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Abstract

Introduction: Health information systems represent an opportunity to improve the care provided to people with multimorbidity. There is a pressing need to assess their impact on clinical outcomes to validate this intervention. Our study will determine whether using a digital platform (METHIS) to manage multimorbidity improves health-related quality of life (HR-QoL).

Methods and Analysis: A superiority, cluster randomised trial will be conducted at Primary Health Care Practices (1:1 allocation ratio). All public practices in the Lisbon and Tagus Valley (LVT) Region, Portugal, not involved in a previous pilot trial, will be eligible. At the participant level, eligible patients will be people with complex multimorbidity, aged 50 years or older, with access to an internet connection and a communication technology device. Participants who cannot sign/read/write and who do not have access to an email account will not be included in the study. The intervention combines a training programme and a customised Information System (METHIS). Both are designed to help clinicians to adopt a Goal-Oriented Care Model approach and to encourage patients and carers to play a more active role in autonomous healthcare. The primary outcome is HR-QoL, measured at 12 months with the physical component scale of the SF-12 questionnaire. Secondary outcomes will also be measured at 12 months and include mental health (mental component Scale SF-12, Hospital Anxiety and Depression Scale). We will also assess serious adverse events during the trial, including hospitalisation and emergency services. Finally, at 18 months, we will ask the general practitioners for any potentially missed diagnoses.

Ethics and Dissemination: The Research and Ethics Committee (LVT Region) approved the trial protocol. Clinicians and patients will sign an informed consent. A data management officer will handle all data, and the publication of several scientific papers and presentations at relevant conferences/workshops is envisaged.

Strengths and limitations of this study:

- This study uses a randomised design to assess the impact of a complex intervention in patient-relevant outcomes defined in the Core Outcome Set for people with multimorbidity. A Cluster Randomised Design minimises the risk of confounding factors influencing the results.
- The training component in the intervention allows for the engagement of health professionals and the decrease in learning time after the implementation of the digital platform.
- As it currently needs to be possible to integrate the digital platform with the official electronic health record, there is possibly a need to duplicate some data entry. This may compromise clinician adherence to the trial.

Keywords: Primary Health Care, Information Management, Research Design, Telemedicine

Introduction

Background and Rationale

Health services are challenged by the increasing prevalence of multimorbidity and polypharmacy in an ageing population (1). Multimorbidity is used for patients who suffer from two or more chronic conditions and require complex care (2). These use healthcare services 3.5 times more often than those without chronic conditions, even after adjustment for socioeconomic variables (3). These patients have poorer clinical outcomes (increased mortality, poorer HR-QoL, more disability), disruption to their personal and social lives, and a more significant financial burden (4–6). Moreover, patients with multimorbidity report several barriers to accessing healthcare services, including inadequate communication from healthcare professionals and non-consideration of their circumstances in managing their care plans (7).

The traditional care approach for multimorbidity patients, supported by multiple single-organ management guidelines, is burdensome and potentially harmful (8–12). New, patient-centred approaches have been proposed, emphasising the need to prioritise patient preferences, and shared goals (13,14). A patient-centred focus potentially allows patients to express their concerns and expectations (leading to greater involvement and adherence) while shifting the health management plan from a vertical to a longitudinal, integrated model (15,16).

The Goal-Oriented Care (GOC) approach is an example of this integration, where healthcare professionals help patients to identify their desired outcomes (goals). These goals can be related to preventing premature mortality or disability, improving “good death”, optimising health-related quality of life, and fostering personal growth and development during the remaining lifespan (17). Goals help healthcare discussions and simplify decision-making when patients have multiple conditions. Important mechanisms for GOC implementation are functional and normative integrations of different providers (18). Many of these can be achieved through information systems. Mobile technologies have been used to support the functional integration of different levels of care, reducing inappropriate referrals and improving access to specialised care (19,20). Point-of-care computer reminders often improve health professionals’ behaviour (21). Even the redesign of digital charts contributes to substantial improvements in adherence to evidence-based practice (22).

Intervention Objectives

Evidence on the impact of Digital Health in the disease management of patients with multimorbidity shows moderate improvements (23,24). However, most studies have used only short follow-ups (<= six months) and rarely assessed patient-oriented outcomes (HR-QoL or mortality), or the complex needs of these patients (24,25). Therefore, this study aims to evaluate the improvement in the quality of life in patients using a digital healthcare platform (METHIS) which assists patients and primary healthcare clinicians in managing multimorbidity within a GOC framework. In addition, it will also assess whether the digital platform impacts anxiety, depression, physical activity, and serious adverse events.

Trial Design

The "METHIS" intervention is a decentralised trial that combines the implementation of a training program and a customised digital platform, which is designed to prompt clinicians to adopt a GOC approach. A cluster randomised trial (CRT) with an assignment ratio of 1:1 in a superiority framework will be conducted. The CRT design will avoid the possible selection bias of individual

randomisation conducted by clinicians. In addition, cluster randomisation will facilitate trial implementation since the practices share an identical electronic health records (EHR) server. The trial is registered on clinicaltrials.gov under the identifier NCT05593835, and the patient timeline can be seen in Figure 1.

Methods and Analysis

Study Setting

The trial will be conducted in primary care practices (henceforward, practices) in the Lisbon and Tagus Valley Region (ARSLVT) within the Portuguese National Health Service. These practices have 4-12 family physicians, 4-12 nurses and 2-6 clinical secretaries.

Eligibility Criteria

All practices in ARSLVT that did not pilot the METHIS digital platform will be eligible at the cluster level. The staff at participating units will constitute the local research team. Eligible patients will be community-dwelling people aged 50 or older with complex multimorbidity (co-occurrence of three or more chronic conditions affecting three or more different body systems) and access to an Internet connection and a communication technology device (26). Exclusion criteria will be the inability to: provide informed consent, to read or write, to access an email or electronic device, even when helped by an informal caregiver.

Intervention

The METHIS intervention will consist of two components (Figure 2).

The first component is a **GOC Training Program** for health professionals. The training program will include the concept of personalised care, methods of goal elicitation, implications of GOC in healthcare practice, and how the METHIS platform can be used to support the application of GOC. The training will be implemented through a blended-learning, continuous education program that NOVA University of Lisbon will credit. It will have three stages: initial face-to-face training, which will happen before the data collection, followed by remote, asynchronous training over 12 months, and a final seminar to discuss the results and inquire about the usability of the GOC model and the METHIS platform. The course will be offered to the intervention group one month before the start of patient recruitment and the control group at least one month after the end of data collection.

The second component is a **GOC Information System**. This will be the digital platform METHIS, designed to nudge clinicians to adopt a GOC and encourage patients and caregivers to take an active role in healthcare. We will adapt an existing platform developed for a pilot study during the COVID-19 pandemic (27), which promotes care coordination and optimises disease prioritisation and patient self-management (28). The METHIS platform is a digital healthcare platform supported by three databases using PostreSQL (based on relational SQL). One of the databases allows adequate internal testing before production. Another database of production (secured with unique access codes) will be created to retrieve data from the practices, and the last database for the research data, where pseudonymised production data can be analysed for research purposes. The platform is integrated (via FCCN Scientific Computation Unit of the Portuguese Fundação para a Ciência e a Tecnologia) with the Software Zoom® to allow encrypted teleconsultations, with a guarantee that each patient connection is unique. The digital platform

is web-based and can be used on multiple devices.

Control

The control group in this trial will receive the best usual care, using the standard EHR available to the practice (29,30). Our understanding of what "best usual care" is for people with multimorbidity is informed by qualitative research in an earlier stage of this project (31). Our results suggest that healthcare professionals often provide disease-driven care. When faced with multiple healthcare problems, they prioritise based on 1) patient complaints, 2) which condition is less well controlled, or 3) which condition is more likely to impact patient HR-QoL adversely. General practitioners and primary care nurses are often unfamiliar with the GOC model. However, they already try to implement some of its principles, such as identifying patient goals and supporting shared decision-making.

Cluster adherence and co-interventions

To promote cluster adherence, we will provide training on how to use the METHIS platform, and create a technical support line to monitor the usage of the METHIS platform by patients and healthcare professionals. Practices will be provided with an aggregate profile of the 23 patients included in the study and reminder materials (e.g. mouse pads). We will also send reminders before the final data collection. To promote individual retention, we will distribute a letter to patients acknowledging their support. We will provide them with an infographic with the baseline characteristics of patients in the project and plans for the next phase. These letters will be sent after the end of participant recruitment and another month before data collection.

All participating practices can implement other interventions to better support managing patients with multimorbidity. The types of health system interventions according to the Taxonomy of Effective Practice and Care Organisation (EPOC) and their permissions during the trial can be consulted (**Appendix 1**) (32). Financial and Governance arrangements are probably not relevant at the primary care practice level since all will be recruited from the same Regional Health Authority, and any changes to the financial or governance arrangements will be simultaneously applied to all.

Outcomes

Primary outcome

Health-related quality of life is a core outcome in multimorbidity studies (33). Participants will be asked to fill in the SF-12 questionnaire at baseline, six months, and 12 months. This questionnaire generates a physical component score (PCS) and a mental component score (MCS). The primary outcome will be the mean difference in the variation of the PCS of SF-12 between baseline and 12 months. The SF-12 can be filled in 2-4 minutes, and it is validated for the Portuguese population (34,35).

