# Opportunities and Limits to Deprescribing in Nursing Homes: Quality Circle Deprescribing Module (QC-DeMo)

# Amended Research Plan

OLD-NH-QC-DeMo

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| Type of Research Project: | Research project using anonymous health-related data |
| Risk Categorisation: | Not applicable |
| Project Identifier: | OLD-NH-QC-DeMo-2017 |
| Project Leader: | Prof Olivier Bugnon<br>Pharmacien-chef<br>Centre de Pharmacie Communautaire,<br>Policlinique Médicale Universitaire,<br>Rue du Bugnon 44 - 1011 Lausanne<br><br>*Affilié à la Section des sciences pharmaceutiques, Université de Genève et Université de Lausanne* |
| Problem to be studied: | Effect of a deprescribing-specific quality-circle module on the use of potentially inappropriate medication in nursing homes of Vaud and Fribourg. |
| Project Duration | December 2017 – March 2019 (possible extension to March 2020) |
| Project Plan Version and Date: | V2, 05.02.2020 |

ACCESS TO RESEARCH DOCUMENTS

All essential documents of promoter and investigators will be stored in study folders, whose management and archival are conform to the Principles of Good Clinical Practices (GCP).

IMPORTANT NOTICE

This protocol has been amended to add a co-primary outcome after receiving approval from the relevant ethics committee. Amendments are denoted in red, and the original parts modified by amendments barred.

**Signature Page**

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| Project number | OLD-NH-QC-DeMo-2017 |
| Project Title | Opportunities and Limits to Deprescribing in Nursing Homes: Quality Circle Deprescribing Module |

The project leader and the methodologist have approved the research plan version 2 (dated 05.02.2020), and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, the Principles of Good Clinical Practice and the local legally applicable requirements.

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Signature

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## SYNOPSIS

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| **Project Leader** | Prof. Olivier Bugnon<br>Pharmacien-chef<br>Centre de Pharmacie Communautaire,<br>Policlinique Médicale Universitaire,<br>Rue du Bugnon 44 - 1011 Lausanne<br><br>*Affilié à la Section des sciences pharmaceutiques,*<br>*Université de Genève et Université de Lausanne* |
| **Project Title:** | Opportunities and Limits to Deprescribing in Nursing Homes: Quality Circle Deprescribing Module |
| **Project ID:** | OLD-NH-QC-DeMo-2017 |
| **Project Plan Version and Date:** | Version 2 of 05.02.2020 |
| **Risk categorisation:** | Not applicable |
| **Type of Research:** | Research project in which anonymous health-related data are used. |
| **Project design:** | Effectiveness-implementation hybrid design: 1) Cluster randomised controlled trial of a nursing-home level intervention; 2) Mixed method approach to evaluate implementation strategies. |
| **Background and Rationale:** | Older people residing in nursing homes (NH) are frequently polymedicated and often prescribed potentially inappropriate medications. Deprescribing has been proposed as a way to reduce the number of drugs they receive and their exposure to harmful treatments.<br>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:** | 1) To evaluate the effect of a deprescribing-specific interdisciplinary quality circle module on the use of potentially inappropriate medication in nursing-home residents.<br>2) To determine the effective strategies to reach and implement deprescribing consensus resulting of said quality circle module. |
| **Endpoints:** | 1) a. The primary outcome is the change at 12 months, relative to baseline, in the proportion of PIMs used in the NHs relative to their total drug consumption;<br>b. The co-primary outcome is the change at 12 months, relative to baseline, in the number of potentially inappropriate defined daily dose per average resident and per day (DDD/res);<br>c. The secondary outcomes are the change at 12 months ~~in the proportions of defined daily doses (DDD) of PIMs used in the NHs~~ in the number of DDD/res considered to avoid or to reevaluate; the number of days in hospital per resident and per year, the number of falls per resident and per year; the number of uses of restraint measures per resident and per year, and the mortality rate.<br>2) The implementation outcomes are the adoption of the deprescribing-specific interdisciplinary quality circle module and the fidelity to it, as well as the adoption of deprescribing consensus; other implementation outcomes, such as costs of the intervention and satisfaction of the healthcare professionals, will also be evaluated. |

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| **Inclusion criteria:** | All NHs already taking part in the pharmaceutical assistance programme of their canton, having a geriatric mission, and whose mean population age is over 65 will be able to participate. |
| **Project assessments, procedures:** | Participating NHs will be randomised in two groups. NHs allocated to the intervention group will hold a QC session on deprescribing, where a local consensus on the deprescribing of specific therapeutic classes will be elaborated.<br><br>The effects will be assessed using anonymous data on the drug consumption of the NH (already routinely collected for the administrative monitoring of the pharmaceutical assistance programme) and NH-level data on falls, hospitalisation, emergency events and death. The implementation outcomes will be evaluated with questionnaires to health care professionals of the intervention group at baseline, 3 months and 12 months. |
| **Number of Participants:** | 62 NHs will be included in this project, 31 in each group (intervention and control). Assuming a normal distribution of the reduction in PIMs proportion and a standard deviation of 7.5%, similar between the two groups, this number of participant will allow for the detection of a 20% relative reduction in the primary outcome, from 22.8% to 18.2%, with 80% power. |
| **Project Duration:** | From December 2017 to March 2019 (possible extension to March 2020) |
| **Project Centre(s):** | Single-centre; the intervention will take place in multiple NHs in the cantons of Vaud and Fribourg. |
| **Statistical Considerations:** | The inclusion of 62 NH will allow for the detection of a 20% relative reduction in the use of PIMs with 80% power.<br><br>The main outcome will be assessed using a generalised linear regression model taking the difference at 12 months in overall PIM proportion as dependent variable. The secondary outcomes will be assessed using the same methodology. The 5% level of significance will be considered for all analyses. |
| **Other methodological Considerations:** | No other methodological considerations. |
| **Risk-Benefit statement:** | In previous studies of deprescribing in older people residing in nursing homes, very few adverse events occurred, none of them serious. Moreover, physicians will retain complete control over NH residents' treatments during the study. It is thus estimated that the intervention poses little to no risk compared to usual care.<br>Possible benefits include a reduced mortality rate and fewer adverse drug reactions, as well as fewer hospital stays and reduced consumption of acute care. The risk-benefits balance of this project is estimated to be clearly positive. |

