Randomised, Controlled Trial of an Individual Deprescribing Intervention for Nursing Homes Residents.

Clinical Study Protocol

Study title in participants' documents	Étude d'une Intervention de Déprescription Individuelle en EMS (étude IDeI)
Study Type:	Clinical trial other than of a therapeutic product, transplant product or trial of transplantation.
Study Categorisation:	Risk category A
Study Registration:	The study will be registered with ClinicalTrials.gov; no registration number is available at the time of submission. In addition, this study will be registered with the Swiss National Clinical Trial Portal (KOFAM).
Study Identifier:	OLD-NH-IDeI-2018 NCT03655405
Sponsor-Investigator	Dr Anne Niquille Pharmacienne FPH, PhD Centre de Pharmacie Communautaire, Policlinique Médicale Universitaire, Rue du Bugnon 44 - 1011 Lausanne
Investigational Intervention:	Deprescribing-focused medication review
Protocol Version and Date:	Protocol version 2, date 27.08.2018

SIGNATURE PAGE

Study number	The study will be registered with ClinicalTrials.org; no registration number available at the time of submission.
Study Title	Randomised, Controlled Trial of an Individual Deprescribing Intervention for Nursing Homes Residents.

The Sponsor-Investigator, Investigators and trial Statistician have approved the protocol version 2, dated 27.08.2018, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the Swiss legislation.

Sponsor - Investigator:

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Pharmacist

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Place / Date

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Investigator:

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TABLE OF CONTENTS

STUDY SYNOPSIS

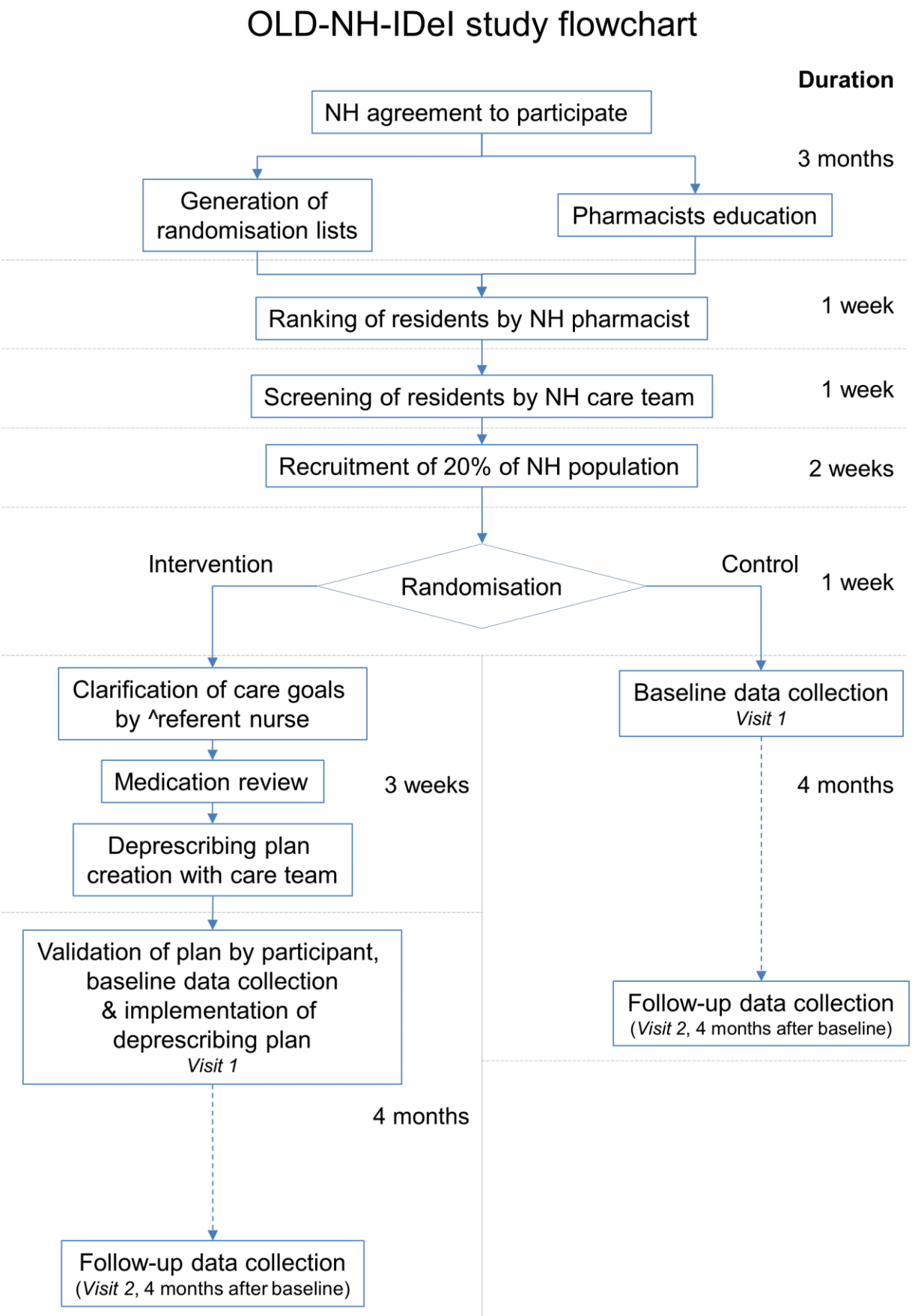
Sponsor-Investigator	Dre Anne Niquille, PhD Pharmacist Centre de Pharmacie Communautaire, Policlinique Médicale Universitaire, Rue du Bugnon 44 - 1011 Lausanne
Study Title:	Randomised, Controlled Trial of an Individual Deprescribing Intervention for Nursing Homes' Residents.
Short Title/Study ID:	OLD-NH-IDeI study
Protocol Version and Date:	Protocol version 2 of 27.08.2018
Trial registration:	The study will be registered with ClinicalTrials.org; no registration number available at the time of submission. In addition, this study will be registered with the Swiss National Clinical Trial Portal (KOFAM).
Study category and Rationale	As the study involves minimum risk for the participant and will be conducted under the constant supervision of health professionals, this study is deemed of risk category A.
Clinical Phase:	Not applicable to this study
Background and Rationale:	Older people residing in nursing homes (NH) are frequently polymedicated and often prescribed potentially inappropriate medications (PIMs). Deprescribing has been proposed as a way to reduce the number of drugs they receive and their exposure to harmful treatments. In the nursing homes of Vaud and Fribourg, physicians, nurses and pharmacists are already working together in quality circles to improve drugs use. This provides an excellent opportunity to implement a deprescribing intervention, using the collaboration already in place.
Objectives:	The primary study objective is to determine the effect of a pharmacist-led, deprescribing-focused medication review on the use of PIMs by NH residents. The main secondary objectives are to determine the safety of this intervention and its effect on the participants' quality of life.
Outcomes:	The primary outcome is the change in the number of PIMs used by participants between baseline and 4 months (end of follow-up). The main secondary outcomes are the mortality rate, hospitalisation rate, number of falls and quality of life measured with EQ-5D-5L. This intervention will also be evaluated on implementation outcomes.
Study design:	This study is a randomised, controlled trial.
Inclusion/Exclusion criteria:	This study will include residents from NHs of Vaud and Fribourg residing in institutions that already took part in a previous study, OLD-NH-QC-DeMo, where a NH-level intervention to promote deprescribing have already taken place. Residents aged 65 years or more, taking 5 or more medications daily and who reside in the NH since at least 4 months are eligible to participate. Potential participants will be excluded from recruitment if their physician judges that discussing deprescribing with them risks destabilising them.

