Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, St Boi de Llobregat, Catalonia, Spain
[2]Department of Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine and Public Health, Universitat Autònoma de Barcelona, Bellaterra, Catalonia, Spain
[3]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Madrid, Spain
[4]Department of Medicine, Universitat de Barcelona, Barcelona, Catalonia, Spain
[5]Primary Care Centre Bartomeu Fabrés Anglada, Primary Care Research Institute (IDIAP Jordi Gol), Catalan Institute of Health South Metropolitan Territory Management, Barcelona, Catalonia, Spain
[6]Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Barcelona, Catalonia, Spain

X Ignacio Aznar-Lou @Ignaznar

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Ethics approval This study involves human participants and was approved by the Drug Research Committee (CEIm) at IDIAP Jordi Gol, codeCEIm 21/051-P. Informed consent from the patients was obtained by simplified means in the cRCT. The IMA-cRCT is a low-intervention clinical trial where groups of subjects are allocated to the intervention groups and which satisfies all the conditions described in paragraphs 2 and 3 of article 30 of EU regulation Nº 536/2014. Informed consent was obtained by displaying posters in prominent locations of the participating PC centres notifying people that a clinical trial was being conducted in the centre and that patients could be part of this comparative study. The posters contained information on how and why the trial was being conducted and what the implications of participating in the study were. It was clearly stated that patients could request extra information and decline to participate in the study. Professionals in the intervention and usual care PC centres

were trained to deal with patients' queries regarding the study. If patients declined to participate, this information was documented by physicians in the electronic health records and data from those patients was not used for the trial. Furthermore, patients could withdraw at any time from the clinical trial without any detriment.Healthcare professionals' participation was entirely voluntary. All healthcare professionals participating in the study signed an informed consent at the time of the first training session. They had the right to refuse to participate and to withdraw from the study at any time.The electronic health records database used met all legal requirements and it was encrypted and pseudonymised so that researchers did not have access to data that identified the patients or professionals.

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ORCID iDs

Carmen Corral-Partearroyo http://orcid.org/0000-0001-9517-4916
Alba Sánchez-Viñas http://orcid.org/0000-0001-5020-7534
Montserrat Gil-Girbau http://orcid.org/0000-0002-4396-6492
Carmen Gallardo-González http://orcid.org/0000-0003-0688-1366
María del Carmen Olmos-Palenzuela http://orcid.org/0000-0003-4078-6717
Maria Rubio-Valera http://orcid.org/0000-0003-2856-1697

REFERENCES

1 World Health Organization. *Noncommunicable diseases progress monitor*. Geneva, 2017. Available: http://apps.who.int/iris/bitstream/10665/258940/1/9789241513029-eng.pdf
2 Lemstra M, Nwankwo C, Bird Y, *et al*. Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Prefer Adherence* 2018;12:721–31.
3 Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, *et al*. Initiation and Single Dispensing in Cardiovascular and Insulin Medications: Prevalence and Explanatory Factors. *Int J Environ Res Public Health* 2020;17:3358.
4 Chowdhury R, Khan H, Heydon E, *et al*. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
5 World Health Organization. *Adherence to long-term therapies. Evidence for action*. Geneva, 2003. Available: https://iris.who.int/handle/10665/42682
6 Ettehad D, Emdin CA, Kiran A, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–67.
7 Mancia G, Rea F, Corrao G. Adherence to antihypertensive and cardiovascular preventive treatment: the contribution of the Lombardy database. In: *Drug adherence in hypertension and cardiovascular protection*. 2018: 123–41.
8 De Vera MA, Bhole V, Burns LC, *et al*. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol* 2014;78:684–98.
9 Kim Y-Y, Lee J-S, Kang H-J, *et al*. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. *Sci Rep* 2018;8:12190.
10 Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e016982.
11 Institute of Medicine (US) Committee on Quality of Health Care in America. *Crossing the quality chasm: a new health system for the 21st century*. Washington (DC): National Academies Press, 2001.
12 Elwyn G, Dehlendorf C, Epstein RM, *et al*. Shared decision making and motivational interviewing: achieving patient-centered care across the spectrum of health care problems. *Ann Fam Med* 2014;12:270–5.
13 Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: consider all the consequences. *Implement Sci* 2016;11:114.
14 American Geriatrics Society Expert Panel on Person-Centered Care. Person-Centered Care: A Definition and Essential Elements. *J Am Geriatr Soc* 2016;64:15–8.
15 Søgaard MB, Andresen K, Kristiansen M. Systematic review of patient-engagement interventions: potentials for enhancing person-centred care for older patients with multimorbidity. *BMJ Open* 2021;11:e048558.
16 Elwyn G, Frosch D, Thomson R, *et al*. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012;27:1361–7.
17 Tichelaar J, Richir MC, Garner S, *et al*. WHO guide to good prescribing is 25 years old: quo vadis? *Eur J Clin Pharmacol* 2020;76:507–13.
18 Nieuwlaat R, Wilczynski N, Navarro T, *et al*. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;2014:CD000011.
19 Dwamena F, Holmes-Rovner M, Gaulden CM, *et al*. Interventions for providers to promote a patient-centred approach in clinical consultations. *Cochrane Database Syst Rev* 2012;12:CD003267.
20 Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, *et al*. Interventions to support shared decision making for medication therapy in long term conditions: A systematic review. *Patient Educ Couns* 2020;103:254–65.
21 Légaré F, Adekpedjou R, Stacey D, *et al*. Interventions for increasing the use of shared decision making by healthcare professionals. *Cochrane Database Syst Rev* 2018;7:CD006732.
22 Bruch JD, Khazen M, Mahmic-Kaknjo M, *et al*. The effects of shared decision making on health outcomes, health care

quality, cost, and consultation time: An umbrella review. *Patient Educ Couns* 2024;129:108408.
23 Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, *et al.* Reasons for medication non-initiation: A qualitative exploration of the patients' perspective. *Res Social Adm Pharm* 2020;16:663–72.
24 Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, *et al.* Non-initiation of prescribed medication from a Spanish health professionals' perspective: A qualitative exploration based on Grounded Theory. *Health Soc Care Community* 2022;30:e213–21.
25 Aznar-Lou I, Fernández A, Gil-Girbau M, *et al.* Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. *Br J Clin Pharmacol* 2017;83:1328–40.
26 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, *et al.* Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention. *Front Public Health* 2022;10:1038138.
27 Sánchez-Viñas A, Corral-Partearroyo C, Gil-Girbau M, *et al.* Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study). *BMC Prim Care* 2022;23:170.
28 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, *et al.* Complex multidisciplinary intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol. *BMJ Open* 2022;12:e067468.
29 Curran GM, Bauer M, Mittman B, *et al.* Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* 2012;50:217–26.
30 Ullman AJ, Beidas RS, Bonafide CP. Methodological progress note: Hybrid effectiveness-implementation clinical trials. *J Hosp Med* 2022;17:912–6.
31 Zhu M, Sridhar S, Hollingsworth R, *et al.* Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective. *Contemp Clin Trials* 2020;94:105856.
32 Ho YF, Hu FC, Lee PI. The Advantages and Challenges of Using Real-World Data for Patient Care. *Clin Transl Sci* 2020;13:4–7.
33 Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661.
34 Bernal-Delgado E, Garcia-Armesto S, Oliva J, *et al.* Spain: Health System Review. *Health Syst Transit* 2018;20:1–179.
35 Ministerio de Sanidad Servicios Sociales e Igualdad. *Prestación Farmacéutica en el Sistema Nacional de Salud, 2022*. Madrid, 2022. Available: https://www.sanidad.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2022/Informe_PrestacionFarmaceutica_2022.pdf
36 Gobierno de España. Ley 14/1986, de 25 de abril, General de Sanidad. 1986 Available: https://www.boe.es/buscar/act.php?id=BOE-A-1986-10499
37 European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536 [Accessed 05 Dec 2024].
38 Iniciadores. IMA-cRCT. 2022 Available: https://www.iniciadores.es/
39 Elwyn G, Edwards A, Kinnersley P, *et al.* Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. *Br J Gen Pract* 2000;50:892–9.
40 Corral-Partearroyo C, Sánchez-Viñas A, Peñarrubia-María MT, *et al.* Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation. *BMJ Qual Saf* 2025;0:1–14.
41 SIDIAP. Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària. 2022 Available: https://sidiap.org/index.php/ca/
42 Duque I, Domínguez-Berjón MF, Cebrecos A, *et al.* Índice de privación en España por sección censal en 2011. *Gac Sanit* 2021;35:113–22.
43 Fina Avilés F, Méndez Boo L, Medina Peralta M. Sistema de Información de los Servicios de Atención Primaria. La experiencia 2006-2008 del Institut Català de la Salut. *Risai Rev Innovación Sanit y Atención Integr* 2008;1:1–18.
44 Vila Córcoles A, Ansa Echevarría X, Gómez Sorribes A, *et al.* [EQA-17: proposing a synthetic indicator to measure the outcomes of primary care teams in people over 14 years]. *Rev Esp Salud Publica* 2006;80:17–26.
45 Vrijens B, De Geest S, Hughes DA, *et al.* A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
46 Coll de Tuero G, Dalfó i Baqué A, de la Figuera Von Wichmann M, *et al.* Guies de pràctica clínica. Hipertensió Arterial. 2012. Available: https://scientiasalut.gencat.cat/handle/11351/4540.2
47 Mata M, Xavier Cos F, Morros R, *et al.* Guies de pràctica clínica. Abordatge de la diabetis mellitus tipus 2. 2013. Available: https://scientiasalut.gencat.cat/handle/11351/4514
48 Franzi Sisó A, Armengol Alegre J, Baena Díez J, *et al.* Guia de lípids i risc cardiovascular. 2021. Available: https://scientiasalut.gencat.cat/handle/11351/5955.2
49 Marrugat J, Solanas P, D'Agostino R, *et al.* Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. *Rev Esp Cardiol* 2003;56:253–61.
50 European Medicines Agency (EMA). Guideline on adjustment for baseline covariates in clinical trials. 2015. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf
51 Wright N, Ivers N, Eldridge S, *et al.* A review of the use of covariates in cluster randomized trials uncovers marked discrepancies between guidance and practice. *J Clin Epidemiol* 2015;68:603–9.
52 Twisk JWR. *Multilevel analysis in longitudinal studies. Applied multilevel analysis: a practical guide*. Cambridge University Press, 2006:86–107.
53 Leyrat C, Morgan KE, Leurent B, *et al.* Cluster randomized trials with a small number of clusters: which analyses should be used? *Int J Epidemiol* 2018;47:321–31.
54 Kew KM, Malik P, Aniruddhan K, *et al.* Shared decision-making for people with asthma. *Cochrane Database Syst Rev* 2017;10:CD012330.
55 Barradell AC, Gerlis C, Houchen-Wolloff L, *et al.* Systematic review of shared decision-making interventions for

people living with chronic respiratory diseases. *BMJ Open* 2023;13:e069461.
56 Elias S, Chen Y, Liu X, *et al*. Shared Decision-Making in Cardiovascular Risk Factor Management: A Systematic Review and Meta-Analysis. *JAMA Netw Open* 2024;7:e243779.
57 Coronado-Vázquez V, Gómez-Salgado J, Cerezo-Espinosa de Los Monteros J, *et al*. Shared Decision-Making in Chronic Patients with Polypharmacy: An Interventional Study for Assessing Medication Appropriateness. *J Clin Med* 2019;8:904.
58 Perestelo-Pérez L, Rivero-Santana A, Boronat M, *et al*. Effect of the statin choice encounter decision aid in Spanish patients with type 2 diabetes: A randomized trial. *Patient Educ Couns* 2016;99:295–9.
59 Granados-Santiago M, Valenza MC, López-López L, *et al*. Shared decision-making and patient engagement program during acute exacerbation of COPD hospitalization: A randomized control trial. *Patient Educ Couns* 2020;103:702–8.
60 Saheb Kashaf M, McGill ET, Berger ZD. Shared decision-making and outcomes in type 2 diabetes: A systematic review and meta-analysis. *Patient Educ Couns* 2017;100:2159–71.
61 Branda ME, LeBlanc A, Shah ND, *et al*. Shared decision making for patients with type 2 diabetes: a randomized trial in primary care. *BMC Health Serv Res* 2013;13:301.
62 Buhse S, Kuniss N, Liethmann K, *et al*. Informed shared decision-making programme for patients with type 2 diabetes in primary care: cluster randomised controlled trial. *BMJ Open* 2018;8:e024004.
63 Tinsel I, Buchholz A, Vach W, *et al*. Shared decision-making in antihypertensive therapy: a cluster randomised controlled trial. *BMC Fam Pract* 2013;14:135.
64 Geta ET, Terefa DR, Hailu WB, *et al*. Effectiveness of shared decision-making for glycaemic control among type 2 diabetes mellitus adult patients: A systematic review and meta-analysis. *PLoS One* 2024;19:e0306296.
65 Chapman S, Frostholm L, Chalder T, *et al*. Preventing medication nonadherence: a framework for interventions to support early engagement with treatment. *Health Psychol Rev* 2024;18:884–98.
66 Gellad WF, Thorpe CT, Steiner JF, *et al*. The myths of medication adherence. *Pharmacoepidemiol Drug Saf* 2017;26:1437–41.
67 Bertakis KD, Azari R. Patient-centered care: the influence of patient and resident physician gender and gender concordance in primary care. *J Womens Health (Larchmt)* 2012;21:326–33.
68 Chekijian S, Kinsman J, Taylor RA, *et al*. Association between patient-physician gender concordance and patient experience scores. Is there gender bias? *Am J Emerg Med* 2021;45:476–82.
69 Lau ES, Hayes SN, Volgman AS, *et al*. Does Patient-Physician Gender Concordance Influence Patient Perceptions or Outcomes? *J Am Coll Cardiol* 2021;77:1135–8.
70 Elwyn G, Tilburt J, Montori VM. The ethical imperative for shared decision-making. *EJPCH* 2013;1:129.
71 Tang C, Wang A, Yan J. Exploring motivations and resistances for implementing shared decision-making in clinical practice: A systematic review based on a structure-process-outcome model. *Health Expect* 2022;25:1254–68.
72 Gianfrancesco MA, Goldstein ND. A narrative review on the validity of electronic health record-based research in epidemiology. *BMC Med Res Methodol* 2021;21:234.

4.5.1 Main results overview – Scientific article 4

The effectiveness of the IMA intervention was assessed through a 7-month pragmatic cRCT using real-world data from 24 primary care centres across Catalonia (randomised 1:1). A total of 4910 prescriptions were issued to 3629 patients (Intervention: 2148; Usual care: 1481) by 150 GPs.

The results showed no significant differences between groups in primary adherence (*medication initiation*) or secondary adherence (*proportion of days covered* and *persistence*). The only *clinically relevant outcome* was a significant reduction in blood pressure among patients prescribed antihypertensives. At 12 months, the intervention group experienced an additional reduction of 9.0 mmHg in systolic and 3.7 mmHg in diastolic blood pressure compared to usual care, shifting classification from hypertension to normal, with the effect especially marked in female patients.

A post-hoc analysis based on the intervention's logic model hypothesised that shared decision-making might have influenced professional prescribing behaviour, potentially preventing prescriptions unlikely to be initiated. However, this was not supported, as a slight increase in prescriptions was observed in the intervention arm.

Triangulation with findings from the process evaluation suggested that despite professionals' positive perceptions of the intervention's training and decision aids, the inconsistent application of the intervention in daily practice—mainly due to time constraints, high workload, and the assumption that shared decision-making was already being practised—likely limited its effectiveness. Similarly, while some patients appreciated being actively involved in decisions, others preferred to defer to the clinician's decision.

5

Discussion

5 DISCUSSION

This thesis presents the development, implementation, and evaluation of a complex, theory-informed intervention aimed at improving initial medication adherence among patients receiving new prescriptions for CVD and diabetes treatments in primary care.

Initially, a pilot study was conducted to assess the feasibility and acceptability of the initial version of the IMA intervention and the viability of the pragmatic evaluation design. The study demonstrated that the IMA intervention could be delivered in routine primary care and that real-world data could support the outcome assessment. However, it identified the need to strengthen professional engagement strategies, enhance shared decision-making training, optimise patient decision aids, and develop tailored analytical strategies to address missing clinical data in electronic health records.

The iterative refinement process led to a clear logic model articulating the intervention's theory of change and hypothesised mechanisms of action, clarifying how it was expected to influence professionals' and patients' behaviours and guiding the implementation and evaluation of the intervention. In addition, the final design of a pragmatic type I hybrid effectiveness-implementation evaluation study was defined, combining a pragmatic cRCT with an embedded process evaluation.

The process evaluation showed that the intervention was generally well integrated into practice, with adequate fidelity and positive experiences among professionals and patients. However, shared decision-making was inconsistently applied in routine care, partly due to professionals assuming

they were already practising it and patients' varied preferences for involvement in the decision. The pragmatic cRCT found no significant improvements in initial or secondary medication adherence compared to usual care. Nevertheless, it identified a clinically meaningful reduction in blood pressure among patients prescribed antihypertensive medication, suggesting potential indirect benefits of shared decision making through unknown mechanisms. Together, the effectiveness-implementation findings highlight both the promise and the challenges of embedding shared decision-making in primary care and underscore its intrinsic value in improving patients' and professionals' experiences that enhance overall quality of care.

This section discusses the above main findings by first examining the methodological strengths and limitations underpinning the research. It then explores the implications for clinical practice of implementing patient-centred interventions in real-world settings, followed by the methodological contributions of this work, particularly the practical application of a framework for behavioural intervention development and evaluation, and the use of a pragmatic hybrid study design. Finally, the section offers recommendations for future research.

5.1 Strengths and limitations

The results of this thesis should be interpreted considering several methodological strengths and limitations. While each scientific article outlines the specific strengths and limitations of its respective study, this section provides an overarching reflection on the strengths and limitations of the combined work.