Secondary outcomes

Mental health status is another central outcome in multimorbidity studies. We will ask participants to complete the Hospital Anxiety and Depression Scale questionnaire (HADS-A and HADS-D, respectively) at baseline, six months, and 12 months. We will calculate the mean difference in the variation in HADS-A and HADS-D between baseline and 12 months. Although HADS was designed for inpatients, it was posteriorly validated in the primary care outpatient

setting (36). A minimum significant difference of 1.5 has been reported in other chronic disorders (37).

Physical activity will be monitored through the number of steps walked daily. To assess the number of steps per day, a smart band with a triaxial Accelerometer will be used in both arms of the trial. Although traditional step counters use pedometers to detect daily step counts, accelerometers are more accurate and sensitive to lower force accelerations (e.g., slow walking), considered the current standard for collecting physical activity data (38–40). Sedentary older adults and individuals with a disability and chronic illness benefit from a physically active lifestyle, with approximately 4,600- 5,500 daily steps. The lowest median values for steps/day found are in disabled older adults (1214 steps/day) and people living with COPD (2237 steps/day) (39).

Serious adverse events (clinician-reported) are the safety outcomes chosen for this trial. In both trial arms, data about patient mortality will be collected and combined with data on emergency department visits and hospital admissions as a proxy for serious adverse events. Family physicians will be asked, at 6 and 12 months after randomisation, to check the life status of enrolled patients and whether patients in the trial were admitted to a hospital or had visited an emergency service since the randomisation date. This information is available through the common Portuguese EHR. Due to legal requirements, the information about hospital admissions and other contacts with healthcare organisations ceases to be open to the attending physician after death.

Potentially missed diagnoses (clinician-reported) will be a second safety outcome. At 18 months, we will ask clinicians in the intervention arm if they know of any severe diagnosis that might have been missed due to the intervention. This report, six months after the intervention phase, is a compromise between avoiding recall bias and allowing enough time for a missed diagnosis to become clinically apparent.

Sample Size

To address our primary outcome, we assumed for the PCS of the SF-12 scale, a mean of 38.3 for the control group, a mean of 41.3 for the intervention group, and a typical standard deviation of 11.3. The mean difference of 3 points used in the sample size calculation is informed by earlier research suggesting that the minimum significant difference for SF-12 in different populations´ diseases ranges between 2 and 3 points (34,35). A conservative intra-cluster correlation coefficient of 0.08, an alpha of 0.05, and a power of 80% were considered. To achieve the desired strength, approximately 600 patients will need to be enrolled in each arm, implying about 20 patients per practice, with a minimum of 30 practices in the intervention arm and 30 in the control arm. The sample size will be corrected considering the 10% losses to follow-up. This means that 1380 participants will have to be enrolled (i.e., 23 participants per cluster).

Recruitment

All potentially eligible practices will be randomly ordered and contacted by a member of the leading research team until the number of clusters obtained in the sample size calculations is reached. These units will be invited to engage in the CRT as members of a local research team. A short questionnaire will be sent to identify primary care teams (family physician plus family nurse) willing to participate and collect the required practice characteristics for minimisation. Eligible participants will be determined by the members of the local research team through a review of records and confirmed by a leading research team member. Participant screening will

continue until the target population is achieved. A random sample of twenty-three participants will be drawn from each practice. Participants will have no financial incentives other than using a smart band for 12 months. The recruitment phase will extend over six months.

Allocation

Clusters will be allocated to the intervention or control groups (1:1) using minimisation with a random element, a method to achieve a good balance regarding baseline characteristics that could influence the outcomes when the number of clusters is small. Cluster variables used in the minimisation will be the type of setting (urban, rural, mixed), patient age distribution (50- 75 years/>75 years), patient-level of education (lower/higher), baseline HR-QoL (below median SF-12 / above median SF-12), baseline mental health status (HADS-A and HADS-D).

After patient recruitment and baseline data collection, the trial manager (i.e., the Data Protection Officer, DPO) will assign a pseudonymised code to each practice and send the practice code and minimisation variables to the statistician, who will then allocate practices into two groups. Members of the local research team will then assess for patient eligibility, and recruitment will be performed by one of the trial researchers. The trial statistician will generate the allocation sequence.

Blinding

Given the nature of the intervention, none of the people involved in the trial will be blinded to the intervention.

Data Collection

Data on HR-QoL, mental health and physical activity will be collected at baseline, six months, and 12 months. For baseline assessment, after signing the informed consent, patients will be invited to fill in the electronic forms with the questionnaires, either using a personal computer or using a tablet. At the 6- and 12-month assessments, participants will be contacted by research team members and asked to fill in the electronic forms at home, using a personal computer or a tablet.

Data on physical activity will be stored locally and uploaded to a cloud-based health repository. For patients on the intervention arm, data will be available for consultation by health professionals and patients on the web platform, either using a personal computer or a tablet. As for patients in the control arm, data will be collected similarly but will not be available for consultation (only by researchers at baseline, at six months, and at 12 months).

Mortality: Members of the local research team will be asked to fill in a small survey at 6 and 12 months after randomisation. They will be asked to check the life status of their enrolled patients in the Portuguese common Electronic Health Record. Data recorded will be life status (alive, dead) and, if relevant, date of death.

Hospital admissions (clinically reported): At 6 and 12 months after randomisation, members of the local research team will be invited to check the number of hospital admissions in the previous 6-12 months in the Portuguese common Electronic Health Record. Data recorded will be the number of admissions (count) and, if relevant, dates of admissions. Due to legal requirements, data will only be available for patients alive at the end of the intervention phase.

Composite outcome: The composite outcome will be defined as the date until death, hospital admission or visit to the emergency department, whichever comes first.

Baseline characterisation of individual participants: Patient month and year of birth (self-reported), gender (self-reported), number of years of education (self-reported), profession, number of hospital admissions in the previous 12 months, active chronic medications, and active chronic health problems (information and ICPC-2 codes in the patient's EHR extracted by the family physician) will be collected.

Baseline characteristics of clusters: After practice (cluster) recruitment, data about the type of setting (urban, rural, mixed) and the number of clinicians (nurses, family physicians, residents) will be collected.

Interactions with the platform (intervention group only): METHIS platform will register the following intervention data: the basic information about the patient's condition (e.g., chronic diseases, medications, care goals, etc.), any teleconsultations done with members of the local research team, any communication exchange between health workers and data registered by both patient (physiologic and biochemical data, SF-12, Mental health, and mobility data) and health workers, members of the local research team (relevant notes over consultations considering patient´s therapeutics).

Potentially missed diagnoses (intervention group only): At 18 months, physicians, and members of the research team, following the intervention group will be invited to report any severe diagnosis that might have been missed due to the use of METHIS. If relevant, missed serious diagnoses and the date of diagnosis will be collected.

Administrative information: Identification data (name, address, e-mail, personal phone number) and data from a significant person/career (name and phone number) will be collected by the local research team. This will be kept in a separate file from clinical data and will be used to send participants updates on the status of the study and to contact participants for the 12 months outcome assessment period.

Data Management

The data collected in this study will come from healthcare professionals and patients at different stages. Given its diverse nature and sources, data will be collected, treated, and analysed in specific datasets. Each dataset will be set up to answer the respective research questions.

A Data Management Plan (DMP) will be formulated and overseen by the Data Protection Officer (DPO). DMP follows GDPR, within FAIR principles, to ensure transparency of results dissemination, notwithstanding data security and privacy. ISO/IEC 27001 will be used as a standard.

Regarding the datasets focused on the digital platform activities, it generates anonymised databases to be worked on by the researchers. Its functionalities enable planning and organising data entry, proper participants' coding, security, and storage, including range checks for data values (e.g., patients will receive an alert whenever the data entry is invalid or out of typical values).

Data Analysis

Individual participants will be analysed according to their randomly allocated group regardless of adherence to the intervention (intention to treat analysis). If participants transfer to another unit within the health region, they will be considered lost to follow-up, even if they move to a practice

conducting the trial. All the collected variables will be summarised using descriptive statistics. Quantitative variables will be summarised by mean, standard deviation, median and range (minimum and maximum values), and qualitative variables will be summarised by absolute (n) and relative frequencies (%).

Both groups will be compared on primary and secondary outcomes using generalised mixed-effects models, accounting for variables used in the minimisation (cluster level). We will report the mean difference between the two groups of the change of HR-QoL (PCS and MCS subscales) from baseline to end of follow-up, the mean difference of the evolution of the HADS scale from baseline to end of follow-up, the mean difference of the change of step count, the hazard ratio for the composite outcome of mortality, hospital admission or visits to accidents and emergencies.

Statistical significance will be assumed for a p-value less than 0.05. The latest version of R software will be used to conduct the analysis.

Data Monitoring

There will be no Data Monitoring Committee assigned in this trial. The trial does not assess a life-threatening situation; the trial is not aimed at an especially vulnerable population, and there is no suspicion that the intervention may harm participants. There will not be any pre-planned interim analyses, nor are we planning on an adaptive trial design.

Although no direct physical or mental harm is expected from using the METHIS platform, patients and members of the local research team in the intervention arm may substitute/postpone face-to-face consultations with remote consultations in which physical examination is not possible. There is a theoretical risk of missing a serious diagnosis, and a safety follow-up phase is planned, where we will receive reports from members of the local research team 18 months after randomisation (6 months after the intervention phase). We will assess whether any patients enrolled in the intervention arm had a missed diagnosis. All the events related to adverse events notified by healthcare professionals, members of the local research team, and patient participants will be registered in the data reporting books and will be available for auditing purposes.