## ABBREVIATIONS

| | |
|---|---|
| AFIPA/VFA | Association Fribourgeois des Institutions pour Personnes Âgées / Vereinigung freiburgischer Alterseinrichtungen |
| AVDEMS | Association Vaudoise des EMS |
| CPC | Centre de Pharmacie Communautaire de la Policlinique Médicale Universitaire de Lausanne |
| EC | Ethics Committee |
| EGEP | Essentials of Good Epidemiological Practice |
| FEDEREMS | Fédération Patronale des EMS vaudois |
| HRA | Federal Act on Research involving Human Beings (Human Research Act, HRA) |
| NH | Nursing Home |
| PAP | Pharmaceutical assistance programme |
| PIM | Potentially Inappropriate Medication |
| PMU | Policlinique Médicale Universitaire |
| QC-DeMo | Quality Circle Deprescribing Module |
| SE | Serious event |
| SPCF | Société des Pharmaciens du Canton de Fribourg |
| SVPh | Société Vaudoise de Pharmacie |

**SCHEDULE OF ASSESSMENTS**

| | 2017 | | | | 2018 | | | | | | | 2019 | | | | 2020 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sep. | Oct. | Nov. | Dec. | Jan. | Feb. | Apr. | Sep. | Oct. | Nov. | Dec. | Jan. | Feb. | Apr. | Feb. | Dec. | Jan. | Feb |
| Recruitment | X | X | | | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | | | | |
| Pharmacist formation | | | X | | | | | | | | | | | | | | | |
| Baseline data collection (January to December 2017) | | | | | X | | | | | | | | | | | | | |
| QC session, collection of consensus, strategies and first implementation questionnaires. | | | | X | X | | | | | | | | | | | | | |
| Compilation of consensus and strategies and communication to participants | | | | | | X | | | | | | | | | | | | |
| Collection of second implementation questionnaire | | | | | | | X | | | | | | | | | | | |
| Collection of third implementation questionnaire | | | | | | | | | | | X | | | | | | | |
| Follow-up data collection (January to December 2018) | | | | | | | | | | | | X | | | | | | |
| Main analysis (if single recruitment round) or intermediate analysis (if two recruitment rounds) | | | | | | | | | | | | | | | X | | | |
| Recruitment (second round) | | | | | | | | X | | | | | | | | | | |
| Randomisation (second round) | | | | | | | | | X | | | | | | | | | |
| Pharmacist formation (second round) | | | | | | | | | | X | | | | | | | | |
| Baseline data collection for second round (January to December 2018) | | | | | | | | | | | | X | | | | | | |
| QC session, collection of consensus, strategies and first implementation questionnaires (second round) | | | | | | | | | | | X | X | | | | | | |
| Compilation of consensus and strategies and communication to participants (second round) | | | | | | | | | | | | | X | | | | | |
| Collection of second implementation questionnaire (second round) | | | | | | | | | | | | | | X | | | | |
| Collection of third implementation questionnaire (second round) | | | | | | | | | | | | | | | | X | | |
| Follow-up data collection for second round (January to December 2019) | | | | | | | | | | | | | | | | | X | |
| Main analysis (if two recruitment rounds) | | | | | | | | | | | | | | | | | | X |

## 1. ADMINISTRATIVE STRUCTURE


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## 2. ETHICAL AND REGULATORY ASPECTS

The research project proposed here aims to study the effectiveness and implementation of an interprofessional quality-circle module on deprescribing, whose objective is to promote the uptake of deprescribing in the NH of Vaud and Fribourg where a PAP is already in place. The planned intervention will deploy its effects at the NH level; individual NH residents will be affected through change in the NH's physician prescribing practices, which will retain her/his usual control over clinical decisions. Although a local consensus of the deprescribing priorities will be set in each NH, all the clinical decisions, including the introduction or the discontinuation of a drug, will be individualised and managed as usual by the residents' physician.

According to its article 2, alinea 2.c, the HRA "*does not apply to research which involves […] anonymously collected or anonymised health-related data*". The research project presented here does fall in this category: all assessments will be made using anonymized health-related data, administrative data collected at the NH level, or data concerning health professional perception of the intervention (see Data collection, page 14).

Furthermore, the intervention studied in this research project is aimed at modifying physicians' and care teams' clinical practices, and not to influence the treatment of specific NH residents. As such, it does not fall under HRA's article 3, alinea l definition of a clinical trial ("*a research project in which persons are prospectively assigned to a health-related intervention in order to investigate its effects on health or on the structure and function of the human body.*"). Given the indirect nature of the intervention, the investigator cannot foresee, nor know, which residents of the participating NHs will be affected by the intervention and which will not.