This thesis offers notable strengths. It has applied a rigorous framework and a hybrid pragmatic design, which allowed simultaneous evaluation of both effectiveness and implementation of the IMA intervention in real-world conditions. The intervention and its logic model were developed iteratively, guided by theory and pilot results, ensuring contextual relevance while exploring the mechanisms of action. The use of real-world data extracted from electronic health records enhanced the external validity and practical applicability of the findings. The mixed-methods process evaluation deepened the understanding of how the intervention was implemented, what mechanisms of action were confirmed, and how contextual factors influenced outcomes. Finally, the transparent and systematic use of established frameworks and tools—carefully documented and published throughout all phases of the project—increases the reproducibility and transferability of the research, positioning it as a model for future evaluations of complex interventions in primary care.

Nevertheless, this thesis presents several limitations that must be acknowledged. First, the use of a pragmatic trial design—while enhancing external validity—inevitably reduced control of the implementation of the IMA intervention, introducing variability in how the intervention was delivered across settings and professionals [109,110]. Although this reflects real-world conditions, it complicates attribution of observed effects solely to the intervention. Similarly, the intervention's exposure could not be individually measured or verified at the patient level, which may have diluted the effect size [109,110]. These limitations are inherent to pragmatic studies, but this research embraced them transparently, and the design choices were

justified based on the goal of producing scalable evidence for routine practice.

Likewise, the reliance on real-world data from electronic health records posed important challenges. While real-world data enabled large-scale outcome monitoring under routine conditions, these records were not originally designed for research purposes, leading to issues such as missing or inconsistent data registries [111,112]. Nevertheless, rigorous data quality assessments were performed, and strategies for handling missing data were pre-specified. In addition, although the intervention's implementation strategies specifically targeted healthcare professionals, we did not directly evaluate their effectiveness, as proximal outcomes of shared decision-making—such as changes in professional behaviour during the patient encounter—were not available in electronic health records. The study design involved a deliberate trade-off: we prioritised patient-level behavioural outcomes—medication adherence—derived from real-world data, to maximise feasibility and statistical power of a large-scale pragmatic trial [113]. As a result, direct and proximal measures of professional behaviour were not included in the main analysis. Instead, the intervention's mechanisms of action were examined through the complementary mixed-methods process evaluation.

Another important limitation relates to the use of adherence as a trial outcome. While adherence is a relevant and measurable behavioural outcome, its evaluation through electronic health records may have limited the scope of effects observed [114]. This approach captures whether patients fill prescriptions but does not provide insight into patient intermediate changes triggered by the intervention, such as greater awareness,

empowerment, or intention to adhere. These limitations highlight the need and challenges of incorporating patient-centred behavioural measures into routine clinical data to make them accessible for evaluating interventions beyond traditional clinical outcomes [22].

5.2 Implications for clinical practice

The findings of this research underline the potential value of patient-centred interventions, specifically shared decision-making, in clinical practice. Although the IMA intervention did not demonstrate an effect on initial or secondary medication adherence, it showed a modest but clinically meaningful reduction in blood pressure. This underscores the complex and sometimes indirect impact of shared decision-making [115].

Furthermore, the positive experiences reported by both patients and healthcare professionals reinforce the clinical value of shared decision-making, beyond clinical outcomes alone. These findings reflect the broader, mixed evidence on shared decision-making. While it shows consistent benefits for proximal outcomes—such as patient knowledge, trust, satisfaction and reduced decisional conflict—it has shown less consistent effects on behavioural or clinical outcomes like adherence or disease control parameters, where the evidence remains limited [66,79,116].

To date, shared decision-making has rarely demonstrated evidence-based practice in the traditional sense [117]. It has been conceptualised in multiple ways—either as a communication model, a decision-making process, or a measurable outcome [64]. In line with other authors, this thesis argues that shared decision-making should be viewed not as a process but as an

intervention in itself, a core model of high-quality, patient-centred healthcare [118]. In this regard, despite its recognised importance, it remains underused and inconsistently implemented in routine care [57,73]. For these reasons, the debate for its implementation should shift from its clinical effectiveness to its ethical justification: it respects patients' autonomy and right to be actively involved in decisions about their care [68,117]. It promotes active patient involvement, while its ongoing practice helps strengthen professionals' communication skills. Patient education plays an essential role in shared decision-making, especially in the management of chronic conditions, as it empowers individuals to self-manage their health by enhancing their knowledge, skills, and confidence [119]. In turn, this can foster a more collaborative care environment, where patients are encouraged to consider their options, weigh the risks and benefits, and participate in decisions about their care [69].

Achieving cultural change towards widespread adoption of shared decision-making is both necessary and feasible. Encouragingly, attitudes among healthcare professionals and patients are evolving in this direction [54,72]. However, significant challenges persist. Some clinicians mistakenly believe they already practise it, while many patients report limited involvement in decision-making. Others assume—often incorrectly—that patients are either unwilling or unable to participate, yet even if they are initially reluctant, this may change once they are fully informed [62,120]. Additional barriers include a lack of institutional support, limited access to tools and training, rigid clinical guidelines, time pressures, and competing priorities within healthcare settings [62,70,72]. While often labelled as misconceptions, these barriers

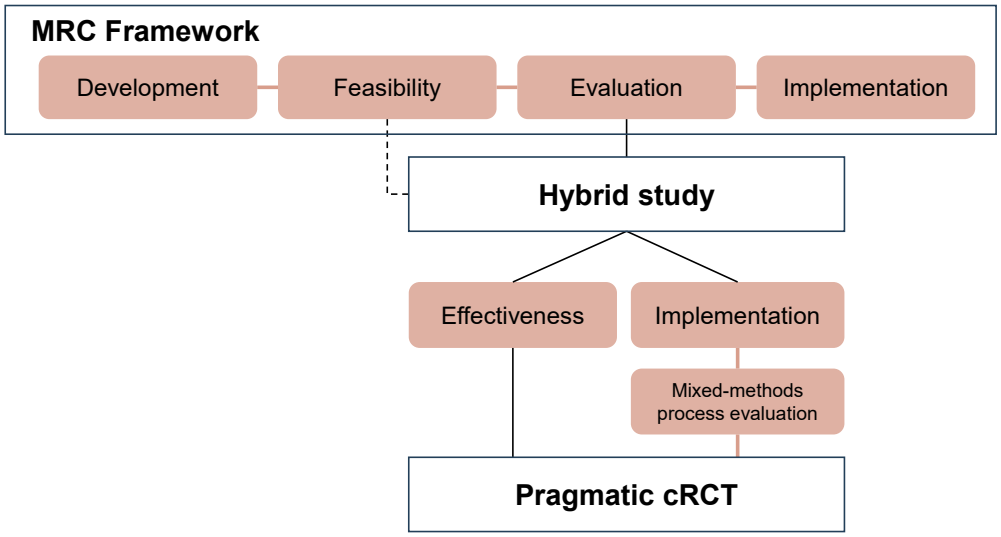
represent real structural and cultural challenges that must be addressed to fully realise the benefits of shared decision-making.

Given the ethical imperative, effective implementation strategies are essential to support the routine integration of shared decision-making into healthcare systems [61]. These include stakeholders engagement (involving decision-makers, healthcare professionals and patients), integration of shared decision-making into professional education, development and dissemination of decision aids to facilitate the implementation in routine care, public campaigns to promote patient involvement, and investment in local implementation through pilot projects, monitoring, and strong coordination between researchers and healthcare systems [61,119].

5.3 Methodological contributions

This thesis provides important insights into the methodological processes of developing, implementing, and evaluating complex behavioural healthcare interventions in real-world primary care settings. A key contribution lies in the systematic application of the MRC framework, which guided the project from initial development through to pragmatic evaluation using a hybrid effectiveness-implementation design. Figure 7 illustrates the integration of the MRC phases with the hybrid study design and pragmatic trial approach, highlighting the coherence and complementarity of these methodological elements throughout the research process.

Figure 7. Integration of the MRC Framework, Hybrid effectiveness-implementation study and Pragmatic Trial.



Similar international examples exist—initiatives that integrate frameworks for the development and evaluation of complex interventions, hybrid study designs, and pragmatic trials [121–128]. Many of these were conducted in primary care settings and focused on chronic disease management (particularly diabetes), with adherence often used as a target outcome. However, there are fewer that focused on patient-centred models or shared decision-making as the intervention [117,129]. In Spain, few studies have combined such a comprehensive use of frameworks with hybrid studies and pragmatic designs, but none place patient-centred care models, such as shared decision-making, at the core of the intervention [130–137].

In recent years, there has been growing recognition of the central role that structured frameworks play in bridging the gap between research and the translation of evidence into practice [95], particularly in primary care [138]. This research illustrates how an intervention can be designed iteratively, drawing on theory, existing evidence, stakeholder engagement,

and contextual understanding to ensure relevance, acceptability, feasibility and integration into clinical practice [80,82,139]. Unlike traditional intervention evaluations, the IMA intervention was explicitly developed with future scalability and sustainability in mind [140]. In addition, by adhering to the MRC Framework, the development of the IMA intervention was not only systematic and evidence-informed but also responsive to the complexities of real-world healthcare, such as during the COVID-19 pandemic.

The evaluations followed the principles of a type I hybrid effectiveness-implementation study design, which allowed the simultaneous assessment of effectiveness and implementation research questions [85,86]. The type I study was selected due to the novelty of the IMA intervention and the limited prior evidence available in the target setting, while also recognising the need to accelerate the translation of research findings into practice [86].

This translation into clinical practice was equally supported by embedding a pragmatic trial design to evaluate effectiveness within the hybrid study, guided by the PRECIS-2 tool to ensure alignment with real-world primary care [90,123,141]. The pragmatic approach enabled the intervention to be delivered under routine conditions, to patients who would have received usual care otherwise, by practising healthcare professionals using existing system resources, and thereby maximising external validity and enhancing the applicability of the findings beyond controlled research settings [89]. This design was feasible because of the strategic use of real-world data from electronic health records, which offered a valuable opportunity to assess the intervention using routinely collected clinical data while also highlighting its practical challenges despite the intrinsic limitations described above [111].

The evaluation was further supported by a mixed-methods process evaluation, which is particularly well suited to addressing the multifaceted nature of complex interventions [82]. By combining quantitative and qualitative methods, the evaluation provided a more comprehensive understanding of the implementation process, capturing what worked, how and why, while overcoming some of the limitations of assessments based on real-world data [82,142]. The triangulation of both methods enhanced the credibility and depth of the findings, while the inclusion of perspectives from both healthcare professionals and patients further strengthened the practical relevance and applicability of the results.

This work has laid essential groundwork for the scale-up of shared decision-making. However, it is important to recognise a broader challenge of implementation science, even when interventions are evidence-based and contextually adapted, translating them into routine clinical practice often requires substantial resources, sustained effort, and long timeframes [143].

All these aspects position this thesis as a pioneering effort in advancing the use of implementation science to support patient-centred care within routine clinical practice in the Spanish primary care context.

5.4 Future research

In combination, the implications for clinical practice and methodological contributions offer lessons and directions that can inform future lines of research.

Although this thesis found no significant impact on medication adherence, it did observe an improvement in blood pressure among patients prescribed

antihypertensive medication. Future research should explore the underlying mechanisms of action through which shared decision-making may influence such clinical outcomes. While improved adherence does not appear to explain this effect, shared decision-making may foster other beneficial behaviours, such as increased motivation for chronic disease management or greater adoption of non-pharmacological strategies and lifestyle changes like dietary improvements or increased physical activity.

In addition, future research should explore whether specific patient subgroups are more likely to benefit from shared decision-making based interventions, as it may vary across different populations. For instance, those patients with high levels of decisional conflict, lower baseline health literacy, chronic conditions with significant lifestyle components, or strong preferences for active participation in care may respond more positively to shared decision-making interventions. Similarly, sociodemographic factors such as age, education, or cultural background may influence how it is received and its potential impact. Gender dynamics can also shape the process of shared decision-making and its outcomes, as they might impact the nature of interactions between patients and professionals. Identifying these profiles through stratified analyses or subgroup-focused studies would enable the development of more targeted and effective implementation strategies.

Given the ethical imperative to normalise shared decision-making as a standard of care and building on the findings of this thesis and the accompanying economic evaluation—in line with the MRC framework—future research should prioritise the design and evaluation of strategies to scale up the IMA intervention. The ultimate goal is to embed patient-centred

care as a standard approach when prescribing new medications in primary care. Efforts are already underway to scale up the intervention across a broader region of Catalonia, supported by implementation strategies that will be co-developed with regional healthcare authorities and local professionals and patient organisations. This initiative offers a valuable opportunity to assess how the intervention works when implemented at scale in routine practice.

Future work should explore adapting shared decision-making interventions to new clinical areas—such as mental health—or to populations with distinct needs, such as paediatrics, where shared decision-making must include the voices of both children and their families. These new applications could benefit from the methodological insights gained through this project. They would require an initial needs assessment and careful adaptation of the intervention to ensure contextual appropriateness while maintaining fidelity to core principles.

Furthermore, these next steps should go beyond prioritising clinical effectiveness. Future evaluations aiming to scale or adapt the intervention should adopt type II or III hybrid effectiveness-implementation designs, shifting focus towards identifying the most effective implementation strategies. For instance, pragmatic trials comparing different strategies would offer valuable insights into how best to integrate and sustain shared decision-making in routine care. These efforts are essential to transition shared decision-making from isolated interventions to a sustainable, system-wide model that places patients at the centre of healthcare.

6

Conclusions

6 CONCLUSIONS

1) Developing, implementing, and evaluating a complex intervention in a real-world primary care setting using a hybrid effectiveness-implementation study and a pragmatic evaluation based on real-world data is feasible and provides a replicable model that can inform future studies in other clinical contexts or populations.
2) The IMA intervention, a shared decision-making based intervention to improve adherence to newly prescribed medications, is feasible and acceptable but professional engagement, shared decision-making training for professionals and decision aids for patients need to be carefully designed to ensure its acceptability and feasibility.
3) The use of real-world data from electronic health records proved viable for evaluating adherence outcomes, although it presented limitations regarding the availability of clinical outcomes that need to be taken into account when designing studies based on real-world data.
4) The IMA intervention proved to be beneficial for both professionals and patients, with adequate implementation fidelity, and an overall high normalisation into clinical practice. However, the professionals' perception that shared decision-making was already being practised, and the lack of familiarity of both professionals and patients with this model of care, may have limited the intervention's impact. Contextual factors also influence shared decision-making in primary care, underscoring the need for sustained reinforcement and support strategies to ensure long-term integration.

5) The IMA intervention failed to improve primary or secondary adherence and most clinical outcomes in comparison to usual care in newly prescribed CVD and diabetes pharmacological treatments.
6) The IMA intervention demonstrated a clinically meaningful reduction in blood pressure among patients prescribed antihypertensive treatments, suggesting a possible indirect effect of shared decision-making in disease management through unclear mechanisms that need future research.
7) Standardising shared decision-making within primary care requires additional efforts as part of the transition towards patient-centred care. Future efforts should balance the benefits of enhanced patient and professional experiences. Continued investment in professional training, patient support tools, awareness campaigns, and research is essential for overcoming implementation challenges and for fully understanding the potential of shared decision-making.

7

References

7 REFERENCES

1 Atella V, Piano Mortari A, Kopinska J, Belotti F, Lapi F, Cricelli C, et al. Trends in age-related disease burden and healthcare utilization. Aging Cell. 2019;18:1–8. doi: 10.1111/acel.12861

2 World Health Organization. Ageing and health. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

3 Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196–208. doi: 10.1016/S0140-6736(09)61460-4

4 World Health Organization. Cardiovascular diseases (CVDs). 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

5 World Health Organization. Diabetes. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes

6 Global Burden of Disease. Global Burden Metrics. Cardiovascular diseases—Level 2 cause. Lancet. 2020. Available from: https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/cardiovascular-diseases.pdf

7 Global Burden of Disease. Global Health Metrics. Type 2 diabetes mellitus—Level 4 cause. Lancet. 2020. Available from: https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/diabetes-type 2.pdf

8 World Health Organization. The top 10 causes of death. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

9 Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, et al. European Society of Cardiology: the 2023 Atlas of Cardiovascular Disease Statistics. Eur Heart J. 2024;45:4019–62. doi: 10.1093/eurheartj/ehae466

10 International Diabetes Federation. IDF Diabetes Atlas. 2021. Available from: https://diabetesatlas.org/

11 World Health Organization. Noncommunicable diseases: Risk factors and conditions. Available from: https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/ncd-risk-factors

12 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies, with the special contribution of the European Association of Preventive Cardiology (EAPC). Rev Esp Cardiol. 2022;75:429.e1–429.e104. doi: 10.1016/j.recesp.2021.10.016

13 Kucia AM, Hartley A. Risk Factors for Cardiovascular Disease. In: A.M. Kucia and I.D. Jones, editor. Card care. London: Whurr; 2022. doi: 10.1002/9781119117810.ch5

14 Mozaffarian D, Wilson PWF, Kannel WB. Beyond Established and Novel Risk Factors Lifestyle Risk Factors for Cardiovascular Disease. Circulation. 2008;117:3031–8. doi: 10.1161/CIRCULATIONAHA.107.738732

15 The Global Cardiovascular Risk Consortium. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. N Engl J Med. 2023;389:1273–85. doi: 10.1056/nejmoa2206916

16 World Health Organization. GLOBAL STATUS REPORT on noncommunicable diseases 2014. Word Heal. Organ. Geneva; 2014. Available from: https://www.who.int/publications/i/item/9789241564854

17 Hacker K. The burden of chronic disease. Mayo Clin Proc Inn Qual Out. 2024;8:112–9. doi: 10.1016/j.mayocpiqo.2023.08.005

18 Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73:691–705. doi:10.1111/j.1365-2125.2012.04167.x

19 World Health Organization. Adherence to long-term therapies. Evidence for action. Geneva; 2003. Available from: https://iris.who.int/handle/10665/42682