Patient and Public Involvement

The METHIS project is based on Design Science Research. In this approach, the methods used always have a participatory research perspective that allows the users of the artefact to be involved at all stages of its development (41). As such, at the beginning of the project, a qualitative study was developed with health professionals to understand and identify the facilitating factors and barriers to changing from the current HIS to the METHIS (31). Currently, the research team is conducting a validation study of the training component with health professionals and a pilot study with the utilization of the platform in which professionals and patients are asked to provide their inputs regarding their experience and preferences.

Ethics and Dissemination

Research Ethics Approval

The trial protocol was approved by the Research and Ethics Committee of ARSLVT (March 2022,

094/CES/INV/2021). Protocol amendments, such as changes to eligibility criteria, outcomes, and analysis, will be submitted for review and reapproval to the Research and Ethics Committee.

Informed Consent

Members of the local research team will sign an informed consent for conducting the trial (**Appendix 2**). Patients will sign an informed consent as participants in the trial.

Confidentiality

Only healthcare professional members of the local research team will have access to each patient's demographic and clinical data. The DPO will be responsible for automatically generating an alphanumeric code that will provide an anonymised table with the previously mentioned variables for researchers and statistical analysis purposes. Data will be stored in a secure server which the DPO can only access.

Access to data

The complete research dataset will be stored in an encrypted and secure location to be accessed for secondary analyses or comparative studies or per request of the patients involved or the Research and Ethics Committee.

Ancillary and post-trial care

If we verify an improvement in HR-QoL and mental health related to care given through the METHIS platform, we will provide access to this platform for practices and patients in the control groups.

Dissemination

The trial protocol, the main paper with the trial results and a short report with the results of the final physician survey will be published in peer-review journals. All team members who fulfil the ICMJE criteria for authorship will be co-authors of these publications.

We will not disclose the database or grant access to data reproduction for legal reasons. However, the research team may make processed data available upon request, with appropriate justification.

Authors' contributions

LVL and BH conceived the study. The following authors contributed to the study design: MGC, ARJM and BH provided specific methodological expertise in the clinical strand, MP, MRM and JG in the technological strand, and MSP, BH and LVL in the pedagogical strand. AP and MA provided specific methodological expertise in statistics in cluster-randomised clinical trials. MRM and MP provided specific methodological expertise in research data management, protection, and confidentiality. MGC, MP, ARJM, MRM, JG, MSP, MA, AP, BH and LVL prepared the initial proposal for funding application. MGC and MP prepared the first draft of this study protocol. MGC, MP, ARJM, MRM, JG, MSP, MA, AP, BH and LVL contributed to rewrites and refinements with important intellectual content; all the authors approved the final manuscript and agreed to be accountable for all aspects of the work. The team acknowledges the health professionals and patients involved in the development and participation of this study.

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Competing interests' statement

All authors and researchers declare no competing interest.

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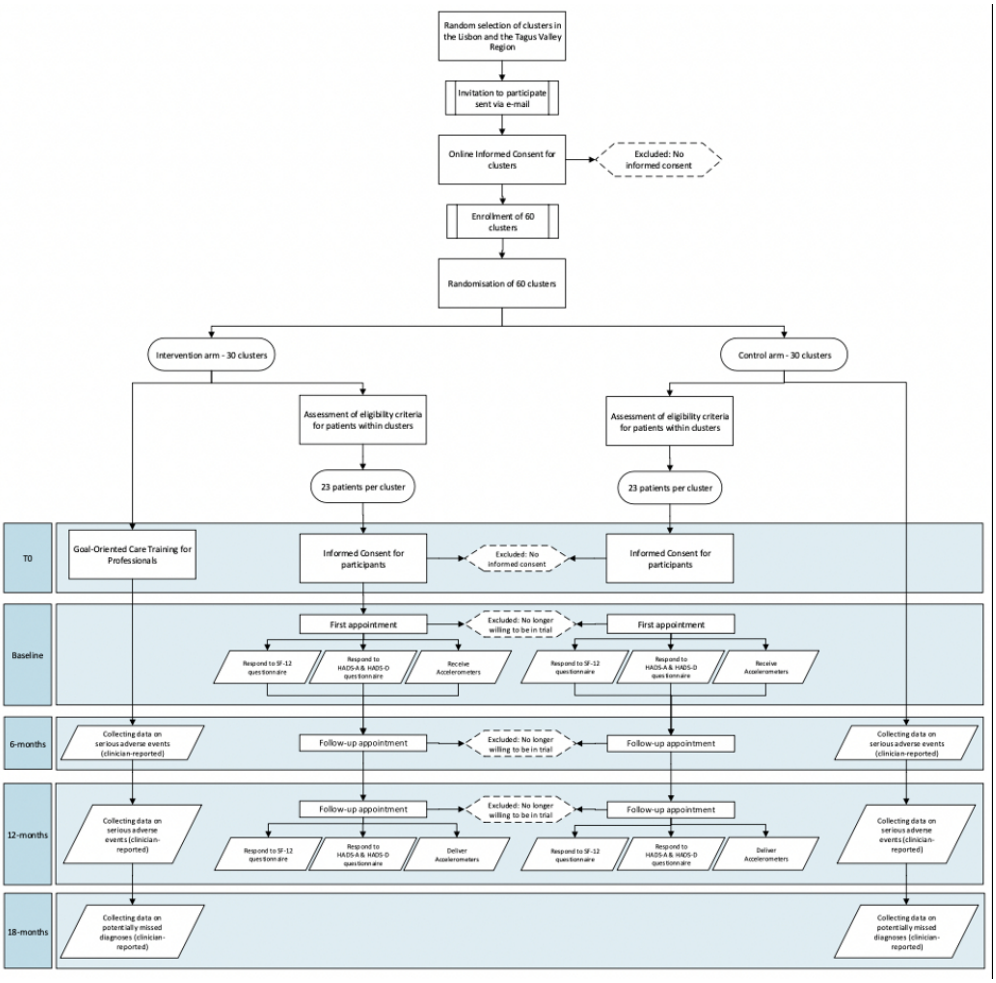
Figure Legend

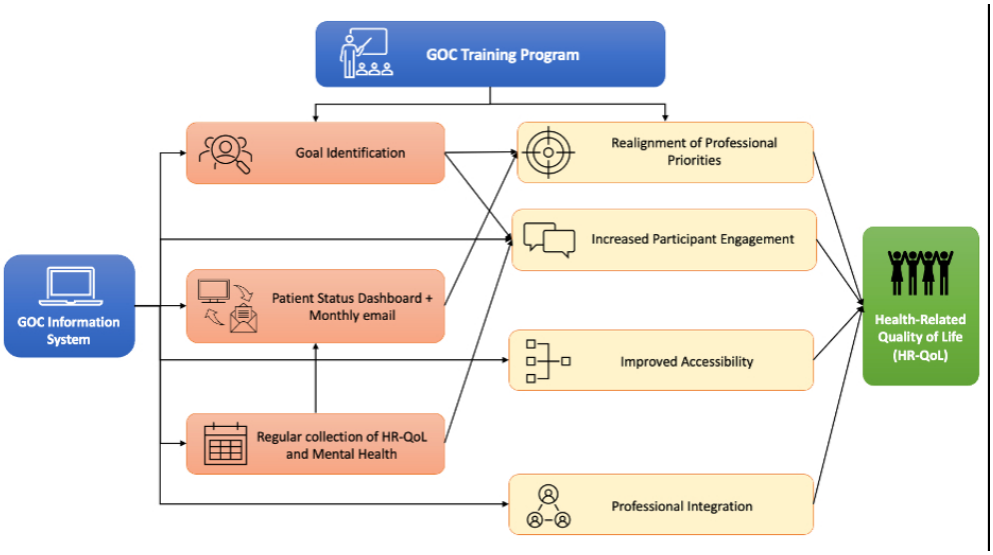
Figure 1 – Participant Timeline

Figure 2 – METHIS Intervention Framework: impact on health-related quality of life



Patient Timeline

166x161mm (144 x 144 DPI)



METHIS Intervention Framework: impact on health-related quality of life

166x91mm (144 x 144 DPI)

Appendix 1

Types of co-interventions that are permitted and non-permitted during trial implementation.

Macro level	**Meso level**	**Permitted during the trial?**
Delivery Arrangements	How and when care is Delivered	Permitted
	Where care is provided and changes to the healthcare environment	Permitted
	Who provides care and how the healthcare workforce is managed	Permitted
	Coordination of care and management of care processes	Permitted
	Information and Communication technology (ICT)	**Discouraged**
Financial Arrangements		Not relevant at the practice level.
Governance Arrangements		Not relevant at the practice level.
Implementation Strategies	Interventions targeted at healthcare organisations	Permitted
	Interventions targeted at healthcare workers	Permitted
	Interventions targeted at specific types of practice, conditions or settings	Not relevant at the practice level.

Model for Informed Consent Form

FORMULÁRIO DE CONSENTIMENTO INFORMADO LIVRE E ESCLARECIDO

Título do estudo:

METHIS: Multimorbilidade e envelhecimento: Ensaio Clínico Randomizado em Cluster de uma abordagem centrada no doente suportada por uma plataforma digital.

METHIS - Multimorbidity and Ageing: Cluster Randomized Trial of a Patient-Centred Approach supported by a digital platform.

Nome da Instituição:

Unidade de Saúde Familiar

Morada da Instituição

INTRODUÇÃO

Gostaríamos de convidá-lo(a) a participar no estudo de investigação clínica: "*METHIS: Multimorbilidade e Envelhecimento*", conduzido na sua Unidade de Saúde Familiar. Este documento contém informação que o(a) ajudará a decidir se deseja participar.

