Deprescribing: a portrait and out-comes of the reduction of Polypharmacy in Portugal (DePil17-20)

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <Number, if available>

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Version Number: v.1.0

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP).

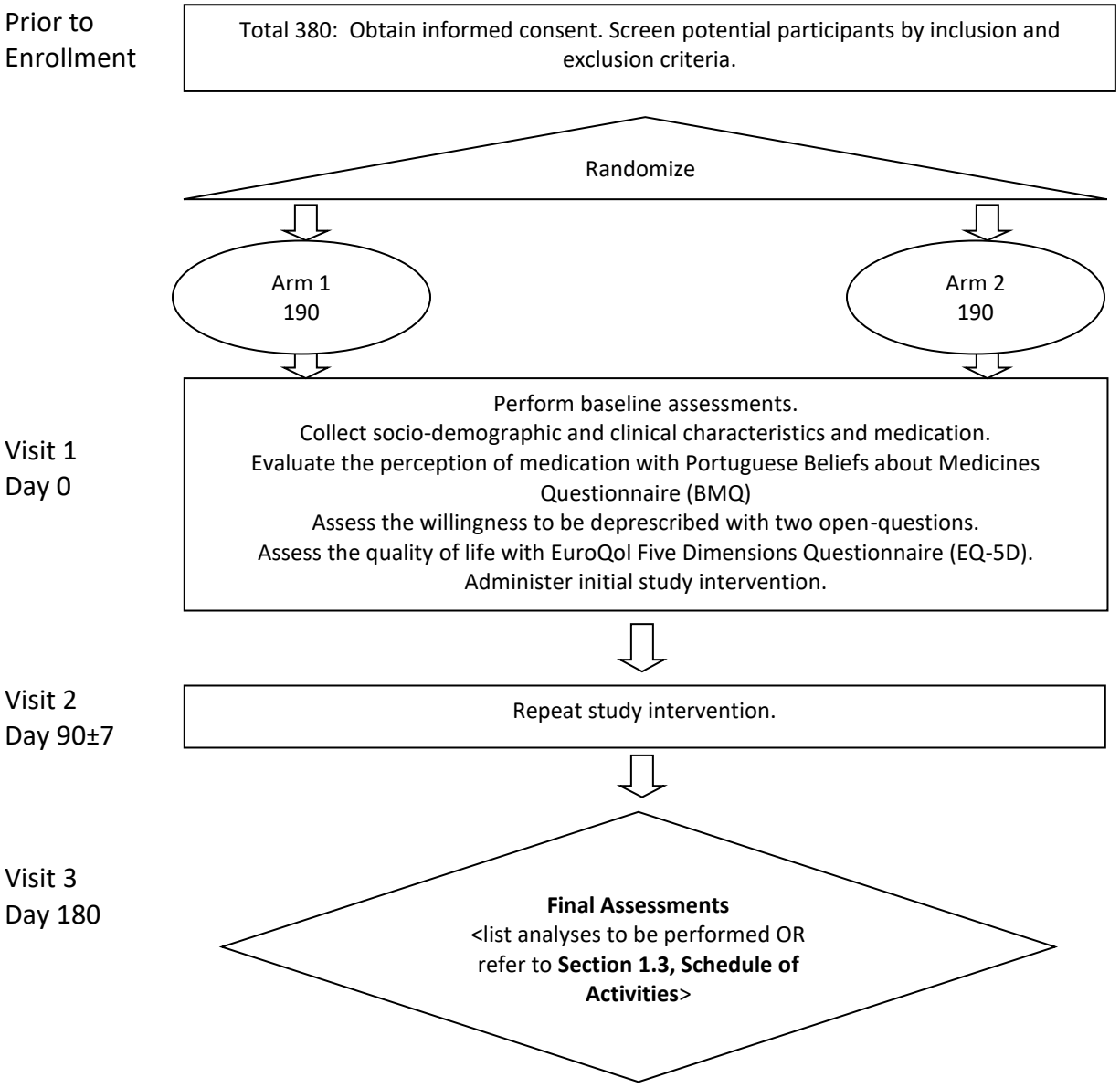
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Deprescribing: a portrait and out-comes of the reduction of Polypharmacy in Portugal (DePil17-20)
Study Description:	This study protocol comprises three phases. The first two phases will be nationwide and aim to evaluate the prevalence and patterns of polypharmacy and assess the barriers and facilitators of deprescribing perceived by older adults, as well as their willingness to be deprescribed and to self-medicate. The third and last phase will be a non-pharmacological randomised clinical study to measure the impact of enablement of older adults in their willingness to be deprescribed and related quality of life.
Objectives:	Primary Objective: Willingness to be deprescribed after the intervention Secondary Objectives: Quality of life after the intervention
Study Population:	Older adults (≥65 years) in Portugal
Description of Study Intervention:	In the intervention group the investigators will give enablement tools and talks with their General Practitioners about how to issue the problem of polypharmacy.
Study Duration:	36 months.
Participant Duration:	6 month.

