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Deprescribing in nursing homes: Protocol for nested, randomised controlled hybrid trials of deprescribing interventions

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ABSTRACT

Introduction: Polypharmacy and the use of potentially inappropriate medication (PIMs) are frequent among nursing home (NH) residents, and are associated with adverse health outcomes like falls, hospitalisation and death. Deprescribing has been proposed as a way to curtail both problems; however, the best way to implement deprescribing and its real impact are still unclear. This article describes nested trials of two consecutive deprescribing interventions, the first at the NH level, and the second at the resident level.

Methods and analysis: The first intervention (QC-DeMo) will be a deprescribing module to be carried out in existing interprofessional quality circles in NHs, with the goal to develop a NH-wide deprescribing consensus. Its effects will be evaluated on the use of PIMs and on patient safety outcomes such as death, hospitalisation and falls. All NHs in the cantons of Vaud and Fribourg with an integrated pharmacy service will be eligible.

The second intervention (IDeI), at the resident level, will be a deprescribing-focused medication review, resulting in the implementation of a deprescribing plan. Its effects will be evaluated on the use of PIMs and chronic medications, and on quality of life. This second trial will take place in the NHs allocated to the intervention group of the first trial. All residents of these NHs over 65 years old, living in the NH for at least 4 months, and taking 5 or more medications will be eligible to participate.

Both trials will be hybrid effectiveness and implementation trials, aiming to understand the implementation process for the interventions, and to identify barriers and facilitators.

Ethics, registration and funding: Both trials were approved by the relevant ethics committee, registered on ClinicalTrials.gov (QC-DeMo: NCT03688542; IDeI: NCT03655405), and funded by the Swiss National Fund for Scientific Research.

Introduction

Background

Elderly people frequently experience polypharmacy, defined as the concurrent use of five drugs or more. Although sometimes necessary to treat multiple conditions, or a severe single condition, polypharmacy has many drawbacks, mainly an increased risk of drug-related problems, and is a heavy burden for both the patient and the healthcare system. It has also been linked to adverse health outcomes, such as lower physical function,[1] hospitalisation,[2,3] and increased frailty.[4] In addition, polypharmacy increases the probability of use of potentially inappropriate medications (PIMs), drugs with adverse risk-to-benefit ratio; PIMs are indeed common in the elderly population, although estimations of their prevalence vary widely between studies.[5–8] Elderly people living in nursing homes (NHs) are especially at risk of polypharmacy and PIM use, as the literature consistently reports high prevalence of both problems in this population.[9–11]

In the last 10 years, deprescribing, "*the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes*",[12] has emerged as a useful way to reduce both polypharmacy and the use of PIMs. The concept has garnered a global interest, with multiple deprescribing networks being formed,[13] symposia taking place,[14] and clinical

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recommendations being produced.[15,16] Deprescribing has been shown to be beneficial for relevant clinical outcomes, such as mortality and falls[17,18]; however, its integration in routine care is complex and requires a good collaboration, both between the healthcare professionals involved and with the patients.[19,20]

Local context

In some NHs of the French speaking part of Switzerland, such good interprofessional collaborations exist, thanks to the implementation of an integrated pharmacy service (IPS). Since 2002 in the canton of Fribourg and 2009 in the canton of Vaud, pharmacists', nurses' and physicians' collaboration is structured by the IPS, in which they take part in regular group discussions, prepared and facilitated by the NH pharmacist, with the goal of improving drug choice and reducing drug costs. Based on quality circle (QC) methodology, each NH continuously develops and updates a local prescribing consensus, based on evidence from the literature adapted to the realities of care in each NH. Physicians and nurses are responsible for implementing the consensus at the patient level, and pharmacists for monitoring their progress at the NH level, using drug consumption data. This IPS achieved a reduction in the cost of drugs, without reducing the quality of care,[21] and improved the appropriate use of antibiotics.[22] However, the use of PIMs remains high in these two cantons: a recent epidemiologic analysis showed that one in three drug doses used in these NHs is potentially inappropriate.[23] Likewise, an unpublished study from a Swiss health insurer showed that NH residents in canton with an active IPS are no less likely to receive PIMs than residents in other cantons (personal communication from A. Jamieson, *Pharmazeutische Betreuung in Pflegeheime*, presented at 3. Zürcher Forum fur Versorgungforschung, Zürich, 2016). Consequently, the need for deprescribing remains in these NHs.