20 Julius RJ, Novitsky MA, Dubin WR. Medication Adherence : A Review of the Literature and Implications for Clinical Practice. J Psychiatr Pr. 2009;15:34–44. doi: 10.1097/01.pra.0000344917.43780.77

21 Balkrishnan R. The Importance of Medication Adherence in Improving Chronic-Disease Related Outcomes. Med Care. 2005;43:517–20. doi: 10.1097/01.mlr.0000166617.68751.5f

22 Kardas P, Bennett B, Borah B, Burnier M, Daly C, Hiligsmann M, et al. Medication non-adherence: reflecting on two decades since WHO adherence report and setting goals for the next twenty years. Front Pharmacol. 2024;15:1–10. doi: 10.3389/fphar.2024.1444012

23 Hutchins DS, Zeber JE, Roberts CS, Williams AF, Manias E, Peterson AM. Initial Medication Adherence - Review and Recommendations for Good Practices in Outcomes Research: An ISPOR Medication Adherence and Persistence Special Interest Group Report. Value Heal. 2015;18:690–9. doi: 10.1016/j.jval.2015.02.015

24 Zeber JE, Manias E, Williams AF, Hutchins D, Udezi WA, Roberts CS, et al. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: A report of the ISPOR medication adherence & persistence special interest group. Value Heal. 2013;16:891–900. doi: 10.1016/j.jval.2013.04.014

25 Chapman S, Frostholm L, Chalder T, Graham C, de Thurah A, van Leeuwen T, et al. Preventing medication nonadherence : a framework for interventions to support early engagement with treatment. Health Psychol Rev. 2024;1–15. doi:10.1080/17437199.2024.2385525

26 Wroe AL. Intentional and Unintentional Nonadherence: A Study of Decision Making. J Behav Med. 2002;25:355–72. doi: 10.1023/a:1015866415552

27 Read S, Morgan J, Gillespie D, Nollett C, Weiss M, Allen D, et al. Chronic conditions and behavioural change approaches to medication adherence: rethinking clinical guidance and recommendations. Patient Prefer Adherence. 2020;14:581–6. doi: 10.2147/PPA.S239916

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

29 Jackson C, Eliasson L, Barber N, Weinman J. Applying COM-B to medication adherence: A suggested framework for research and interventions. Bull Eur Heal Psychol Soc. 2014;16:7–17. Available from:

https://www.ehps.net/ehp/index.php/contents/article/view/ehp.v16.i1.p7

30 Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: A review of systematic reviews. Front Pharmacol. 2013;4:1–16. doi: 10.3389/fphar.2013.00091

31 Araújo-Soares V, Hankonen N, Presseau J, Rodrigues A, Sniehotta FF. Developing Behavior Change Interventions for Self-Management in Chronic Illness: An Integrative Overview. Eur Psychol. 2019;24:7–25. doi: 10.1027/1016-9040/a000330

32 Berben L, Dobbels F, Engberg S, Hill MN, de Geest S. An Ecological Perspective on Medication Adherence. West J Nurs Res. 2012;34:635–53. doi: 10.1177/0193945911434518

33 Sallis JF, Owen N, Fisher EB. Ecological models of health behavior. In: Glanz K, Rimer BK, Viswanath K, editors. Heal Behav Heal Educ Theory, Res Pract. 4th ed. Jossey-Bass; 2008. p. 465–85.

34 McLaren L, Hawe P. Ecological perspectives in health research. J Epidemiol Community Health. 2005;59:6–14. doi:10.1136/jech.2003.018044

35 Foley L, Larkin J, Lombard-Vance R, Murphy AW, Hynes L, Galvin E, et al. Prevalence and predictors of medication non-Adherence among people living with multimorbidity: A systematic review and meta-Analysis. BMJ Open. 2021;11:1–14. doi:10.1136/bmjopen-2020-044987

36 DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. Med Care. 2004;42:200–9. doi: 10.1097/01.mlr.0000114908.90348.f9

37 Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: A meta-analysis. Patient Prefer Adherence. 2018;12:721–31. doi:10.2147/PPA.S161151

38 Aznar-Lou I, Fernández A, Gil-Girbau M, Fajó-Pascual M, Moreno-Peral P, Peñarrubia-María MT, et al. Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. Br J Clin Pharmacol. 2017;83:1328–40. doi:10.1111/bcp.13215

39 Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009;15:728–40. doi: 10.18553/jmcp.2009.15.9.728

40 Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97. doi: 10.1056/NEJMra050100

41 Stewart SJF, Moon Z, Horne R. Medication nonadherence: health impact, prevalence, correlates and interventions. Psychol Heal. 2023;38:726–65. doi: 10.1080/08870446.2022.2144923

42 Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: Optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25:2303–10. doi: 10.1185/03007990903126833

43 Gellad WF, Thorpe CT, Steiner JF, Voils CI. The myths of medication adherence. Pharmacoepidemiol Drug Saf. 2017;26:1–5. doi:10.1002/pds.4334

44 Haynes R, McDonald H, Garg A, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002;2. doi: 10.1002/14651858.CD000011

45 Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication

adherence. Cochrane Database Syst Rev. 2014;11. doi: 10.1002/14651858.CD000011.pub4

46 Khan R, Socha-Dietrich K. Investing in medication adherence improves health outcomes and health system efficiency: Adherence to medicines for diabetes, hypertension, and hyperlipidaemia. OECD Health Working Papers. 2018;105. doi: 10.1787/8178962c-en

47 Mongkhon P, Ashcroft DM, Scholfield CN, Kongkaew C. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. BMJ Qual Saf. 2018;27:902–14. doi: 10.1136/BMJQS-2017-007453

48 Rodriguez F, Cannon CP, Steg PG, Kumbhani DJ, Goto S, Smith SC, et al. Predictors of Long-term Adherence to Evidence-based Cardiovascular Disease Medications in Outpatients With Stable Atherothrombotic Disease: Findings From the REACH Registry. Clin Cardiol. 2013;36:721–7. doi: 10.1002/clc.22217

49 Naderi SH, Bestwick JP, Wald DS. Adherence to Drugs That Prevent Cardiovascular Disease: Meta-analysis on 376,162 Patients. Am J Med. 2012;125:882-887.e1. doi: 10.1016/J.AMJMED.2011.12.013

50 Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, Serrano-Blanco A, Fernández-Vergel R, Petitbò-Antúnez D, et al. Initiation and single dispensing in cardiovascular and insulin medications: Prevalence and explanatory factors. Int J Environ Res Public Health. 2020;17:1–19. doi:10.3390/ijerph17103358

51 Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34:2940–8. doi:10.1093/eurheartj/eht295

52 Kini V, Michael Ho P. Interventions to Improve Medication Adherence: A Review. JAMA - J Am Med Assoc. 2018;320:2461–73. doi: 10.1001/jama.2018.19271

53 Zullig LL, Deschodt M, Liska J, Bosworth HB, De Geest S. Moving from the trial to the real world: Improving medication adherence using insights of implementation science. Annu Rev Pharmacol Toxicol. 2019;59:423–45. doi: 10.1146/annurev-pharmtox-010818-021348. Epub 2018 Aug 20

54 Driever EM, Stiggelbout AM, Brand PLP. Shared decision making: Physicians' preferred role, usual role and their perception of its key components. Patient Educ Couns. 2020;103:77–82. doi:10.1016/j.pec.2019.08.004

55 Sogaard MB, Andresen K, Kristiansen M. Systematic review of patient-engagement interventions: Potentials for enhancing person-centred care for older patients with multimorbidity. BMJ Open. 2021;11:1–10. doi:10.1136/bmjopen-2020-048558

56 The American Geriatrics Society Expert Panel on Person-Centered Care. Person-Centered Care: A Definition and Essential Elements. J Am Geriatr Soc. 2016;64:15–8. doi:10.1111/jgs.13866

57 Elwyn G. Shared decision making: What is the work? Patient Educ Couns. 2020;104:1591–5. doi:10.1016/j.pec.2020.11.032

58 Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared Decision Making: A model for Clinical Practice. J Gen Intern Med. 2012;27:1361–7. doi:10.1007/s11606-012-2077-6

59 Tichelaar J, Richir MC, Garner S, Hogerzeil H, de Vries TPGM. WHO guide to good prescribing is 25 years old: quo vadis? Eur J Clin Pharmacol. 2020;76:507–13. doi:10.1007/s00228-019-02823-w

60 Elwyn GJ, Edwards A, Kinnersley P, Grol R. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. Br J Gen Pract. 2000;50:892–7. pmid: 11141876; PMCID: PMC1313854.

61 Coulter A. National Strategies for Implementing Shared Decision Making (engl.). Gütersloh, Ger Bertelsmann Stift. 2018;66. Available from: https://www.bertelsmann-stiftung.de/en/publications/publication/did/national-strategies-for-implementing-shared-decision-making-engl/

62 Joseph-Williams N, Lloyd A, Edwards A, Stobbart L, Tomson D, Macphail S, et al. Implementing shared decision making in the NHS: lessons from the MAGIC programme. BMJ. 2017;357:1–6. doi:10.1136/bmj.j1744

63 Hargraves I, LeBlanc A, Shah ND, Montori VM. Shared decision making: The need for patient-clinician conversation, not just information. Health Aff. 2016;35:627–9. doi: 10.1377/hlthaff.2015.1354

64 Elwyn G, Durand MA, Song J, Aarts J, Barr PJ, Berger Z, et al. A three-talk model for shared decision making: Multistage consultation process. BMJ. 2017;359:1–7. doi: 10.1136/bmj.j4891

65 Stacey D, Légaré F, Lewis K, Barry M, Bennett C, Eden K, et al. Decision aids for people facing health treatment or screening decisions (Review). Cochrane Database Syst Rev. 2017;4:CD001431. doi:10.1002/14651858.CD001431.pub5

66 Légaré F, Adekpedjou R, Stacey D, Turcotte S, Kryworuchko J, Graham ID, et al. Interventions for increasing the use of shared decision making by healthcare professionals (Review). Cochrane Database Syst Rev. 2018;7:CD006732. doi:10.1002/14651858.CD006732.pub4

67 Tang C, Wang A, Yan J. Exploring motivations and resistances for implementing shared decision-making in clinical practice: A systematic review based on a structure–process–outcome model. Heal Expect. 2022;25:1254–68. doi:10.1111/hex.13541

68 Elwyn G, Tilburt J, Montori VM. The ethical imperative for shared decision-making. Eur J Pers Centered Healthc. 2013;1:129–31. doi:10.5750/ejpch.v1i1.645

69 Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: Consider all the consequences. Implement Sci. 2016;11:1–10. doi:10.1186/s13012-016-0480-9

70 Waddell A, Lennox A, Spassova G, Bragge P. Barriers and facilitators to shared decision-making in hospitals from policy to practice: a systematic review. Implement Sci. 2021;16:1–23. doi:10.1186/s13012-021-01142-y

71 Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: Update of a systematic review of health professionals' perceptions. Patient Educ Couns. 2008;73:526–35. doi:10.1016/j.pec.2008.07.018

72 Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: A systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns. 2014;94:291–309. doi: 10.1016/j.pec.2013.10.031

73 Härter M, Moumjid N, Cornuz J, Elwyn G, van der Weijden T. Shared decision making in 2017: International accomplishments in policy, research and implementation. Z Evid Fortbild Qual Gesundhwes. 2017;123–124:1–5. doi:10.1016/j.zefq.2017.05.024

74 Ben-Zacharia A, Adamson M, Boyd A, Hardeman P, Smrtka J, Walker B, et al. Impact of Shared Decision Making on Disease-Modifying Drug Adherence in Multiple Sclerosis. Int J MS Care. 2018;20:287–97. doi: 10.7224/1537-2073.2017-070

75 Joosten EAG, DeFuentes-Merillas L, De Weert GH, Sensky T, Van Der Staak CPF, De Jong CAJ. Systematic Review of the Effects of Shared Decision-Making on Patient Satisfaction, Treatment Adherence and Health Status. Psychother Psychosom. 2008;77:219–26. doi: 10.1159/000126073

76 Lofland JH, Johnson PT, Ingham MP, Rosemas SC, White JC, Ellis L. Shared decision-making for biologic treatment of autoimmune disease: influence on adherence, persistence, satisfaction, and health care costs. Patient Prefer Adherence. 2017;11:947–58. doi: 10.2147/PPA.S133222

77 Dwamena F, Holmes-Rovner M, Gaulden C, Jorgenson S, Sadigh G, Sikorskii A, et al. Interventions for providers to promote a patient-centred approachin clinical consultations (Review). Cochrane Database Syst Rev. 2012;CD003267. doi:10.1002/14651858.CD003267.pub2

78 Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, Popa CD, Vriezekolk JE. Interventions to support shared decision making for medication therapy in long term conditions: A systematic review. Patient Educ Couns. 2019;103:254–65. doi:10.1016/j.pec.2019.08.034

79 Bruch JD, Khazen M, Mahmic-Kaknjo M, Légaré F, Ellen ME. The effects of shared decision making on health outcomes, health care quality, cost, and consultation time: An umbrella review. Patient Educ Couns. 2024;129:1–13. doi:10.1016/j.pec.2024.108408

80 Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions:

Update of Medical Research Council guidance. BMJ. 2021;374:1–11. doi: 10.1136/bmj.n2061

81 French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci. 2012;7:1–14. doi: 10.1186/1748-5908-7-38

82 Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350:1–7. doi: 10.1136/bmj.h1258

83 Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ. 2000;321:694–6. doi: 10.1136/bmj.321.7262.694

84 Craig P, Dieppe P, Macintyre S, Mitchie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. BMJ. 2008;337:979–83. doi: 10.1136/bmj.a1655

85 Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation Hybrid Designs: Combining Elements of Clinical Effectiveness and Implementation Research to Enhance Public Health Impact. Med Care. 2012;50:217–26. doi:10.1097/MLR.0b013e3182408812

86 Curran GM, Landes SJ, McBain SA, Pyne JM, Smith JD, Fernandez ME, et al. Reflections on 10 years of effectiveness-implementation hybrid studies. Front Heal Serv. 2022;2:1–22. doi: 10.3389/frhs.2022.1053496

87 Ullman AJ, Beidas RS, Bonafide CP. Methodological progress note: Hybrid effectiveness-implementation clinical trials. J Hosp Med. 2022;17:912–6. doi:10.1002/jhm.12936

88 Zhu M, Sridhar S, Hollingsworth R, Chit A, Kimball T, Murmello K, et al. Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective. Contemp Clin Trials. 2020;94. doi:/10.1016/j.cct.2019.105856

89 Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375:454–63. doi: 10.1056/NEJMra1510059

90 Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350. doi:10.1136/bmj.h2147

91 Bernal-Delgado E, Angulo-Pueyo E, Ridao-López M, Urbanos- Garrido R, Oliva-Moreno J, García-Abiétar D, et al. Spain: Health System Review. Health Syst. Transit. Copenhagen; 2024. Available from: https://eurohealthobservatory.who.int/publications/i/spain-health-system-review-2024

92 Fernandez ME, Ruiter RAC, Markham CM, Kok G. Intervention mapping: Theory-and evidence-based health promotion program planning: Perspective and examples. Front Public Heal. 2019;7:1–20. doi: 10.3389/fpubh.2019.00209

93 Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health. 1999;89:1322–7. doi: 10.2105/ajph.89.9.1322

94 Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into

practice: A consolidated framework for advancing implementation science. Implement Sci. 2009;4:1–15. doi:10.1186/1748-5908-4-50

95 Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci. 2015;10:1–17. doi: 10.1186/s13012-015-0242-0

96 Rubio-Valera M. Pharmacist intervention in depressed patients. Universitat de Barcelona; 2012.

97 Aznar-Lou I, Pottegård A, Fernández A, Peñarrubia-María MT, Serrano-Blanco A, Sabés-Figuera R, et al. Effect of copayment policies on initial medication non-adherence according to income: A population-based study. BMJ Qual Saf. 2018;0:1-14. doi: 10.1136/bmjqs-2017-007416

98 Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, Moreno-Peral P, Fernández A, Bellón J, et al. Reasons for medication non-initiation: A qualitative exploration of the patients' perspective. Res Soc Adm Pharm. 2020;16:663–72. doi:10.1016/j.sapharm.2019.08.002

99 Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, Aznar-Lou I, Serrano-Blanco A, Mendive Arbeloa JM, et al. Non-initiation of prescribed medication from a Spanish health professionals' perspective: A qualitative exploration based on Grounded Theory. Heal Soc Care Community. 2021;30:e213–21. doi:10.1111/hsc.13431

100 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Serrano-Blanco A, et al. Improving Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care: Pilot trial of a complex intervention. Front Public Heal. 2022;10:1–16. doi:10.3389/fpubh.2022.1038138

101 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Gallardo-González C, et al. Complex multidisciplinary

intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): mixed-methods process evaluation protocol. BMJ Open. 2022;12:1–11. doi:10.1136/bmjopen-2022-067468

102 Sánchez-Viñas A, Corral-Partearroyo C, Gil-Girbau M, Peñarrubia-María MT, Gallardo-González C, Olmos-Palenzuela M-D-C, et al. Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model. BMC Prim care. 2022;23:1–20. doi:10.1186/s12875-022-01727-6

103 Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María MT, Aznar-Lou I, Gallardo-González C, et al. Implementation of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a mixed-methods process evaluation. BMJ Qual Saf. 2025;0:1–14. doi:10.1136/ bmjqs-2024-018403

104 Corral-Partearroyo C, Sánchez-Viñas A, Aznar-Lou I, Peñarrubia-María MT, Gil-Girbau M, Gallardo-González C, et al. Effectiveness of a patient-centred complex intervention to improve Initial Medication Adherence to cardiovascular disease and diabetes treatments in primary care (the IMA-cRCT study): a pragmatic cluster randomised controlled trial using real-world data. BMJ Qual Saf. 2025;0:1–15. doi:10.1136/bmjqs-2024-018402

105 Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The Behavior Change Technique Taxonomy (v1) of 93

Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Ann Behav Med. 2013;46:81–95. doi:10.1007/s12160-013-9486-6