However, the investigators choose to submit this research project the Commission Cantonale d'Éthique de la Recherche, to ensure that our interpretation of the legislative texts are correct. In keeping with spirit of the HRA, anonymity of the participating NHs is guaranteed when data obtained through this research project will be presented at scientific meetings or published in scientific journals. The informed consent of all NH professionals taking part in the intervention will also be required. Given the anonymity of data collected (see Data collection, page 14) and the total control retained by the physicians over individual residents' care throughout the project, the consent of NH residents is not required.

## 3. INTRODUCTION

### 3.1 Background

*Polypharmacy*, or the use of five or more concurrent medications, is frequent among the elderly [1], and especially those residing in NHs [2]. 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) [3] and may lead to decreased health outcomes and quality of life [4].

Inherent risks posed by polypharmacy are amplified by the use of *potentially inappropriate medications* (PIMs), drugs whose potential for harm surpass their expected benefits [5]. PIMs have been a major concern for the geriatric care community since the early 1990s, with the publication of Beers' seminal paper [6]. Their use is associated with worse health outcomes, more frequent hospitalisation and increased risk of death[7, 8]. Elderly people residing in NHs are frequently exposed to such drugs: a meta-analysis by Morin et al [9] 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[10].

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" [11], deprescribing has the potential to improve elderly people's well-being and health outcomes [12]. A recent meta-analysis indeed concluded on the positive effect of patient-centred deprescribing intervention on mortality [13]. Since the first occurrence of the term in the scientific literature[14], deprescribing has gathered interest in various countries, such as Australia[15], Canada[16], the United States[17], New

Zealand[18], Belgium[19], the Netherlands[20], and France[21]. Outside of the academic world, deprescribing is also gaining traction, with initiatives such as guidelines published by the Canadian Deprescribing Network [22]or the MedStopper online tool [23].

To our knowledge, no initiatives have been launched to try and implement deprescribing in the Swiss NHs. One reason for that may be that, to be successful, deprescribing must rely on interprofessionnal collaborations [24] that may not be as developed in Switzerland as in other countries. Such interprofessionnal collaborations do however exist in Switzerland: since 2002 in the canton of Fribourg and 2010 in the canton of Vaud, pharmaceutical assistance programmes (PAP) are in place in the NHs of those cantons. These programmes consist of interprofessionnal quality circles bringing together physicians, nurses and pharmacists, with the goal of improving 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.

The present study is part of a larger research project intituled "Opportunities and Limits to Deprescribing in Nursing Homes" (OLD-NH). As part of this project, two qualitative studies exploring the context surrounding the withdrawal of medications in the Swiss NH are under way. The present study is the first in the intervention phase of OLD-NH; the second study, to be started one year after this one, will assess the impact of a deprescribing intervention at the resident level in NH that already implemented the intervention proposed in this study. The whole research project is funded by the Swiss National Fund for Scientific Research, through the National Research Programme 74 "Smarter Health Care"[25].

## 3.2 Rationale for the research project

The pharmaceutical assistance programs already in place in Vaud and Fribourg have shown a positive effect on the cost of medication[26]; however, the analysis made by Helsana [10] shows that these programs have little to no effect on PIM use in the NH: the prevalence of PIM was not different in the NHs with or without PAP. The intervention tested in this study aims to reduce PIM use, which could positively impact NH residents' health status and lower medications adverse effects, and thus lower hospitalisations and further reduce drug costs.

Beside a reduction in polypharmacy and PIM use, the intervention could also lead to improvements in the underuse of helpful medications, which is another problem befalling older people. Studies have indeed shown that patients experiencing overuse of medications are the most likely to experience underuse of useful treatments [27, 28]. Reducing the number of unnecessary drugs could thus lead to an increased use of the useful ones.

Most deprescribing studies have been focused on clinical interventions targeting individual patients, frequently using medication review-like methods. While effective [13], these interventions are extremely intensive, and thus have a high cost: they require that, on top of routine care, highly trained professionals analyse the medications of individual patients and provide clinical advice to the care team. On the other hand, less intensive interventions, for example educational ones, have not shown to be effective [13]. The intervention assessed in this study sits in between these two extremes: while less intensive than a full-blown review of individual residents' medications, the engagement of the whole care team resulting from a NH-wide consensus on the best way to deprescribe specific inappropriate medications is more likely to result in positive outcomes for the residents than a purely educational intervention. The good collaboration already established through the PAPs in the NHs between nurses, physicians and pharmacists further enhances the chances of success of the intervention.

As our setting is the healthcare system, we opted for a hybrid design to evaluate simultaneously the effectiveness and the implementation of the intervention, to maximise the creation of knowledge useful both for policy makers and easily transferable to practitioners. This approach also gives us the opportunity to study and optimise the implementation strategies adopted by each NH to support the application of his deprescribing consensus.

The findings of the study could help the development and implementation of new deprescribing practice models with a better cost-effectiveness ratio.

## 3.3 Risk-Benefit Assessment

Studies show that enacting deprescribing induces very little acute adverse events [29, 30]: in a study of deprescribing in 422 NH residents in the United Kingdom [29], only 7 adverse events occurred following the discontinuation of more than 700 medicines. None of those 7 events led to significant harm to the residents; the measures taken to resolve these events included the reinstatement of the stopped medication, treatment of a urinary tract infection, and adaptation of an insulin regimen and closer monitoring of blood pressure. In another trial of deprescribing in Australian NH, there were no differences in the occurrence of adverse events between the intervention and control groups [30].