Research project

NHs with IPS provide a suitable setting to trial deprescribing interventions, given that interprofessional collaborations are already established. Our research group launched the Opportunities and Limits to Deprescribing in Nursing Homes (OLD-NH) in 2017, with the support of the Swiss National Science Foundation, within a National Research Program called "Smarter Health Care" (www.nrp74.ch). The goals of the OLD-NH project are 1) to quantify the use of PIMs in the NHs of Vaud and Fribourg through an epidemiologic analysis; 2) to better understand the needs of both patients and professionals around deprescribing through qualitative studies; and 3) to trial deprescribing interventions in these NHs. The results of the epidemiologic analysis and qualitative studies have already been published[23–25]; this article describes the protocol for the interventional phase of OLD-NH.

Methods

Design overview

The intervention phase of OLD-NH consists of nested trials of two consecutive deprescribing interventions. The first intervention is a deprescribing module to be carried out in existing QCs, aiming to reach and implement a local deprescribing consensus that will deploy its effect at the NH level. The second intervention will be a deprescribing-focused medication review (MR; a MR is a structured evaluation of a patient's medicines aiming to optimise medicines use and improve health outcomes),[26] addressing both medication over-, mis- and underuse at the resident level, and resulting in the creation of an individualised drug-regimen modification plan. It will be trialed in the NHs allocated to the intervention arm of the first trial, and will start one year after the first intervention.

Fig. 1 details the flow of these two trials; they will be hybrid type 2, evaluating both the effects of the interventions and their implementation,[27] as there are many barriers to implementing deprescribing interventions into everyday practice.[28]

First intervention: Quality Circle-Deprescribing Module (QC-DeMo)

The initial protocol is available in Appendix 1, and the amended protocol in Appendix 2.

Population and recruitment

The study for the QC-DeMo intervention will take place in NHs of Vaud and Fribourg; all NHs caring for a mainly geriatric population and having entered the IPS at least one year before recruitment, to ensure that interprofessional collaboration is well established, will be eligible. No individual residents will be recruited for this study. The agreement of all involved healthcare professionals (physicians, head nurses and pharmacists) and the direction of the NH to take part in the study will be formalised by the signature of a document describing the procedures of the study.

Recruitment will start in September 2017, with a planned intervention period between Decembre 2017 and January 2018. The investigators will recruit NHs by direct contact with the NH pharmacists; the professional associations of NHs in Fribourg and Vaud will support the recruitment through direct mailings to their members, as will the professional association of NH physicians in Vaud. In case of insufficient recruitment, a second recruitment round will take place in 2018, with the intervention taking place between December 2018 and January 2019. If so, data of the two recruitment rounds will be pooled for analysis.

Randomisation and blinding

NH physicians in Switzerland sometimes attend multiple NHs. Therefore, a risk of contamination of the control group exists if two NH sharing a physician are allocated to different groups. Moreover, some large NHs have multiple attending physicians. Participating NHs will therefore be clustered by physicians for randomisation: all NH sharing at least one physician will be grouped in a cluster, and clusters will then be randomised in a 1:1 ratio. 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.

In case of a second recruitment round, the NHs sharing a physician with a NH of the first round will be allocated to the same group. The remaining NH clusters will be randomised between intervention and control, with a randomisation ratio adjusted to maintain balance in the number of clusters between the two groups.

Given the nature of the intervention, no blinding is possible at the NH level or for the investigators. Therefore, only the statistician performing the analysis will be blinded.

Intervention

The QC-DeMo intervention consists of a QC session, prepared and facilitated by the NH pharmacist, with the goal of producing a local deprescribing consensus for the NH.

All pharmacists participating in the study are experienced in conducting QCs. Those working within the NHs assigned to the intervention group will take part in a half-day education session where the material for the QC module (slides, relevant scientific literature and guidelines), and the study procedures and questionnaires will be made available to them. The content of the course, developed by the investigators, comprises 1) an overview of the problems posed to older people by polypharmacy and PIMs; 2) an in-depth description of the process of deprescribing and of its challenges; 3) the presentation of useful clinical tools; and 4) a selection of guidelines and evidence supporting the deprescribing of specific therapeutic classes (e.g. proton-