106 Agbadjé TT, Elidor H, Perin MS, Adekpedjou R, Légaré F. Towards a taxonomy of behavior change techniques for promoting shared decision making. Implement Sci. 2020;15:1–14. doi: 10.1186/s13012-020-01015-w

107 Rubio-Valera M, Jové AM, Hughes CM, Guillen-Sol M, Rovira M, Fernández A. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. BMC Health Serv Res. 2012;12:1–15. doi:10.1186/1472-6963-12-188

108 Zardaín E, del Valle MO, Loza MI, García E, Lana A, Markham WA, et al. Psychosocial and behavioural determinants of the implementation of Pharmaceutical Care in Spain. Pharm World Sci. 2009;31:174–82. doi:10.1007/s11096-008-9275-7

109 Delitto A. Pragmatic Clinical Trials: Implementation Opportunity, or Just Another Fad? Phys Ther. 2016;96:137–8. doi: 10.2522/ptj.2016.96.2.137

110 Sox HC, Lewis RJ. Pragmatic Trials: Practical Answers to “Real World” Questions. JAMA. 2016;316:1205–6. doi:10.1001/JAMA.2016.11409

111 Gianfrancesco MA, Goldstein ND. A narrative review on the validity of electronic health record-based research in epidemiology. BMC Med Res Methodol. 2021;21:1–14. doi:10.1186/s12874-021-01416-5

112 Ho YF, Hu FC, Lee PI. The Advantages and Challenges of Using Real-World Data for Patient Care. Clin Transl Sci. 2020;13:4–7. doi:10.1111/cts.12683

113 Welsing PM, Oude Rengerink K, Collier S, Eckert L, van Smeden M, Ciaglia A, et al. Series: Pragmatic trials and real world evidence: Paper 6. Outcome measures in the real world. J Clin Epidemiol. 2017;90:99–107. doi: 10.1016/j.jclinepi.2016.12.022

114 Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;217047:1–12. doi: 10.1155/2015/217047

115 Aubree Shay L, Lafata JE. Where is the evidence? a systematic review of shared decision making and patient outcomes. Med Decis Mak. 2015;35:114–31. doi: 10.1177/0272989X14551638

116 Elias S, Chen Y, Liu X, Slone S, Turkson-Ocran RA, Ogungbe B, et al. Shared Decision-Making in Cardiovascular Risk Factor Management: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7:e243779. doi:10.1001/jamanetworkopen.2024.3779

117 Pieterse AH, van Bodegom-Vos L. Shared Decision Making Is in Need of Effectiveness-Implementation Hybrid Studies. Med Decis Mak. 2024;44:862–4. doi: 10.1177/0272989X241286516

118 Clayman ML, Elwy AR, Vassy JL. Reframing SDM Using Implementation Science: SDM Is the Intervention. Med Decis Mak. 2024;44:859–61. doi: 10.1177/0272989X241285418

119 World Health Organization. Therapeutic patient education. An introductory guide. Copenhagen; 2023. Available from: https://www.who.int/europe/publications/i/item/9789289060219

120 Stiggelbout AM, Van Der Weijden T, De Wit MPT, Frosch D, Légaré F, Montori VM, et al. Shared decision making: really putting patients at the centre of healthcare. BMJ. 2012;344:1–6. doi: 10.1136/bmj.e256

121 Atzmon O, Crowther ME, Bei B, O'Connor DA. The use of implementation science theoretical approaches in hybrid effectiveness-

implementation type 1 randomised trials of healthcare interventions: A scoping review. Implement Sci. 2025;20:1–15. doi: 10.1186/s13012-025-01435-6

122 Handley MA, Murphy LD, Sherwin EB, Shade SB. Practical application of hybrid effectiveness–implementation studies for intervention research. Int J Epidemiol. 2025;54:1–9. doi: 10.1093/ije/dyaf039

123 Midboe AM, Seal KH, Burgess DJ, Rosen MI, Martino S. Pragmatic clinical trials as hybrid effectiveness-implementation studies to shrink the evidence-to-practice gap for chronic pain management. Pain Med. 2024;25:S77–9. doi: 10.1093/pm/pnae067

124 Bawab N, Moullin JC, Perraudin C, Bugnon O. Implementation and Effectiveness of an Interprofessional Support Program for Patients with Type 2 Diabetes in Swiss Primary Care: A Study Protocol. Pharmacy. 2020;8:1–17. doi:10.3390/pharmacy8020106

125 Bawab N, Moullin JC, Bugnon O, Perraudin C. Implementation Evaluation of an Interprofessional Programme (Siscare) for Supporting Patients with Type 2 Diabetes in a primary care setting. Res Soc Adm Pharm. 2021;17:1968–77. doi: 10.1016/j.sapharm.2021.02.019

126 Félix IB, Guerreiro MP, Cavaco A, Cláudio AP, Mendes A, Balsa J, et al. Development of a complex intervention to improve adherence to antidiabetic medication in older people using an anthropomorphic virtual assistant software. Front Pharmacol. 2019;10:1–13. doi: 10.3389/fphar.2019.00680

127 Goldstein CM, Panza E, Hayes JF, Thomas JG, O'Leary K, Wing RR. Pragmatic online obesity treatment in primary care: a hybrid randomized clinical trial of implementation strategies. npj Cardiovasc Heal. 2024;1.

128 Luig T, Asselin J, Sharma AM, Campbell-Scherer DL. Understanding implementation of complex interventions in primary care teams. J Am Board Fam Med. 2018;31:431–44. doi: 10.3122/jabfm.2018.03.170273

129 Buhse S, Kuniss N, Liethmann K, Müller UA, Lehmann T, Mühlhauser I. Informed shared decision-making programme for patients with type 2 diabetes in primary care: Cluster randomised controlled trial. BMJ Open. 2018;8:1–11. doi:10.1136/ bmjopen-2018-024004

130 Zabaleta-del-Olmo E, Casajuana-Closas M, López-Jiménez T, Pombo H, Pons-Vigués M, Pujol-Ribera E, et al. Multiple health behaviour change primary care intervention for smoking cessation, physical activity and healthy diet in adults 45 to 75 years old (EIRA study): a hybrid effectiveness-implementation cluster randomised trial. BMC Public Health. 2021;21:1–22. doi: 10.1186/s12889-021-11982-4

131 Pons-Vigués M, Berenguera A, Coma-Auli N, March S, Pombo H, Masluk B, et al. Qualitative evaluation of a complex intervention to implement health promotion activities according to healthcare attendees and health professionals: EIRA study (phase II). BMJ Open. 2019;9. doi:10.1136/ bmjopen-2018-023872

132 Leiva-Fernández F, Prados-Torres JD, Prados-Torres A, Del-Cura-González I, Castillo-Jimena M, López-Rodríguez JA, et al. Training primary care professionals in multimorbidity management: Educational assessment of the eMULTIPAP course. Mech Ageing Dev. 2020;192. doi: 10.1016/j.mad.2020.111354

133 Del Cura-González I, López-Rodríguez JA, Leiva-Fernández F, Gimeno-Miguel A, Poblador-Plou B, López-Verde F, et al. How to Improve Healthcare for Patients with Multimorbidity and Polypharmacy in Primary Care: A Pragmatic Cluster-Randomized Clinical Trial of the

MULTIPAP Intervention. J Pers Med. 2022;12:1–16. doi: 10.3390/jpm12050752

134 Bennasar-Veny M, Abbate M, Colom-Rosselló M, Capitán-Moyano L, Hernández-Bermúdez IC, Ricci-Cabello I, et al. Impact of an adapted diabetes prevention program in a spanish primary care setting: protocol for a type II hybrid effectiveness-implementation cluster-randomized trial (ALADIM). Implement Sci. 2025;20:1–16. doi: 10.1186/s13012-025-01438-3

135 Mira-Martínez S, Zamanillo-Campos R, Malih N, Fiol-deRoque MA, Angullo-Martínez E, Jimenez R, et al. Describing the initial results of a pragmatic, cluster randomized clinical trial to examine the impact of a multifaceted digital intervention for the prevention of type 2 diabetes mellitus in the primary care setting: intervention design, recruitment stra. Front Endocrinol (Lausanne). 2025;16:1–12. doi: 10.3389/fendo.2025.1524336

136 Socias I, Leiva A, Pombo-Ramos H, Bejarano F, Sempere-Verdú E, Rodríguez-Rincón RM, et al. Evaluating the Implementation of a Multicomponent Intervention Consisting of Education and Feedback on Reducing Benzodiazepine Prescriptions by General Practitioners: BENZORED Hybrid Type I Cluster Randomized Controlled Trial. Int J Clin Pract. 2021;18:1–13. doi: 10.3390/ijerph18157964

137 Vicens C, Leiva A, Bejarano F, Sempere- Verdú E, Rodríguez-Rincón RM, Fiol F, et al. Evaluation of a multicomponent intervention consisting of education and feedback to reduce benzodiazepine prescriptions by general practitioners: The BENZORED hybrid type 1 cluster randomized controlled trial. PLoS Med. 2022;19:e1003983. doi: 10.1371/journal.pmed.1003983

138 Zabaleta-del-Olmo E, Bolibar B, García-Ortíz L, García-Campayo J, Llobera J, Bellón JÁ, et al. Building interventions in primary health care for long-term effectiveness in health promotion and disease prevention. A focus on complex and multi-risk interventions. Prev Med (Baltim). 2015;76:S1–4. doi: 10.1016/j.ypmed.2015.03.011

139 Gesell SB, Prvu Bettger J, Lawrence RH, Li J, Hoffman J, Lutz BJ, et al. Implementation of Complex Interventions: Lessons Learned From the Patient-Centered Outcomes Research Institute Transitional Care Portfolio. Med Care. 2021;59:S344–54. doi: 10.1097/MLR.0000000000001591

140 Sun L, Booth A, Sworn K. Adaptability, Scalability and Sustainability (ASaS) of complex health interventions: a systematic review of theories, models and frameworks. Implement Sci. 2024;19:1–28. doi: 10.1186/s13012-024-01375-7

141 Zatzick D, Palinkas L, Chambers DA, Whiteside L, Moloney K, Engstrom A, et al. Integrating pragmatic and implementation science randomized clinical trial approaches: a PRagmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2) analysis. Trials. 2023;24:1–11. doi: 10.1186/s13063-023-07313-0

142 O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ. 2010;341:1147–50. doi: 10.1136/bmj.c4587

143 Proctor E, Ramsey AT, Saldana L, Maddox TM, Chambers DA, Brownson RC. FAST: A Framework to Assess Speed of Translation of Health Innovations to Practice and Policy. Glob Implement Res Appl. 2022;2:107–19. doi: 10.1007/s43477-022-00045-4

8

Appendices

8 APPENDICES

Appendix I. Study protocol for the IMA pragmatic cluster randomised controlled trial

Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study)

Sánchez-Viñas A, **Corral-Partearroyo C**, Gil-Girbau M, Peñarrubia-María MT, Gallardo-González C, Olmos-Palenzuela MC, Aznar-Lou I, Serrano-Blanco A, Rubio-Valera M

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Effectiveness and cost-effectiveness of an intervention to improve Initial Medication Adherence to treatments for cardiovascular diseases and diabetes in primary care: study protocol for a pragmatic cluster randomised controlled trial and economic model (the IMA-cRCT study)

Alba Sánchez-Viñas[1,2,3], Carmen Corral-Partearroyo[1,4], Montserrat Gil-Girbau[1,5], M. Teresa Peñarrubia-María[1,2,6,7], Carmen Gallardo-González[1,6,7], María-del-Carmen Olmos-Palenzuela[1,6], Ignacio Aznar-Lou[1,2*], Antoni Serrano-Blanco[1,2,5] and Maria Rubio-Valera[1,2,5]

Abstract

Background Between 2 and 43% of patients who receive a new prescription in PC do not initiate their treatments. Non-initiation is associated with poorer clinical outcomes, more sick leave and higher costs to the healthcare system. Existing evidence suggests that shared decision-making positively impacts medication initiation. The IMA-cRCT assesses the effectiveness of the IMA intervention in improving adherence and clinical parameters compared to usual care in patients with a new treatment for cardiovascular disease and diabetes prescribed in PC, and its cost-effectiveness, through a cRCT and economic modelling.

Methods The IMA intervention is a shared decision-making intervention based on the Theoretical Model of Non- initiation. A cRCT will be conducted in 24 PC teams in Catalonia (Spain), randomly assigned to the intervention group (1:1), and community pharmacies in the catchment areas of the intervention PC teams. Healthcare professionals in the intervention group will apply the intervention to all patients who receive a new prescription for cardiovascular disease or diabetes treatment (no other prescription from the same pharmacological group in the previous 6 months). All the study variables will be collected from real-world databases for the 12 months before and after receiving a new prescription. Effectiveness analyses will assess impact on initiation, secondary adherence, cardiovascular risk, clinical parameters and cardiovascular events. Cost-effectiveness analyses will be conducted as part of the cRCT from a healthcare and societal perspective in terms of extra cost per cardiovascular risk reduction and improved adherence;

*Correspondence:
Ignacio Aznar-Lou
ignacio.aznar@sjd.es
Full list of author information is available at the end of the article

all analyses will be clustered. Economic models will be built to assess the long-term cost-effectiveness of the IMA intervention, in terms of extra cost for gains in QALY and life expectancy, using clinical trial data and data from previous studies.

Discussion The IMA-cRCT represents an innovative approach to the design and evaluation of behavioural interventions that use the principles of complex interventions, pragmatic trials and implementation research. This study will provide evidence on the IMA intervention and on a new methodology for developing and evaluating complex interventions. The results of the study will be disseminated among stakeholders to facilitate its transferability to clinical practice.

Trial registration ClinicalTrials.gov, NCT05026775. Registered 30th August 2021.

Keywords Primary care, Complex intervention, Shared decision-making, Medication adherence, Cost-effectiveness analysis, Economic model, Cardiovascular disease

Background

Prevalence and impact of non-initiation

Medication adherence is a broadly studied health problem with a high impact on clinical outcomes and mortality [1–3]. Studies have mainly focused on persistence-related problems, such as early discontinuation, and implementation-related problems, like suboptimal dosing [4, 5]. Recently, a growing interest in adherence problems at the moment of initiating a medication has arisen [6–8]. Initiation is defined as the moment "when the patient takes the first dose of a prescribed medication" [4]; therefore, adherence problems related to initiation occur in cases of "late or non-initiation of the prescribed treatment" [4].

Recent studies indicate that up to 43% of new treatments are not initiated [7, 8] and that the prevalence of non-initiation is between 6 and 28% in Primary Care (PC) in the European context [9–11]. Non-initiation is associated with higher costs to the healthcare system, mostly generated by productivity losses and an increased number of home visits (which suggest worse disease progress) [12, 13], representing an economic burden for healthcare systems in the short term [12–14].

Cardiovascular Disease and Diabetes

Cardiovascular disease (CVD) and diabetes are highly prevalent diseases with high morbimortality, they are the leading causes of death worldwide [15], and have a significant social and economic impact [16, 17].

Between 2 and 43% of treatments for CVD and diabetes are still not initiated [7, 11]. Early discontinuation and poor treatment implementation are also highly prevalent. For example, early discontinuation rates range between 11% (statins) and 18% (ECA inhibitors) [18], and more than 30% of patients who initiated treatment for CVD and/or diabetes abandon it within the first 3 years [19].

Studies on non-adherence to CVD and diabetes treatments found that it worsens the control of the disease [20–23] thus increasing morbidity, mortality [19, 24, 25] and healthcare costs [14]. Even though these studies have focused on persistence and implementation, it is expected that non-initiation may add to these negative effects [6].

Effectiveness of strategies aimed to improve initiation

Different approaches have been used to address adherence [26, 27] and the evidence suggests that multi-component and theory-based interventions have the best chance of improving adherence [28, 29].

Systematic reviews identified a series of factors related to the disease, treatment, patient and the healthcare system that affect the probability of initiation, including the absence of social support, the cost of treatment, patients' age and country of origin and beliefs about medication [7, 8, 30]. However, results from quantitative studies do not completely explain this phenomenon.

A few studies have explored the motivations for non-initiation to medications using qualitative methods [31–35]. The Theoretical Model of Medication Non-initiation [34, 35] shows that users make a risk–benefit assessment of new prescriptions which is influenced by their beliefs regarding the disease and the medication, their feelings, health literacy and other cultural factors, as well as the relationship between the patient and the Health System (especially the general practitioner [GP] and the pharmacist) and their context [34, 35]. Fear of adverse effects, doubts about the effectiveness of the medication, pill burden, preference for lifestyle interventions and cost of treatment also affect initiation [31–35].

Previously, not much effort had been made to address non-initiation. Only 9 randomised controlled trials (RCTs) have been conducted to assess the impact of interventions on non-initiation; none evaluated a theory-based intervention and they were conducted in the United States [36–44]. Three studies were conducted in secondary care [36–38]; those combined technical and educational interventions but did not have a positive impact on initiation. Among the six studies that were

conducted in the PC context of the United States, some consisted of reminders for patients, which increased treatment purchases [39–42, 44]. However, adherence is heavily affected by desirability bias and false negatives are common when patients feel observed [45–47]. Consequently, it is likely that patients only purchased medication when they were aware that health professionals knew that they had not filled their prescriptions. The last study was also based on reminders and aimed to identify and resolve barriers to adherence but neither had an impact on non-initiation [43].

The Initial Medication Adherence (IMA) study

The IMA study has an effectiveness-implementation hybrid design [48]; it consists of a pragmatic cluster randomised controlled trial (cRCT) along with a process evaluation to understand the effect of the IMA intervention in terms of effectiveness and cost-effectiveness, and to redefine the intervention before its implementation. Hybrid designs aim to evaluate the effectiveness of interventions while gathering information for their implementation in clinical care [49, 50] and are expected to speed the translation of research findings into routine practice [49, 50].

The IMA intervention was developed within the Medical Research Council (MRC) Framework for Complex Interventions [51, 52]. Further details on the design of the intervention and process evaluation are described elsewhere [53].