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 [28]. 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 is currently less than 3 years. The risk incurred by residents of the participating NH is thus deemed to be no greater than usual care. The benefits, however, can be very important: as previously stated, deprescribing can lead to reduced mortality and fewer adverse drug reactions. Deprescribing could also reduce the need for hospitalisation or acute medical care, thus freeing resources in the health system. For these reasons, the risk-benefit ratio of this study is deemed to be positive, both for the residents of the participating NH and the health system in general.

Data needed to assess the impact of the intervention will be aggregated at the NH level. The risk posed by unwanted data access is thus very low: no personally identifying information will be collected, and all health-related data will be aggregated (see section 5.3, page 14).

# 4. OBJECTIVES, OUTCOMES AND OTHER STUDY VARIABLES

## 4.1 Objectives

1) Effectiveness study:

The primary objective of this study is to evaluate the effect of an interprofessionnal quality circle module on the use of PIMs in the participating NHs. Our hypothesis is that the proposed intervention will lead to a reduction in the use of PIMs.

The secondary objectives are the evaluation of the effects of the intervention on the consumption of PIMs measured by their defined daily dose (DDD), the mortality rate, the use of hospital care, the number of falls and the use of restraints.

2) Implementation study:

The final objective of this study is to determine the effective strategies to reach and implement deprescribing consensus resulting of a deprescribing-specific interdisciplinary quality circle module.

## 4.2 Primary and secondary endpoint/outcome(s)

1) Effectiveness study:

The primary outcome is the difference in the proportion of galenic units considered as potentially inappropriate, relative to the total number of galenic units used in the NH, between baseline and 12 months. Each drug used in the NH will be assessed for appropriateness using a custom screening tool combining criterion from the Beers' list [6], the STOPP tool [31] and the NORGEP-NH list [32].

The co-primary outcome is the change in the number of potentially inappropriate defined daily dose per average resident and per day (DDD/res), between the first and second year of the study. The defined daily dose (DDD) for each drug will be computed according to its active ingredient and route of administration.

Secondary outcomes include the difference in ~~PIMs use taking into account the DDD for each drug used in the participating NHs~~ the number of DDD/res categorised either possibly or probably inappropriate, the annual mortality rate, the number of hospitalisation days per mean resident and per year, the number of falls per mean resident and per year, and the number of times restraint measures are used per mean resident and per year.

2) Implementation study:

The main implementation outcomes will be the adoption of the deprescribing-specific interdisciplinary quality circle module and the fidelity to it, as well as the adoption of deprescribing consensus; other implementation outcomes as costs of the intervention, satisfaction of the healthcare professionals will also be evaluated. A list of all implementation outcomes is available in Annex 1.

# 5. PROJECT DESIGN

## 5.1 Type of research and general project design

This project has an effectiveness-implementation hybrid design.

1) Effectiveness study:

The effectiveness is evaluated by a cluster-randomised controlled trial of an interprofessionnal quality-circle module on deprescribing. The unit of analysis for this study is the NH; all data will be aggregated at the NH level, and no data regarding individual residents will be provided to the investigators.

Participating NHs will be randomised between intervention and control groups (ratio 1:1), clustered according to their responsible physician. NHs allocated to the intervention group will hold a QC session on the topic of deprescribing and will produce a local consensus on how to deprescribe specific therapeutic classes in the NH.

2) Implementation study:

The implementation study is based on a mixed method approach combining quantitative and qualitative evaluation of the implementation strategies of the deprescribing-specific interdisciplinary quality circle module as well as the resulting deprescribing consensus. Only the intervention group will be concerned by most of the evaluations.

## 5.2 Recruitment and Screening

Participants will be recruited among the NHs currently taking part in their respective cantonal pharmaceutical assistance programmes. The investigators have direct access to these NHs and their respective pharmacists through their mandate for the monitoring of these two programmes.

All NHs of Vaud and Fribourg with a mainly geriatric mission and that have been part of the programmes for more than a year will be offered the possibility to participate in this study by direct mailing from the investigators. Pharmacists providing the pharmaceutical assistance for these NHs will also be directly informed, and nurses and physicians will be contacted through their respective professional societies. The approval of all partners (NH direction, head nurse, responsible physician and pharmacist) will be required for enrolment (see Annex 2 for agreement to participate).

In case of insufficient recruitment, a second recruitment round will take place in 2018. The NHs agreeing to take part in this second round will be randomised as described in section 5.3, page 13; those allocated to the intervention group will then hold a QC session between December 2018 and January 2019. Data of the two recruitment rounds will be pooled for analysis (see section 8.2, page 18).

## 5.3 Procedures

For clarity, the following section only describes activities planned for the first recruitment round. If a second round is necessary (see above), all activities will be held the following year in the NHs participating in this second round.

**Randomisation:**

Some responsible physicians work in multiple NHs; this could lead to contamination of the control group. Moreover, some NHs have multiple responsible physicians; these two factors lead to the apparition of clusters of physicians working in the same NHs and which could amplify contamination of the control group. To account for this factor, after inclusion and before randomisation, NHs will be clustered by physicians: all NHs sharing at least one physician will be placed in the same cluster. NHs sharing no physician with another will be placed in clusters of size one.

A random list of A (intervention) and B (control) will be used to allocate NHs clusters to groups. The list will be constructed by generating a random list of numbers comprised between 0 and 1, with uniform distribution; numbers below 0.5 will be assigned the letter A, the others the letter B. The list will be of the same length as the list of included NHs clusters, and will be generated using Stata version 14.1.