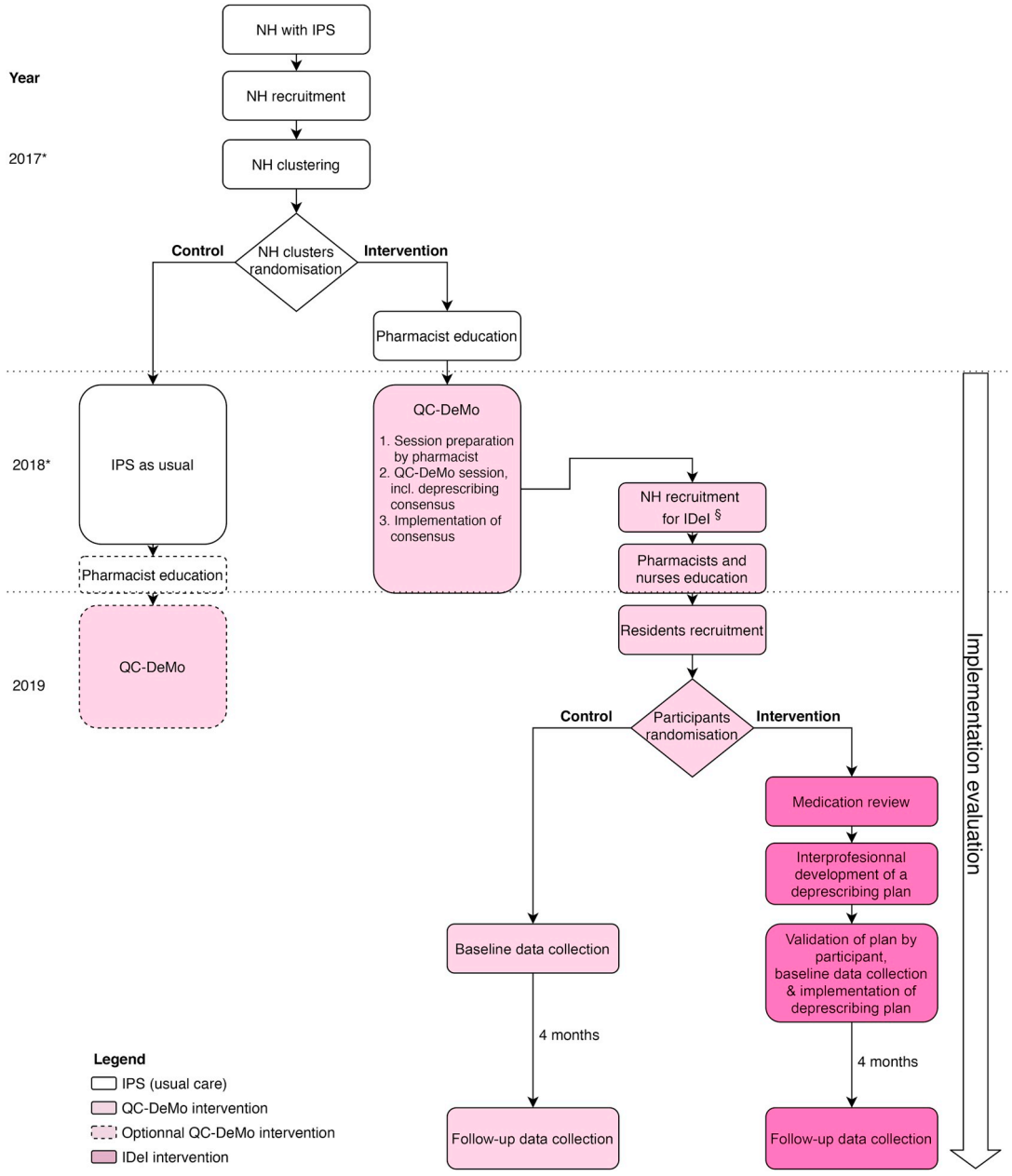

Fig. 1. Flow-chart for the QC-DeMo and IDeI studies. NH: nursing home; IPS: integrated pharmacy service; QC-DeMo: Quality Circle-Deprescribing Module; IDeI: Individual Deprescribing Intervention. *: 2018 and 2019 for QC-DeMo round 2; §: only for NH of QC-DeMo round 1; shapes with dashed outline: optional steps, no obligation for NH of the control group to enact the intervention.

pump inhibitors or cholesterol-lowering drugs). See Table 1 for a complete list of drug classes covered during the education session.

In the two months following the education session, NHs in the intervention group will hold a QC session prepared by the pharmacists. This session will address both generalities about polypharmacy, PIMs and deprescribing, and an in-depth discussion of the evidence and guidelines for deprescribing therapeutic classes selected by the pharmacists based on their use in the NH. The data necessary to select the specific therapeutic classes discussed during the session are routinely collected and analysed by the NHs' pharmacists as part of the IPS.