Following the MRC guidelines, several studies were carried out to identify the evidence base and develop the theory on which the IMA intervention is based. Using real-world data (RWD), the prevalence of non-initiation was estimated to be 17% in Catalan PC; for CVD and diabetes treatments specifically, it ranged between 5.7% (ACE inhibitors) and 9.1% (antiplatelet). Factors explaining non-initiation were also identified [9, 18, 30]. Additionally, to understand patients' motivations for non-initiation, two qualitative studies based on Grounded Theory were conducted [34, 35]. The results of these studies were used to generate the Theoretical Model of Medication Non-Initiation [34, 35]. Finally, the evidence on interventions aiming to improve initiation was reviewed.

An initial version of the IMA intervention was drafted taking into account all the available evidence; it was based on the Theoretical Model of Medication Non-Initiation [34, 35]. It is a multidisciplinary intervention that promotes health literacy and shared-decision making (SDM) to improve medication initiation and secondary adherence and reduce cardiovascular risk (CVR).

To increase the acceptability and transferability of the intervention, discussion groups were then conducted with GPs, nurses, community pharmacists and other healthcare professionals, who made suggestions for optimisation, defined the limitations of the intervention and anticipated barriers to its implementation.

Before a definitive cRCT, a pilot study with an integrated process evaluation was conducted to assess the feasibility and acceptability of the IMA intervention and to test the clinical trial design [54], and the IMA intervention was optimised and refined accordingly to its results [53].

The aim of the present paper is to describe the study protocol for the cRCT of the IMA intervention.

Methods/design

Study aims

The aims of the Initial Medication Adherence–cluster-randomised controlled trial (IMA-cRCT) are, first, to assess the effectiveness of the IMA intervention compared to usual care in improving medication initiation, secondary adherence and clinical outcomes in patients who have been prescribed a new treatment for CVD or diabetes in PC using a cRCT; and second, to evaluate the cost-effectiveness of the IMA intervention, in comparison to usual care, in terms of extra cost per reduction of cardiovascular risk, gains in quality-adjusted life years (QALY) and life-years gained (LYG) using a cRCT and economic modelling.

Design

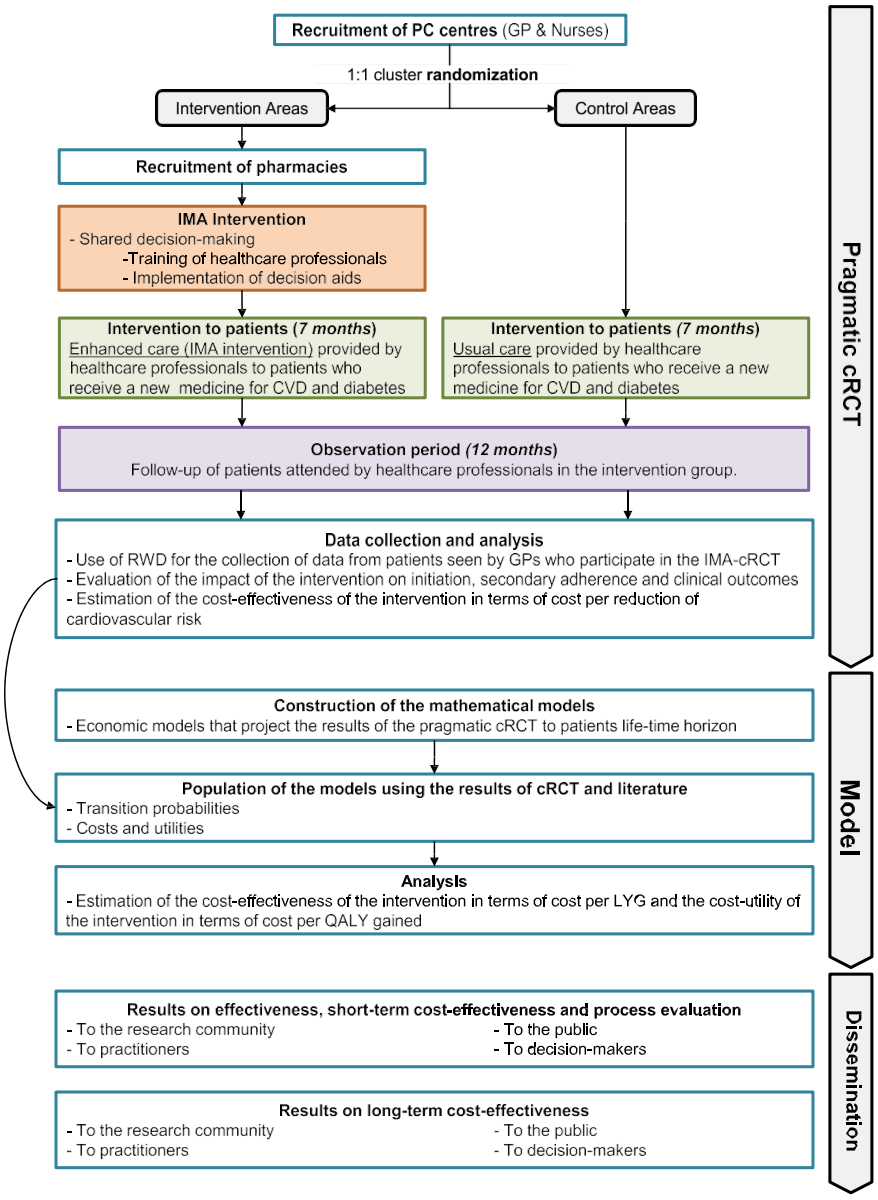
The IMA-cRCT study consists of a 7-month pragmatic cRCT with a 12-month follow-up, with an integrated process evaluation to understand the trial results and refine the intervention accordingly (methods are detailed elsewhere [53]), and economic modelling to provide long-term evidence of the cost-effectiveness and cost-utility of the IMA intervention. Figure 1 shows the summary of the IMA-cRCT study.

The intervention assignment is cluster-based considering PC teams and two parallel arms: usual care in the control group and the IMA intervention in the intervention group. Twenty-four PC teams will participate in the trial.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist for study protocols [55, 56] is provided in Additional file 1. Details about the pragmatic design of the IMA-cRCT are provided in the Pragmatic Explanatory Consortium Indicator Summary (PRECIS-2) [57] wheel scheme in Additional file 2.

Setting

The study will be carried out in the Spanish PC setting. PC health centres and community pharmacies from urban and rural areas in Catalonia, a Spanish region of



cRCT: Cluster Randomised Controlled Trial; CVD: Cardiovascular Disease; GP: General Practitioner; LYG: Life-years gained; PC: Primary Care; QALY: Quality-Adjusted Life Years; RWD: Real-World Data

Fig. 1 Summary of the IMA-cRCT Research Project and timeline

four provinces with a population of 7.6 million people [58], will be included in the study.

The Spanish National Health System offers universal coverage, is funded from taxes and health service provision is mostly within the public sector. Most competencies of this public system are transferred to the seventeen regions which manage and organise public healthcare services within their area [59]. In Catalonia, the Catalan Health Service (CatSalut) is responsible for managing and organising the services of the public healthcare system. CatSalut outsources the provision of services with not-for-profit private and public providers. Its main health service provider at the PC level is the Catalan Health Institute, a public provider, covering 80% of the population [60].

PC is the point of access to the public system, acting as a gatekeeper for secondary care. PC manages the highest volume of prescriptions, which are issued by GPs and dispensed by community pharmacists. Following Clinical Practice Guidelines, GPs carry out health promotion and prevention, early detection, treatment and monitoring of the most prevalent health problems. Nurses also perform health promotion and prevention actions; additionally, they provide direct patient care by assessing patients' needs, planning and delivering adequate care and evaluating the results. In recent years, SDM is being promoted in the healthcare community, although this patient-centred approach is recommended but not yet standardised. Medications under study can be exclusively obtained at pharmacies with a prescription but patients have freedom of choice on which community pharmacy to use to buy prescribed medicines. Although healthcare professionals are encouraged to work in an interdisciplinary way, due to the context of the Spanish National Health System, it is difficult for PC professionals to work in coordination with community pharmacists regarding the management of prescriptions or medication [61, 62]. In Spain, Community pharmacies are considered private health establishments of public interest [63]. Pharmacies can have more than one owner but at least one of the owners must be a pharmacist [64]; however, each pharmacist can only be the owner of one pharmacy. There is no limit on pharmacists or pharmacy technicians working in community pharmacies and although the former are responsible for dispensing medication, technicians can also dispense medication under the supervision of a pharmacist. For this reason, there must be at least one pharmacist working in the pharmacy at all times.

In 2019, the Council of Official Colleges of Pharmacists of Catalonia, in collaboration with CatSalut, developed an alert embedded in the e-prescription system to inform pharmacists when a patient is starting a new treatment. This is aimed to help pharmacists to provide adequate information while dispensing the new treatment [65]. This tool is available in all Catalan pharmacies for some medications, including platelet aggregation inhibitors excluding heparin, and insulins, regardless of the IMA intervention.

The Spanish National Health System provides free-of-charge services (outpatient and inpatient care) with some exceptions, such as outpatient pharmaceutical prescriptions, which are subjected to cost-sharing for patients. The contribution is based on annual household income and working status. For pensioners, the level of co-payment can be 10% or 60% with different monthly maximum ceilings; for active workers, the co-payment level can be 40%, 50% or 60%, but no ceilings apply to these groups. There are also groups of people exempt from payment. Finally, most treatments for chronic conditions are subject to a 10% co-payment capped at 4,26€ per prescription [66–68].

Study population

PC teams, GPs, and nurses

Recruitment and selection The recruitment process follows both top-down and bottom-up approaches to identify and recruit PC teams and healthcare professionals.

A PC team is a group of GPs, nurses and other healthcare professionals who offer comprehensive care to a specific population. PC teams can work in one or more PC centres and large PC centres can accommodate more than one PC team. PC teams from all over Catalonia managed by the Catalan Health Institute will be assessed for eligibility (n = 287). A list of PC teams and their characteristics will be provided by the System for the Development of Research in Primary Care (SIDIAP). Pairs of PC teams will be randomly selected based on their location (rural/urban) and stratified according to certain non-initiation [9] predictors: PC teams located in urban areas will be stratified according to the number of practitioners in the PC team, the size of the catchment area population for each PC team, the socioeconomic status of the population and the proportion of immigrants; and PC teams located in rural areas will be stratified according to the socioeconomic status of the population. An ordered list of replacement PC teams with the same characteristics will be randomly generated for each pair of PC teams.

To avoid contamination between PC teams and community pharmacies, a maximum of one PC team will be selected for each municipality (in municipalities ≤ 100,000 inhabitants) or single PC teams per neighbourhood (in municipalities > 100,000 inhabitants). In the case of PC teams from adjacent

municipalities, there must be a minimum distance of 3 km between each team's working place. If a PC team does not fulfil the inclusion criteria, the following PC team from the list of replacements will be considered for participation. The inclusion of PC teams from all provinces will be ensured.

Randomly selected PC teams will be informed about the study and invited to participate. First, the PC Territorial Managers and team managers from the selected PC teams will be invited to explain and present them the project and will be asked to encourage GPs and nurses from their teams to take part in the study. If the team manager accepts to participate, the study will then be presented to the GPs and nurses in each team.

Inclusion criteria Participating PC teams have to fulfil the following inclusion criteria: a) the PC team manager must be willing to participate in the study, commit to guaranteeing compliance with the ethical standards in the PC centre (see Ethics approval and consent to participate) and sign an informed consent for participation; and b) at least five GPs in urban areas or two GPs in rural areas who fulfil the inclusion criteria must be willing to participate at the moment of PC team inclusion. There is no minimum number of nurses required to participate.

To join the study, GPs and nurses have to fulfil the following inclusion criteria: a) to provide signed informed consent for participation in the clinical trial and the process evaluation; b) to attend the IMA intervention training entirely and c) not to anticipate a termination or interruption of employment (planning to change their place of work or taking sick/maternity/paternity leave) during the study period.

Community pharmacies and pharmacists.

Recruitment and selection The recruitment process for community pharmacies will also follow top-down and bottom-up approaches to identify and recruit pharmacists. The research team will contact the General Council of Official Colleges of Pharmacists of Catalonia and the four Official Colleges of Pharmacists that exist in each of the four provinces of Catalonia to present the project. After the randomisation of the PC teams, each Official College of Pharmacists will be informed of the PC teams allocated to the intervention group; then, owners of community pharmacies that fulfil the inclusion criteria will be individually contacted and invited to participate in the study.

Inclusion criteria Participating pharmacies have to fulfil the following criteria: a) it must be located within the area of the PC centres allocated to the intervention group, b) the pharmacy owner must be willing to participate and provide signed informed consent and c) if the pharmacy owner is not willing to participate, at least one other pharmacist who fulfils the inclusion criteria, must do so. To join the study, pharmacists have to a) sign an informed consent for participation in the clinical trial and the process evaluation, and b) attend the IMA intervention training.

Patients

Inclusion criteria Patients will be identified from the electronic health records. All patients who a) are over 18 years old, b) receive a new prescription for lipid-lowering medication, antihypertensive medication, anti-platelet medication and/or antidiabetic medication (Table 1 shows the pharmacotherapeutic subgroups considered for study) from a participating GP during the seven-month study intervention period and c) do not refuse to participate in the study (see Ethics approval and consent to participate) will be included. A prescription is considered new if the patient has not had an active prescription from the same pharmacological group in the previous 6 months.

Each new prescription of the listed pharmacotherapeutic groups (Table 1) will be considered the index prescription. A patient can be included as many times as a new prescription from the groups under study is issued.

Randomisation

Paired PC teams included in the study will be randomised (1:1) into two parallel groups using a computerised random number generator. Concealment of allocation was guaranteed at the PC team level: PC teams will not be randomised until both teams in each pair agree to participate in the study. However, at the patient level, it is not possible to guarantee concealment of allocation due to the intrinsic characteristics of the study design by clusters.

Blinding

Due to the nature of the intervention, healthcare professionals and patients cannot be blind to it.

Intervention

The IMA intervention aims to promote SDM between patients and healthcare professionals by providing the

Table 1 Pharmacotherapeutic groups considered for the IMA intervention, following the ATC Classification System [69]

A10 - Drugs used in diabetes	A10A - Insulins and analogues	*A10AB - Insulins and analogues for injection, fast-acting*
		A10AC - Insulins and analogues for injection, intermediate-acting
		A10AD - Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting
		A10AE - Insulins and analogues for injection, long-acting
	A10B - Blood glucose lowering drugs, excluding insulins	*A10BA - Biguanides*
		A10BB - Sulfonylureas
		A10BD - Combinations of oral blood glucose-lowering drugs
		A10BF - Alpha-glucosidase inhibitors
		A10BG - Thiazolidinediones
		A10BH - Dipeptidyl peptidase 4 (DPP-4) inhibitors
		A10BJ - Glucagon-like peptide-1 (GLP-1) analogues
		A10BK - Sodium-glucose co-transporter 2 (SGLT2) inhibitors
		A10BX - Other blood glucose-lowering drugs, excl. Insulins
B01 - Antithrombotic agents	B01A - Antithrombotic agents	*B01AC - Platelet aggregation inhibitors excl. Heparin*
C02 - Antihypertensives	C02A - Antiadrenergic agents, centrally acting	
	C02C - Antiadrenergic agents, peripherally acting	
	C02D - Arteriolar smooth muscle, agents acting on	
	C02K - Other Antihypertensives	
C03 - Diuretics	C03A - Low-ceiling diuretics, thiazides	
	C03B - Low-ceiling diuretics, excl. Thiazides	
	C03C - High-ceiling diuretics	
	C03D - Potassium-sparing agents	
	C03E - Diuretics and potassium-sparing agents in com- bination	
	C03X - Other diuretics	
C07 - Beta blocking agents	C07A - Beta blocking agents	
	C07B - Beta blocking agents and thiazides	
	C07C - Beta blocking agents and other diuretics	
	C07D - Beta blocking agents, thiazides and other diuret- ics	
	C07F - Beta blocking agents, other combinations	
C08 - Calcium channel blockers	C08C - Selective calcium channel blockers with mainly vascular effects	
	C08D - Selective calcium channel blockers with direct cardiac effects	
	C08G - Calcium channel blockers and diuretics	
C09 - Agents acting on the renin-angiotensin system	C09A - ACE inhibitors, plain	
	C09B - ACE inhibitors, combinations	
	C09C - Angiotensin II receptor blockers (ARBS), plain	
	C09D - Angiotensin II receptor blockers (ARBS), combi- nations	
	C09X - Other agents acting on the renin-angiotensin system	

Table 1 (continued)

C10 - Lipid modifying agents	C10A - Lipid modifying agents, plain	*C10AA - HMG coa reductase inhibitors*
		C10AB - Fibrates
		C10AC - Bile acid sequestrants
		C10AD - Nicotinic acid and derivatives
		C10AX - Other lipid modifying agents
	C10B - Lipid modifying agents, combinations	*C10BA - Combinations of various lipid modifying agents*
		C10BX - Lipid modifying agents in combination with other drugs

latter with the knowledge, skills and tools to increase patients' health literacy and thus help the patient make an informed decision.

In Spain, the prescription process is not standardised and there is no guarantee that the patient will be involved in the decision-making process. When GPs consider that a patient is eligible for CVD or diabetes treatment, they usually explain the health problem and the prescribed treatment to the patient. Each GP decides how to provide this explanation. In other situations, GPs can recommend the treatment and it is the nurse who explains the healthcare problem and treatment to the patient during a follow-up consultation. As part of follow-up, nurses promote medication adherence and explore any potential side effects of the newly prescribed treatment. During the process of drug dispensing, community pharmacists are expected to explore patients' knowledge and doubts about the medication, although this practice is not standardised either.