A sua participação no estudo é voluntária. Está no direito de recusar participar e a sua decisão não será prejudicial nem afetará a assistência médica a que tem direito.

Antes de decidir sobre a sua participação, é importante que leia cuidadosamente e compreenda a informação apresentada neste documento, onde estão descritos os objetivos do estudo.

Se aceitar participar neste estudo deverá assinar o presente Formulário de Consentimento Informado Livre e Esclarecido, do qual receberá uma cópia assinada e datada. Não serão recolhidos quaisquer dados para oestudo até que tenha lido e assinado este documento.

Este estudo está a ser conduzido de acordo com a Lei 21/2014, de 16 de abril (Lei da Investigação Clínica), na sua redação atual, e com toda a legislação e diretrizes Nacionais e Europeias aplicáveis e foi avaliado e aprovado pela Comissão de Ética Competente desta instituição (Comissão de Ética para a Saúde da Administração Regional de Saúde de Lisboa e Vale do Tejo, I.P.) e pela Comissão de Ética da Nova Medical School aos quais pertencem os Investigadores que desenvolveram o projeto.

Objetivo do Estudo:

O presente estudo pretende avaliar se a Plataforma METHIS influencia a qualidade de vida, saúde mental e atividade física dos doentes com multimorbilidade.

Por que estou a ser convidado para participar no estudo?

Está a ser convidado a participar neste estudo porque:

- É utente inscrito(a) numa Unidade de Saúde Familiar que aceitou participar no estudo;
- Foi considerado pelo seu médico(a) ou enfermeiro(a) assistente como tendo multimorbilidade complexa, ou seja, por ser portador de três ou mais problemas de saúde que afetam três ou mais sistemas de órgãos do corpo humano;
- Tem acesso a dispositivos de tecnologia que permitem comunicação (computador, tablet, etc.) e tem acesso a ligação de internet.

O que irá acontecer se eu decidir participar no estudo?

Se concordar em participar neste estudo, depois de ler cuidadosamente as informações presentes neste documento e de assinar o Formulário de Consentimento Informado, poderá ser alocado a um dos dois braços do estudo. Os utentes no braço da intervenção terão acesso a consultas através de uma plataforma digital chamada METHIS enquanto os utentes no braço de controlo serão acompanhados pelos seus médicos de família pelo método tradicional.

Todos os participantes do estudo serão convidados a preencher questionários sobre qualidade de vida (SF- 12), saúde mental (HADS-A e HADS-D), e a reportar o número de passos dados, no início do estudo e passados 12 meses, quando o estudo terminar.

Os resultados do estudo permitirão avaliar se a utilização da plataforma digital METHIS que utiliza uma abordagem centrada no doente contribui para melhores resultados em termos de qualidade de vida, saúde mental e atividade física dos utentes com multimorbilidade.

Os dados obtidos através do estudo serão tratados de forma anonimizada. Os resultados serão publicados em revistas e congressos científicos.

Qual a duração do estudo?

O estudo terá a duração de um ano e meio desde a primeira consulta após ser incluído(a) no estudo.

Quais são os possíveis benefícios que terei por participar no estudo?

Caso se verifique que a plataforma METHIS contribui para a melhoria de qualidade de vida, saúde mental e atividade física dos utentes com multimorbilidade, os utentes que participam no estudo no braço de intervenção poderão usufruir deste tipo de cuidados.

Os utentes no braço de controlo poderão solicitar acompanhamento através desta plataforma, após conclusão do estudo, se se verificar que a sua utilização é benéfica.

Existem riscos associados com a minha participação no estudo?

Não se prevê que haja riscos associados à participação no estudo

Irei receber alguma compensação ou ter alguma despesa pela participação neste estudo?

Os participantes não irão receber compensações monetárias nem terão despesas associadas à participação no estudo.

O que acontecerá se não participar no estudo ou se optar por terminar a minha

participação no estudo?

A sua participação é voluntária e poderá decidir não participar ou terminar a sua participação no estudo, a qualquer momento, sem prejuízo dos seus cuidados médicos. Caso decida não participar no estudo, ou terminar a sua participação antes da conclusão do estudo o(a) seu(sua) médico(a) irá garantir que o seu acompanhamento clínico continuará a ser prestado dentro da prática clínica habitual. Caso decida terminar a sua participação no estudo, os dados recolhidos não serão utilizados.

Como será protegida a minha privacidade?

A sua privacidade será protegida conforme o previsto na Legislação Portuguesa e Comunitária aplicável (incluindo a Lei 58/2019 e o Regulamento Europeu 2016/679, relativos à proteção de dados pessoais).

O acesso aos dados requeridos pelo estudo é necessário para poder participar. Todas as pessoas/entidades que poderão ter acesso aos seus dados descodificados estão sujeitas a dever de sigilo profissional.

Poderá a qualquer momento retirar a sua autorização para a utilização e partilha dos seus dados pessoais, incluindo dados de saúde, através do(a) médico(a) do estudo. Se essa for a sua decisão, não poderá continuar a participar no estudo.

É-lhe reconhecido, nos termos da lei, o direito de solicitar o acesso ou a retificação dos seus dados que se encontrem incorretos. Poderá também pedir para receber os dados pessoais que facultou para o estudo num formato eletrónico padronizado, ou pedir que essa informação seja transmitida a outra pessoa à sua escolha.

Os resultados do estudo poderão ser utilizados em relatórios ou em apresentações científicas nos congressos clínicos ou científicos, ou ainda publicados em revistas científicas, mantendo a confidencialidade dos seus dados.

Quem poderei contactar se tiver alguma dúvida?

Caso tenha perguntas ou dúvidas a colocar sobre o estudo deverá contactar o(a) médico(a) responsável pelo estudo:

Nome do(a) Médico(a) do estudo:

Contacto:

Quaisquer questões sobre os seus direitos e deveres como participante no contexto deste estudo clínico podem ser colocadas à seguinte comissão de ética independente, que avaliou e emitiu parecer favorável para este estudo:

Comissão de ética para a saúde: Comissão de Ética para a Saúde da Administração Regional de Saúde de Lisboa e Vale do Tejo, I.P.

Avenida Estados Unidos da América, Lote 77 - 11º piso

1749-096 Lisboa;

21 842 5203; 21 842 5123

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT05593835
	2b	All items from the World Health Organization Trial Registration Data Set	1-20
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Protocol for a Cluster Randomised Trial of a Goal-Oriented Care approach for multimorbidity patients supported by a digital platform

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Communication, Health informatics, Patient-centred medicine
Keywords:	Information management < BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, MEDICAL EDUCATION & TRAINING, PRIMARY CARE, STATISTICS & RESEARCH METHODS

Protocol for a Cluster Randomised Trial of a Goal-Oriented Care approach for multimorbidity patients supported by a digital platform

July 2023, Version 2.0

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Abstract

Introduction: Health information systems represent an opportunity to improve the care provided to people with multimorbidity. There is a pressing need to assess their impact on clinical outcomes to validate this intervention. Our study will determine whether using a digital platform (METHIS) to manage multimorbidity improves health-related quality of life (HR-QoL).

Methods and Analysis: A superiority, cluster randomised trial will be conducted at Primary Health Care Practices (1:1 allocation ratio). All public practices in the Lisbon and Tagus Valley (LVT) Region, Portugal, not involved in a previous pilot trial, will be eligible. At the participant level, eligible patients will be people with complex multimorbidity, aged 50 years or older, with access to an internet connection and a communication technology device. Participants who cannot sign/read/write and who do not have access to an email account will not be included in the study. The intervention combines a training programme and a customised Information System (METHIS). Both are designed to help clinicians to adopt a Goal-Oriented Care Model approach and to encourage patients and carers to play a more active role in autonomous healthcare. The primary outcome is HR-QoL, measured at 12 months with the physical component scale of the SF-12 questionnaire. Secondary outcomes will also be measured at 12 months and include mental health (mental component Scale SF-12, Hospital Anxiety and Depression Scale). We will also assess serious adverse events during the trial, including hospitalisation and emergency services. Finally, at 18 months, we will ask the general practitioners for any potentially missed diagnoses.

Ethics and Dissemination: The Research and Ethics Committee (LVT Region) approved the trial protocol. Clinicians and patients will sign an informed consent. A data management officer will handle all data, and the publication of several scientific papers and presentations at relevant conferences/workshops is envisaged.

Strengths and limitations of this study:

- This study uses a randomised design to assess the impact of a complex intervention in patient-relevant outcomes defined in the Core Outcome Set for people with multimorbidity. A Cluster Randomised Design minimises the risk of confounding factors influencing the results.
- The training component in the intervention allows for the engagement of health professionals and the decrease in learning time after the implementation of the digital platform.
- As it currently needs to be possible to integrate the digital platform with the official electronic health record, there is possibly a need to duplicate some data entry. This may compromise clinician adherence to the trial. However, any additional burden will be addressed in order to mitigate it.

Keywords: Primary Health Care, Information Management, Research Design, Telemedicine

Introduction

Background and Rationale

Health services are challenged by the increasing prevalence of multimorbidity and polypharmacy in an ageing population (1). People with multimorbidity use healthcare services 3.5 times more often than those without chronic conditions, even after adjustment for socioeconomic variables (2). These patients have poorer clinical outcomes (increased mortality, poorer HR-QoL, more disability), disruption to their personal and social lives, and a more significant financial burden (3–6). Moreover, patients with multimorbidity report several barriers to accessing healthcare services, including inadequate communication from healthcare professionals and non-consideration of their circumstances in managing their care plans (7).