Measurements and procedures:	The drug regimen, quality of life and common drug-related complaints will be assessed at baseline and after 4 months in both arms. Data collection will be made by NH pharmacist and nurses, after education by the investigators.
Study Intervention:	The intervention tested in this study is a medication review followed by the creation of a deprescribing plan. The review will be conducted by the NH pharmacist and focused on deprescribing of inappropriate medications. It's results will help the NH care team (physician, nurse and pharmacist) create a deprescribing plan for each participant. Once validated by the participant, this plan will be put into practice.
Control Intervention :	Participants allocated to the control group will be cared for by the NH care team as usual.
Number of Participants with Rationale:	18 NHs are eligible for participation, and we anticipate that half of them will agree to take part in the study. With an average of 50 beds per NH and the inclusion of 20% of residents, we expect that 106 participants will enrol across 10 NHs. We did not perform power calculation, as no data are available on the number of PIMs used by the 20% of residents taking the most drugs regularly.
Study Duration:	The expected duration for the study is 9 months, from October 2018 to June 2019. Data analysis will take place until the end of 2019.
Study Schedule:	October 2018 to June 2019
Investigators:	Prof. Olivier Bugnon Centre de Pharmacie Communautaire, Policlinique Médicale Universitaire, Rue du Bugnon 44 - 1011 Lausanne olivier.bugnon@hospvd.ch Tel : 021 314 48 42 / 43 (secretary) Damien Cateau Centre de Pharmacie Communautaire, Policlinique Médicale Universitaire, Rue du Bugnon 44 - 1011 Lausanne damien.cateau@hospvd.ch Tel : 021 314 48 46
Study Centre:	This study is monocentric; however, the intervention will take place in different NHs of the Cantons of Vaud and Fribourg.
Statistical Considerations:	Generalised linear mixed models will be used for the analysis of outcomes relative to individual participants; outcomes at the NH level will be analysed using t-tests or Mann-Whitney, according to distribution.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees,
CA	Competent Authority
CEC	Competent Ethics Committee
CER-VD	Commission cantonale d'éthique de la recherche sur l'être humain du Canton de Vaud
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DDD	Defined Daily Dose
GCP	Good Clinical Practice
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings
IIT	Investigator-initiated Trial
ITT	Intention to treat
NH	Nursing Home
PI	Principal Investigator
PIM	Potentially Inappropriate Medication
RCT	Randomised, Controlled Trial
SUSAR	Suspected Unexpected Serious Adverse Reaction

STUDY FLOW-CHART



1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Investigator

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1.4 Laboratory

No laboratory will be involved in this study.

1.5 Monitoring institution

Monitoring will be ensured by Charles Meier, a pharmacist at the Centre de Pharmacie Communautaire.

1.6 Data Safety Monitoring Committee

As defined in ICH's GCP guidelines, section 1.25 [1], the role of the data safety monitoring committee is *"to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial."*

The anticipated duration of the trial as a whole (9 months) and for individual participants (4 months) are short and extremely close: most participants will enter the study at the same time, and no intermediate data collection and analysis are planned. Thus, all participants will have entered the study before any individual participant completes it. As no intermediate data collection and analysis are planned, a data safety monitoring committee would not have the opportunity to review data and inform the sponsor on whether to continue, modify, or stop the trial. For this reason, no data safety monitoring committee will be constituted.

1.7 Other relevant Committee, Person, Organisation or Institutions

No other committee, person, organisation or institution other than the participating NHs will take part in this study.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The recruitment of participants will begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

This study will be registered with the ClinicalTrials.gov registry; registration is ongoing and no registration number is available at the time of submission. Registration will be completed before inclusion of the first patients.

In addition, this study will be registered with the Swiss National Clinical Trial Portal.

2.2 Categorisation of study

As this trial is not one of a drug, medical device, or transplant, it is classified as an "Other Clinical Trial", according to ClinO article 60.

Since all treatments alterations conducted must be judged as safe by the treating physician caring for each participant (see section 8.1.1, page 20) and will be conducted in a setting with constant monitoring, the risks are judged minimal by the investigators. The data collection methods involve no blood or tissue sampling, nor the collection of broad health-related data; the burden of the trial is thus deemed minimal. For these reasons, this study is of category A, according to ClinO article 61.1.

2.3 Competent Ethics Committee (CEC)

As this project will take place in the cantons of Vaud and Fribourg, the Commission cantonale d'éthique de la recherche sur l'être humain of Canton de Vaud (CER-VD) is competent. Investigators will submit the present study protocol to the CER-VD for approval. No patient will be recruited before reception of the written agreement of the CER-VD.

The end of the study will be reported to the CER-VD within 90 days of completion (last collection of data); the study report will be submitted within one year of completion. In case of premature study end or study interruption, the CER-VD will be informed within 15 days.

2.4 Competent Authorities

No approvals from other competent authorities are necessary for this research project, as it is of risk category A.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki [2], the guidelines of Good Clinical Practice (GCP) issued by ICH [1], as well as the Swiss Law and Swiss regulatory authority's requirements. The CER-VD will be informed about

study end, in agreement with the Swiss law; given the duration of the study, no interim reports are planned.

2.6 Declaration of interest

The sponsor, investigators and statistician declare no conflicts of interest, be they intellectual, financial or of any other kind.

2.7 Patient Information and Informed Consent

Each participant, or her/his legal representative if applicable, will be informed of the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant or his/her representative will be informed that the participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information and consent form (see Annex 1) describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. For participants unable to consent because of cognitive impairment, the consent of their legal representatives will be necessary (see Annex 2). Participants or their representative will be given at least 24 hours to review the documents before deciding to enrol or not in the study.

The formal consent of a participant, or of her/his representative, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The participant or her/his representative, after being given enough time to read and consider the statement, will read and date the informed consent form, and will be given a copy of the signed document. The consent form will also be signed and dated by the investigator's representative at the same time as the participant sign, and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study are considered confidential and will not be disclosed to third parties. Subject confidentiality will be further ensured by the use of code numbers in all collected data.

For data verification purposes, authorised representatives of the Sponsor or of the CER-VD may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely if the NHs where the study takes place express concerns regarding the safety of the participants. The CER-VD will be informed within 15 days in case of premature termination.

2.10 Protocol amendments

Substantial amendments proposed by the sponsor or investigators will only be implemented after approval of the CER-VD.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CER-VD. Such deviations will be documented and reported to the sponsor and the CER-VD as soon as possible.

All non-substantial amendments will be mentioned in the final report to the CER-VD.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Polypharmacy, or the use of five or more concurrent medications, is frequent among the elderly [3], and especially those residing in NHs [4]. While appropriate in many cases, especially when multiple concurrent drugs are required to adequately treat a health condition, for example diabetes, polypharmacy has been shown to increase the risk of adverse drugs events (ADE) [5] and may lead to decreased health outcomes and quality of life [6].

Inherent risks posed by polypharmacy are amplified by the use of potentially inappropriate medications (PIMs), drugs whose potential for harm surpass their expected benefits [7]. PIMs have been a major concern for the geriatric care community since the early 1990s, with the publication of Beers' seminal paper [8]. Their use is associated with worse health outcomes, more frequent hospitalisation and increased risk of death [9, 10]. Elderly people residing in NHs are frequently exposed to such drugs: a meta-analysis by Morin et al [11] found that at least 43% of NH residents worldwide receive at least one PIM each year; in Europe, this figure goes up to 49%. A study conducted by the Helsana health insurance showed that Swiss NH residents are not better off than their European counterparts: at least 45% of NH residents insured by Helsana receive at least one PIM every quarter [12].