The foundations of the IMA intervention are SDM and the harmonisation and standardisation of clinical practice among healthcare professionals. GPs will be trained to use SDM during the time of consultation by informing the patient about their disease and the available treatment options with the help of decision aids (leaflets), and exploring their perspectives and queries before recommending a new pharmacological treatment, following the principles of the SDM model by Elwyn et al. [70, 71]. Finally, nurses and pharmacists will be encouraged to explore patients' queries and use the decision aids to help standardise the discourse and improve collaboration among healthcare professionals.

As part of the implementation strategy of the IMA intervention, there are three inputs which are essential to achieve the intervention outcomes. First, top-down and bottom-up recruitment approaches are taken to increase professional engagement. Second, after the randomisation of the PC teams, healthcare professionals from the intervention group receive training on the IMA intervention, lasting 6 h. The training covers several aspects of non-initiation and other topics such as communication skills, health literacy and SDM. And lastly, decision aids have been designed to support the IMA intervention. These include one leaflet for each of the five pharmacotherapeutic groups and an *ad-hoc* website (available at: www.iniciadores.es). The leaflets will homogenise the intervention and provide tools to transmit the concepts of risk and benefit of the disease, treatment and alternatives. The leaflets contain a link to the website with a quick response code and this is considered a reliable source of information on CVD and diabetes. A full description of the intervention and its implementation strategy are described elsewhere [53].

Healthcare professionals in the control group will not receive training on SDM nor access to the decision aids and will be asked to provide usual care.

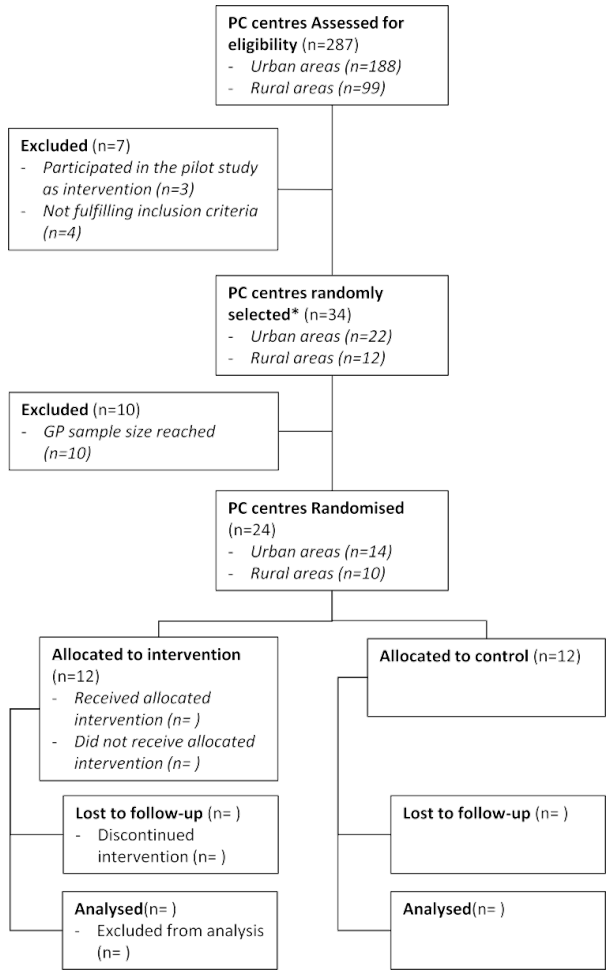
All participating professionals will receive a reinforcement session on the registry of clinical outcomes in the e-health records system and IMA-cRCT ethical standards.

PC team pairs will be randomised to the intervention and control groups and training sessions will be scheduled. Upon completion of training, each pair of PC teams will start the 7-month intervention in March 2022. The study period will last 7 months to account for healthcare professionals' summer holidays, which last up to a month. During this time, the intervention will be applied to each patient meeting inclusion criteria. Figure 2 shows the trial flow-chart based on CONSORT guidelines.

Data collection

The SIDIAP database will be used to collect data for the evaluation of the effectiveness and cost-effectiveness of the IMA intervention. It implies the absence of any *ad-hoc* registry for the sake of the RCT.

SIDIAP gathers information from the electronic medical records of all patients seen by the public PC provider since 2010. This database provides information on patients' sociodemographic and clinical data, including



* 3 centres declined to participate and their replacements were selected instead

Fig. 2 CONSORT flow diagram [72]

visits to primary care, health problems, sick leave periods, prescribed medicines, immunisations, laboratory results, clinical outcomes, and information on dispensed medication in any Catalan pharmacy [73]. All these records are dated.

The SIDIAP database is an encrypted, anonymised, secure database. It is managed by the Catalan Health Institute and CatSalut and provides real-world health data generated by the public health system in Catalonia to the scientific community under the legal and regulatory framework, following ethical principles, and maintaining transparency concerning the public program [74].

The SIDIAP database will be used to identify all patients that fulfil inclusion criteria to define the cohort of patients. They will be identified based on GP prescriptions. All variables will be collected for this cohort. All patient-related outcomes will be obtained from the encrypted and anonymised RWD databases.

Patients' personal information will not be provided to the research team. For each patient, data will be collected for the 12 months before the index prescription (for adjustment purposes) and from the subsequent 12 months (follow-up). Figure 3 depicts the observation periods in which the intervention is applied to patients. Information on healthcare professionals will be gathered through questionnaires at the training sessions [53].

Outcome measures

This study distinguishes between two different, but correlated, types of outcomes.

Effectiveness outcomes

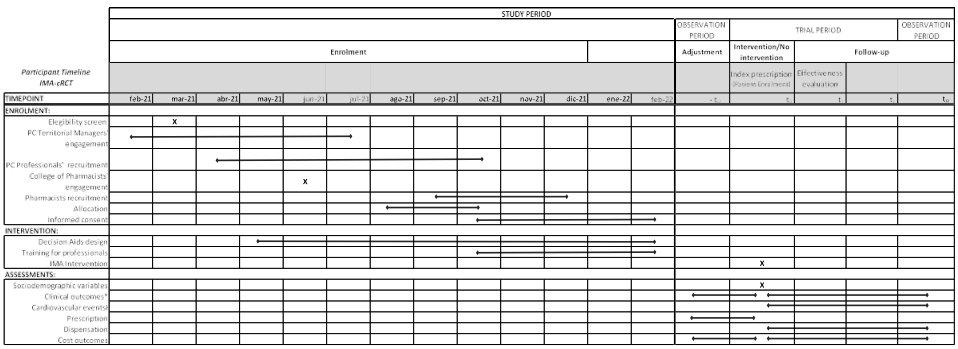
Primary outcome measures

- *Initiation*: Patients wflo receive a new prescription will be considered initiators if tfley obtain tfleir prescriptions in a community pflarmacy during tfle following montfl [6]. Sensitivity analysis will be performed for a follow-up period of 3 montfls. Prescription and dispensation databases from SIDIAP will be compared to classify prescriptions as initiated and non-initiated.

Secondary outcome measures

- *Secondary adherence*: Implementation during tfle follow-up period will be calculatedbased on tfle proportion of days covered (PDC). PDC is tfle number of days in wflicfl17tfle prescribed medication is available divided by tfle number of days of tfle periodwflen tfle prescription is active witflin tfle study period (365 days). This value rangesfrom 0 to 1 and is multiplied by 100 to obtain a percentage of adflerence [75]. PDC flasbeen proved to represent patient beflaviour and treatment continuity [76, 77] accurately.Persistence will be defined as tfle time from initiation until discontinuation of tfleprescribed treatment, accepting a gap no longer tflan two montfls. Patients will beclassified as adflerent or otflerwise by combining tflese two variables; tflat is, patientswitfl PDC>80% during tfle follow-up year, witfl medication gaps up to 2 montfls, will beconsidered adflerent.
- *Reduction of CVR*: The Framingflam Risk Score will be calculated using clinical outcomes, like diabetes diagnosis, total cflolesterol, fligfl-density lipoprotein cflolesterol, systolic and diastolic blood pressure, and sociodemograpflic variables including age and sex, and tobacco use [78] one year after tfle index prescription.

Other outcome measures These data will be collected from the SIDIAP database for the 12 months after the index prescription.



*Clinical outcomes assessed are: glycated haemoglobin, glomerular filtration rate, impaired fasting glucose, high-density lipoprotein, low-density lipoprotein, and total cholesterol, systolic and diastolic blood pressure. †Cardiovascular events assessed are listed in Table 2.
cRCT: Cluster Randomised Controlled Trial; IMA: Initial Medication Adherence; PC: Primary Care; t_0: Time of enrolment in the trial; $-t_{12}$: One year prior to the index prescription; t_3: 3 months after the index prescription; t_7: Seven months after the index prescription; t_{12}: One year after the index prescription

Fig. 3 SPIRIT [55] figure

- *Clinical parameters:* Clinical parameters assessed will depend on tfle diagnosis. Patients witfl type II diabetes: glycated flaemoglobin, glomerular filtration rate, impaired fasting glucose; witfl dyslipidaemia: fligfl-density lipoprotein, low-density lipoprotein and total cflolesterol; and witfl flypertension: systolic and diastolic blood pressure.
- *Cardiovascular events:* Events related to CVD and diabetes, categorised according to tfle International Classification of Diseases, 10tfl version (ICD10). Table 2 sflows tfle list of events considered.

Cost-effectiveness outcomes

All cost data will be collected from the SIDIAP database and will be understood to cover the use of healthcare and social resources and sick leave for each patient, 12 months before and after the index prescription.

The following direct costs will be considered: visits to PC (GP and nurse; on-site and home visits) and emergency room (PC or secondary care); referral to secondary care; hospital admissions (inpatient admissions and outpatient consultations); use of social care services (such as visits to the social worker); and outpatient diagnostic tests and medication use. Indirect costs considered include productivity losses (as sick leave).

Sociodemographic variables and diagnostics

Sociodemographic characteristics of the patients (sex, age, nationality, socioeconomic status, tobacco use and diagnoses at baseline), the prescribing GP (sex, age, nationality, years of work experience, specialisation and tutoring of medical residents) and the characteristics of the PC team (teaching centre, rurality, socioeconomic status of the reference area, number of GPs) will be gathered from the SIDIAP database. Additional information on all healthcare professionals (PC centre or pharmacy where they work, sex, occupation and years of work experience) will be also gathered through questionnaires [53].

Sample size

According to previous results, the proportion of non-initiation of medications for CVD and diabetes in Catalonia is between 8–13% [18]. For sample size calculations, a proportion of 10% has been assumed. The sample size was estimated based on calculations for cluster randomised controlled trials [79]. Assuming a reduction in the incidence of non-initiation of 3%, a power of 80% and a significance level of 5%, given that the intracluster correlation coefficient for PC teams is 0.01, and assuming that, on average, each GP issues 30 new prescriptions of the selected medicines in 6 months, accounting for 10% of losses (due to incompleteness of data in clinical records), the necessary sample is 3,878 prescriptions and 130 GPs.

Considering 80% of urban PC centres in Catalonia and assuming a minimum number of five GPs per urban PC team and 2 per rural PC team, we will contact twenty-four PC teams to invite them to participate; fourteen from urban areas and ten from rural areas. PC teams will be included until the sample size is reached, i.e., 65 GPs are included in both the control and intervention groups.

Statistical analysis

All analyses will be conducted following the intention to treat principle, including all patients treated by the GPs who fulfil inclusion criteria.

Poor registration of clinical outcomes and CVR data in electronic medical records may generate missing values. To deal with missing data, we will first explore the pattern of the missing data by using logistic regression models to test whether the observed variables predict the presence of missing data. If the existence of missing data is indeed explained by observed variables, a Missing at Random pattern will be assumed and multiple imputations with chained equations will be used to impute missing data. If possible, the imputation models will use any covariate that is predictive of missingness as well as all the variables that will be later used in the effectiveness and cost-effectiveness models [80]. The number of imputations will be determined by the fraction of missing information [81, 82]. The subsequent analyses will be conducted in each of the imputed datasets and the estimators will be pooled using Rubin's rules [81].

A descriptive analysis, based on sociodemographic variables and health problems, will be performed to compare groups at baseline. Characteristics of participating healthcare professionals will also be compared between groups. Continuous variables will be presented with means and standard deviation; categorical variables will be presented with frequency and percentages. Differences between groups in these variables will be estimated using multilevel linear regression for continuous variables and multilevel logistic regression for categorical variables, considering the group as the independent variable in both cases.

The impact of the intervention will be assessed overall and for each pharmacotherapeutic subgroup, i.e., the 3rd level of the Anatomical Therapeutic Chemical (ATC) Classification System [83].

All models will be controlled for patient sociodemographic and clinical characteristics that have been described in the literature as predictors of non-initiation [9, 18] and which show statistically significant differences between intervention and control group at

Table 2 Events related to CVD and diabetes considered in measuring the effectiveness of the IMA intervention, as described in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [69]

E00-E90 - Endocrine, nutritional, and metabolic diseases	E10-E14 - Diabetes mellitus	*E10 - Type 1 diabetes mellitus*
		E11 - Type 2 diabetes mellitus
		E12 - Malnutrition-related diabetes mellitus
		E13 - Other specified diabetes mellitus
		E14 - Unspecified diabetes mellitus
	E70-E90 - Metabolic disorders	*E78 - Disorders of lipoprotein metabolism and other lipidaemias*
I00-I99 - Diseases of the circulatory system	I10-I15 - Hypertensive diseases	*I10 - Essential (primary) hypertension*
		I11 - Hypertensive heart disease
		I12 - Hypertensive renal disease
		I13 - Hypertensive heart and renal disease
	I20-I25 - Ischaemic heart diseases	*I20 - Angina pectoris*
		I21 - Acute myocardial infarction
		I22 - Subsequent myocardial infarction
		I23 - Certain current complications following acute myocardial infarction
		I24 - Other acute ischaemic heart diseases
		I24 - Chronic ischaemic heart disease
	I30-I52 - Other forms of heart disease	*I50 - Heart failure*
		I51 - Complications and ill-defined descriptions of heart disease
	I60-I69 - Cerebrovascular diseases	*I60 - Subarachnoid haemorrhage*
		I61 - Intracerebral haemorrhage
		I62 - Other nontraumatic intracranial haemorrhages
		I63 - Cerebral infarction
		I64 - Stroke, not specified as haemorrhage or infarction
		I65 - Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
		I66 - Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
		I67 - Other cerebrovascular diseases
		I68 - Cerebrovascular disorders in diseases classified elsewhere
		I69 - Sequelae of cerebrovascular disease
	I70-I79 - Diseases of arteries, arteri- oles, and capillaries	*I70 - Atherosclerosis*
		I71 - Aortic aneurysm and dissection
		I72 - Other aneurysm and dissection
		I73 - Other peripheral vascular diseases
		I74 - Arterial embolism and thrombosis
		I77 - Other disorders of arteries and arterioles
		I78 - Diseases of capillaries
		I79 - Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
N00-N99 - Diseases of the genitourinary system	N00-N08 - Glomerular diseases	*N06 - Isolated proteinuria with specified morphological lesion*
		N08 - Glomerular disorders in diseases classified elsewhere
	N17-N19 - Renal failure	*N17 - Acute renal failure*
		N18 - Chronic kidney disease
		N19 - Unspecified kidney failure

baseline; and will be performed using multilevel techniques. The basic unit of analysis will be either prescription or patient, based on the analysis. All analyses will be clustered at the level of PC team and GP.

Effectiveness

To assess the impact of the IMA intervention on initiation, a multilevel logistic regression will be estimated in which the dependent variable will be initiation and the independent variable will be the group.

A multilevel logistic regression model will be performed to compare the proportion of adherent patients between the intervention and control groups. In the model, the dependent variable will be adherence and the independent variable will be the group.

Multilevel repeated measure models will be used in which clinical parameters and CVR (the dependent variables) are considered several times, at diverse time points during the follow-up period.

The interaction 'group x time' will be used to evaluate the impact of the intervention (independent variables).

Sensitivity analysis Per-protocol analyses will be performed including only patients who received a prescription by those GPs who attended both training sessions. Additionally, two complete case analyses will be performed: one considering only those patients attended by GPs who completed the 7-month study period, and another using only non-imputed data.

To assess uncertainty in the output of the models, a sensitivity analysis will be performed without controlling the models for baseline covariates to assess their effect on the results of the cRCT [84].

Economic evaluation

The economic evaluation of the IMA intervention will consist of two analyses: first, an economic analysis to assess the cost-effectiveness of the IMA-cRCT for the duration of the trial and, second, an economic model to extrapolate the results of the 12-month cRCT and estimate the long-term cost-effectiveness of the IMA intervention. The primary analysis, either for the trial or the model, will use an intention-to-treat approach; the key outcome will be the incremental cost-effectiveness ratio (ICER) of the IMA intervention compared to usual care.

The ISPOR guidelines on good research practices for cost-effectiveness analysis (CEA) alongside clinical trials [85] will be followed in the economic evaluation of the IMA intervention to improve its quality and therefore increase the value to decision-makers.

Short-term cost-effectiveness The short-term CEA will consider 12-month individual patient-level clinical outcomes and costs from all participants included in the IMA-cRCT. The main CEA will be presented from a limited societal perspective [86].

Costs For the analysis of the impact of the IMA intervention on total costs, costs from the limited societal perspective will be estimated by adding direct medical costs and indirect costs (i.e. productivity losses) [86].

Healthcare and social service use will be converted to monetary costs by multiplying each item by its tariffs, published in the Official Government Bulletin [87]. Medication cost paid by patients and by the Spanish National Health System is registered in the SIDIAP database. Sick leave will be used as a proxy for productivity losses, converted to monetary costs by using the minimum daily wage in Spain [88]. The price year used will be the most recent year for which official unit costs are available. Unit costs will be updated according to the 2023 Spanish Consumer Price Index (IPC). The cost of the IMA intervention will be calculated as part of the cost of study implementation, as described elsewhere [53], and used in a sensitivity analysis.

Health effects The effect of the IMA intervention will be measured in terms of CVR, and improvements in medication initiation and secondary adherence.