One of the most often used definition of multimorbidity is the coexistence of two or more chronic conditions (2). This means that people with multimorbidity are a very heterogeneous group, making it very challenging to identify what matters most to patients. One important contribution is the Core Outcome Set for multimorbidity, which identified 17 outcomes that should be assessed in clinical trials involving people with multimorbidity. (8) The authors recommend that all studies assess health-related quality of life, mental health outcomes, and mortality; and that researchers also consider among 14 other outcomes, related to patient activities, physical activity, function, and health system outcomes. This core outcome set was developed to improve clinical trials, which assess the average effects of interventions in groups of patients. The relative importance of these outcomes may not be directly transferable to clinical practice.

Clinical guidelines help to translate the evidence of clinical trials and other forms of research into clinical practice, policy and healthcare organization. However, the traditional care approach for people with multimorbidity, has been supported by multiple single-organ management guidelines, which is burdensome and potentially harmful (9–13). New, patient-centred approaches have been proposed, emphasising the need to prioritise patient preferences, and agreed shared treatment goals (14,15). A patient-centred focus of multimorbidity management potentially allows patients to express their concerns and expectations (leading to greater involvement and adherence) while shifting the health management plan from a vertical disease-oriented model to a person-centred model (16,17).

The Goal-Oriented Care (GOC) approach is an example of a person-centred model, where healthcare professionals help patients to identify their desired goals. These goals (I.e., health concerns and expectations) can be related to preventing premature mortality or disability, improving “good death”, optimising health-related quality of life, and fostering personal growth and development during the remaining lifespan (18). Goals help to prioritise healthcare discussions and to simplify decision-making when patients have multiple conditions. Important mechanisms for GOC implementation are functional integration, whereby care is adapted to lead providers to adopt a GOC approach (e.g., IT systems designed for GOC) and normative integration, where clinical guidelines compel providers to use the GOC approach (e.g. providing training to health professionals on GOC) (19). Many of these can be achieved through information systems. Mobile technologies have been used to support the functional integration of different levels of care, reducing inappropriate referrals and improving access to specialised care (20,21). Point-of-care computer reminders often lead to modest improvements in health professionals’ behaviour (22). Even the redesign of digital charts has led to substantial improvements in adherence to evidence-based practice (23).

Intervention Objectives

Evidence on the impact of Digital Health in the disease management of patients with multimorbidity appears to lead to moderate improvements (24,25). However, most studies have used only short follow-ups (<= six months) and rarely assessed patient-oriented outcomes (HR-QoL or mortality) or the complex needs of people living with multimorbidity (25,26). Therefore, this study aims to evaluate the improvement in the quality of life in patients using a primary healthcare digital platform (METHIS: Multimorbidity Management Health Information System) which assists patients and primary healthcare clinicians in managing multimorbidity within a GOC framework. In addition, it will also assess whether the digital platform impacts anxiety, depression, physical activity, and serious adverse events.

Trial Design

The "METHIS" intervention is a decentralised trial that combines the implementation of a training program and the use of a customised digital platform, which is designed to prompt clinicians to adopt a GOC approach. A 12-month cluster randomised trial (CRT) (planned for 1 June 2025) with an assignment ratio of 1:1 in a superiority framework will be conducted. The CRT design will avoid the possible selection bias of individual randomisation conducted by clinicians. In addition, cluster randomisation will facilitate trial implementation since the practices share an identical electronic health records (EHR) server. The trial is registered on clinicaltrials.gov under the identifier NCT05593835, and the patient timeline can be seen in **Figure 1**.

Methods and Analysis

Study Setting

The trial will be conducted in primary care practices (henceforward, practices) in the Lisbon and Tagus Valley Region (ARSLVT) within the Portuguese National Health Service. These practices have 4-12 family physicians, 4-12 nurses and 2-6 clinical secretaries.

Eligibility Criteria

All practices in ARSLVT that did not pilot the METHIS digital platform will be eligible at the cluster level. The staff at participating units will constitute the local research team. Eligible patients will be community-dwelling people aged 50 or older with complex multimorbidity (co-occurrence of three or more chronic conditions affecting three or more different body systems) and access to an Internet connection and a communication technology device (27). Exclusion criteria will be the inability to: provide informed consent, to read or write, inability to access an email or electronic device, even when helped by an informal caregiver.

Intervention

The METHIS intervention will consist of two components (**Figure 2**).

The first component is a **GOC Training Program** for health professionals. The training program will include the concept of personalised care, methods of goal elicitation and goal-setting, implications of GOC in healthcare practice, and how the METHIS platform can be used to support the application of GOC. The training will be implemented through a blended-learning, continuous education program that NOVA University of Lisbon will credit. It will have three stages: initial face-to-face training, which will happen before the data collection, followed by remote,

asynchronous training over 12 months, and a final seminar to discuss the results and inquire about the usability of the GOC model and the METHIS platform. The course will be offered to the intervention group one month before the start of patient recruitment and the control group at least one month after the end of data collection.

The second component is a **GOC Information System**. We will adapt the platform developed from a pilot study during the COVID-19 pandemic (METHIS)(28). The prototype was developed with the input of clinicians, but patients were not involved. Briefly, the platform was designed to nudge clinicians to adopt a GOC approach and encourage patients and caregivers to take an active role in healthcare (28–30). It is is a web-based platform with several modules. To ensure each user only has access to the features and information relevant to them, patients can access patient-specific features, while clinicians are given access to a different set of capabilities tailored to their needs. A goal-setting module will help the process of goal-elicitation. Patients will have information on the relevance of this process, while clinicians will have prompts to guide them during the process. A health literacy module will give patients access to education materials and to the outputs of decision aids that were used during clinical appointments. Clinicians can add new education materials or decision aids to a preset library available in the information system. Patients can contribute with self-monitoring data, which will allow them to track their monitoring data. Clinicians will have access to a summary of this self-monitoring data in the patient record. There will be a dashboard with patient goals and a timeline with self-monitoring data relevant to their goals to help patients and clinicians monitor the achievement of goals. Patient goals will be highlighted on every screen, to nudge patients and clinicians in every interaction with the system. Service and features of the information system may be changed during pilot implementation, according to feedback from patients and clinicians. Appendix 1 provides more information about the platform.

Control

The control group in this trial will be the best usual care, using the standard EHR available to primary care practices (31,32). Our understanding of what “best usual care” is for people with multimorbidity is informed by qualitative research in an earlier stage of this project (33). Our results suggest that healthcare professionals often provide disease-driven care. When faced with multiple healthcare problems, they prioritise based on 1) patient complaints, 2) which condition is less well controlled, or 3) which condition is more likely to impact patient HR-QoL adversely. General practitioners and primary care nurses are often unfamiliar with the GOC model. However, they already try to implement some of its principles, such as identifying patient goals and supporting shared decision-making.

Cluster adherence and co-interventions

We will use a mix of strategies to help promote cluster adherence. We will provide an easy access support line to assist participants with technical difficulties. We will use physical items (e.g., mouse pads, pens, and notepads) to remind them of the study. We will simplify trial related processes using an aggregate profile of patients in the study. We will provide clinicians with regular updates about the progress of the trial, including the number of participants recruited and any preliminary results use letters before final at collection. These letters will be sent after the end of participant recruitment and another month before data collection.

All participating practices can implement other interventions to better support managing patients with multimorbidity. The types of health system interventions according to the

Taxonomy of Effective Practice and Care Organisation (EPOC) and their permissions during the trial can be consulted (**Appendix 2**) (34). Financial and Governance arrangements are probably not relevant at the primary care practice level since all will be recruited from the same Regional Health Authority, and any changes to the financial or governance arrangements will be simultaneously applied to all.

Outcomes

Primary outcome

Health-related quality of life is a core outcome in multimorbidity studies (8). Participants will be asked to fill in the SF-12 questionnaire at baseline, six months, and 12 months. This questionnaire generates a physical component score (PCS) and a mental component score (MCS). The primary outcome will be the mean difference in the variation (delta) of the PCS of SF-12 between baseline and 12 months. The SF-12 can be filled in 2-4 minutes, and it is validated for the Portuguese population. Minimum significant differences validated across large populations and multiple disease categories are a change between 2 and 3 points from the population mean of 50 (35,36).

Secondary outcomes

Mental health status is another core outcome in multimorbidity studies. We will ask participants to complete the Hospital Anxiety and Depression Scale questionnaire (HADS-A and HADS-D, respectively) at baseline, six months and 12 months. We will calculate the mean difference in the variation (delta) in HADS-A and HADS-D between baseline and 12 months. Although HADS was designed for inpatients, it was posteriorly validated in the primary care outpatient setting (37). A minimum significant difference of 1.5 has been reported in other chronic disorders (38).

Physical activity will be monitored through the number of steps walked daily. To assess the number of steps per day, a smart band with a triaxial Accelerometer will be used in both arms of the trial. Although traditional step counters use pedometers to detect daily step counts, accelerometers are more accurate and sensitive to lower force accelerations (e.g., slow walking), considered the current standard for collecting physical activity data (39–41). Most accelerometer-based fitness wearables measure acceleration in three directions (42). They can be used to estimate the type of movement, count steps, calculate energy expenditure and intensity, and estimate sleep patterns. Although the validity and reliability of these metrics vary, they found high reliability for steps and distance (43). Sedentary older adults and individuals with a disability and chronic illness benefit from a physically active lifestyle, with approximately 4,600-5,500 daily steps. The lowest median values for steps/day found are in disabled older adults (1214 steps/day) and people living with COPD (2237 steps/day) (40).