At the end of the session, a consensus for deprescribing specific therapeutic classes in the NH will be developped, and strategies devised to implement each chosen deprescribing measure. This consensus will then be enacted by the NH team; physicians will retain complete control over therapeutic choices for individual residents, including the choice to enact the consensus or not.

As a reminder, the pharmacists will send the consensus and strategies to the NH team two weeks after the session; they will also include a specific chapter about deprescribing in their annual report, and will be encouraged 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, shared to all NHs in the intervention group during the three months following the QC session, to foster discussion and ideas about deprescribing among the NH team and reinforce its implementation. Participating NHs will be encouraged to monitor progress on the implementation of the consensus, and will be free to hold supplementary QC during the year if needed.

Comparator

NHs allocated to the control group will pursue usual care for their

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Table 1
Drugs classes covered during the pharmacists education for QC-DeMo and rationale for deprescribing.

Drug class (ATC code)	Rationale for deprescribing	Tools presented
Biphsphonates (M05BA & M05BB)	Lack evidence for efficacy after 5+ years of treatment	
Lipid modifying agents (C10)	Negative risk/benefit ratio in people aged 85 or more if used in primary prevention	
Antihypertensives (C02)	Higher blood pressure targets for very old patients	
Proton-pump inhibitors (A02BC)	Frequent overprescribing	CDN alg.
	Side-effects in case of long-term use	
Antidepressants (N06A)	Frequent overprescribing	
Benzodiazepines (N05B & N05C)	Side effects in case of long-term use	CDN alg.
Antipsychotics (N05A)	Lack of evidence for use in dementia-associated symptoms	CDN alg.
Glucose-lowering drugs (A10B)	Higher HbA_{1C} targets for very old patients	CDN alg.
	Risk of adverse events if blood sugar too low	
Anti-dementia drugs (N06D)	Lack of efficacy; high costs	CDN alg.
Urinary spasmolytics (G04BD) and anticholinergic drugs	Lack of efficacy (urinary spasmolytics)	RMS tool
	Frequent side effects	

QC-DeMo: Quality Circle-Deprescribing Module; HbA_{1C}: glycated haemoglobin; CDN alg.: Canadian Deprescribing Network algorithm, available on www.deprescribing.org; RMS tool: detection tool for anticholinergic drugs published in Revue Médicale Suisse.[29]

residents for the duration of study. After study completion, they will be offered the opportunity to enact the intervention, and a separate education session will then be organised for their pharmacists, with the same content as the one for the intervention group pharmacists.

Outcomes

The primary outcome for the study is the change in the proportion of potentially inappropriate galenic units used in the NH between the first and second year of the study.

The appropriateness of each drug used in the participating NHs will be identified by a custom screening tool combining criteria from the 2015 Beers' list[30] and the Norwegian General Practice – Nursing Home criteria,[31] and classified as either "to avoid" or "to reevaluate". The proportion of potentially inappropriate galenic units will be computed by dividing the number of potentially inappropriate galenic units by the total number of galenic units. This outcome was used to compute the sample size.

Work on an epidemiologic analysis,[23] finalised by the investigators after the start of the study, made the use of another outcome technically possible: the number of potentially inappropriate Defined Daily Dose (DDD) per average resident and per day (DDD/res). This outcome is judged more robust than the primary, as it will not be influenced by the change in the use of non-inappropriate drugs, and will be able to reflect the potential changes in the doses of drugs resulting from the intervention, which the primary outcome can not. Therefore, the investigators chose to add the change in the number of DDD/res between the first and second year of the study as co-primary outcome. This addition was decided before the completion of data acquisition and before any analysis was carried out; the exact methodology for computation of this outcome can be found in the amended protocol in Appendix 2. Briefly: the number of DDD used in the NH will be computed according to the volume of drugs used and their respective DDD, and then divided by the total number of days spent in the NH during the year. Potentially inappropriate drugs will be identified with the same criteria as for the primary outcome. Drugs will be excluded from analysis if a DDD cannot be computed (e.g. vaccines or dermatological products), or if some information lack (e.g. some pharmacy-compounded products).

Secondary outcomes are listed in Table 2.

Sample size

Based on the IPS monitoring data for the NHs in Fribourg, the mean proportion of potentially inappropriate galenic units 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 was 0.8% (CI_{95} [-1.1%; 2.7%], SD 5.3%); the Pearson correlation coefficient ρ between values of the outcome for 2014 and 2015 was 0.54 (CI_{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.[35] Our hypothesis is that the QC-DeMo intervention 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 PIMs between the control and intervention groups. The standard deviation of the difference at 12 months (SDdiff) was estimated with the following formula, assuming a common standard deviation of 6.3% at baseline and 12 months:

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

By varying the correlation coefficient ρ along the confidence interval, plausible values of SDdiff were estimated to be between 4.1% (ρ = 0.7) and 7.5% (ρ = 0.3). A value of ρ = 0.3 (SDdiff = 7.5%) was chosen as 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%), 66 NHs, 33 per group, will have to be included.