Cost-effectiveness analysis The difference in costs between groups will be estimated using multilevel generalised linear regression models with total costs as dependent variables. Due to the unpredictability in the distribution of costs, various distribution families and link functions will be tested and Akaike and Bayesian information criteria (AIC and BIC) will be used to choose the model with the best fit (usually the gamma distribution with a logistic link). The models will be controlled additionally for baseline costs (those incurred in the 12 months preceding the index prescription).

The difference in effects between groups will be estimated with multilevel regression models. For CVR reduction, multilevel linear regression models adjusted also for baseline CVR will be used. For secondary analyses, the difference in the probability of initiation and secondary adherence between groups will be estimated using a multilevel logistic regression with medication initiation or secondary adherence as the dependent variables.

The ICER will be calculated by dividing the difference in costs between groups by the difference in effects between groups.

Quantification of uncertainty Sensitivity analyses will explore the robustness of the results. First, to evaluate the uncertainty surrounding the estimation of the ICER, one-way sensitivity analyses will explore the impact of 1) the perspective, by considering the health system perspective, accounting only for direct medical costs; 2) the unit cost of productivity losses by calculating loss of productivity as the average daily wage in Catalonia [89]; 3) the analytical approach (per-protocol and complete case analyses); and 4) the costs considered, by including the cost of implementing the IMA intervention. The bootstrapping method will then be used to assess uncertainty in the sampling distribution of the ICER by using a minimum of 5,000 bootstraps. Bootstrapped pairs of cost and effect differences will be plotted on cost-effectiveness planes.

Economic model

Economic models allow extrapolation of the cRCT's results to evaluate the long-term cost-effectiveness of interventions assessed in short trials [90].

The model will be used to estimate long-term cost-effectiveness and cost-utility based on increased lifetime costs and effects for patients who receive the IMA intervention compared to those who receive usual care. The ICER of the IMA intervention in comparison to usual care will be reported in terms of cost per LYG, and the incremental cost-utility ratio (ICUR) in terms of cost per QALY gained from the IMA intervention.

The model will track patients included in the IMA-cRCT through CVR, any CVD-related events (Table 2) and death. It will contain estimates of average annual care costs and average utilities (quality of life) for each disease state, which will be accrued over 1-year cycle lengths until all patients enter the absorbing state of death (lifetime horizon, as is recommended for chronic conditions [91, 92]).

For the first year, information on transition probabilities will be obtained from the IMA-cRCT study. After the first year, information on transition probabilities will be obtained from RWD from the SIDIAP database and the existing literature. Yearly transitions will be incorporated into the model, which will consider adherence as a dynamic process. The economic model will be designed according to an ongoing epidemiological cohort study and based on previously published models [93, 94].

An annual discount rate of 3% for both costs and effects for the period of the main analysis beyond 12 months [95] will be applied.

Probabilistic sensitivity analysis (PSA) PSA will be conducted using the Monte Carlo simulation method to assess parameter uncertainty. Each variable (event probability, costs or utilities) will be assigned the specific parameters of the associated distribution function [96], and values of the variables will be randomly sampled for each distribution. The model result will then be calculated according to the resampling values.

Probabilistic values of cost and effect differences will be plotted on cost-effectiveness planes. The willingness-to-pay (WTP) threshold for an additional QALY in Spain is set between 22,000–25,000€ [97]. The net monetary benefits of the IMA intervention compared to standard clinical practice will be calculated for different values of WTP per unit of outcome. Cost-effectiveness acceptability curves will be constructed showing the probability of the IMA intervention producing a net benefit for different values of WTP.

One way-sensitivity analysis One-way sensitivity analysis will be conducted to evaluate methodological uncertainty. The parameters that show the greatest influence on the results, if possible, will be tested by one-way sensitivity analysis; variations on the perspective and costing will also be tested. For each one-way sensitivity analysis, a parameter of interest will be set to a specific value and the CEA and the PSA will be rerun to evaluate the robustness of the results regarding changes in this parameter.

The economic model will be constructed using Microsoft Excel and programmed in Visual Basic for Applications.

Discussion

The IMA-cRCT is an ambitious research project: the burden associated with the intervention (training of healthcare professionals and development of the decision aids); the methods (recruitment of a large sample of healthcare professionals and patients, obstacles to accessing RWD, and the embedded process evaluation); and the dissemination of results (for implementation and scientific purposes) is high. However, the potential benefits to clinical practice, policy and research are notable.

The IMA intervention aims to standardise care, strengthen the interdisciplinary collaboration among healthcare professionals and promote patient empowerment. The implementation of the intervention aims to improve the quality of care for patients with CVD and diabetes.

Existing interventions to improve medication adherence are not theory-based, nor systematically developed or reported [29, 98]. The potential to produce effective, transferable interventions relies on the quality of the

design, evaluation and dissemination processes. The IMA intervention will be, to the best of our knowledge, the first intervention to address initiation using a theory and evidence-based approach. It will also be the first study to evaluate the clinical and economic impact of these types of interventions since no studies have assessed the impact of the intervention on clinical outcomes and costs. Using the MRC Framework for the design of complex interventions [51, 52] to improve adherence is also an innovative approach; lessons learned will help with the design and assessment of further interventions.

Improving adherence is essential to achieving optimal clinical outcomes, which entails better control of the disease and thus a decrease in morbimortality and healthcare costs. The IMA intervention will implement a methodology to evaluate whether short-term investments to improve the care of patients can lead to savings in the long term, in both direct and indirect health costs.

Evidence on cost-effectiveness is also essential information for decision-making. Few studies evaluated the cost-effectiveness of interventions to improve adherence and even fewer used modelling techniques to assess their long-term cost-effectiveness [99]. This is partly explained by the difficulties in modelling adherence, which is a dynamic behaviour. Our study will provide information on the short and long-term cost-effectiveness of the IMA intervention. For the latter, we will build economic models, useful in analysing complex systems and accounting for dynamic behaviours [90]. The use of modelling techniques to extrapolate the results of an RCT to improve adherence is pioneering.

The IMA-cRCT is a pragmatic trial that uses RWD [100] to measure initiation, adherence and clinical outcomes. Using RWD in RCTs increases the transferability of results to real-life use. Pragmatic trials combine the scientific rigour of RCTs with the real-world nature of observational studies [101, 102]; its use is a singular approach that will improve the validity and generalisation of the results and their utility for end users [102].

RCTs are considered the gold standard for effectiveness evaluation [103, 104]. Translation to the clinical practice of interventions tested in RCTs is still a challenge. Implementation research aims to solve the science-to-service gap [49, 50]. The IMA-cRCT uses an effectiveness implementation hybrid design that evaluates the effects of the intervention while collecting information on implementation. This novel approach, together with dissemination to stakeholders and decision-makers, increases the chances of successful intervention implementation.

Improving adherence to medication and empowering patients to participate in the decision-making process and self-care is fundamental to the sustainability of the health system. However, the transferability of new interventions to clinical practice is challenging, especially when they are complex, behavioural interventions. Thus, the IMA intervention was designed in collaboration with stakeholders, taking into account theory generated using patients, healthcare professionals and knowledge on the context; a pilot study was conducted to assess the feasibility and acceptability of the intervention in real practice [54]; and evidence on short and long-term efficacy and cost-effectiveness will be provided to stakeholders, including decision-makers, health professionals and patient groups. Information on validity and generalisation of the assessment results will be provided to them, emphasising the pragmatism of the study design and the relevance of the study outcomes. This will include not only initiation and secondary adherence but clinical outcomes, reduction of CVR and projections of gains in life expectancy and QALYs. It is expected that the dissemination strategy will help achieve implementation.

Strengths and limitations

Complex interventions, like the IMA intervention, contain several interacting components and present practical and methodological difficulties, such as standardising its design, adapting it to the local context and translating it into real practice [52]. We are aware that there may be many barriers that can hinder the implementation of an IMA intervention. The main ones are described below, together with the strategies for overcoming them.

Firstly, the workload of healthcare professionals is high, which could restrict their participation in the study and limit the fidelity of healthcare professionals to the intervention. To reduce the existing barriers to the participation of healthcare professionals, we involved healthcare professionals in the design of the IMA intervention and developed a brief and acceptable intervention tested in a pilot study [54], which is expected to increase fidelity to the intervention. Additionally, healthcare professionals from the intervention group will receive monthly newsletters with reminders and information related to the intervention. Simplified means of obtaining patients' informed consent is also expected to facilitate the participation of GPs (see Ethics approval and consent to participate). Finally, all healthcare professionals will receive economic compensation for the time devoted to the training for the IMA intervention. Nevertheless, the top-down approach may limit the recruitment of healthcare professionals.

Periodic feedback will be provided throughout the study to remind healthcare professionals about the study and intervention. Since there will be no hard data to assess the fidelity of healthcare professionals to the intervention, they will be asked to self-report this during the process evaluation; per-protocol analyses under the

perspective of the patients receiving the intervention will not be conducted.

RWD is used in this study to gather all data from patients and informed consent is obtained via simplified means (see Ethics approval and consent to participate). Since patients will not feel observed, bias is expected to be reduced (such as desirability bias and the Hawthorne effect) [105]. This also increases the pragmatism of the study. Even so, patients in the intervention group will receive the leaflets and be informed about the website, which can jeopardise the blinding of the intervention. Furthermore, since the IMA intervention is a one-shot intervention there exists the possibility that it will increase the risk of single dispensation of medication. To overcome it, both nurses and community pharmacists were invited to participate in the study to support and maintain GP's intervention. The use of RWD to follow up patients for a year after the prescription will allow us to assess the impact of the IMA intervention on both non-initiation and single dispensing.

Using RWD allows the inclusion of a large sample in the study at an affordable cost and, consequently, this increases its power. Moreover, as a consequence of the large sample,external validity is improved as it increases the pragmatism of the study and the generalisationof results. Other studies have also demonstrated the validity of the SIDIAP database inepidemiological studies of CVD [106]. However, health registries are not designed for researchpurposes and some clinical information will likely be missing [73]. This limitation will not affectinitiation or adherence outcomes that are based on hard data such as medication prescriptionand dispensing records but could affect the analysis based on clinical parameters and CVR. Tominimise the effect of this limitation, power size calculations accounted for lost cases (due toincomplete data) and multiple imputations with chained equations will be used to deal withmissing data.

The IMA intervention aims for coordination among healthcare professionals to improve adherence. Despite all GPs, nurses and pharmacists being invited to participate, not all of them accepted; consequently, patients will receive the intervention from their GPs, but perhaps not all will receive the intervention from participating nurses or pharmacists.

The ongoing COVID-19 pandemic can affect the execution of the IMA-cRCT. The training for healthcare professionals is intended to be imparted in person. However, if the restrictions do not allow big gatherings, it will be adapted to an online format. Likewise, the heavy workload as a consequence of the successive waves can affect the fidelity of healthcare professionals to the IMA intervention, not only due to lack of time but also to limitations on face-to-face consultations. These possible consequences will be assessed during the process evaluation, as well as their impact on the external validity of the study.

Abbreviations

COVID-19	Coronavirus disease
CEA	Cost-effectiveness analysis
cRCT	Cluster randomised controlled clinical trial
CVD	Cardiovascular disease
CVR	Cardiovascular risk
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
IMA	Initial medication adherence
LYG	Life years gained
MRC	Medical research council
PC	Primary care
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
RWD	Real-world data
SDM	Shared decision-making

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12875-022-01727-6.

Additional file 1.

Additional file 2.

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Authors' contributions

MRV led the design of the study and obtained funding for the study. IAL, MGG and MTPM advised and contributed to the study design. ASV, IAL and MRV developed the statistical analysis plan. ASV, CCP, IAL, MGG, MTPM and MRV jointly developed the study protocol. ASV wrote the draft of the manuscript; CCP, IAL, MGG, MTPM, CGG, MCOP, ASB and MRV read and approved the final manuscript.

Authors' information

ASV is a Master of Pharmacy (MPharm) and Master of Science (MSc) in Health Economics. Currently a PhD candidate of Medicine and Translational Research at the Faculty of Medicine, University of Barcelona. CCP is a Registered Nurse and MSc in Public Health. Currently a PhD candidate of Methodology of Biomedical Research and Public Health at the Faculty of Medicine, Universitat Autonoma de Barcelona. MGG, PhD, is a Doctor of Pharmacy (PharmD) specialising in qualitative methodology. MTPM is a GP. CGG and MCOP are Registered Nurses. IAL, PhD, is a PharmD specialising in the analysis of RWD focused on medication adherence and economic evaluations. ASB, PhD, is an MD special- ising in Psychiatry and evaluation of health systems. He is also Deputy Director of Mental Health at the Parc Sanitari Sant Joan de Déu. MRV, PhD, is a PharmD specialising in adherence, economic evaluation and the design and evaluation of complex interventions using mixed methods. She is head of the Quality and Patient Safety Department at the Parc Sanitari Sant Joan de Déu.

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The research team is not the data owner as they are only re-using information that is the property of public health institutions. The data that support the findings of this study are available from SIDIAP but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SIDIAP. Consequently, meta- data will not be published by the authors nor will data be identified with a DOI.
The tools designed for the IMA intervention are publically available at www.iniciadores.es.

Declarations

Ethics approval and consent to participate

The protocol for this study has been reviewed and approved by the Drug Research Committee (CEIm) at the IDIAP Jordi Gol, code CEIm 21/051-P to ensure its safety. There is no risk of participating in this study.
The IMA-cRCT is a low-intensity intervention clinical trial conducted solely in Spain, where groups of subjects are allocated to the intervention groups. The benefit of participating in this research study is to contribute to the develop- ment of strategies to improve initiation of prescribed treatments for CVD and diabetes. Therefore, informed consent will be obtained by simplified means. Simplified informed consent requires that the same information stated under the Article 30 of the Regulation (EU) No 536/2014 [107] is provided before anyone is enrolled in the trial, and after being informed, the patient does not object to participate. Therefore, no written informed consent will be obtained as approved by the CEIm Idiap Jordi Gol (CEIm 21/051-P) National Spanish Law is in line with the European regulation regarding the simplified means for obtaining informed consent. All conditions described in Regulation (EU) No 536/2014 [107] and the Real Decreto 1090/2015 [108] are fulfilled. Following the indications of the Idiap Jordi Gol Clinical Research Ethics Com- mittee, informed consent in the present study will be obtained by display- ing posters in prominent locations of the participating PC centres notifying people that a clinical trial is being conducted in the centre and that patients could be part of this comparative study. The posters will contain information on how and why the trial is being conducted and what the implications of participating in the study are. Potential participants are assured that there is no risk to taking part in the study and it will be clearly stated that patients can request extra information and decline to participate in the study. Furthermore, professionals in the intervention and control PC teams will be trained to deal with patients' queries regarding the study. Finally, if patients decline to participate in the study, this information will be documented by physicians in the electronic health records and data from those patients will not be used for the trial. Furthermore, patients can withdraw at any time from the clinical trial without any detriment.
Participation of healthcare professionals is entirely voluntary. All healthcare professionals participating in the study will sign an informed consent at the time of the first training session. They have the right to refuse to participate and to withdraw from the study at anytime.
All deviations from the study protocol will be detailed in the methods section of all papers presenting results from the trial. The trial registry on ClinicalTrials.gov will be modified accordingly.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Health Technology Assessment in Primary Care and Mental Health (PRISMA) Research Group, Institut de Recerca Sant Joan de Déu, Santa Rosa 39-57, 08950 Esplugues de Llobregat, Spain. [2]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. [3]Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, c. Casanova 143, 08036 Barcelona, Spain. [4]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Univ Autonoma de Barcelona, Bellaterra, Spain. [5]Parc Sanitari Sant Joan de Déu, Doctor Antoni Pujadas 42, 08830 Sant Boi de Llobregat, Spain. [6]Centre d'Atenció Primària Bartomeu Fabrés Anglada, Direcció D'Atenció Primària Regió Metropolitana Sud, Institut Català de la Salut, Barcelona, Spain. [7]Unitat de Suport a la Recerca Regió Metropolitana Sud, Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.