Serious adverse events (clinician-reported) are the safety outcomes chosen for this trial. In both trial arms, data about patient mortality will be collected and combined with data on emergency department visits and hospital admissions as a proxy for serious adverse events. Family physicians will be asked, at 6 and 12 months after randomisation, to check the life status of enrolled patients and whether patients in the trial were admitted to a hospital or had visited an emergency service since the randomisation date. This information is available through the common Portuguese EHR. Due to legal requirements, the information about hospital admissions and other contacts with healthcare organisations ceases to be open to the attending physician after death.

Potentially missed diagnoses (clinician-reported) will be a second safety outcome. At 18 months, we will ask clinicians in the intervention arm if they know of any severe diagnosis that might have been missed due to the intervention. This report, six months after the intervention phase, is a compromise between avoiding recall bias and allowing enough time for a missed diagnosis to become clinically apparent.

Sample Size

To address our primary outcome, it was assumed that for the PCS of the SF-12 scale, a mean of 38.3 for the control group, a mean of 41.3 for the intervention group, and a typical standard deviation of 11.3. The mean difference of 3 points used in the sample size calculation is informed by earlier research suggesting that the minimum significant difference for SF-12 in different populations´ diseases ranges between 2 and 3 points (35,36). A conservative intra-cluster correlation coefficient of 0.08, an alpha of 0.05, and a power of 80% were still considered. To achieve the desired strength, approximately 600 patients will need to be enrolled in each arm, implying about 20 patients per practice, with a minimum of 30 practices in the intervention arm and 30 in the control arm. The sample size will be corrected considering the 10% losses to follow-up. This means that 1380 participants will have to be enrolled (i.e., 23 participants per cluster).

Recruitment

All potentially eligible practices will be randomly ordered and contacted by a member of the leading research team until the number of clusters obtained in the sample size calculations is reached. These units will be invited to engage in the CRT as members of a local research team. A short questionnaire will be sent to identify primary care teams (family physician plus family nurse) willing to participate and collect the required practice characteristics for minimisation.

Eligible participants will be determined by the members of the local research team through a review of records and confirmed by a leading research team member. Participant screening will continue until the target population is achieved. A random sample of twenty-three participants will be drawn from each practice. Participants will have no financial or non-financial incentives other than using a smart band for 2 months. The recruitment phase will extend over six months.

Once contacted, patients will be provided with an informed consent form and any queries they may have will be addressed. Most contacts will be made through their healthcare professionals to maintain trust and anonymity.

Allocation

Clusters will be allocated to the intervention or control groups (1:1) using minimisation with a random element, a method to achieve a good balance regarding baseline characteristics that could influence the outcomes when the number of clusters is small. Cluster variables used in the minimisation will be the type of setting (urban, rural, mixed), patient age distribution (50- 75 years/>75 years), patient-level of education (lower/higher), baseline HR-QoL (below median SF-12 / above median SF-12), baseline mental health status (HADS-A and HADS-D).

After patient recruitment and baseline data collection, the trial manager (i.e., the Data Protection Officer, DPO) will assign a pseudonymised code to each practice and send the practice code and minimisation variables to the statistician, who will then allocate practices into two groups. Members of the local research team will then assess for patient eligibility, and recruitment will be performed by one of the trial researchers. The trial statistician will generate the allocation

sequence.

Blinding

Given the nature of the intervention, none of the people involved in the trial (participants, care providers and outcome assessors) will be blinded to the intervention.

Data Collection

Data on HR-QoL, mental health and physical activity will be collected at baseline, six months and 12 months. For baseline assessment, after signing the informed consent, patients will be invited to fill in the electronic forms with the questionnaires, either using a personal computer or using a tablet. At the 6- and 12-month assessment, participants will be contacted by research team members and asked to fill in the electronic forms at home, using a personal computer or a tablet.

Data on physical activity will be stored locally and uploaded to a cloud-based health repository. For patients on the intervention arm, data will be available for consultation by health professionals and patients on the web platform, either using a personal computer or a tablet. As for patients in the control arm, data will be collected similarly but will not be available for consultation (only by researchers at baseline, at six months, and at 12 months).

Mortality: Members of the local research team will be asked to fill in a small survey at 6 and 12 months after randomisation. They will be asked to check the life status of their enrolled patients in the Portuguese common Electronic Health Record. Data recorded will be life status (alive, dead) and, if relevant, date of death.

Hospital admissions (clinically reported): At 6 and 12 months after randomisation, members of the local research team will be invited to check the number of hospital admissions in the previous 6-12 months in the Portuguese common Electronic Health Record. Data recorded will be the number of admissions (count) and, if relevant, dates of admissions. Due to legal requirements, data will only be available for patients alive at the end of the intervention phase.

Composite outcome: The composite outcome will be defined as the date until death, hospital admission or visit to the emergency department, whichever comes first.

Baseline characterisation of individual participants: Patient month and year of birth (self-reported), gender (self-reported), number of years of education (self-reported), profession, number of hospital admissions in the previous 12 months, active chronic medications, and active chronic health problems (information and ICPC-2 codes in the patient's EHR extracted by the family physician) will be collected.

Baseline characteristics of clusters: After practice (cluster) recruitment, data about the type of setting (urban, rural, mixed) and the number of clinicians (nurses, family physicians, residents) will be collected.

Interactions with the platform (intervention group only): METHIS platform will register the following intervention data: the basic information about the patient's condition (e.g., chronic diseases, medications, care goals, etc.), any teleconsultations done with members of the local research team, any communication exchange between health workers and data registered by both patient (physiologic and biochemical data, SF-12, Mental health, and mobility data) and health workers, members of the local research team (relevant notes over consultations considering patient´s therapeutics).

Potentially missed diagnoses (intervention group only): At 18 months, physicians, and members of the research team, following the intervention group will be invited to report any severe diagnosis that might have been missed due to the use of METHIS. If relevant, missed serious diagnoses and the date of diagnosis will be collected.

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Data Management

The data collected in this study will come from healthcare professionals and patients at different stages. Given its diverse nature and sources, data will be collected, treated, and analysed in specific datasets. Each dataset will be set up to answer the respective research questions.

A Data Management Plan (DMP) will be formulated and overseen by the Data Protection Officer (DPO). DMP follows GDPR, within FAIR principles, to ensure transparency of results dissemination, notwithstanding data security and privacy. ISO/IEC 27001 will be used as a standard.

Regarding the datasets focused on the digital platform activities, it generates anonymised databases to be worked on by the researchers. Its functionalities enable planning and organising data entry, proper participants' coding, security, and storage, including range checks for data values (e.g., patients will receive an alert whenever the data entry is invalid or out of typical values).

Data Analysis

Individual participants will be analysed according to their randomly allocated group regardless of adherence to the intervention (intention to treat analysis). If participants transfer to another unit within the health region, they will be considered lost to follow-up, even if they move to a practice conducting the trial. All the collected variables will be summarised using descriptive statistics. Quantitative variables will be summarised by mean, standard deviation, median and range (minimum and maximum values), and qualitative variables will be summarised by absolute (n) and relative frequencies (%).

Both groups will be compared on primary and secondary outcomes using generalised mixed-effects models, accounting for variables used in the minimisation (cluster level). We will report the mean difference between the two groups of the change of HR-QoL (PCS and MCS subscales) from baseline to end of follow-up, the mean difference of the evolution of the HADS scale from baseline to end of follow-up, the mean difference of the change of step count, the hazard ratio for the composite outcome of mortality, hospital admission or visits to accidents and emergencies.

Statistical significance will be assumed for a p-value less than 0.05. The latest version of R software will be used to conduct the analysis.

Data Monitoring

There will be no Data Monitoring Committee assigned in this trial. The trial does not assess a life-threatening situation; the trial is not aimed at an especially vulnerable population, and there is no suspicion that the intervention may harm participants. There will not be any pre-planned interim analyses, nor are we planning on an adaptive trial design.

Although no direct physical or mental harm is expected from using the METHIS platform, patients and members of the local research team in the intervention arm may substitute/postpone face-to-face consultations with remote consultations in which physical examination is not possible. There is a theoretical risk of missing a serious diagnosis, and a safety follow-up phase is planned, where we will receive reports from members of the local research team 18 months after randomisation (6 months after the intervention phase). We will assess whether any patients enrolled in the intervention arm had a missed diagnosis. All the events related to adverse events notified by healthcare professionals, members of the local research team, and patient participants will be registered in the data reporting books and will be available for auditing purposes.

Patient and Public Involvement

The METHIS project is based on Design Science Research. In this approach, the methods used always have a participatory research perspective that allows the users of the artefact to be involved at all stages of its development (44). Needs assessment (before the intervention) and evaluation (after the evaluation) is done with qualitative methods. The intervention builds on a qualitative study with primary care clinicians during the development of the METHIS information system prototype. In this project, health professionals identified facilitating factors and barriers to changing from the current HIS to METHIS (33). Clinicians also identified the required features of the information system. We will seek patients' insights on the best design for the intervention, through a series of interviews and focus groups with patients. Qualitative data will be collected during a pilot implementation of the intervention in two primary care practices. This will be used to refine the patient interface for the information system.(33). To assess the intervention, we will also gather a group of participants and conduct a focus group in the intervention arm.