1.2 SCHEMA


Prior to Enrollment
Total 380: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria.
Randomize
Arm 1
190
Arm 2
190
Visit 1
Day 0
Perform baseline assessments.
Collect socio-demographic and clinical characteristics and medication.
Evaluate the perception of medication with Portuguese Beliefs about Medicines Questionnaire (BMQ)
Assess the willingness to be deprescribed with two open-questions.
Assess the quality of life with EuroQol Five Dimensions Questionnaire (EQ-5D).
Administer initial study intervention.
Visit 2
Day 90±7
Repeat study intervention.
Visit 3
Day 180
Final Assessments
<list analyses to be performed OR refer to Section 1.3, Schedule of Activities>

2 INTRODUCTION

Polypharmacy is defined as the simultaneous taking of five or more drugs. It's present in 30-70% of older adults (1) and it's a significant predictor of the risk of falls (2) and other iatrogenic complications (3), inappropriate prescriptions (4), reduced patient's adherence (5), drug interactions (6), hospital admissions (7) and mortality (8). It is estimated that at least 75% of this adverse event is potentially preventable (9).

It is necessary to distinguish between appropriate and inappropriate medications (10), because as people get older the benefit/risk ratio of medications changes meaning that medications that were once appropriately prescribed may have become inappropriate (11). Potentially Inappropriate Medications (PIMs) are those for which the harms outweigh the benefits (12). Available data indicate that 20 to 65% of older adults are taking at least one PIM, leading to a high risk of adverse drug reactions, morbidity and mortality (13). There is a lot of information available to guide prescribers to start and maintain drug therapies that are safe and effective, but there is lack of knowledge concerning its reduction and/or withdrawal so maintaining safety and effectiveness (3, 8).

Deprescribing can be defined as the withdrawal of PIMs, under medical supervision, with the objective of managing the polypharmacy and improving health outcomes (14). However, it isn't risk's deprived, it can cause abstinence syndrome, rebound effects, pharmacokinetic/pharmacodynamic changes in the metabolism of not interrupted drugs and recurrence of symptoms that were in treatment by the withdrawn drug (1, 2).

So the decision to deprescribe results from a careful weighting between the therapeutic objectives and the risk/benefit ratio (15, 16).

Several deprescribing processes have been proposed in the literature (2, 17) and involve revision of all actual medications, identification of inappropriate medications (considering harms and benefits of medication use in the individual and in the setting of life expectancy and care goals), prioritisation of medications for withdrawal, withdrawal of medications (often with tapering) and close monitoring and support and also with documentation of the improvement in health and quality of life and the reduction of adverse effects (18).

There are several tools which have been developed in order to aid identifying PIMs in older adults. The most commonly employed explicit tools are the Beers criteria and the STOPP/START criteria (Screening Tool of Older Person's Prescriptions and Screening Tool to Alert Doctors to Right Treatment) that are lists of medications which are generally inappropriate in older adults (or in the presence of certain conditions) due to an increased risk and/or decreased need/benefit. The STOPP/START criteria also offer a list of medications that should be initiated in older adults with certain conditions. However, there are also implicit tools, which are questions to take in account during our clinical judgement, to assess the medication appropriateness, for example the Medication Appropriateness Index (19).

Several studies have established that the implementation of a deprescribing process is feasible in practice (20, 21) and may result in favourable patient health and quality of life outcomes (22) and a few strategies seem effective or promising (23). Most of these studies are limited by variable methodologies, single settings, short follow-up periods and/or lack of clinical outcome measurements (24).

But there is inconsistent reporting of the patient willingness to have a medication deprescribed (2, 18). The direct involvement of patients and their caregivers in the choice and administration of drugs has long been known to be very important, but it isn't usually applied, so many patients complain about lacking this opportunity in the decision-making process (25, 26). It is assumed that older people generally do not like to take multiple medications, but there is also evidence that they may be reluctant to accept their doctor's proposal to stop some of them (13, 16, 18). So it's important to understand this incongruity between not liking to take multiple medications and reluctance to accept the proposal to stop them.

3 OBJECTIVES AND ENDPOINTS

Primary objective is to assess the enablement of older adults while being Deprescribed in the rise of Willingness to be Deprescribed.

Secondary objective is to assess the enablement of older adults while being Deprescribed in the rise of their Quality of Life outcome.