Data collection

Necessary data for the primary outcomes and all secondary outcomes regarding drug consumption will be provided by the central monitoring for the IPS. Such data will be aggregated at the NH level; no data on individual residents will be collected. As these data require extensive processing before being exploitable, they will be available six months after the end of each calendar year (e.g. data for 2018 will be available in July 2019). Anticipated study completion date will thus be July 2019 if only one recruitment round is needed, and July 2020 if two rounds are needed.

Data for the security outcomes (falls, hospitalisation, use of restraints, death) will be collected on a yearly basis, using electronic questionnaires, directly from participating NHs.

Statistical analysis

The analysis will follow the intention-to-treat approach. If the primary outcome follows a not too skewed distribution and variances between intervention groups are equal, NH groups will be compared at 12 months by means of linear least-square regression under adjustment for baseline. In case of heteroscedasticity, a robust estimation of the variance will be applied. If the outcome does not follow a sufficiently normal distribution, a generalised linear model (GLM) will be applied with the most appropriate distribution and link function. Residual diagnostics will be used to check the quality of the statistical model. If it is not possible to find an acceptable model, the two NH groups will be

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Table 2
Secondary outcomes for the QC-DeMo and IDeI trials.

Trial	Secondary outcomes	Measurement method
QC-DeMo	Change in the number of DDD to avoid *	Idem primary outcome
	Change in the number of DDD *	Idem primary outcome
	Change in the number of hospital days *	Questionnaire submitted to NH
	Change in the mortality rate	Questionnaire submitted to NH
	Change in the number of falls *	Questionnaire submitted to NH
	Change in the number of restraint measures *	Questionnaire submitted to NH
IDeI	Change in the number of potentially inappropriate DDDs prescribed	Comparison of baseline and follow-up treatment plans, linked to the ATC/DDD set
	Change in the number of regular drugs prescribed	Comparison of baseline and follow-up treatment plans
	Change in the number of chronic DDDs prescribed	Comparison of baseline and follow-up treatment plans, linked to the ATC/DDD set
	Number of new drugs prescribed as a result of the intervention	Comparison of deprescribing plan and medication plan at follow-up
	Number of drug reintroduction	Comparison of deprescribing plan and final treatment plan
	Change in health-related quality of life	EQ-5D-5L questionnaire, either auto-administered or by proxy
	Change in the number of common drug-related complaints presented by the participant	Ad-hoc questionnaire
	Mortality rate	Number of participant having died divided by the total number of participants
	Hospitalisation rate	Number of participant having been hospitalised divided by the total number of participants
	Number of days spent in hospital	Ad-hoc questionnaire filled by nurses at follow-up
	Falls: • Number of falls • Proportion of participants having experienced at least one fall • Number of falls in participants having fallen at least once	Ad-hoc questionnaire filled by nurses at follow-up
	Number of days where physical or environmental restraints have been used	Ad-hoc questionnaire filled by nurses at follow-up

DDD: defined daily dose; ATC: Anatomical Therapeutic Chemical classification; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels questionnaire[32]; *: computed per average resident and per day (number of days spent in the nursing home during the year, divided by 365).

compared by means of a Mann-Whitney test without baseline adjustment.

The same procedure will be used to compare the differences between baseline and 12 months for the change in the number of DDD/res to avoid and to reevaluate (two variables), and for the mortality rate.

The other secondary outcomes, being counts, are likely to follow a Poisson distribution. Therefore, a GLM with family Poisson and logarithmic link function will be applied first.

Implementation evaluation

Based on the on the Framework for the implementation of services in pharmacy (FISpH), the implementation process of the QC-DeMo intervention will be evaluated at each phase: exploration, preparation, operation and sustainability.[39] The implementation outcomes measured will be: awareness, adoption and reach of the intervention, the fidelity to it, as well as its cost, acceptability and maintenance.

Data collection for the implementation evaluation will imply observations and the completion of ad-hoc questionnaires by nurses, physicians and pharmacists in both groups at baseline and after 12 months. The questionnaires will be adapted to each profession involved, and filled in anonymously.