Given the variable size of the clusters, this may lead to the constitution of two groups of unequal size. However, given the relatively small size of expected clusters (the largest possible cluster we are aware of regroups eight NH; most clusters will only include two NHs), this should not lead to a dramatic unbalance between the two groups.

**Intervention:**

Pharmacists of the NHs assigned to the intervention group will take part in a course where the material for the quality circle module (slides, relevant scientific literature and guidelines) will be made available to them. The content of the course was developed at the CPC. It comprises an overview of the problems posed to older people by polypharmacy and the use of PIMs, an in-depth description of the process of deprescribing and of the challenges to enacting it, a selection of useful clinical tools, and a selection of guidelines to deprescribe specific therapeutic classes (for example, proton-pump inhibitors or cholesterol-lowering drugs).

In the two months following course completion, every NH in the intervention group will hold a QC session prepared by the pharmacist based on the course. This session will address both generalities about polypharmacy, PIMs and deprescribing, and an in-depth discussion of the guidelines for deprescribing therapeutic classes selected by the pharmacist on the basis of their use in the NH. It is to be noted that the data necessary to select the specific therapeutic classes discussed during the session are both routinely collected and analysed by the NHs' pharmacists, due to their participation in their respective cantonal pharmaceutical assistance programme.

At the end of the session, participants will be required to build a consensus for deprescribing specific therapeutic classes in the NHs. This consensus will then be enacted by the care team, according to their best clinical knowledge. In addition, the participants will be encouraged to think about the strategies to implement each deprescribing measures chosen for the consensus. Physicians will retain complete control over therapeutic choices for individual residents, including the choice to enact the consensus or not.

In addition, the pharmacist will be required to send the consensus with strategies to the other participants two weeks after the session, to include a specific chapter about deprescribing in their PAP annual report for 2017 and to discuss the implementation of the consensus during the presentation of this report to the NH team.

All consensus and implementation strategies chosen by the participating NHs will be collected by the investigators, compiled and, after anonymization, communicated to the participants during the first trimester of 2018.

**Data collection:**

Assessment of this project's outcomes will be made using anonymised data, provided by the CPC monitoring team. These data will comprise, for every NH and every year:

- Mission of the NH (geriatric, psycho-geriatric, or mixed);
- Number of beds in the NH;
- Mean age of NH residents;
- Gender repartition of the residents;
- Total number of days spent at the NH;

- Total number of days sent in the hospital;
- Total number of deaths in the NH;
- Designation, pharmacode, number of boxes and total cost of every drug used in the NH during the year.

Some data will be collected directly in the NHs; these data will be aggregated at the NH level:

- Total number of falls in the NH;
- Total number of residents having fallen, if available;
- Total number of falls having resulted in a hospital stay, if available;
- Total number of falls having resulted in supplementary care, if available;
- Total number of hospital stays, if available;
- Total number of residents having had an hospital stay, if available;
- Total number of hospital stays resulting from a demand of the GP, on-call GP or the resident's family, if available;
- Total number of restraint measures enacted during the year, if available.

All data will be collected on a yearly basis. Data collected directly at the NH will be collected by nurses, using a CRF hosted on the REDCap instance maintained by the École de Pharmacie Genève-Lausanne (University of Geneva). Its access will be restricted to the investigators.

**Implementation evaluation:**

To evaluate the implementation of the intervention, participants in the intervention group will be asked to fill a specific questionnaire at the end of the QC session (baseline) and after 12 months. The questionnaires at baseline are available in annexes 3 to 6. The questionnaires at 12 months will include an evaluation of the implementation strategies related to the local deprescribing consensus; as such, they are not elaborated to date, as those strategies will be elaborated by the participants during the QC session.

A supplementary questionnaire will be sent to the pharmacists to monitor the implementation process after the QC session within the first trimester of 2018 (see Annex 6).

A copy of each presentation support prepared by the pharmacists to lead the discussion within the QC session and the final version of each consensus with implementation strategies will have to be sent to the investigators. The presence of the specific chapter in the PAP annual report will also be checked.

Between 4 and 6 months after the QC session, the head nurse or his surrogate will be reach to evaluate the efficacy of each implementation strategies. A global feedback will be sent to each participants. After 12 months, the effectiveness of each consensus and implementation strategies defined during the QC session will be systematically asked.

## 5.4 Methods of minimising bias

To account for the other influences on the prescribing practices of physicians, a controlled design has been chosen. Thus, external influence from medical literature, expert opinions, treatment guidelines or other sources should equally impact NHs in the intervention and control groups.

Randomisation will increase the likelihood that the characteristics of participating NHs are similar between the two groups. To account for the fact that some physicians are responsible for more than one NH, thus allowing for "bleeding" of the intervention between the two groups, randomisation will be clustered at the physician level (see section 5.3, page 13 for details).

Previous discussions with the prospective participants and their professional associations show that there is a great interest for deprescribing among partners. We fear that a purely controlled design will prevent the participation of some of the most interested NHs, thus minimising the effect of the intervention. To reduce this risk, we will offer the possibility to participants randomized to the control group to enact the intervention one year after the start of the study. At this point, all NH in the intervention group will have submitted to the intervention and its effects will have full deployed.

Finally, assessments of the study outcomes will be conducted while maintaining allocation blinding, ensuring that no analysis bias occurs.

Given that the unit of analysis is the NH, the risk of loss to follow-up is deemed inexistent. Data collection will take place in the same way as it already routinely does in a satisfactory way, thus reducing the risk of missing data.