In the past years, the concept of deprescribing emerged in the literature as a potential way to address both polypharmacy and PIMs. Defined as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" [13], deprescribing has the potential to improve elderly people's well-being and health outcomes [14]. A recent meta-analysis indeed concluded on the positive effect of patient-centred deprescribing intervention on mortality [15]. Since the first occurrence of the term in the scientific literature[16], deprescribing has gathered interest in various countries, such as Australia[17], Canada[18], the United States[19], New Zealand[20], Belgium[21], the Netherlands [22, 23], and France[24]. Outside of the academic world, deprescribing is also gaining traction, with initiatives such as guidelines published by the Canadian Deprescribing Network [25] or the MedStopper online tool [26].

In Switzerland, preoccupations relative to the medication regimen of NH residents are present as well: the not-for-profit organisation *patient safety switzerland* launched, in 2016, an initiative called *progress! La sécurité de la médication en EMS* (Drug safety in NH) [27]. This initiative led to the publication in 2018 of a preliminary report highlighting the need for concrete solutions to be investigated regarding polypharmacy and the use of inappropriate medications by NH residents [28]. To our knowledge, however, apart from the QC-DeMo study (see below), no initiatives have been launched to try to implement deprescribing in the Swiss NHs. One of the reasons could be that, to be successful, deprescribing must rely on interprofessionnal collaborations [29] that may not be as developed in Switzerland as in other countries. Such collaborations do however exist locally in Switzerland: since 2002 in the canton of Fribourg [30] and 2010 in the canton of Vaud, pharmaceutical assistance programmes (PAP) are in place in the NHs of those cantons. These programmes consist of interprofessional quality circles bringing together physicians, nurses and pharmacists on a regular basis, to improve medications prescribing and use in the NH through the building of local treatment consensus. These existing and successful, local collaborations are an opportunity to develop deprescribing in the Swiss NHs.

This study takes part in a larger research program entitled "Opportunities and Limits to Deprescribing in Nursing Homes" (OLD-NH), funded by the Swiss National Fund for Scientific Research, through the National Research Programme 74 "Smarter Health Care" [31]. The OLD-NH program started with a first phase consisting of two qualitative studies exploring the context surrounding the withdrawal of medications in the Swiss NHs. The first study was focused on the professionals' point of view (protocol submitted to the CER-VD in 2016 and declared as out of the HRA's scope), and the second on the NH residents' perspectives (protocol 2017-00211 accepted on 10.04.2017 by the CER-VD). Both these studies have been completed and their results informed the design of the present study.

The second phase of OLD-NH consists of two interventional studies; the first one, OLD-NH-QC-DeMo, is ongoing (protocol submitted to the CER-VD in 2017 and confirmed as out of HRA's scope, Req-2017-01009). This first study is a RCT of a Quality Circle Deprescribing Module (QC-DeMo), in which participating NHs allocated to intervention held an interprofessional quality circle bringing together nurses, pharmacists and physician, with the goal of defining a local deprescribing consensus focused on the most widely used PIMs. The physicians were then free to implement or not the deprescribing consensus in residents receiving the targeted PIMs, based on their clinical judgement.

The study described in this protocol is the second in the intervention phase of OLD-NH. It aims to test the effects of an additional intervention in the NHs who already held the QC-DeMo intervention and implemented the deprescribing consensus.

3.2 Intervention to be investigated

The intervention investigated is a pharmacist-led medication review, focused on the deprescribing of inappropriate medications, resulting in the creation, validation and application of an individual deprescribing plan by the NH care team.

After performance by the pharmacist, the results of the medication review will be discussed with the clinical staff of participating NHs (pharmacist, treating physician, and head nurse), with the goal of producing a treatment modification plan tailored to the needs of each participant (deprescribing plan). The deprescribing plan will then be discussed with the participant or her/his representative before being enacted.

Details of the intervention are presented in section 8 (page 20).

3.3 Preclinical Evidence

Not applicable to this study.

3.4 Clinical Evidence to Date

Deprescribing has already been shown to be an effective way to reduce the number of drugs used by older people living in NH: an Australian study randomised 95 participants to a deprescribing intervention or usual care [32]. Participants in the intervention group received a lower number of drugs (-2.0 ± 0.9) 12 months after intervention than participants in the control group. This reduction did not increase mortality, falls or hospital admissions, and did not negatively influence cognitive functions, quality of life or sleep.

A 2016 systematic review found that deprescribing could be safely enacted in older people [15]: in randomised trials, individual deprescribing interventions led to a lower mortality, without lowering cognitive functions, increasing the risk of falls, or increasing the occurrence of adverse events.

Studies indeed show that enacting deprescribing induces very little acute adverse events: in a study of deprescribing in 422 NH residents in the United Kingdom [33], only seven adverse events occurred following the discontinuation of more than 700 medicines. None of those seven events led to significant harm to the residents; the measures taken to resolve these events included the reinstatement of the stopped medication, the treatment of a urinary tract infection, the adaptation of an insulin regimen, and closer monitoring of blood pressure. In the previously cited trial of deprescribing in Australian NHs [32], there were no differences in the occurrence of adverse events between the intervention and control groups.

These findings were confirmed by a recent study of deprescribing in Dutch NHs residents [23]: reducing the number of medication prescribed to 159 NH residents did not worsen their clinical condition or their quality of life, compared to 193 residents which were not subject to the deprescribing intervention.

In case of acute adverse reaction after the withdrawal of a drug, corrective measures, including reinstating the treatment, can be put into practice extremely quickly given the close monitoring of residents in NHs. The risks of stopping long-term preventive treatments (for example cholesterol-lowering drugs) are less well known; however, the benefits of such preventive drugs in the very elderly are also not well established: most preventive drug have not been studied in this population [6]. The benefits of these treatments in the adult population are, in general, expected to occur in a timeframe longer than the average life expectancy of NH residents: the mean duration of stay in the NHs of Fribourg and Vaud was less than 3 years in 2015 [34].

3.5 Dose Rationale

Not applicable to this study.

3.6 Explanation for choice of comparator

The intervention will be compared to usual care: participants affected to the control group will still benefit from the interprofessional collaboration already in place, including the effects of the deprescribing consensus resulting from the NH's participation in OLD-NH-QC-DeMo (see page 9).

This comparator was chosen because the goal of this study is to investigate the effects of an individual deprescribing intervention following the NH-wide approach evaluated in the QC-DeMo study, from which residents of the whole NH benefit.

3.7 Risks / Benefits

As discussed previously (see section 3.4 before), deprescribing inappropriate medication lead to few adverse events and does not worsen the clinical condition or quality of life of older people; it can also lead to a reduction in mortality.

In addition to these reassuring results from the literature, the participants' treating physicians will remain in complete control of their treatment (see section 8.1.1, page 20). The risks incurred by residents taking part in this study is thus deemed minimal, and no greater than usual care.

No threat to the study (competing trial, change in the regulatory framework, or otherwise) is anticipated.

3.8 Justification of choice of study population

Older people living in NHs were chosen as study population because of the high number of drugs they receive and the high rate of PIMs use [35] among them, which make them more likely to benefit from a deprescribing intervention. In addition, the good collaboration already in place between physicians, nurses, and pharmacists in the NHs taking part in the QC-DeMo study provide an ideal ground to implement deprescribing at an individual level.