At the end of the deprescribing QC session for the intervention group, and during a regularly scheduled QC session for the control group, baseline questionnaires will ask about previous deprescribing experiences and state of the interprofessional collaboration in the NH. In addition, in the intervention group, pharmacists will be asked to evaluate the education session that they attended; physicians and nurses will rate the deprescribing QC session that they attended on appropriateness and likelihood of positive outcomes.

A supplementary questionnaire will be sent every three months to the pharmacists of NHs in the intervention group, to monitor the implementation process after the QC session. They will be asked about the activities and time that occupied them outside the program and the predominant activities that they have led during these periods.

At 12 months, nurses, physicians and pharmacists of the intervention NHs will fill a second questionnaire to evaluate the implementation strategies related to the local deprescribing consensus, the degree of implementation of the consensus, and its effectiveness. Barriers and facilitators for each implementation strategies will be collected, as well as adoption, fidelity and maintenance data.

Second intervention: Individual Deprescribing Intervention (IDeI)

The IDeI trial will take place in the NHs that were allocated to the intervention group during the first round of the QC-DeMo trial (see Fig. 1). IDeI consists of a MR with a particular focus on deprescribing, followed by the construction and implementation of a drug-regimen modification plan. This review will take into account the clinical situation of the participant, i.e. pathologies, disabilities, drug regimen, and their therapeutic and life goals. The complete protocol for this trial is available in Appendix 3; it will take place between October 2018 and June 2019.

NH recruitment and pharmacists and nurses education

Six months after the QC session, eligible NHs will be invited to take part in this second study; the agreement of all healthcare professionals involved and of the NH direction will again be required and documented. Participating NH will designate a member of the nursing staff to coordinate activities of the study in the NH.

The NH pharmacist will perform the MR for the participating residents. They will receive education on the methodology of performing MRs prior to the study, by attending a postgraduate course organised by the Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva; the investigators will cover the cost of the course. For questions about specific drugs, diseases, or interactions, the pharmacists will be able to solicit the investigators, who have access to more academic and clinical resources. A separate education session will be organised in each NH for pharmacists and nurses, to present the conduct and documents of the study, and introduce them to the data capture platform (REDCap).[40,41]

Population and NH residents recruitment

NH residents aged 65 years and over, taking regularly five or more drugs, and living in the NH since at least four months are eligible to take part in the study. If the 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.

Many NH residents in Switzerland present cognitive problems, rendering them unable to provide consent for participation; however, excluding them would bias the results, greatly reducing the external validity of the findings of the study. Therefore, if an eligible resident is not capable of consent, a legal representative will be sollicitated to consent in their stead.

The eligible residents will be offered to enter the study in descending order of number of drugs prescribed (from most drugs prescribed to least), based on a ranking prepared by the NH pharmacist. Recruitment will be performed by the nurse responsible for the study in the NH, and will continue until 20% of the residents of the NH have been included, or until participation has been offered to all residents. An estimated 100 residents will be included in the study, based on a mean of 50 residents per NH and a forecast of 10 NHs participating in the study. As no data on pre-trial use of PIMs are available, no power calculation will be performed. Consent forms for participants and representatives are available in Appendix 4.

Randomisation and blinding

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 of size 2, to ensure equilibrium between groups, even in case of incomplete recruitment in the NH. The lists will be used to populate the randomisation module of the REDCap instance used for the trial; randomisation will be performed by the NH staff, upon completion of the inclusion questionnaire hosted on REDCap.

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 (see Implementation evaluation), investigators will not be blinded either. Thus, only the statistician will be blinded; unblinding will occur only after analysis completion.

Intervention

Pharmacists will perform a complete MR based on the medical data found in the residents' records at the NH, with insights provided by nurses and physicians about the care goals for the participants. The results of the review will be structured propositions of drug regimen modification, tailored to the clinical situation of the participants. These propositions will include regimen modifications (administration form, time, dose, or frequency), withdrawal or tapering of non-beneficial drugs (deprescribing), and introduction of new drugs in case of prescribing omission. These propositions will be discussed with the nurses and physicians, with the goal of developing a deprescribing plan that will be validated with the participants or their representatives before being enacted. The propositions resulting from the review and the deprescribing plan will be prepared following templates provided by the investigators.

Comparator

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

Outcomes

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. Number of medications will be extracted from the treatment plans, and appropriateness status determined using the results of STOPP/START analysis performed by the pharmacists.

The secondary outcomes, also measured at 4 months after baseline, are listed in Table 2.