# 6. PROJECT POPULATION

## 6.1 Inclusion criteria

This study is open to all NH of Vaud and Fribourg:

- Who have been part of their cantonal pharmaceutical assistance programme for more than 1 year at the time of recruitment;
- Who have a geriatric or psychogeriatric mission, or a mainly geriatric population;
- Whose residents' mean age is at least 65 years.

## 6.2 Exclusion criteria

No exclusion criteria will be enforced.

## 6.3 Criteria for withdrawal / discontinuation of participants

Participating NHs will have to withdraw from the study if one of the partners (physician, head nurse, pharmacist or NH direction) withdraws its consent to participate, if the mission of the NH become exclusively psychiatric, or if the mean age of its residents becomes less than 65 years.

# 7. PROJECT ASSESSMENTS

## 7.1 Project flow chart

See Schedule of assessments, page 8.

## 7.2 Assessments of primary outcome

The primary endpoint of this study will be the difference in the overall proportion of PIMs used in each NH between baseline and 12 months. This endpoint will be assessed using the drug consumption data collected by the CPC monitoring team for the monitoring of the two cantonal PAPs; these data will be anonymised before transmission to the investigators (see section 5.3, page 13 for data collection).

PIM status for each line of drug consumption data will be assessed using a custom screening tool combining criterion from the Beers' list [6], STOPP tool [31] and NORGEP-NH list [32]. This tool will classify each data line as "not inappropriate", "possibly inappropriate" or "probably inappropriate". At both time points, the proportion of PIM will be computed for each NH as the ratio of the number of galenic units classified as "inappropriate" (sum of possibly and surely inappropriate) to the total number of galenic units used in the NH over the course of the past year. The primary outcome will be the difference of the two resulting proportions.

The co-primary endpoint for this study will be the change in the number of potentially inappropriate DDD/res between baseline and 12 months. For each NH, the total number of DDD used will be computed according to the active ingredient of the drug and its administration route. The total number of DDD will be divided by the total number of days spent in the NH for the year to calculate the number of DDD/res.

**Rationale for the addition of a co-primary outcome:** work on the same topic carried out by the investigators during the study revealed that the change in number of potentially inappropriate DDD/res is a more robust outcome, as it captures the adaptations of the doses of PIMs used and, unlike the proportion of potentially inappropriate galenic, is independent of the total amount of drugs. This addition of a co-

primary outcome was decided before the completion of data collection, and before any analysis of the data collected to date had been carried out. The investigators stress that this addition is in no way related to a supposed lack of effectiveness of the intervention; rather, it has been decided to try and reflect the effects of the intervention in the most accurate way possible.

## 7.3 Assessment of secondary outcomes

This study includes ~~eight~~ six secondary outcomes; ~~four~~ two of them are efficacy outcomes: the change ~~in proportion of possibly inappropriate galenic units, of probably inappropriate galenic units (see 7.2 Assessments of primary outcome before), of possibly inappropriate DDDs and of probably inappropriate DDDs~~ in number of possibly inappropriate DDD/res and of probably inappropriate DDD/res.

The other four are both efficacy and safety outcomes: the mean number of hospital days per mean resident and per year, the mortality rate, the number of falls per mean resident and per year, and the number of restraint measures enacted per mean resident and per year. All four are calculated at the NH level.

- Number of hospital days per mean resident and per year: for each year (see Schedule of assessment, page 8), the total number of days spent in the hospital (i.e. days spent outside of the NH for medical reasons) and the total number of days spent in the NH.
- Mortality rate: the number of residents having died, for each year and for each NH, will be provided by the CPC monitoring team.
- Number of fall per mean resident and per year NH will report the total number of falls during the year.
- Use of restraint measures: NH will report the number of times restraint measures have been enacted in the NH during the year.

The availability of certain data regarding falls, hospital stays and the use of restraints in the NHs of Vaud is uncertain (see Data collection, page 14). These data will be analysed only if the majority of NHs are able to provide them.

Data processing is described in section 8.2, page 18.

## 7.4 Assessment of implementations outcomes

As the implement study is descriptive, all implementation outcomes (list available in Annex 1) will be summative.

# 8. STATISTICAL METHODOLOGY

## 8.1 Determination of sample size

Based on the retrospective data collected for the administrative monitoring of the Fribourg PAP, the mean proportion of PIM in the NH of Fribourg in 2015 was 22.8% (SD 6.3%). The natural year-on-year variation of the outcome was calculated between 2014 and 2015: the mean difference is 0.8% ($IC_{95}$ -1.1% - 2.7%, SD 5.3%); the correlation coefficient ρ between values of the outcome for 2014 and 2015 is 0.54 ($IC_{95}$ 0.29 – 0.72).

Studies of deprescribing have shown relative reductions in the number of PIMs ranging from 6.4% [33] to 31%[34]; one of the largest studies so far showed a 19.7% reduction in the number of PIMs [30]. Our hypothesis is that the intervention proposed in this study will reduce the proportion of PIMs used by 20%, in relative term.

We aim to detect an absolute difference of 4.6% (22.8% × 0.2) in the one-year reduction of the proportion of PIM between the control and intervention groups. The standard deviation of the difference at 12 months ($SD_{diff}$) was estimated with the following formula, assuming that the standard deviation at baseline and 12 months were the same and equal to 6.3%:

$$Var_{diff} = Var_{baseline} + Var_{12\ months} - 2 \cdot \rho \cdot SD_{baseline} \cdot SD_{12\ months}$$

By varying the correlation coefficient ρ along the confidence interval, plausible values of $SD_{diff}$were estimated to be between 4.1% (ρ=0.7) and 7.5% (ρ=0.3). A value of ρ=0.3 ($SD_{diff}$ = 7.5%) was chosenas a conservative estimate for the calculation of the sample size, given the moderate correlation between the values for 2014 and 2015. To detect a difference between a mean difference of 0 in the control group and 4.6 in the intervention group (common SD of 7.5%, risks of α and β errors of 5% and 20%), 66NH, 33 per group, will have to be included. With an optimistic estimate of ρ = 0.7, the number of NH to include would decrease to 36. However, as this could lead to a lack of statistical power, a conservative estimate has been preferred.