4 STUDY DESIGN

This is a three-phase study:

1. Cross-sectional, analytical study of the prevalence and patterns of polipharmacy, namely sociodemographic and clinical profiles (age, genre, area of residence and years of study) and about medication (number of drugs and their active component), in older adults attending Primary Care in Portugal.
2. Cross-sectional, triangulation study of older adults' perception of Barriers to and Facilitators of Deprescribing, Willingness to be Deprescribed and Willingness to Self-medicate.
3. Non-pharmacological randomised clinical study of the impact of enablement of older adults in their willingness to be Deprescribed and related Quality of Life.

Phase I: prevalence of polypharmacy in older adults attending primary care in Portugal

Design

Cross-sectional, analytical study.

Setting

Primary Care Centres in Portugal will be randomly selected from the five main-land Portuguese Healthcare Administrative Regions and two Autonomous Regions (Madeira and Azores), in order to obtain a national geographical representative sample.

Sample size

Since the prevalence of polypharmacy in older adults is unknown, we used as base of population all older adults in Portugal. For the study, we used a 95% confidence interval (CI) and a maximum precision error of 5%, so a minimum of 385 patients should be recruited.

Study procedures

This phase of the study starts in November 2017.

General Practitioners (GPs) sampling is made according to existing files of previous projects adherent GPs, in other epidemiological studies. After the selection of GPs, those who accept to participate will recruit their own patients. Assuming that a GP will be able to include at least 6 patients in a 3-week period, a total of 65 GPs will be enrolled in the study: 21 in North of Portugal (31.7%), 16 in Centre of Portugal (24.7%), 18 in Lisbon-Tejo Valley (27.4%), 5 in Alentejo (8.4%), 3 in Algarve (4.3%), 1 in Azores (1.6%) and 1 in Madeira (1.9%) in accordance with the distribution of Portuguese old adult population (≥65 years) in Portugal according with Pordata (www.pordata.pt).

Enrolled GPs will be instructed to collect all necessary data about all older adults (≥65 years) patients attending a primary care consultation during the period of study: 5 days on 3 consecutive weeks (Monday and Tuesday on week 1; Wednesday and Thursday on week 2; and Friday on week 3).

Data collection

The collection of the data will occur in November 2017.

GPs will be responsible for collecting all data about patients' sociodemographic characteristics, as well as morbidity and medication, during their consultations.

Data will be electronically stored in a database specifically designed for this study using MS Access 2010. Data will be encrypted and password protected. Information will be treated in strict confidentiality to protect the privacy of patients. The investigators will have no access to the data of the patient, except the one provided by the GP meaning that the only person to know who is being studied is the GP.

Before the collection of data, there will be online reunions with the GPs participating in the study.

Phase II: patients' perception of barriers to and facilitators of deprescribing, willingness to be deprescribed and actual self-medication in adult patients with polypharmacy attending primary care in Portugal

Objectives

To assert reasons and facilitators, willingness to be deprescribed and actual self-medication

Design

Cross-sectional, analytical study.

Setting

It will be the same of the phase I.

Sample size

A minimum of 385 patients will be included in phase II in order to obtain a sample with a 95% CI and a maximum precision error of 5%.

Study procedures

This phase of the study is expected to start in June 2018.

Again, GPs sampling will be made according to existing files and those who accept to participate will recruit their own patients. Patients from phase I can be enrolled in phase II. Assuming that a GP will be able to include at least 6 patients in a 3-week period, a total of 65 GPs has to be enrolled in the study, with the same distribution of the phase I. Enrolled GPs will be instructed to invite all older adult (≥65 years) patients attending the primary care consultation to participate in the study during 5 days on 3 consecutive weeks (Monday and Tuesday on week 1; Wednesday and Thursday on week 2; and Friday on week 3). Those willing to participate in the study must give written informed consent and present willingness and ability to comply with the study requirements.

Exclusion criteria will be: Being acutely unwell in the last three weeks, and refuse to participate.

Data collection

The collection of the data will occur in June 2018.

Patient's socio-demographic and clinical characteristics and medication will be registered using the same methodology as described in phase I.

Perception of medication will be evaluated using Portuguese general BMQ, the willingness to be deprescribed will be assessed with two open-questions (one to assess the facilitators and the other to assess the barriers), and the actual self-medication will be evaluated with an analogic visual scale (0 to 10) about the need to self-medicate and its justification.

For those not knowing how to write or read, someone of their knowledge, will fill in the open questions, with their answers.

In case of less than 5% of answers of the open questions, two patient groups will be invited to make a focus group asserting reasons for accepting deprescribing.