The broad inclusion criteria (see section 7.1, page 19) for this study imply the possibility that NH residents incapable of judgement because of cognitive impairment, for example suffering of dementia, will be included in the study. These residents are amongst the most vulnerable, but their inclusion is essential to the conduct of this study, as they constitute a large proportion of the NH population: in Europe, over 60% of NH residents exhibit cognitive impairment [36], and it is estimated that 2/3 of residents in Swiss NHs are affected by a dementia-like pathology [37]. While the proportion of residents with cognitive impairment is not precisely known in Vaud or Fribourg, the last available statistics on the subject indicate that at least 40% of NH residents are diagnosed with a dementia [38]. In 2016, 42% of NH beds in Vaud were in institutions with a psychogeriatric mission [39]. No data are available for the canton of Fribourg, but we have no reason to believe that the situation is different. Excluding residents presenting a cognitive impairment would greatly reduce the external validity of the findings of this study, thus limiting their transferability.

For cognitively impaired residents, their legal representative will have to consent to participation. Representatives will be contacted directly by the NH team and be given the same explanations as NH residents capable of judgement (see section7.2, page 19 and Annex 1). A specific information and consent form has been prepared for this situation (Annex 2).

We have a priori no idea of how eligible residents with cognitive impairment rending them unable to communicate could express their disagreement to participate to the study. However, their cognitive state will be taken into account by the healthcare team and their representative to validate their participation, and to establish the deprescribing plan. In case of deprescribing, any sign of discomfort or symptoms related to the withdrawn drug will be addressed and the reintroduction of stopped drugs remain possible at any time.

4. STUDY OBJECTIVES

4.1 Overall objective

The purpose of this study is to evaluate the effects of a deprescribing intervention, a pharmacist-led, deprescribing-focused medication review followed by the creation of a deprescribing plan with the NH care team, on the use of PIMs in select NHs, as well as its implementation. The study will be conducted in NHs included in the intervention arm of the OLD-NH-QC-DeMo study (see section 3.1, page 13), as the effects of the intervention tested here is cumulative with the deprescribing intervention tested at the NH level in the QC-DeMo study.

4.2 Primary objective

This study seeks primarily to determine the effect of the intervention on the number of PIMs used by NH residents, compared to usual care.

4.3 Secondary objectives

Secondary objectives are to evaluate the effects of the medication review on the participants' health-related quality of life and the prevalence of common complaints related to drugs frequently used by elderly people.

4.4 Implementation objectives

Implementation objectives are to assess the acceptability, adoption, feasibility, appropriateness, penetration, fidelity, sustainability and costs of the intervention.

4.5 Safety objectives

This study aims to assess the safety of the deprescribing intervention in terms of mortality, hospitalisation, falls and the use of restraints.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary endpoint of the study is the change in the number of PIMs prescribed to participants between baseline and 4 months. It was chosen because the main effect of the intervention will be to reduce the number of inappropriate medications prescribed to participants.

5.2 Secondary Outcomes

Secondary outcomes are:

1. The change between baseline and 4 months in the number of potentially inappropriate Defined Daily Doses (DDDs) prescribed to participants;
2. The change between baseline and 4 months in the number of regular drugs prescribed to participants;
3. The change between baseline and 4 months in the number of regular DDDs prescribed to participants;
4. The number of new drugs prescribed as a result of the intervention;
5. The change in health-related quality of life between baseline and follow-up, measured with EQ-5D-5L[1] [40] (see Annex 4 for the questionnaires);
6. The change in the number of common drug-related complaints presented by the participant between baseline and follow-up (see Annex 5 for the questionnaire on common complaints);

5.3 Implementation outcomes

Implementation outcomes are:

1. The number of pharmacist's propositions validated by the care team;
2. The rate of pharmacist's propositions validated by the care team;
3. The number of validated propositions accepted by the participants or their relatives;
4. The rate of validated propositions accepted by the participants or their relatives;
5. The number of accepted propositions implemented within 4 months;
6. The rate of accepted propositions implemented within 4 months;
7. The drug reintroduction rate;
8. The satisfaction of the participants and the healthcare professionals, measured using ad-hoc questionnaires;
9. The perception of the intervention of participants' relatives', evaluated using an ad-hoc questionnaire;
10. The time needed to enact the whole intervention;
11. The delay between the acceptation of validated propositions by the participant and their implementation;
12. The impact of the diminution of the volume of PIMs on medications costs;
13. The cost of training healthcare professionals for the intervention.
14. The change in the burden of care for NH staff, measured using the NeuroPsychiatric Inventory – Nursing Home (NPI-NH) [2] (Annex 6).
15. The study refusal rate at recruitment stage and the number of participants withdrawing from the study;
16. The number of calls received by of the Centre de Pharmacie Communautaire Pharmaceutical Assistance team (see section 8.1.1, page20).

[1]Authorisations for the use of the EQ-5D-5L questionnaires for auto-administration and for administration by proxy have been granted by the EuroQol Group.
[2] Authorisation for the use of the NPI-NH questionnaire has been granted by the copyright holder.

5.4 Safety Outcomes

Safety outcomes are:

1. The mortality rate, defined as the number of participant having died between baseline and completion of the follow-up period, divided by the total number of participants;
2. The hospitalisation rate, defined as the number of participant having been hospitalised between baseline and completion of the follow-up period, divided by the total number of participants;
3. The number of days spent in hospital between baseline and completion of the follow-up period;
4. The causes of hospitalisation;
5. The number of falls between baseline and follow-up;
6. The proportion of participants having experienced at least one fall;
7. The number of falls in participants having fallen at least once;
8. The number of days where restraints measures have been used.

5.5 Demographic information

In order to describe the population of the study, the year of birth of participants, their gender and their date of entry in the NH will be collected.

6. STUDY DESIGN

6.1 General study design and justification of design

This study is a randomised, controlled trial of a deprescribing intervention, consisting of a pharmacist-led, deprescribing-focused medication review, resulting in the creation, validation and application of a personalized deprescribing plan by the NH care team. The study will take place in NHs already included in the intervention arm of the OLD-NH-QC-DeMo study (see section 3.1, page 13), as it aims to test the cumulative effect of the medication review and the deprescribing quality circle tested at the NH level in the QC-DeMo study. All stakeholders in the NH will have to agree for the NH to take part in the IDeI study; agreement will be documented in writing (

The participants will be residents of the participating NHs which are prescribed the most drugs (see chapter 7, page 19 for details), and thus most at risk of PIM use [41-44]; if NH care team judges that discussing the possibility of deprescribing with a specific resident will destabilise her/him, this resident will be excluded from participation. The residents will be offered the option to participate in descending order of number of drugs prescribed (from most drugs prescribed to least), based on a ranking prepared by the NH pharmacist. After inclusion, participants will be randomly allocated to either the control of intervention groups, based on pre-specified, NH-specific randomisation lists (see section 6.2.1 below for details). Inclusion will continue until 20% of the residents of the NH have been included. An estimated 100 residents will be included in the study, based on a mean of 50 residents per NH and 10 NH participating in the study.

After randomisation, the record of participants allocated to the intervention group will be searched by the nurse responsible for the study in the NH ("study nurse") for clearly stated objectives of care. If no objectives are present in the record, the referent nurse for this participant will be interviewed by the pharmacist to clarify these objectives. The referent nurse will also provide a list of drugs taken by the participant without supervision of the NH staff (self-medication). Using this information and the content of the participant's records in the NH and in the pharmacy, the pharmacist will then conduct the medication review according to the formation received; the medication review process is described in chapter 8, page 20. Based on the results of the medication review, a deprescribing plan will be decided by the NH care team (head nurse, physician(s) responsible for the resident(s), and pharmacist). This plan will also include proposition for the introduction of new drugs if prescription omissions (sub-optimal treatment) are detected by the medication review. Each item of this plan will then be presented for validation to the participant or her/his representative. Once validated, baseline data collection will occur and the deprescribing plan will be implemented.