Data collection

Data for the evaluation of the outcomes will be collected by the responsible nurses and pharmacists. Nurses will assist participants in completing the quality of life (QoL) and common complaints questionnaires, or fill them in their place if a medical condition prevents the participant from doing so. They will also complete the NeuroPsychiatric Inventory-Nursing Home version.[36] Pharmacists will extract the medication list of participants from the NH records and analyse it using the French translation of the second version of the screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START),[37] using the online implementation made available by the French Caisse Nationale d'Assurance Maladie.[38]

Baseline data collection for both groups will occur after the validation of the deprescribing plan to the participants of the intervention group; follow-up data collection will be performed after four months. Data will be collected and managed using the REDCap electronic data capture tools hosted at Unisanté.

In case of death of a participant during the follow-up period, their treatment plan on the day preceding death will be considered. For participants hospitalised at the end of the follow-up period, the treatment on their last day of presence in the NH will be considered. In both cases, no questionnaire for secondary outcomes will be filled.

Statistical analysis

The analysis will follow the intention-to-treat approach. The primary outcome, being a count, likely follows a Poisson distribution; after confirmation by visual inspection of the relevant plots and calculation of means and variance, groups will be compared using multilevel mixed-effect Poisson regression, with adjustment for baseline value and clustering by NH. If the outcome follows another distribution, a GLM with the most appropriate distribution and link function will be applied. Residual diagnostics will be used to check the quality of the statistical model. In the case of overdispersion (variance $>$ mean), a negative binomial distribution model will be tried.

The same procedure will be used for the secondary outcomes; for the outcomes involving defined daily doses, a mixed-effect linear regression model will be applied first, as they are more likely to follow a normal distribution.

Implementation evaluation

As for the QC-DeMo intervention, the implementation evaluation of IDeI will be based on the FISpH with focus on the implementation process and outcomes, as well as the impact of intervention.[39] The six main implementation outcomes that will be evaluated are: 1) acceptation of the IDeI intervention, measured by observation of validated and effective treatment changes; 2) acceptability of the intervention by professionnals and participants, measured by ad-hoc questionnaires; 3) perception of the intervention by participants' relatives, measured by an ad-hoc questionnaire; 4) time needed to enact the whole intervention, self-reported by the healthcare professionnals; 5) change in the burden of care for NH staff, measured using the NeuroPsychiatric Inventory – Nursing Home (NPI–NH); and 6) costs of the intervention and costs-savings generated.

Patients and public involvement

The views on deprescribing and possible interventions of nurses, pharmacists and physicians active in NHs eligible for participation in the QC-DeMo trial were collected through focus groups and individual interviews in the exploratory phase of OLD-NH.[25] Nurses, pharmacists and physicians participating in the QC-DeMo trial were invited to take part in a focus group on the design of the IDeI trial, especially on the design of the intervention.

Ethical considerations and registration

For organizational reasons, the two trials described in this paper have been submitted separately to the *Commission cantonale d'éthique de la recherche sur l'être humain* of Canton de Vaud (CER-VD), the relevant ethics committee, as only the IDeI trial falls under the Swiss law for research on human subjects. However, both trials were always intended to be carried out as described here, and have been submitted as such to the Swiss National Science Foundation, which funds the whole OLD-NH research project through the National Research Program 74 "Smarter Health Care".[42]

The CER-VD confirmed that the QC-DeMo trial does not fall under the applible Swiss law for research on human subjects (decision 2017-01009), and approved the IDeI trial (decision 2018-01279). Both trials were separately registered on ClinicalTrials.gov (QC-DeMo: NCT03688542; IDeI: NCT03655405), and IDeI was also registered on the Swiss national registry of clinical trials (SNCTP000002975), as required by Swiss law.

Discussion

This article presents a pragmatic, nested study of two consecutive deprescribing interventions, in NHs where interprofessional collaborations are well-established and successful.

In the past decade, numerous studies have anchored deprescribing as a safe and powerful tool to enhance clinical outcomes for elderly patients and nursing home residents.[17,18] Accordingly, the research effort around this topic has shifted to finding the best ways to deprescribe safely and efficiently. This was illustrated at the 2018 Bruyère Evidence-Based Deprescribing Guidelines Symposium,[14] where the priority areas for future research identified by the participants included items such as understanding the implementation of deprescribing in routine practice, conducting pharmacoeconomic studies, or a need to focus on patient-important outcomes.[43] Thanks to their hybrid nature and their articulation between interventions at the NH level and the resident level, the trials described in this paper will contribute evidence to some of these priority areas, such as understanding the implementation process, the evaluation of interventions at different levels of the healthcare system, and the pharmacoeconomic impact of deprescribing.