Phase III: impact of enablement of older adults in their willingness to deprescribe and quality of life

Design

Non-pharmacological randomised clinical study, intended to last for six months.

Setting

Primary Care Centres in Portugal will be randomly selected from six Health Centres of Centre of Portugal (Aveiro, Castelo Branco, Coimbra, Guarda, Leiria and Viseu)

Sample size

Will be created two groups with a minimum of 190 patients each (one will be the intervention group and the other the control).

Study procedures

This phase of the study is expected to start in September 2019 and will last for 6 months.

Again, GPs sampling will be made according to existing files and those who accept to participate will recruit their own patients. Patients from previous phases can be enrolled in phase III. Assuming that a GP will be able to include at least 6 patients, a total of 64 GPs has to be enrolled in the study. Enrolled GPs will be instructed to invite all older adult (≥65 years) patients attending to the primary care consultation to participate in the study during until obtaining the sample size and being randomized according to the table for study entry. The geographical areas of work, the Districts, will be randomized for entry into exposed and unexposed groups. Those patients willing to participate in the study must give written informed consent and present willingness and ability to comply with the study requirements.

Exclusion criteria: Being acutely unwell in the last three weeks, and refuse to participate.

Two groups will be created with a minimum of 190 patients each, one of which will be composed from patients from the region of Aveiro, Coimbra and Guarda and the other from patients from the region of Castelo Branco, Leiria and Viseu. In the intervention group we will give enablement tools and talks with their GPs about how to issue the problem of polypharmacy. The information given in this group will result from the knowledge obtained in phase II in the shape of small leaflets and other information materials to be made according to the best practice, to be given and remembered at scheduled times to the intervention group.

Data collection

The collection of the data will occur in the beginning and end of phase II.

Patient's socio-demographic and clinical characteristics and medication will be registered using the same methodology as described in phase I.

Perception of medication will be evaluated using Portuguese general BMQ, the willingness to be deprescribed will be assessed with two open-questions (the same as phase II), and the quality of life we will assessed with EQ-5D.

For those not knowing how to write, someone of their knowledge, will fill in the open questions.

5 STUDY POPULATION

Older adult (≥65 years) patients attending to the primary care consultation in Portugal.

Exclusion criteria: Being acutely unwell in the last three weeks, and refuse to participate.

6 STUDY INTERVENTION

In the intervention group we will give enablement tools and talks with their GPs about how to issue the problem of polypharmacy.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 EFFICACY ASSESSMENTS

List and description of the procedures/evaluations to be used*:*

- Portuguese Beliefs about Medicines Questionnaire
  - For evaluation of the perception of medication
- EuroQol Five Dimensions Questionnaire
  - For assessment of the quality of life
- Two open-questions (one to assess the facilitators and the other to assess the barriers)
  - For assessment of the willingness to be deprescribed

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

No adverse events are expected to occur.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

The investigators' hypothesis is that the intervention will result in statistical higher willingness to be deprescribed and better quality of life.

8.2 SAMPLE SIZE DETERMINATION

According to the older adults population in the Centre of Portugal and with a 95% confidence interval and a maximum precision error of 5%, so a minimum of 380 patients should be recruited.

8.3 STATISTICAL ANALYSES

Descriptive statistics will be computed for all variables together with 95% CI whenever relevant and applicable. Associations between qualitative-independent variables will be tested using $\chi 2$ test. Comparisons between two or more independent groups regarding a quantitative variable are to be conducted using analysis of variance (ANOVA) or Kruskal-Wallis non-parametric test, if normality assumption is not met. ANCOVA may also be used to adjust for potential confounding factors. Associations between quantitative independent variables will be analysed using Pearson's or Spearman's correlation coefficient depending on normality assumption. All tests will be two-sided, considering a significance level of 0.05.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 CONFIDENTIALITY AND PRIVACY

Information will be treated in strict confidentiality to protect the privacy of patients. The investigators will have no access to the data of the patient, except the one provided by the GP meaning that the only person to know who is being studied is the GP.

Data will be electronically stored in a database specifically designed for this study using MS Access 2010. Data will be encrypted and password protected.

9.1.3 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Pedro Augusto Simões, Master degree, Doctor
University of Beira Interior
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9.1.4 PUBLICATION AND DATA SHARING POLICY

The investigators will publish the results in peer-reviewed journal. There is no provision for data sharing.

9.1.5 CONFLICT OF INTEREST POLICY

The investigators don't have any conflict of interest.

9.2 ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMQ	Beliefs about Medicines Questionnaire
CI	Confidence Interval
EQ-5D	EuroQol Five Dimensions Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PIM	Potentially Inappropriate Medication
START	Screening Tool to Alert Doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions

9.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

10 REFERENCES

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