Participants allocated to the control group will receive usual care. Baseline data collection for them will occur after inclusion. Follow up data collection will occur 4 months after baseline data collection for both groups. The duration of the study will be 4 months for the participants allocated to the control group. For participants allocated to the intervention group, the realisation of the medication review by the pharmacist, the discussion of its results with the treating physicians, the creation of the deprescribing plan, and its discussion with the participant will induce a delay before baseline data collection, estimated of maximum 2 months; thus, the total duration of the study could be up to 6 months in this group. Participants allocated to both groups will be monitored as usual by the NH care team (treating physician and nurses) during and after the duration of the study. In addition, the NH care team will mention specific monitoring measures in the deprescribing plan, according to the drugs being deprescribed and the clinical situation of the participant.

6.2 Methods of minimising bias

6.2.1 Randomisation

Participants will be randomised between the intervention and control groups at the time of inclusion, in a 1:1 ratio at the level of the NH. For each NH agreeing to participate, a randomisation list of length equal to 20% of the number of beds of the NH will be generated by the investigators, using the tool provided at www.randomization.com. These lists will be created using randomly permutated blocks, to ensure a relative equilibrium between groups, even in case of incomplete inclusion in the NH. The lists will then be loaded in the REDCap randomisation module for this institution.

Allocation will be made at the end of completion of the inclusion CRF by the NH nurse (see Annex 10).

6.2.2 Blinding procedures

Given the nature of the intervention, NH staff (pharmacist, physician and nurses) cannot be blinded to the allocation. As the data collected differ between participants in the intervention and control groups,

investigators will not be blinded either.

Thus, only the statistician will be blinded: he will not have access to the raw data, and all data extracted for analysis will be communicated to him with groups coded A and B. Unblinding will occur only after analysis completion. Descriptive statistics will be performed after completion of the primary analysis, as the data relative to the treatment changes enacted in the intervention group will allow the differentiation of the groups by the statistician.

6.2.3 Other methods of minimising bias

Assessment of quality of life will be made using the EQ-5D-5L, which has been validated in large studies across Europe [45], and tested in NH residents with cognitive impairment [46].

Assessment of the burden of care will be made with the NeuroPsychiatric Index – Nursing Home, a validated questionnaire for the assessment of changes in patient's behaviour and the impact of said changes on carer and staff [47].

6.3 Unblinding Procedures

As participants, NH care teams and the investigators will not be blind to the allocation, no unblinding procedure is necessary: the NH care team, without regard to the allocation of participants, will deal with all eventual adverse events resulting from the intervention. In addition, as no intermediate analyses are planned, no event will trigger the need for unblinding before study completion.

7. STUDY POPULATION

The study will be conducted in the NH allocated to the intervention group of the OLD-NH-QC-DeMo study (see section 3.1, page 13 for details and Annex 7 for the list of eligible NHs).

7.1 Eligibility criteria

All residents of the NHs mentioned in Annex 7 are eligible for participation if:

- They are 65 years old or older;
- They take 5 or more regular drugs;
- They have been resident of the NH for at least 4 months at inclusion;

If the NH head nurse and a resident's treating physician judge that discussing the possibility of deprescribing will lead to their destabilisation, this resident will be excluded from recruitment.

7.2 Screening and recruitment

Screening for participants will take place in the NH and will be performed by the NH care team (treating physician, head nurse and pharmacist). It will consist of two phases: ranking and screening.

Ranking: pharmacists will rank the residents in decreasing order of number of regular drugs prescribed, based on the treatment regimen recorded in the patients' file at the time of ranking.

Screening: with the ranking performed, the NH care team will decide which residents will be excluded from recruitment, as the discussion of deprescribing with them could destabilise them. After screening, a list of residents eligible for recruitment, ranked in decreasing order of PIMs use, will be prepared by the pharmacist.

Recruitment of residents will be made by the nurse responsible for the study in the NH, using the information and consent form (Annex 1 and Annex 2). Participation will initially be offered to a number of residents equal to 20% of the capacity of the NH (number of beds); residents or their representative will be given at least 24 hours of reflexion to decide whether to enter the study. For every resident declining to enter, participation will be offered to the next eligible resident, following the ranking list. Recruitment will continue until 20% of the population of the NH has been recruited, or until participation has been offered to all residents.

No compensation, monetary or otherwise, will be offered to participants.

7.3 Assignment to study groups

After recruitment, participants will be randomised between control and intervention groups. Randomisation will be made using the inclusion CRF; after randomisation, the allocation group will be recorded in a NH-specific list, to be stored with the study documents. This list will comprise the name of the

participants, their identifying code and allocated group. Allocation will be communicated to the treating physician and the participants.

7.4 Criteria for withdrawal of participants

Participants, or their representative if applicable, can withdraw from the study at any time, without justification.

The NH care team can withdraw participants from the study if they estimate that the safety of the participant is not guaranteed anymore. However, we do not anticipate this to happen: if the clinical status of the particiapnt does not allow for treatment alterations, the NH care team will simply not enact the planned treatment modifications. . In addition, a stopped or tapered drug can be reintroduced at any time during the study. The treating physician will indeed remain in control of the participant's care at all time.

Participants withdrawing during the study will not be replaced.

8. STUDY INTERVENTION

8.1 Identity of Investigational Intervention

8.1.1 Experimental Intervention

The intervention tested in this study is a medication review focused on deprescribing, followed by the construction and implementation of a deprescribing plan. A medication review is "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes." [48] This review will take into account the clinical situation of the participant, including pathologies, disabilities, current drug regimen, and her / his therapeutic and life goals.

The responsible pharmacist of the NH where the participant resides will perform the medication review. They will receive education on the realisation of medication review prior to the study by attending the "Medication review" module of the Certificate in Advanced Studies "Pharmacie Clinique: prestations dans les soins de base" [3]. Through the study, pharmacists will be able to solicit the clinical advices of the *Centre de Pharmacie Communautaire* Pharmaceutical Assistance team for performing of the reviews.

The results of the review will be structured propositions of drug regimen modification, according to the clinical situation of participant and the risk/benefit balance of each prescribed drug for her-/him-self. These propositions will include regimen modifications (modification of galenic forms or administration time or frequency), withdrawal or tapering of non-beneficial drugs (deprescribing), and introduction of new drugsin case of prescribing omission (sub-optimal treatment). These propositions will be discussed with nurse and treating physician of the NH, with the goal to create a deprescribing plan that will be proposed to the participant. The propositions resulting from the review and the deprescribing plan will be prepared following the model documents in Annex 8.

8.1.2 Comparator

The comparator will be usual care, as routinely provided in the NHs where the study takes place.

8.1.3 Packaging, Labelling and Supply (re-supply)

Not applicable to this study.

8.1.4 Storage Conditions

Not applicable to this study.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

See section 8.1.1 and Annex 8 for details on the intervention.

8.2.2 Control Intervention

See section 8.1.2 for details on the comparator.

[3]https://www.unige.ch/formcont/cours/cas-pharmacie-clinique-prestations-dans-les-soins-de-base-2018

8.3 Dose / Device modifications

Not applicable to this study.

8.4 Compliance with study intervention

As part of the monitoring, (see section 12.3, page 30), the investigators will conduct a weekly check of the progress of inclusion, intervention and data collection. Regular consultation of the CRFs and uploaded documents will ensure that any deviation from the protocol are detected early and that corrective measures can be implemented in a timely manner.