Ethics and Dissemination

Research Ethics Approval

The trial protocol was approved by the Research and Ethics Committee of ARSLVT (March 2022, 094/CES/INV/2021). Protocol amendments, such as changes to eligibility criteria, outcomes and analysis, will be submitted for review and reapproval to the Research and Ethics Committees. If the protocol amendment involves changes related to patient data or significant changes that deem the previous consent invalid, patient participants will be invited to fill in a new informed consent that explains the changes made to the protocol.

Informed Consent

Members of the local research team will sign an informed consent for conducting the trial (**Appendix 3**). Patients will sign an informed consent as participants in the trial.

Confidentiality

Only healthcare professional members of the local research team will have access to each patient's demographic and clinical data. The DPO will be responsible for automatically generating an alphanumeric code that will provide an anonymised table with the previously mentioned variables for researchers and statistical analysis purposes. Data will be stored in a secure server which the DPO can only access.

Access to data

The complete research dataset will be stored in an encrypted and secure location to be accessed for secondary analyses or comparative studies or per request of the patients involved or the Research and Ethics Committee.

Ancillary and post-trial care

If we verify an improvement in HR-QoL and mental health related to care given through the METHIS platform, we will provide access to this platform for practices and patients in the control groups.

Dissemination

The trial protocol, the main paper with the trial results and a short report with the results of the final physician survey will be published in peer-review journals. All team members who fulfil the ICMJE criteria for authorship will be co-authors of these publications.

We will not disclose the database or grant access to data reproduction for legal reasons. However, the research team may make processed data available upon request, with appropriate justification.

Authors' contributions

LVL and BH conceived the study. The following authors contributed to the study design: MGC, ARJM and BH provided specific methodological expertise in the clinical strand, MP, MRM and JG in the technological strand, and MSP, BH and LVL in the pedagogical strand. AP and MA provided specific methodological expertise in statistics in cluster-randomised clinical trials. MRM and MP provided specific methodological expertise in research data management, protection and confidentiality. MGC, MP, ARJM, MRM, JG, MSP, MA, AP, BH and LVL prepared the initial proposal for funding application. MGC and MP prepared the first draft of this study protocol. MGC, MP, ARJM, MRM, JG, MSP, MA, AP, BH and LVL contributed to rewrites and refinements with important intellectual content; all the authors approved the final manuscript and agreed to be accountable for all aspects of the work. The team acknowledges the health professionals and patients involved in the development and participation of this study.

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Competing interests' statement

All authors and researchers declare no competing interest.

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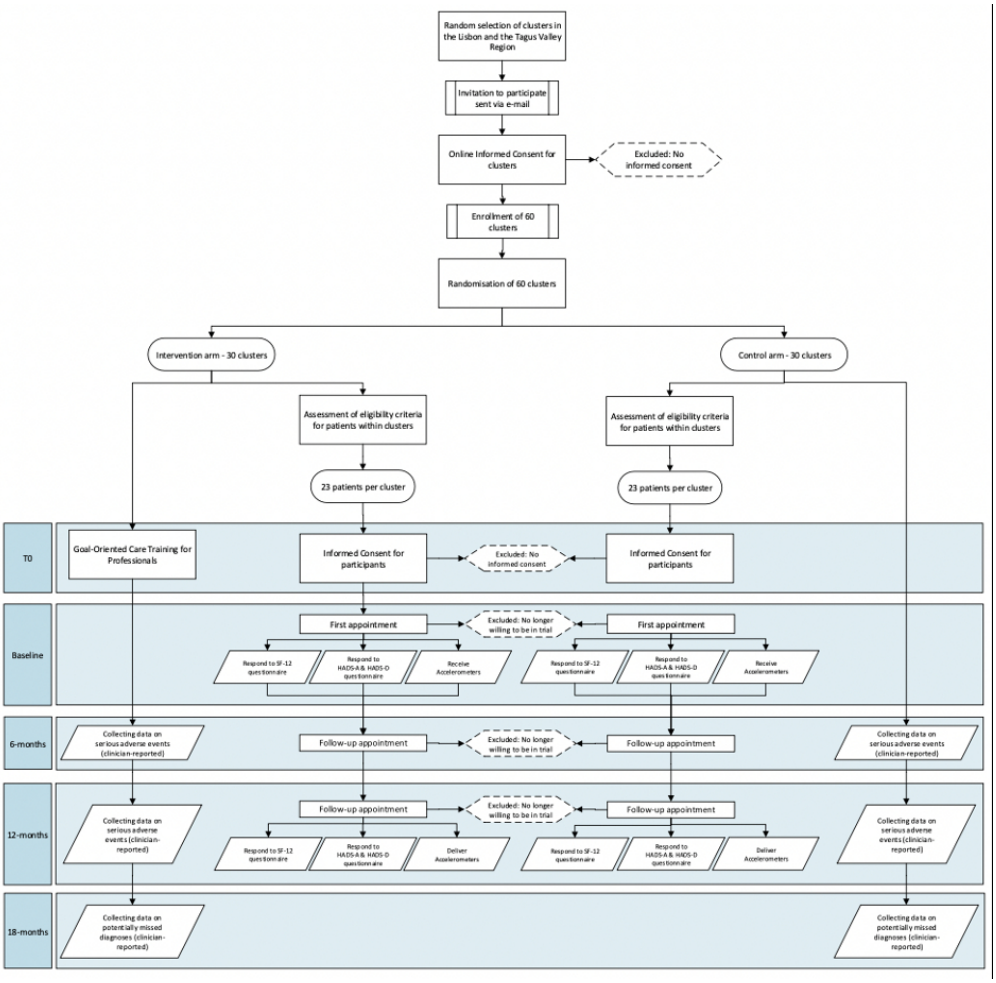
Figure Legend

Figure 1 – Participant Timeline

Figure 2 – METHIS Intervention Framework: impact on health-related quality

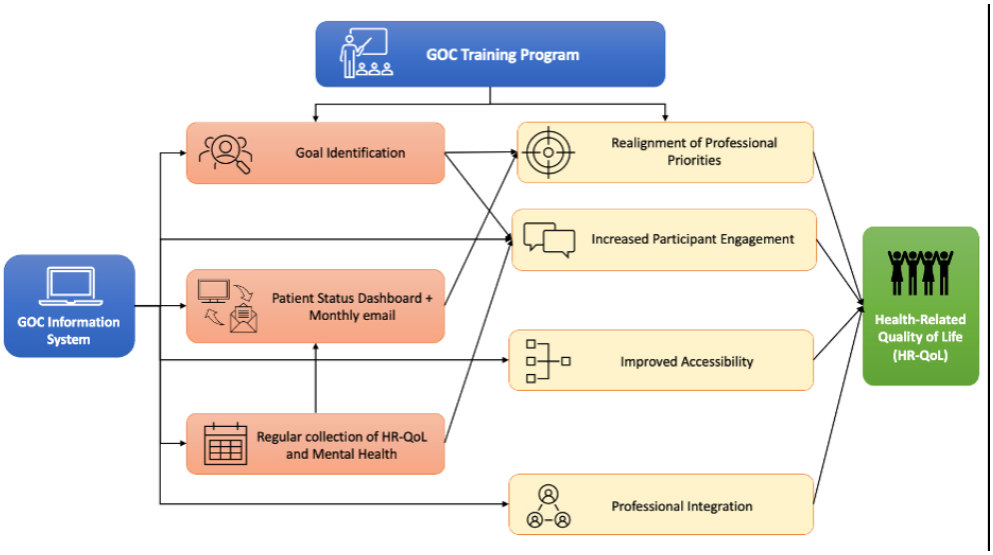
Appendices

Appendix 1 – METHIS Digital Healthcare Platform Technical Datasheet
Appendix 2 – Types of co-interventions
Appendix 3 – Consent Form



Participant Timeline

166x161mm (144 x 144 DPI)



METHIS Intervention Framework: impact on health-related quality

166x91mm (144 x 144 DPI)

METHIS Digital Healthcare Platform Technical Datasheet

Brief description:

The primary healthcare digital platform (METHIS: Multimorbidity Management Health Information System) allows physicians and nurses to monitor patients with chronic diseases. It is designed to provide features to facilitate de Goal-Oriented care approach for managing chronic patients in primary healthcare services. It focuses on improving health outcomes by self-monitoring the health profile with the healthcare professionals and enhancing communication and proximity with the healthcare team.

Each type of user profile—clinician or patient—has a home dashboard set up with the main features according to its shape (if patient, physician, nurse, or clinical secretary), with direct links to the information they need most. Administrator profiles allow the customization of features and the upload and refresh of databases whenever required. Both testing and training, together with the research platform versions, are of added value, allowing innovation in real-time, retrieving usability to secondary data analytics, and giving a voice to users' feedback for continuous improvement.