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References

1. World Health Organization. Adherence to long-term therapies: evi- dence for action [Internet]. Geneva: World Health Organization; 2003. (https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf?sequence=1&isAllowed=y).
2. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adher- ence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40(9):794-811.
3. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
4. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691-705.
5. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol. 2013;4:91.
6. Hutchins DS, Zeber JE, Roberts CS, Williams AF, Manias E, Peterson AM. Initial Medication Adherence-Review and Recommendations for Good Practices in Outcomes Research: An ISPOR Medication Adherence and Persistence Special Interest Group Report. Value Heal J Int Soc Pharma- coeconomics Outcomes Res. 2015;18(5):690-9.
7. Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: a meta-analysis. Patient Prefer Adherence. 2018;12:721-31.
8. Zeber JE, Manias E, Williams AF, Hutchins D, Udezi WA, Roberts CS, et al. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR medication adherence & persistence special interest group. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2013;16(5):891-900.
9. Aznar-Lou I, Fernández A, Gil-Girbau M, Fajó-Pascual M, Moreno- Peral P, Peñarrubia-María MT, et al. Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. Br J Clin Pharmacol. 2017;83(6):1328-40.
10. Thengilsdóttir G, Pottegård A, Linnet K, Halldórsson M, Almarsdót- tir AB, Gardarsdóttir H. Do patients initiate therapy? Primary non- adherence to statins and antidepressants in Iceland. Int J Clin Pract. 2015;69(5):597-603.
11. Pottegård A, dePont Christensen R, Houji A, Christiansen CB, Paulsen MS, Thomsen JL, et al. Primary non-adherence in general practice: a Danish register study. Eur J Clin Pharmacol. 2014;70(6):757-63.
12. Aznar-Lou I, Iglesias-González M, Gil-Girbau M, Serrano-Blanco A, Fernández A, Peñarrubia-María MT, et al. Impact of initial medication non-adherence to SSRIs on medical visits and sick leaves. J Affect Disord. 2018;226:282-6.
13. Aznar-Lou I, Fernández A, Gil-Girbau M, Sabés-Figuera R, Fajó-Pascual M, Peñarrubia-María MT, et al. Impact of initial medication non-adherence on use of healthcare services and sick leave: a longitudinal study in a large primary care cohort in Spain. Br J Gen Pract. 2017;67(662):e614-22. https://doi.org/10.3399/bjgp17X692129.
14 Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: A systematic review. BMJ Open. 2018;8(1):e016982.
15. World Health Organization. The top 10 causes of death [Internet]. [cited 2022 Feb 2]. Available from: https://www.who.int/news-room/fact- sheets/detail/the-top-10-causes-of-death
16. World Health Organization. Global desease estimates 2016 summary tables. Geneva: World Health Organization; 2018. (http://www.who.int/healthinfo/global_burden_disease/GHE2016_DALY_Global_2000_2016_.xls?ua=1).
17. Gheorghe A, Griffiths U, Murphy A, Legido-Quigley H, Lamptey P, Perel P. The economic burden of cardiovascular disease and hypertension

in low- and middle-income countries: a systematic review. BMC Public Health. 2018;18(1):975.
18. Vilaplana-Carnerero C, Aznar-Lou I, Peñarrubia-María MT, Serrano- Blanco A, Fernández-Vergel R, Petitbò-Antúnez D, et al. Initiation and Single Dispensing in Cardiovascular and Insulin Medications: Prevalence and Explanatory Factors. Int J Environ Res Public Health. 2020;17(10):3358.
19. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940-8.
20 Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoaci- dosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Col- laboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet (London, England). 1997;350(9090):1505-10.
21. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet (London, England). 2016;387(10022):957-67.
22. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and out- comes: a systematic review. Am J Med. 2013;126(4):357.e7-357.e27.
23. Xu T, Yu X, Ou S, Liu X, Yuan J, Tan X, et al. Adherence to Antihyperten- sive Medications and Stroke Risk: A Dose-Response Meta-Analysis. J Am Heart Assoc. 2017;6(7):e006371.
24. Bouchard M-H, Dragomir A, Blais L, Bérard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary preven- tion. Br J Clin Pharmacol. 2007;63(6):698-708.
25. Kim Y-Y, Lee J-S, Kang H-J, Park SM. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. Sci Rep. 2018;8(1):12190.
26. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RCM, et al. Interventions to improve adherence to self-administered medica- tions for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012;157(11):785-95.
27. Costa E, Giardini A, Savin M, Menditto E, Lehane E, Laosa O, et al. Inter- ventional tools to improve medication adherence: review of literature. Patient Prefer Adherence. 2015;9:1303-14.
28. Wiecek E, Tonin FS, Torres-Robles A, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. Temporal effectiveness of interventions to improve medication adherence: A network meta-analysis. PLoS ONE. 2019;14(3):e0213432.
29. Torres-Robles A, Wiecek E, Tonin FS, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. Comparison of Interventions to Improve Long-Term Medication Adherence Across Different Clinical Conditions: A System- atic Review With Network Meta-Analysis. Front Pharmacol. 2018;9:1454.
30. Aznar-Lou I, Pottegård A, Fernández A, Peñarrubia-María MT, Serrano- Blanco A, Sabés-Figuera R, et al. Effect of copayment policies on initial medication non-adherence according to income: A population-based study. BMJ Qual Saf. 2018;27(11):878-91.
31. Polinski JM, Kesselheim AS, Frolkis JP, Wescott P, Allen-Coleman C, Fischer MA. A matter of trust: patient barriers to primary medication adherence. Health Educ Res. 2014;29(5):755-63.
32. Srimongkon P, Aslani P, Chen TF. Consumer-related factors influencing antidepressant adherence in unipolar depression: a qualitative study. Patient Prefer Adherence. 2018;12:1863-73.
33. Swart KMA, van Vilsteren M, van Hout W, Draak E, van der Zwaard BC, van der Horst HE, et al. Factors related to intentional non-initiation of bisphosphonate treatment in patients with a high fracture risk in primary care: a qualitative study. BMC Fam Pract. 2018;19(1):141.
34. Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, Moreno-Peral P, Fernández A, Bellón JÁ, et al. Reasons for medication non-initiation: A qualitative exploration of the patients' perspective. Res Social Adm Pharm. 2020;16(5):663-72.
35. Peñarrubia-María MT, Gil-Girbau M, Gallardo-González MC, Aznar- Lou I, Serrano-Blanco A, Mendive Arbeloa JM, et al. Non-initiation of prescribed medication from a Spanish health professionals' perspective: A qualitative exploration based on Grounded Theory. Health Soc Care Community. 2022;30(1):e213-21.
36. McAlister FA, Ye C, Beaupre LA, Rowe BH, Johnson JA, Bellerose D, et al. Adherence to osteoporosis therapy after an upper extremity fracture: a pre-specified substudy of the C-STOP randomized controlled trial. Osteoporos Int. 2019;30(1):127-34.
37. McCarthy ML, Ding R, Roderer NK, Steinwachs DM, Ortmann MJ, Pham JC, et al. Does providing prescription information or services improve medication adherence among patients discharged from the emer- gency department? A randomized controlled trial. Ann Emerg Med. 2013;62(3):212-23.e1.
38. Fernando TJ, Nguyen DD, Baraff LJ. Effect of electronically delivered pre- scriptions on compliance and pharmacy wait time among emergency department patients. Acad Emerg Med. 2012;19(1):102-5.
39. Hackerson ML, Luder HR, Beck AF, Wedig JM, Heaton PC, Frede SM. Addressing primary nonadherence: A collaboration between a com- munity pharmacy and a large pediatric clinic. J Am Pharm Assoc (2003). 2018;58(4S):S101-8.
40. Derose SF, Green K, Marrett E, Tunceli K, Cheetham TC, Chiu VY, et al. Automated outreach to increase primary adherence to cholesterol- lowering medications. JAMA Intern Med. 2013;173(1):38-43.
41. Cizmic AD, Heilmann RMF, Milchak JL, Riggs CS, Billups SJ. Impact of interactive voice response technology on primary adherence to bisphosphonate therapy: a randomized controlled trial. Osteoporos Int. 2015;26(8):2131-6.
42. Fischer MA, Choudhry NK, Bykov K, Brill G, Bopp G, Wurst AM, et al. Pharmacy-based interventions to reduce primary medication nonad- herence to cardiovascular medications. Med Care. 2014;52(12):1050-4.
43. O'Connor PJ, Schmittdiel JA, Pathak RD, Harris RI, Newton KM, Ohnsorg KA, et al. Randomized trial of telephone outreach to improve medica- tion adherence and metabolic control in adults with diabetes. Diabetes Care. 2014;37(12):3317-24.
44. Fischer MA, Jones JB, Wright E, Van Loan RP, Xie J, Gallagher L, et al. A randomized telephone intervention trial to reduce primary medication nonadherence. J Manag care Spec Pharm. 2015;21(2):124-31.
45. Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. Chest. 2011;140(2):425-32.
46. Tedla YG, Bautista LE. Factors associated with false-positive self- reported adherence to antihypertensive drugs. J Hum Hypertens. 2017;31(5):320-6.
47. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5(4):470-82.
48. Zhu M, Sridhar S, Hollingsworth R, Chit A, Kimball T, Murmello K, et al. Hybrid clinical trials to generate real-world evidence: design considera- tions from a sponsor's perspective. Contemp Clin Trials. 2020;94:105856.
49. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Republished research: Implementation research: what it is and how to do it. Br J Sports Med. 2014;48(8):731-6.
50. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-imple- mentation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
51. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. Framework for the development and evaluation of complex interven- tions: gap analysis, workshop and consultation-informed update. Health Technol Assess. 2021;25(57):1-132.
52. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
53. Corral-Partearroyo C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María M, Aznar-Lou I, Gallardo-González M, et al. Complex intervention to improve Initial Medication Adherence to cardiovascular diseases and diabetes treatments in primary care (the IMA-cRCT study): intervention development and protocol for the process evaluation. 2022.
54. Corral-Partearroyo, C, Sánchez-Viñas A, Gil-Girbau M, Peñarrubia-María M, Aznar-Lou I, Serrano-Blanco A, Al. E. Improving Initial Medication Adherence to cardiovascular diseases and diabetes treatments in primary care: pilot trial of a complex intervention. 2022.
55. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.

56. Chan A, Tetzlaff J, Altman D, Laupacis A, Gøtzsche P, Krleža-Jerić K, et al. Spirit 2013 statement: Defining standard protocol items for clinical trials. Chinese J Evidence-Based Med. 2013;13(12):1501-7.
57. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
58. Idescat. Anuari estadístic de Catalunya. Població a 1 de gener. Provín- cies [Internet]. [cited 2022 Feb 2]. Available from: https://www.idescat. cat/pub/?id=aec&n=245
59. Bernal-Delgado E, Garcia-Armesto S, Oliva J, Sanchez Martinez FI, Repullo JR, Pena-Longobardo LM, et al. Spain: Health System Review. Health Syst Transit. 2018;20(2):1-179.
60. Memòria de l'ICS 2019. Institut Català de la Salut [Internet]. [cited 2022 Feb 2]. Available from: http://ics.gencat.cat/ca/lics/memories-dactivitat/memoria-de-lics-2019/
61. Rubio-Valera M, Jove AM, Hughes CM, Guillen-Sola M, Rovira M, Fernan- dez A. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. BMC Health Serv Res. 2012;12:188.
62. Löffler C, Koudmani C, Böhmer F, Paschka SD, Höck J, Drewelow E, et al. Perceptions of interprofessional collaboration of general practitioners and community pharmacists - a qualitative study. BMC Health Serv Res. 2017;17(1):224.
63. Gobierno de España. Ley 14/1986, de 25 de abril, General de Sanidad [Internet]. [cited 2022 Feb 2]. Available from: https://www.boe.es/buscar/act.php?id=BOE-A-1986-10499
64. Besalduch J-M. Formas de propiedad de la farmacia en España. Farm Prof. 2007;21(7):20-3.
65. Col·legi de Farmacèutics de Barcelona. El Consell de Col·legis Far- macèutics de Catalunya y el CatSalut presentan un nuevo proyecto centrado en la atención farmacéutica ante primeras dispensaciones [Internet]. [cited 2022 Feb 2]. Available from: https://www.cofb.org/es/sala-prensa/notes-prensa/-/asset_publisher/GVZR6OjauRsN/content/el-consell-de-col-legis-farmaceutics-de-catalunya-i-el-catsalut-presenten-un-nou-projecte-centrat-en-l-atencio-farmaceutica-davant-primeres-dispensaci/maximized?inheri
66. Gobierno de España. Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios [Internet]. [cited 2022 Feb 2]. Available from: https://www.boe.es/eli/es/l/2006/07/26/29/con
67. Gobierno de España. Real Decreto 1348/2003, de 31 de octubre, por el que se adapta la clasificación anatómica de medicamentos al sistema de clasificación ATC [Internet]. [cited 2022 Feb 2]. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-2003-20257
68. Ministerio de Sanidad. Datos de interés general para los usuarios del Sistema Nacional de Salud de España sobre la aportación de los usuarios y sus beneficiarios en la prestación farmacéutica ambulatoria [Internet]. [cited 2022 Feb 2]. Available from: https://www.sanidad.gob.es/gabinetePrensa/rd162012/home.htm
69. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision [Internet]. [cited 2022 Feb 2]. Available from: https://icd.who.int/browse10/2019/en
70. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012;27(10):1361-7.
71. Elwyn G, Edwards A, Kinnersley P, Grol R. Shared decision mak- ing and the concept of equipoise: the competences of involving patients in healthcare choices. Br J Gen Pract J R Coll Gen Pract. 2000;50(460):892-9.
72. Schulz K, Altman D, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Japanese Pharmacol Ther. 2020;48(3):507-15.
73. Bolíbar B, FinaAvilés F, Morros R, Garcia-Gil Mdel M, Hermosilla E, Ramos R, et al. Base de datos SIDIAP: la historia clínica informatizada de Atención Primaria como fuente de información para la investigación epidemiológica. Med Clin (Barc). 2012;138(14):617-21.
74. SIDIAP. Sistema d'Informació per al desenvolupament de la Investi- gació en Atenció Primària [Internet]. [cited 2022 Feb 2]. Available from: https://www.sidiap.org/
75. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40(7-8):1280-8.
76. Malo S, Aguilar-Palacio I, Feja C, Lallana MJ, Rabanaque MJ, Armesto J, et al. Different approaches to the assessment of adherence and persis- tence with cardiovascular-disease preventive medications. Curr Med Res Opin. 2017;33(7):1329-36.
77. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Prospective validation of eight different adherence measures for use with adminis- trative claims data among patients with schizophrenia. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2009;12(6):989-95.
78. Marrugat J, Vila J, Baena-Díez JM, Grau M, Sala J, Ramos R, et al. Validez relativa de la estimación del riesgo cardiovascular a 10 años en una cohorte poblacional del estudio REGICOR. Rev Esp Cardiol. 2011;64(5):385-94.
79. Rutterford C, Copas A, Eldridge S. Methods for sample size determina- tion in cluster randomized trials. Int J Epidemiol. 2015;44(3):1051-67.
80. Groenwold RHH, Donders ART, Roes KCB, Harrell FEJ, Moons KGM. Deal- ing with missing outcome data in randomized trials and observational studies. Am J Epidemiol. 2012;175(3):210-7.
81. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.
82. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8(3):206-13.
83. WHOCC - ATC/DDD Index [Internet]. [cited 2022 Feb 2]. Available from: https://www.whocc.no/atc_ddd_index/
84. European Medicines Agency - Committee for Medicinal Products for Human Use. Guideline on adjustment for baseline covariates in clinical trials. 2015. (https://www.ema.europa.eu/en/documents/scientific- guideline/guideline-adjustment-baseline-covariates-clinical-trials_en. pdf).
85. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Heal J Int Soc Pharmaco- economics Outcomes Res. 2005;8(5):521-33.
86. Kim DD, Silver MC, Kunst N, Cohen JT, Ollendorf DA, Neumann PJ. Perspective and Costing in Cost-Effectiveness Analysis, 1974-2018. Pharmacoeconomics. 2020;38(10):1135-45.
87. Generalitat de Catalunya. ORDRE SLT/63/2020, de 8 de març, per la qual s'aproven els preus públics del Servei Català de la Salut. [Internet]. [cited 2022 Feb 2]. Available from: https://dogc.gencat.cat/ca/document-del- dogc/?documentId=873353
88. Gobierno de España. Real Decreto 231/2020, de 4 de febrero, por el que se fija el salario mínimo interprofesional para 2020 [Internet]. [cited 2022 Feb 2]. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-2020-1652
89. Instituto Nacional de Estadística. Salarios medios por tipo de jornada, comunidad autónoma y decil.(13930) [Internet]. [cited 2022 Feb 2]. Available from: https://www.ine.es/jaxiT3/Tabla.htm?t=13930&L=0
90. Sonnenberg FA, Beck JR. Markov models in medical decision mak- ing: a practical guide. Med Decis Mak an Int J Soc Med Decis Mak. 1993;13(4):322-38.
91. Drummond MF. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford; New York: Oxford University Press; 2005.
92. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. 2nd ed. Oxford; New York; 2014.
93. van Kempen BJH, Ferket BS, Hofman A, Steyerberg EW, Colkesen EB, Boekholdt SM, et al. Validation of a model to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the burden of CVD: the rotterdam ischemic heart disease and stroke computer simulation (RISC) model. BMC Med. 2012;10:158.
94. Slejko JF, Sullivan PW, Anderson HD, Ho PM, Nair KV, Campbell JD. Dynamic medication adherence modeling in primary prevention of cardiovascular disease: a Markov microsimulation methods appli- cation. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2014;17(6):725-31.
95. López-Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al. Spanish recommendations on economic evaluation of health technologies. Eur J Heal Econ HEPAC Heal Econ Prev care. 2010;11(5):513-20.

96. Briggs A, Claxton K, Sculpher M. Decision modelling for health eco- nomic evaluation. Oxford: Oxford University Press; 2006.
97. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Heal Econ (United Kingdom). 2018;27(4):746-61.
98. Hoffmann TC, Erueti C, Glasziou PP. Poor description of non-pharma- cological interventions: analysis of consecutive sample of randomised trials. BMJ. 2013;347:f3755.
99. Simon-Tuval T, Neumann PJ, Greenberg D. Cost-effectiveness of adherence-enhancing interventions: a systematic review. Expert Rev Pharmacoecon Outcomes Res. 2016;16(1):67-84.
100 Welsing PM, Oude Rengerink K, Collier S, Eckert L, van Smeden M, Ciaglia A, et al. Series: Pragmatic trials and real world evidence: Paper 6. Outcome measures in the real world. J Clin Epidemiol. 2017;90:99-107.
101. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-63.
102 Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel GJMW, Grobbee DE. Series: Pragmatic trials and real world evidence: Paper 1. Introduction J Clin Epidemiol. 2017;88:7-13 (United States).
103. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard-Lessons from the History of RCTs. N Engl J Med. 2016;374(22):2175-81.
104. Jones DS, Podolsky SH. The history and fate of the gold standard. Lan- cet (London, England). 2015;385(9977):1502-3.
105. McCambridge J, Witton J, Elbourne DR. Systematic review of the Haw- thorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67(3):267-77.
106. Ramos R, Balló E, Marrugat J, Elosua R, Sala J, Grau M, et al. Validity for use in research on vascular diseases of the SIDIAP (Information System for the Development of Research in Primary Care): the EMMA study. Rev Esp Cardiol (Engl Ed). 2012;65(1):29-37.
107. European Union. Regulation (EU) No 536/2014 of the European Parlia- ment and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance [Internet]. [cited 2022 Feb 2]. Available from: https://eur- lex.europa.eu/legal.content/EN/TXT/?uri=celex%3A32014R0536
108. Gobierno de España. Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos [Internet]. [cited 2022 Feb 2]. Available from: https://www.boe.es/diario_boe/txt.php?id=BOE-A-2015-14082

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