8.5 Data Collection and Follow-up for withdrawn participants

No further data collection will occur for participants withdrawing from the study. Data already collected will be anonymised and used in the analysis.

Withdrawn participants will be monitored as usual by the NH care team.

8.6 Trial specific preventive measures

All interventions part of usual care deemed necessary by the NH care team are allowed before and during the trial, in both arms. Specifically, modifying or stopping a treatment is allowed in the patients allocated to the control group, and restarting a withdrawn treatment is allowed in the intervention group.

The interventions other than the ones specified in the deprescribing plan will not be collected, as they are of no interest to the study outcome and would impose too big a workload on the NHs care team.

8.7 Concomitant Interventions

See section 8.6

8.8 Study Drug / Medical Device Accountability

Not applicable to this study.

8.9 Return or Destruction of Study Drug / Medical Device

Not applicable to this study.

9. STUDY ASSESSMENTS

9.1 Study flow chart

See page 9 for the study flow-chart.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome is the change in the number of PIMs between baseline and 4 months. To identify PIMs, NH pharmacists will use the online implementation of the STOPP/START tool provided by the French *Caisse Nationale d'Assurance Maladie*, found at https://aide-a-la-decision.ameli.fr/revision-ordonnance/ [4]. This tool requires the pharmacist to enter the patients' pathologies and treatments, but no other information. No information are stored on the website once the analysis has been performed. An example of such analysis can be found in Annex 9.

The pharmacist will then upload the PIM report and the participants' treatment plan into the CRF (see Annex 10). The investigators will then transcribe the medication plan for each participant into an investigator-reserved CRF (see Annex 11), including the PIM status of each treatment. This analysis will be made at baseline and 4 months.

The total number of PIMs at every time point for each participant will then be computed by the investigators, and difference in the number of PIMs between baseline and follow-up computed for each participant.

[4] Authorisation for the use of this tool has been granted by its co-conceptor, Dr Pierre-Olivier Lang.

9.2.2 Assessment of secondary outcomes

9.2.2.1 Change in the number of potentially inappropriate DDDs

The number of DDDs for each treatment of each participant will be computed taking into account the regimen (once a day, twice a day, etc.), the dose prescribed, and the DDD for the specific medication, as specified by the WHO Collaborating Centre for Drug Statistics Methodology [5]. The PIM status for each treatment will then be assessed as for the primary outcome, and the change between baseline and 4 follow-up computed. Some drugs and specific preparations will be excluded from this analysis, as no DDDs can be computed for them. The exclusion list can be found in Annex 15.

9.2.2.2 Change in the total number of regular drugs

The total number of regular drugs, without regard for PIM status, will be extracted from the medication plans collected for the assessment of the primary outcome. Regular drugs are defined as drugs with a fixed administration schedule, i.e. not "reserve" drugs. The change between baseline and follow-up will then be computed.

9.2.2.3 Change in the total number of regular DDDs

The total number of regular DDDs will be computed as previously described (see 9.2.2.1), without regard for PIM status, and the change between baseline and follow-up calculated.

9.2.2.4 Change in health-related quality of life (using EQ-5D-5L)

The results of the quality of life questionnaire for each quality of life dimension, as well as the measurement on the visual analogue scale, will be extracted from the questionnaire uploaded at baseline and follow-up in an investigator-reserved CRF (see Annex 12). The total score for each visit and the change between baseline and follow-up will then be computed by the investigators.

9.2.2.5 Change in the number of common complaints

The number of common complaints will be extracted from the questionnaires collected at baseline and follow-up, using an investigator-reserved CRF (see Annex 13), and the change between baseline and follow-up calculated for each participant.

9.2.3 Assessment of implementation outcomes

9.2.3.1 Number and rate of pharmacist propositions validated by the care team, of validated propositions accepted by the participants, and of accepted propositions implemented within 4 months.

Those 6 outcomes will be computed from the information provided on the deprescribing plans at baseline and follow-up.

9.2.3.2 Drug reintroduction rate

The drug reintroduction rate will be computed by dividing the number of drugs having be restarted at follow-up by the total number of drugs having been stopped.

9.2.3.3 Satisfaction of the participants

Ad-hoc short questionnaire currently in development

9.2.3.4 Satisfaction of healthcare professionals

Ad-hoc short questionnaire currently in development

9.2.3.5 Perception of the intervention by participants' relatives

Ad-hoc short questionnaire currently in development

9.2.3.6 Time needed for the implementation of the intervention;

Ad-hoc short questionnaire currently in development

9.2.3.7 Delay between the acceptation of validated proposition by the participant and their implementation

The time taken for implementation of accepted propositions will be extracted from the deprescribing plans at baseline and follow-up.

[5]https://www.whocc.no/atc_ddd_index/

9.2.3.8 Impact of the intervention on drug costs;

The monthly cost of treatment for both baseline and follow-up drug treatment will be calculated based on the public price of prescribed drug on December 31st, 2018, taking into account the dose regimen. The impact of the intervention on drug costs will then be computed by subtracting the baseline costs from the follow-up for each participant.

9.2.3.9 Cost of training healthcare professionals for the intervention.

The cost of training will be calculated by multiplying the number of hours spent in training by participating pharmacists by the mean cost of employment of a pharmacist in the canton of Vaud (information to be provided by the Société Vaudoise de Pharmacie).

9.2.3.10 Neuro-Psychiatric Inventory – Nursing Home

The NPI-NH questionnaire will be extracted using an investigator reserved CRF (see Annex 14), the score will be calculated for each visit, and the difference in NPI-NH score computed by the investigators.

9.2.3.11 The study refusal rate at recruitment stage and the number of participants withdrawing from the study;

The result of each proposition to join the study will be recorded on the list of eligible residents prepared by the pharmacist (see section 7.2, page 19). Participants withdrawing from the study will be recorded on the follow-up CRF (see Annex 10).

9.2.3.12 The number of calls received by of the Centre de Pharmacie Communautaire Pharmaceutical Assistance team (see 8.1.1)

The number of calls relative the IDeI study will be extracted post-hoc from the monitoring system of the CPC. No participant information will be provided to or collected by the CPC Pharmaceutical Assistance team.

9.2.4 Assessment of safety outcomes

9.2.4.1 Mortality rate

All deaths will be recorded by the NH nurse responsible for the study, using the follow-up CRF. The mortality rate will then be computed by the investigators.

9.2.4.2 Hospitalisation rate

All hospitalisations will be documented by the NH nurse using the follow-up CRF, by reporting the beginning and end dates for each hospital stay. If no hospital stay occur during the trial period, the follow-up CRF will be completed accordingly. Elective hospitalisations will be excluded from analysis. The number of participants having been hospitalised will then be computed, and the hospitalisation rate calculated.

9.2.4.3 Number of days spent in the hospital

Using the dates entered in the follow-up CRF, the total number of days spent in the hospital will be computed.

9.2.4.4 Causes of hospitalisation

Causes of hospitalisation will be reported in the follow-up CRF.

9.2.4.5 Number of falls

The number of falls having occurred to each participant will be reported in the CRF for follow-up data collection. The number of falls for each group will then be computed by the investigators.

9.2.4.6 Number of participants having fallen

The number of participants having fallen will be computed by investigators using data on the number of falls.

9.2.4.7 Number of falls in participants with at least one fall

The number of falls having occurred to participants that have fallen at least once will be computed by the investigators.