Choice of interventions

A meta-analysis by Page et al.[17] showed that patient-centered deprescribing interventions have more effects than educational ones. Most of these patient-centered interventions consisted of MRs, led either by pharmacists or by physicians. In another meta-analysis of studies carried out in NHs, Kua et al.[18] showed that MRs are the only intervention with a significant impact on mortality and the number of falls. MRs, however, are costly to perform, requiring time from well-trained professionals that may not be available in every NH.[44]

We decided to build on the existing activities of the IPSs to test an intermediate deprescribing intervention, QC-DeMo, designed to be less costly than a MR, but with better chances of success than a purely educational one. We anticipate that the engagement of the whole NH team resulting from a NH-wide consensus supported by self-designed implementation strategies is more likely to induce change in drug-use patterns than a strictly educational intervention.

This first intervention will not, however, address all PIMs use and polypharmacy problems, because the consensus produced by the QC may not be applicable to all NH residents, given their specific health conditions. Thus, after enough time for QC-DeMo to deploy its effects, the IDeI will target the residents that are still most at risk of PIMs use.

Strengths and limitations

The main strength of the studies presented in this article is their "real-world" setting: the interventions tested will be carried out by field professionals with minimum additional training and minimal clinical support from the investigators, which will enhance the external validity of the findings. The hybrid design of these trials, analysing effectiveness and implementation processes in parallel, will facilitate dissemination in case of positive findings. The nested design will enable the combined effect of two interventions to be trialed in the same setting, providing evidence on the interest of implementing more widely any of the two interventions, or both.

For the IDeI study, participation will be offered to potential participants in decreasing order of number of drugs used. This strategy was chosen to enrol the residents most at risk of PIMs use, and thus the most likely to benefit from deprescribing; the number of drugs was chosen as a proxy for PIMs use, as it is easy to assess and a predictor of both PIMs use[45,46] and adverse events such as falls.[47] This recruitment strategy could, however, prove problematic: it is indeed possible that participants using the most drugs are the ones in which discontinuation is the most difficult, either because each drug is necessary for managing their clinical situation, or they do not wish to discontinue specific drugs.

These trials present other limitations, mainly regarding the choice of outcomes. First, the effects of QC-DeMo will not be evaluated at the resident level, and will therefore only provide information on prescribing process outcomes; humanistic outcomes such as quality of life, which are of great importance in NHs,[48] will not be evaluated, because doing so would require the informed consent of every individual resident, which is unlikely to be given in a timely fashion. The main outcome was chosen as data on pre-trial use of PIMs in the eligible NHs were available, enabling the calculation of a sample size. Likewise, the IDeI intervention will be evaluated on a proxy main outcome, the number of PIMs, and not on a clinical one like death or hospitalisation, or a humanistic one such as QoL. Such outcomes would require much larger studies, which are not feasible given the available funding. Additionally, as the population in Swiss NHs is extremely frail (the median age is over 80 years old, and up to 70% of residents suffer from cognitive dysfunction),[49,50] achieving a meaningful reduction in death or an improvement in QoL by acting on medication only is unlikely. This supposition was later confirmed by a meta-analysis by Pruskowski et al. that showed that deprescribing interventions do not significantly improve or degrade QoL.[51]

This extreme frailty of the population explains another limitation of the IDeI trial: its short follow-up period, which does not allow for the detection of the long-term effects of the reduction in PIMs use, such as changes in cognitive function or propensity to fall. A longer follow-up period in this population would increase loss to follow-up due to death: the average duration of a NH stay in the cantons of Vaud and Fribourg was indeed slightly over 2 years on average in 2017.[52]

The particular setting in which these interventions are trialed is both a strength and a limitation: on the one hand, well-stablished interprofessional collaborations and a closed setting like a NH improve the chances of success of the interventions, as many studies described the lack of collaboration and fragmentation of care as a barrier to deprescribing.[53–55] On the other hand, the characteristics of the NHs will limit the transferability of the findings to other settings, particularly in ambulatory care, where care fragmentation is widespread and interprofessional collaboration may be less developed. This emphasises the importance of running effectiveness and implementation studies in parallel.

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CRediT authorship contribution statement

Damien Cateau: Conceptualization, Funding acquisition, Project administration, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Pierluigi Ballabeni:** Methodology, Formal analysis, Writing - review & editing. **Stephanie Mena:** Writing - original draft, Writing - review & editing. **Olivier Bugnon:** Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Anne Niquille:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interests

The authors declare no competing interests with regard to these trials.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sapharm.2020.05.026.

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