Given that 82 NH meet inclusion criteria in the canton of Vaud and 42 in the canton of Fribourg, we expect that approximately2/3 of the participants will be recruited in Vaud, and 1/3 in Fribourg.

## 8.2 Data processing

**Data pooling:**

If a second recruitment round occurs in 2018 (see section 5.2, page 13), the data collected during the two rounds will be pooled before the main analysis. The year of integration in the study will be considered the baseline year (i.e. 2017 for the NHs of the first round, 2018 for the second round). The main analysis will then take place after data follow-up collection for the second round (planned in January 2020).

**Primary outcome:**

As described in section 7.2 (page 16), drug consumption data will be processed using a list of inappropriate drugs, to elicit each line's appropriateness status (probably inappropriate, possible inappropriate, not inappropriate). For each data line, the number of galenic units will be determined by lookup in a database, created by the CPC, containing information about therapeutic products used in Switzerland. The overall proportion of galenic units considered inappropriate (possibly and probably inappropriate) will then be computed for each NH using the following formula:

$$\frac{(total\ number\ of\ inappropriate\ galenic\ units\ used\ during\ the\ period)}{(total\ number\ of\ galenic\ units\ used\ during\ the\ period)}$$

The difference between baseline and 12 months will then be computed for each NH.

**Co-primary outcome:**

Using the same dataset as for the primary outcome and the same appropriateness classification tool, the overall number of potentially inappropriate DDD/res (possibly and probably inappropriate) will be computed using the following formula:

$$\frac{(number\ of\ boxes\ used)\cdot(number\ of\ galenic\ units\ per\ box)\cdot(dose\ per\ galenic\ unit)}{(DDD\ according\ to\ ATC\ code\ and\ administration\ route)\cdot(days\ spent\ in\ the\ NH\ during\ the\ year)}$$

**Secondary outcomes:**

~~Difference in proportion of probably inappropriate galenic units and of possibly inappropriate galenic units: the difference in the proportion of possibly inappropriate drugs and of probably inappropriate drugs will be computed for each NH using the same method as for the primary outcome.~~

~~Difference in proportion of probably inappropriate DDDs and of possibly inappropriate DDDs: for each data line, the number of DDDs will be computed by multiplying the number of galenic units with the number of DDD per galenic unit. The latter is present in the database used created by the CPC for the monitoring of the cantonal PAPs. The change in proportion of possible inappropriate DDDs and probably inappropriate DDDs will then be computed as for the primary outcome.~~

Difference in number of possibly and probably inappropriate DDD/res: the change between baseline and 12 months will be computed for each category as for the co-primary outcome.

Number of hospital days per mean resident and per year: for each year, NH will report the total number of days spent in the hospital (i.e. days spent outside of the NH for medical reasons). The total number of days spent in the NH will be provided by the CPC monitoring team; the mean number of days in hospital per year and per mean resident will then be computed using the following formula:

$$(total\ number\ of\ days\ in\ hospital)/(total\ number\ of\ days\ spent\ in\ NH)/365$$

If other data regarding hospitalisations are analysed (see section 7.3), they will be processed as described here for the total number of falls.

Mortality rate: NH will report the number of residents having died during each year. The annual mortality rate will then be computed for each NH using the following formula:

$$(total\ number\ of\ deaths)/(total\ number\ of\ days\ spent\ in\ NH)/365$$

Number of falls per mean resident and per month: for each year, NH will report the number of falls. The monthly number of falls per mean resident will then be computed for each NH using the following formula:

$$(total\ number\ of\ falls)/(total\ number\ of\ days\ spent\ in\ NH)/365$$

If other data regarding falls are analysed (see section 7.3), they will be processed as described here for the total number of falls.

Number of restraints measures per mean resident and per month: for each year, NH will report the number of restraint measures episodes enacted. The number of falls per mean resident and per year will then be computed for each NH using the following formula:

$$(total\ number\ of\ restraint\ measures\ episodes)/(total\ number\ of\ days\ spent\ in\ NH)/365$$

## 8.3 Planned analysis

**Descriptive statistics**

Participating NH will be described, by group, in terms of number of beds, mean age of residents, mission (geriatric, psycho-geriatric or mixed), and number of nurses, physicians and pharmacists. Each implementation outcome (list available in Annex 1) will be presented with a suited summative data.

**Inferential statistics**

The main outcome is the difference in the overall proportion of PIMs used in the NH 12 months after intervention, relative to baseline. The primary analysis will test the difference in the overall proportion of PIMs between the intervention and control groups using a generalised linear regression model, taking the difference in overall proportion of PIMs at 12 months as the dependant variable, and the group allocation (binary variable) and baseline overall proportion of PIMs as independent variables (two-sided $\alpha = 0.05$). The analysis will be made immediately after the completion of follow-up data collection.

The same analysis will be carried out for the co-primary outcome, with the overall number of potentially inappropriate DDD at 12 months as dependent variable, adjusted for baseline value, taking into account the group allocation.