Applications & Features		Patient	Clinician
Dashboard module	Access to goals that were set between patient and clinician	✓	✓
	Health Profile and Actions Progression monitoring through a Timeline	✓	✓
Patient record module	Register self-monitoring data (vitals, physical activity markers, patient-reported outcome scales, perception of goal-attainment)	✓	
	Upload self-monitoring data (through a personal electronic device)	✓	
	Track their own monitoring data through time	✓	
	access a summary of self-monitoring data		✓
	Register of Diary Log (SOAP) for Consultations		✓
	Access to Diagnostics, Therapeutics and Management Plan		✓
Goal setting module	Explains why is goal-setting important and will encourage patients to think on valued activities and abilities before appointment with facilitator	✓	
	Provides scripts for the different steps in the Patient Priorities Identification Process: 1. Introduction to patient priorities and value clarification process; 2. Adapting values into health outcome goals and exploring patient preferences; 3. Discussing trade-offs; 4. Encouraging patients to communicate their priorities.		✓
Health literacy module	Access to a library of patient education materials	✓	✓
	Receive summary of decision aid	✓	✓
	Add new decision aids or patient education materials		✓
	Support for video-consultations	✓	✓
	Schedule an appointment	✓	✓
	Message the patient		✓

Specifications:

- Web-based app with three relational databases using PostgreSQL.
- Staging database to enable proper testing and training.
- Production database to collect Family Healthcare Unit (USF) data.
- Research database, with anonymized data from the production database.
- Integration with Zoom (Zoom API) to allow for synchronous teleconsultations.
- Login personal and private profile (clinical secretary, nurse, physician, patient)
- Electronic devices/sensors integration (API).
- Integrated views of the patient's demographic information, chronic conditions, medication, exams, and personal goals.
- Integrate records of patients' diseases (ICPC-2), authorized medicines (INFARMED, 2021), and biochemical and physiological parameters for chronic disease monitoring.
- Admin login and profile for system, performance, and permissions management.
- Data profiling tree by healthcare regional groups to local Healthcare units.
- User's registration in the platform, generates an invitation by email to access and reset private password and complete the personal profile.
- Users has access to the platform by login with private credentials.
- Users have direct access to teleconsultations or tasks through the direct links in the notifications and reminder emails. Any information uploaded to the platform will be automatically logged.

Appendix 2

Types of co-interventions that are permitted and non-permitted during trial implementation.

Macro level	**Meso level**	**Permitted during the trial?**
Delivery Arrangements	How and when care is Delivered	Permitted
	Where care is provided and changes to the healthcare environment	Permitted
	Who provides care and how the healthcare workforce is managed	Permitted
	Coordination of care and management of care processes	Permitted
	Information and Communication technology (ICT)	**Discouraged**
Financial Arrangements		Not relevant at the practice level.
Governance Arrangements		Not relevant at the practice level.
Implementation Strategies	Interventions targeted at healthcare organisations	Permitted
	Interventions targeted at healthcare workers	Permitted
	Interventions targeted at specific types of practice, conditions or settings	Not relevant at the practice level.

Model for Informed Consent Form

FORMULÁRIO DE CONSENTIMENTO INFORMADO LIVRE E ESCLARECIDO

Título do estudo:

METHIS: Multimorbilidade e envelhecimento: Ensaio Clínico Randomizado em Cluster de uma abordagem centrada no doente suportada por uma plataforma digital.

METHIS - Multimorbidity and Ageing: Cluster Randomized Trial of a Patient-Centred Approach supported by a digital platform.

Nome da Instituição:

Unidade de Saúde Familiar

Morada da Instituição

INTRODUÇÃO

Gostaríamos de convidá-lo(a) a participar no estudo de investigação clínica: "*METHIS: Multimorbilidade e Envelhecimento*", conduzido na sua Unidade de Saúde Familiar. Este documento contém informação que o(a) ajudará a decidir se deseja participar.

A sua participação no estudo é voluntária. Está no direito de recusar participar e a sua decisão não será prejudicial nem afetará a assistência médica a que tem direito.

Antes de decidir sobre a sua participação, é importante que leia cuidadosamente e compreenda a informação apresentada neste documento, onde estão descritos os objetivos do estudo.

Se aceitar participar neste estudo deverá assinar o presente Formulário de Consentimento Informado Livre e Esclarecido, do qual receberá uma cópia assinada e datada. Não serão recolhidos quaisquer dados para oestudo até que tenha lido e assinado este documento.

Este estudo está a ser conduzido de acordo com a Lei 21/2014, de 16 de abril (Lei da Investigação Clínica), na sua redação atual, e com toda a legislação e diretrizes Nacionais e Europeias aplicáveis e foi avaliado e aprovado pela Comissão de Ética Competente desta instituição (Comissão de Ética para a Saúde da Administração Regional de Saúde de Lisboa e Vale do Tejo, I.P.) e pela Comissão de Ética da Nova Medical School aos quais pertencem os Investigadores que desenvolveram o projeto.

Objetivo do Estudo:

O presente estudo pretende avaliar se a Plataforma METHIS influencia a qualidade de vida, saúde mental e atividade física dos doentes com multimorbilidade.

Por que estou a ser convidado para participar no estudo?

Está a ser convidado a participar neste estudo porque:

- É utente inscrito(a) numa Unidade de Saúde Familiar que aceitou participar no estudo;
- Foi considerado pelo seu médico(a) ou enfermeiro(a) assistente como tendo multimorbilidade complexa, ou seja, por ser portador de três ou mais problemas de saúde que afetam três ou mais sistemas de órgãos do corpo humano;
- Tem acesso a dispositivos de tecnologia que permitem comunicação (computador, tablet, etc.) e tem acesso a ligação de internet.

O que irá acontecer se eu decidir participar no estudo?

Se concordar em participar neste estudo, depois de ler cuidadosamente as informações presentes neste documento e de assinar o Formulário de Consentimento Informado, poderá ser alocado a um dos dois braços do estudo. Os utentes no braço da intervenção terão acesso a consultas através de uma plataforma digital chamada METHIS enquanto os utentes no braço de controlo serão acompanhados pelos seus médicos de família pelo método tradicional.

Todos os participantes do estudo serão convidados a preencher questionários sobre qualidade de vida (SF- 12), saúde mental (HADS-A e HADS-D), e a reportar o número de passos dados, no início do estudo e passados 12 meses, quando o estudo terminar.

Os resultados do estudo permitirão avaliar se a utilização da plataforma digital METHIS que utiliza uma abordagem centrada no doente contribui para melhores resultados em termos de qualidade de vida, saúde mental e atividade física dos utentes com multimorbilidade.

Os dados obtidos através do estudo serão tratados de forma anonimizada. Os resultados serão publicados em revistas e congressos científicos.

Qual a duração do estudo?

O estudo terá a duração de um ano e meio desde a primeira consulta após ser incluído(a) no estudo.

Quais são os possíveis benefícios que terei por participar no estudo?

Caso se verifique que a plataforma METHIS contribui para a melhoria de qualidade de vida, saúde mental e atividade física dos utentes com multimorbilidade, os utentes que participam no estudo no braço de intervenção poderão usufruir deste tipo de cuidados.

Os utentes no braço de controlo poderão solicitar acompanhamento através desta plataforma, após conclusão do estudo, se se verificar que a sua utilização é benéfica.

Existem riscos associados com a minha participação no estudo?

Não se prevê que haja riscos associados à participação no estudo

Irei receber alguma compensação ou ter alguma despesa pela participação neste estudo?

Os participantes não irão receber compensações monetárias nem terão despesas associadas à participação no estudo.

O que acontecerá se não participar no estudo ou se optar por terminar a minha

participação no estudo?

A sua participação é voluntária e poderá decidir não participar ou terminar a sua participação no estudo, a qualquer momento, sem prejuízo dos seus cuidados médicos. Caso decida não participar no estudo, ou terminar a sua participação antes da conclusão do estudo o(a) seu(sua) médico(a) irá garantir que o seu acompanhamento clínico continuará a ser prestado dentro da prática clínica habitual. Caso decida terminar a sua participação no estudo, os dados recolhidos não serão utilizados.

Como será protegida a minha privacidade?

A sua privacidade será protegida conforme o previsto na Legislação Portuguesa e Comunitária aplicável (incluindo a Lei 58/2019 e o Regulamento Europeu 2016/679, relativos à proteção de dados pessoais).

O acesso aos dados requeridos pelo estudo é necessário para poder participar. Todas as pessoas/entidades que poderão ter acesso aos seus dados descodificados estão sujeitas a dever de sigilo profissional.

Poderá a qualquer momento retirar a sua autorização para a utilização e partilha dos seus dados pessoais, incluindo dados de saúde, através do(a) médico(a) do estudo. Se essa for a sua decisão, não poderá continuar a participar no estudo.

É-lhe reconhecido, nos termos da lei, o direito de solicitar o acesso ou a retificação dos seus dados que se encontrem incorretos. Poderá também pedir para receber os dados pessoais que facultou para o estudo num formato eletrónico padronizado, ou pedir que essa informação seja transmitida a outra pessoa à sua escolha.

Os resultados do estudo poderão ser utilizados em relatórios ou em apresentações científicas nos congressos clínicos ou científicos, ou ainda publicados em revistas científicas, mantendo a confidencialidade dos seus dados.

Quem poderei contactar se tiver alguma dúvida?

Caso tenha perguntas ou dúvidas a colocar sobre o estudo deverá contactar o(a) médico(a) responsável pelo estudo:

Nome do(a) Médico(a) do estudo:

Contacto:

Quaisquer questões sobre os seus direitos e deveres como participante no contexto deste estudo clínico podem ser colocadas à seguinte comissão de ética independente, que avaliou e emitiu parecer favorável para este estudo:

Comissão de ética para a saúde: Comissão de Ética para a Saúde da Administração Regional de Saúde de Lisboa e Vale do Tejo, I.P.

Avenida Estados Unidos da América, Lote 77 - 11º piso

1749-096 Lisboa;

21 842 5203; 21 842 5123

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	1-11
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 11
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 3

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.