9.2.4.8 Number of days with use of restraints

The number of days with use of restraints will be reported in the follow-up CRF. Restraints measures are defined as the use of mechanical restraints (bed barriers, bindings) or movement detectors placed in the participants' room (alarm bedmat).

9.2.4.9 Adverse events

See section 10, page 26, for the reporting of adverse events.

9.2.4.10 Laboratory parameters

No laboratory values will be collected.

9.2.4.11 Vital signs

No vital signs will be collected.

9.2.5 Assessments in participants who prematurely stop the study

In case of participant death before completion of follow-up, the follow-up CRF (staged for completion at visit 2) will be completed within 7 days by the pharmacist and nurse. For the assessment of the treatment plan regarding PIM status, the pharmacist will take into account the treatment plan of the day preceding death. No information will be collected regarding quality of life and common complaints.

If a participant is hospitalised at the date of the follow-up visit, the same procedure as for the participant having died is applied. The treatment plan of the day preceding the hospitalisation will be taken into account.

If a participant wishes to stop the study before the follow-up visit, she/ he will be offered to complete the quality of life and common complaints questionnaire before exiting the study.

9.3 Procedures at each visit

As not all NH nurses and pharmacists have laptop computers or tablets at their disposal to perform the various questionnaires at each visits, the questionnaires will be completed in paper form with the participant or her/his representative, and uploaded into the CRF after visit completion. Transcription of uploaded documents will be made by the investigators into specific CRFs.

9.3.1 Visit 1: Baseline data collection

Timeframe: immediately after inclusion for control group; at the time of implementation of the deprescribing plan for the intervention group.

Action performed with the participant:

- Completion of the baselineEQ-5D-5L questionnaire (using the paper version), by the pharmacist and the nurse, in presence of the participant or her/his representative;
- Completion of the baseline common complaints questionnaire (see Annex 5);
- Planning of the follow-up visit.

Action performed after the visit, in the absence of the participant:

- Upload of the baseline EQ-5D-5L questionnaire into the CRF;
- Upload of the baseline common complaints questionnaire into the CRF;
- Upload of the current medication plan into the CRF;
- Performing and upload of the PIM assessment, as described in section 9.2.1;
- Upload of the deprescribing plan (see Annex 8) into the CRF;
- Completion of the NPI-NH questionnaire (see Annex 6) by the nurse referent for the participant, and upload by the pharmacist into the CRF.

9.3.2 Visit 2: Follow-up data collection

Timeframe: 4 months (16 weeks) after visit 1.

Action performed with the participant:

- Completion of the follow-up EQ-5D-5L questionnaire (using the paper version), either by the participant or her/his representative;
- Completion of the follow-up common negative symptoms questionnaire (see Annex 5);

Action performed after the visit, in the absence of the participant:

- Completion of the CRF part regarding death, falls and hospitalisation;
- Upload of the follow-up EQ-5D-5L questionnaire into the CRF;
- Upload of the follow-up common complaints questionnaire into the CRF;
- Upload of the current medication plan into the CRF;
- Performing and upload of the PIM assessment, as described in section 9.2.1;
- Upload of the updated deprescribing plan (see Annex 8) into the CRF;
- Completion of the NPI-NH questionnaire (see Annex 6) by the nurse referent for the participant,

and upload by the pharmacist into the CRF.

9.3.3 Collection of implementation data

The collection of implementation-specific data (satisfaction with the intervention, perception of participants' relatives, etc.) will happen after conclusion of follow-up. Ad-hoc questionnaires will be used for the collection of this information. Questionnaires provided to the participants' relatives about their perception of the intervention (see section 9.2.3.5, page 22) will include the participant's identification code, to enable the investigators to link these information to the objective data collected on the participant. No health-related data will be collected at this stage.

10. SAFETY

10.1 Definition and assessment of (serious) adverse events and other safety related events

As the intervention trialled in this study is not specific to a single drug or drug class, no specific Adverse Events (AEs) can be predicted: potential AEs depend on the drugs having been stopped and the participant's health status.

Adverse Events will thus be defined as any unfavourable and unintended sign, symptom, or disease for which a causal relationship with the intervention cannot be excluded.

Serious Adverse Events are defined as AEs that:

- result in death,
- are life-threatening,
- require in-patient hospitalization, or
- result in persistent or significant disability/incapacity [6].

SAEs will be followed by the NH team until resolution.

10.1.1 Assessment of Causality

Causality will be assessed by the Investigators, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after reintroduction of suspected drug Recurrence after new withdrawal
Probably	Temporal relationship Improvement after reintroduction of suspected drug No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out

10.1.2 Unexpected Adverse Drug Reaction

Not applicable to this study.

10.1.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Not applicable to this study.

10.1.4 Assessment of Severity

The severity of SAEs will be graded using the definition of the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 [49]. The gradation is implemented in the REDCap CRF for collection of SAEs (Annex 16).

[6] Given the population and setting of the study, congenital anomalies or birth defects are implausible.

10.2 Reporting of serious adverse events (SAE) and other safety related events

10.2.1 Reporting of SAEs

All SAEs will be reported to the investigators within a week of occurrence by the study nurse, using a specific CRF (see Annex 16). The investigators will contact the NH care team to discuss in details the situation. If necessary, the advice of a geriatrician (Dr Pierre-Olivier Lang, CHUV) will be solicited by the investigators for the discussion of the SAE with the NH care team. For the cases where a causal link with the intervention remains probable or definitive after investigation, the CER-VD will be informed within 24 hours via BASEC. In all cases, reported SAEs will be reported to the CER within 15 days via BASEC.

10.2.2 Reporting of SUSARs

Not applicable to this study.

10.2.3 Reporting of Safety Signals

Not applicable to this study.

10.2.4 Reporting and Handling of Pregnancies

Not applicable to this study, as all participants must be 65 years old or more.

10.2.5 Periodic reporting of safety

As the duration of this study is less than a year, no interim safety reports will be submitted. Safety will be assessed in the final report to the EC.

10.3 Follow up of Serious Adverse Events

All participants with ongoing SAEs at the end of the study will be followed by the NH team.

11. STATISTICAL METHODS

11.1 Hypothesis

The null hypothesis (H_0) is that the intervention has no effect on the use on PIMs by NH residents. The alternate hypothesis (H_1) is that the intervention has an effect.

11.2 Determination of Sample Size

No data on the repartition of the number of PIMs used by NH residents in Vaud and Fribourg are available prior to the study. This, no power calculation can or determination of the sample size needed can be made in advance.

We anticipate that half of the 18 eligible NH will agree to take part in the study; with a mean number of beds of 59 in these NHs, the recruitment of 20% of the population should lead to the inclusion of 106 residents.

11.3 Statistical criteria of termination of trial

As no interim analyses are planned, no criteria for the discontinuation of the trial have been set.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The analyses will be performed following the intention to treat approach.

11.4.2 Descriptive statistics

The participants will be described, by group, in terms of age, gender, and length of stay in the NH at inclusion. Their drug regimen at baseline and follow-up will be described in terms of number of regular treatments, classified according to the Anatomical Therapeutic Chemical classification. Drugs withdrawn or added as a result of the intervention will be described in the same way.

Implementation outcomes will be analysed in descriptive terms only; no statistical tests will be performed on these data.

11.4.3 Primary Analysis

The comparison of the primary outcome (change in number of PIMS between baseline and 4 months) between groups will be performed by means of generalised linear mixed models (GLMM), with patient representing a random effect clustered within NH and the allocation group as a fixed effect.