Generalised linear models will also be used to assess differences in secondary outcomes between the two groups will be tested with the same method as the primary outcome, taking the baseline value and the group allocation as the independent variables, with two-sided $\alpha = 0.05$. If enough supplementary data on falls and hospitalisations are available (see section 7.3 page 19), they will be analysed as the number of falls, respectively the number of hospital days, per mean resident and per year.

All analyses will be made using the Stata statistical package (StataCorp LP, College Station, TX, USA).

### 8.3.1 Datasets to be analysed

All retrospective data collected will be used for the main analysis. If some NH allocated to the intervention group do not hold the QC session but provide their data, they will be included in the analysis. The statistician performing the analysis will be blinded to the allocation; groups will be identified as A and B.

Subgroups analysis will be made, both for the primary and secondary outcomes, for the following subgroups:

- NH of Vaud;
- NH of Fribourg;
- NH with a geriatric mission;
- NH with a psychogeriatric mission;
- NH having held the QC session.

### 8.3.2 Handling of missing data

Given the nature of the retrospective data collected and the collection mechanisms, we expect that no data will be missing. The supplementary recruitment (see section 8.1, page 17) will ensure that, if any drop-out occurs, the statistical power will remain sufficient to conduct the analyses.
NH with missing drug consumption data will be excluded from all analyses; NH lacking data for one or more of the secondary outcomes will be excluded from this specific analysis.

### 8.3.3 Ancillary analysis

No ancillary analyses are planned.

### 8.3.4 Deviations from the original statistical plan

All deviations from the planned analyses will be documented in the final project report, and will be justified.

# 9. DATA AND QUALITY MANAGEMENT

## 9.1 Data handling and record keeping / archiving

All documents (agreements to participate, etc.) will be securely archived at the CPC; access to these documents will be restricted to the investigators.

Data from the participating NH and pharmacists will be sent to the investigators via the REDCap instance managed by the PMU; this REDCap instance will also be used for the storage of the raw data. This platform's built-in rights management system and audit trail ensure that only the investigators will have access to the data and that all consultations and modifications are logged. Data will be stored in a coded form; the coding key will be held by the Bureau Qualité Recherche of the PMU, which is not a part of the research project.

Data exported from REDCap for processing and analysis will be stored in a secure location on the PMU infrastructure, accessible only to the investigators.

## 9.2 Confidentiality, Data Protection

All data collected for this study are strictly confidential and will be accessible to the investigators and their delegates only, in a coded form (no non-coded data will be collected). The EC will have access to all data, including in raw form, for purposes of monitoring, audit and inspection.

After study completion, the results will be published in academic journals (see section 10.1, page 21). Upon request of the editors, processed data will be made available to them; however, no data allowing the identification of the participating NH, partners or residents will be provided.

## 9.3 Coding

While they are not health-related personal data, data relative to the participating NH will be coded. The coding key will be stored on the PMU secure infrastructure and is not accessible to people outside of the CPC.

## 9.4 Archiving and destruction

All data will be archived for 10 years after the conclusion of the research project, on the secure infrastructure of the PMU. Raw data will be stored on the REDCap instance, while exported, processed and analysed data will be stored in a secure folder of the IT infrastructure of the PMU. Access will remain exclusive to the investigators through the archival period.

# 10. PUBLICATION AND DISSEMINATION POLICY

## 10.1 Publication of results

The results of the effectiveness study will be published in academic journals with the following authorship order:

Damien Cateau, Pierluigi Ballabeni, Pierre-Olivier Lang, Olivier Bugnon, Anne Niquille.

The results of the implementation study will be published in academic journals with the following authorship order:

First author to be defined, Damien Cateau, Clemence Perraudin, Joanna Moullin, Olivier Bugnon, Anne Niquille.

In case of other people would significantly contribute to a manuscript, they will be add to those authorship orders.

The results will be presented at academic conferences, as well as in academic, professional and public conferences. Presentations of the results will be organised for the participating NHs.

## 10.2 Data sharing

The data collected during this research project will not be accessible to third parties.

## 11. FUNDING AND SUPPORT

This research project is funded by the Swiss National Fund for Scientific Research, through the National research Project 74 "Smarter Health Care" (80%) and by a direct contribution (20%) from the science fund of Prof Bugnon at the PMU in Lausanne. These funding cover the investigators' salaries and administrative costs. The investigators attest that no conflict of interest exists for this research project.

Participants (pharmacists, physicians and NH personal) from the canton of Vaud will be remunerated for their work in the project through their participation in the cantonal pharmaceutical assistance programme. The remuneration scale for each participant is fixed by the canton. For the remuneration of participants in Fribourg, a grant request has been submitted to the AFIPA-santésuisse joint fund. The remuneration scale will be the same as for the participants in Vaud.

Administrative support in contacting the participants will be provided by the relevant professional associations (AVDEMS, FEDEREMS and SVPh for Vaud, AFIPA/VFA and SPCF for Fribourg).

## 12. INSURANCE

As this project is outside of HRA's scope, no specific insurance was contracted. All eventual damages are covered by the insurance policies of the PMU.

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## 14. APPENDICES

Annex 1: Data collected for the implementation study

Annex 2: Agreement to participate in the study

Annex 3: QC-DeMo Questionnaire T0 Pharmaciens

Annex 4: QC-DeMo Questionnaire T0 Médecins

Annex 5: QC-DeMo Questionnaire T0 Infirmiers

Annex 6: QC-DeMo Questionnaire T3-5 Pharmaciens

Annexes 7 – 10: CV of investigators