11.4.4 Secondary Analyses

The same GLMM models as for the primary outcomes will also be used to compare all patient-level secondary outcomes between the intervention groups. NH-level outcomes will be compared between allocation groups by mean of t-tests if the outcomes follow a normal distribution, by means of Mann-Whitney otherwise.

11.4.5 Interim analyses

No interim analyses are planned.

11.4.6 Safety analysis

At the end of the trial, all the participant-level safety outcomes will be compared between intervention groups by means of the same GLMM models mentioned above. Mortality and hospitalisation rates (NH-level) will be compared using t-tests or Mann-Whiteny tests, as appropriate (see section 11.4.4).

Causes of hospitalisation will be described, but no statistical tests will be performed in this outcome.

11.4.7 Deviations from the original statistical plan

All deviations from the original analysis plan will be described and justified in the final report submitted to the CER.

11.5 Handling of missing data and drop-outs

Multiple imputation will be used to replace participant-level outcome data missing in cases where the latter are missing at random for more than 5% and less than 40% of participants [50].

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

Electronic CRFs, hosted on REDCap (see section 12.2.1), will be used for data collection. As the nurses and pharmacists of the NH where the study takes place do not all have access to laptop or tablet computers, data collection at the bed of the participant will be made using paper forms. The forms will be uploaded into the eCRF after each visit. All other collected data will be entered directly into the eCRF. The responsible pharmacist and study nurse of the NH where the participant resides are the only ones authorised for data entry and upload in the CRFs.

Participants will be identified by a participant number generated automatically upon inclusion.

12.1.2 Specification of source documents

All demographic data (age, gender, date of entry in the NH), data regarding the medication plan, hospitalisations, falls, use of restraints and death will be extracted from the participant's record in the NH, which is considered the source document.

For other data, the source documents are as follow:

- Informed consent form: paper form signed by the participant or her/his representative;
- Randomisation number: eCRF (automatically generated);
- Visit date: eCRF;
- EQ-5D-5L questionnaires: paper questionnaire filled by the participant / at the participant's bed;
- Common complaints: paper questionnaire filled with the participant / at the participant's bed;
- NPI-NH: paper questionnaire filled by the referent nurse;
- PIM assessment: electronic form obtained after analysis of the PIMS, as described in section 9.2.1;
- Deprescribing plan: paper form filled and updated by pharmacist, nurse and physician;

All source documents will be filed in a designated folder provided by the investigators; this folder will be kept in the NH nurse office.

Information specific to the implementation outcomes will be collected after the end of the study; source documents will be ad-hoc questionnaires that have yet to be developed.

12.1.3 Record keeping / archiving

All data will be archived at the PMU for 10 years after study termination.

12.2 Data management

12.2.1 Data Management System

The REDCap data acquisition platform (Vanderbilt University) will be used to collect all data relative to the participants. The instance used is hosted on the IT infrastructure of the Policlinique Médicale Universitaire, and maintained and administered by its IT department (head: M. Julien Thabard).

12.2.2 Data security, access and back-up

Access to the data is restricted to the sponsor, investigators and administrators of the database, using nominative accounts. All access prior to database extraction will be made through REDCap, which includes an audit trail enabling tracing back all data access and modification.

Pharmacists and study nurses of the NHs collaborating with the study will have access to the REDCap platform with nominative accounts. They will have access only to the CRFs concerning the residents of their NH taking part in the study, and will not be able to edit or view the data entered by the other NHs' teams.

12.2.3 Analysis and archiving

After completion of follow-up data collection and data validation, the database will be locked and all data relative to outcomes exported outside of the REDCap platform. All data will remain on the IT infrastructure of the PMU at all time after data extraction. All collected data will be archived for 10 years after study completion.

12.2.4 Electronic and central data validation

Data entered in the CRF will be validated by the definition of a range of possible values for each data collected.

After completion of follow-up data collection, all data will be checked by the investigators for coherence and plausibility. In case of incoherence or implausibility, the pharmacists and / or nurses will be contacted for clarification. REDCap's built-in audit trail will ensure that all modifications made during the validation phase are recorded and justified.

12.3 Monitoring

Monitoring of the study will be ensured by researchers active at the Policlinique Médicale Universitaire, mandated by the sponsor and independent from the study investigators.

The monitor and investigators will visit each NH priori to inclusion of the first participant to ensure that all study document are correctly stored and answer the NH team questions regarding the conduct of the study.

During the study, the monitor will monitor the activities taking place in the NHs on a weekly basis via REDCap dashboards. In particular, the signature of the informed consent form will be certified in the inclusion CRF (see Annex 10). In case of non-conformity, the monitor will contact the NH team for clarification and, if necessary, visit the NH.

The monitor will conduct a visit in all NH during the course of the study, after inclusion of the first participant and before the end of follow-up of the last participant, to ensure that the study is conducted according to the protocol. He will, in particular, ascertain that:

- all study documents, particularly information and consent forms, are correctly completed and stored;
- all adverse events are reported to the investigators in a timely fashion.

12.4 Audits and Inspections

No external audits or inspections are planned. The CER-VD will have constant access to all documents and data, and the sponsor and investigators will answer their eventual questions in case of inspection.

12.5 Confidentiality, Data Protection

Access to the protocol, data and documents of the study are restricted to the sponsor, investigators, statistician and database administrator. Participating NHs' pharmacists and nurses will have access to the data relative to their NHs' residents and to the study documents until the completion of follow-up data collection.

12.6 Storage of biological material and related health data

Not applicable to this study.

13. PUBLICATION AND DISSEMINATION POLICY

Results from the study will be presented at national and international scientific conferences and meetings, and published in peer-reviewed periodicals. Results will also be presented to stakeholders (professional associations, policymakers) and, upon request, to the team of the NHs where the study takes place.

All data presented in scientific congresses or to stakeholders, or published, will respect the anonymity of participants.

14. FUNDING AND SUPPORT

14.1 Funding

This study is partly funded be the Swiss National Fund for Scientific Research, through the National Research Program 74 "Smarter Health Care". This funding covers Mr Cateau's and Dr Ballabeni's salaries.

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14.2 Other Support

The Policlinique Médicale Universitaire provides material support to this study by providing the REDCap instance used for the study free of charge, as well as administrative and logistic support (premises, computer system, prints, etc.).

15. INSURANCE

As this study is of category A, according to ClinO art 12 alinea b, no particular insurance is required for this study. All eventual damages are covered by the insurance policies of the PMU.

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17. APPENDICES

Annex 1: Participant information and consent form

Annex 2: Information and consent form for participants' representative

Annex 3: Form for the documentation of NH stakeholders' agreement to participate

Annex 4: EQ-5D-5L questionnaires for completion by the participant or the pharmacist

Annex 5: Questionnaire about common complaints for completion by the participant or the pharmacist

Annex 6: NPI-NH questionnaire (submitted here in English, pending the reception of the French version)

Annex 7: List of eligible NHs

Annex 8: Model documents for propositions resulting from the medication review and preparation of the deprescribing plan

Annex 9: Example of PIM analysis provided by the online STOPP/START tool

Annex 10: CRFs for inclusion, first visit and follow-up visit

Annex 11: Investigator-reserved CRFs for the extraction of drug regimen

Annex 12: Investigator-reserved CRF for the extraction of quality of life questionnaire

Annex 13: Investigator-reserved CRF for the extraction of common complaints

Annex 14: Investigator-reserved CRF for the extraction of NPI-NH

Annex 15: Exclusion list for the analysis of DDDs

Annex 16: CRF for reporting of serious adverse events

Annex 17: Sponsor, Investigators and Statistician curriculum vitae