Impact of a deprescribing tool on the use of sedative hypnotics among older patients: study protocol for a cluster randomised controlled trial in Swiss primary care (the HYPE trial)

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ABSTRACT

Introduction Benzodiazepines and other sedative hypnotics (BSH) are potentially inappropriate and harmful medications in older people due to their higher susceptibility for adverse drug events. BSH prescription rates are constantly high among elderly patients and even increase with higher age and comorbidity. Deprescribing BSH can be challenging both for healthcare providers and for patients for various reasons. Thus, physicians and patients may benefit from a supportive tool to facilitate BSH deprescribing in primary care consultations. This study intends to explore effectiveness, safety, acceptance and feasibility of such a tool.

Methods and analysis In this prospective, cluster randomised, controlled, two-arm, double-blinded trial in the ambulatory primary care setting, we will include general practitioners (GPs) from German-speaking Switzerland and their BSH consuming patients aged 65 years or older, living at home or in nursing homes. GPs will be randomly assigned to either intervention or control group. In the intervention group, GPs will participate in a 1-hour online training on how to use a patient support tool (decision-making guidance plus tapering schedule and non-pharmaceutical alternative treatment suggestions for insomnia). The control group GPs will participate in a 1-hour online instruction about BSH epidemiology and sleep hygiene counselling. This minimal intervention aims to prevent unblinding of control group GPs without jeopardising their ‘usual care’.

The primary outcome will be the percentage of patients who change their BSH use (ie, stop, reduce or switch to a non-BSH insomnia treatment) within 6 months from the initial consultation.

Expected benefit Based on the results of the study, we will learn how GPs and their patients benefit from a supportive tool that facilitates BSH deprescribing in primary care consultations. The study will emphasise on exploring barriers and facilitators to BSH deprescribing among patients and providers. Positive results given, the study will improve medication safety and the quality of care for patients with sleeping disorders.

Ethics and dissemination The study has been approved by the Ethics Committee of the Canton of Zurich (KEK-ZH

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study, with its prospective, cluster randomised, controlled, two-arm, double-blind core trial, is particularly well suited to investigate both the efficacy and implementation of the proposed standardised intervention.

⇒ The pragmatic design of the study takes into account the many challenges, for example, regarding recruitment or protocol adherence by providers and patients, which researchers often face in the outpatient primary care setting.

⇒ By including patient-related outcome measures, patient-related experience measures and implementation issues, we are responding to the current call for more patient-relevant and feasible outcomes.

⇒ A panel of patient and public representatives is involved in the conceptualisation of the study from the outset and contributed their valuable perspective throughout.

⇒ The restriction to German-speaking Switzerland will limit the generalisability and a selection bias among general practitioners may occur despite randomisation.

INTRODUCTION

Prescription rates of benzodiazepines and sedative hypnotics (BSH) are constantly high for older people.1 Prevalence rates of BSH use for patients aged 65 years or older vary between 9% and 54%, depending on age and comorbidity.2 A Canadian study demonstrated a high BSH incidence rate of 16% during hospital stay among previously BSH-naïve patients, and 87% of these BSH were prescribed inappropriately.3

Ref no. 2023-00054, 4 April 2023. Informed consent will be sought from all participating GPs and patients. The results of the study will be publicly disseminated.

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BSH use is associated with increased rates of falls, injuries, fractures, cognitive impairment, delirium, hospitalisations, entries into nursing home, cost and increased mortality, with an average OR for these adverse events (AEs), compared with non-consumers, of roughly 2–4. 

Although many of the harmful events are considered multifactorial, a reduction in BSH use would prevent many AEs, and therefore, public healthcare and the individual would benefit. Consequently, BSH are widely recognised as potentially inappropriate medication, and movements such as ‘Choosing Wisely’ are campaigning to avoid them.

The first deprescribing guidelines have started to tackle the overuse of BSH successfully, in new inpatient prescriptions (‘Less sedatives for your older relatives’ toolkit) and in ambulatory care (‘Drowsy without feeling lousy’ toolkit). However, data about the effectiveness of BSH deprescribing are still scarce. It seems that psychotropic drugs are among the most resistant to deprescribing, despite intensive intervention. General practitioners (GPs)—as the main prescribers of BSH—and because of their trusting relationships with their patients—are predestined to make an important contribution to more restrained BSH use.

There is an urgent need to develop interventions in this area and explore their effectiveness and implementation. BSH deprescribing interventions may improve the quality and safety of care, particularly for older and frail patients taking BSH, thus enabling them to maintain their activities of daily living and their autonomy.

Hypothesis and primary objective

We hypothesise that a BSH deprescribing guidance for GPs and patients is efficient, safe, feasible and acceptable among the target groups. The guidance consists of two elements: first, a support tool with a (shared) decision-making guide, a BSH tapering schedule, and a catalogue of alternative (ie, non-BSH) approaches to improve sleep quality. As its second element, the guidance includes an online tutorial on how to use the support tool.

The study aims to investigate the effectiveness (and safety) of said guidance. Additionally, it aims at exploring barriers, facilitators and other implementation issues of BSH deprescribing among patients and GPs.

METHODS AND ANALYSIS

Study design

Prospective parallel controlled, cluster randomised, double-blind, single-centre clinical trial with 6 months follow-up among Swiss primary healthcare providers and their older patients living either at home or in nursing homes (figure 1). The study is designed to evaluate, in parallel with effectiveness outcomes, implementation feasibility and acceptability through mixed methods and according to the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework. To optimise feasibility and acceptance of the study procedures and materials, they will be pilot tested with three GPs before the start of the main study. The evaluation of the pilot test consisted of a short online 5-point Likert scale questionnaire about the feasibility and acceptance of the different study steps and free-text boxes for further comments.

Patient and public involvement

The research questions and the outcomes were guided by the priorities, experiences and preferences of patients. We gathered this valuable input through multiple sessions with a panel of 12 patients and citizens. This panel and other contributors such as a GP panel, a nurse panel and an academic expert panel played a significant role in shaping the study design, recruitment strategy, study procedures and the patient support tool. Once the study concludes, we will share the final results with the study GPs in a clear and accessible summary. We will then request the GPs to convey this information in lay language to their study patients. In order to assess the potential burden of the intervention, we will ask the study patients to share their experiences concerning this matter at T1 (6 months after the initial consultation). This feedback will be instrumental in understanding the impact of the intervention and improving its effectiveness in the future.

Study population

Practising in the German-speaking part of Switzerland will be the only inclusion criterion for GPs (imposed for reasons of feasibility), and there will be no exclusion criteria with regard to GPs. For patients, the following criteria will apply:

- Aged 65 years or older.
- Living at home or in a nursing home.
- Taking BSH for at least 2 weeks.
- Registered as patient in the practice records of the recruiting GP.
- Willing to discuss their sleep and sleep behaviour with their GP.
- Able to provide the relevant outcome information (eg, rating on the quality-of-life scale).
- Provided informed consent.

Patient exclusion criteria (any of)

- Life expectancy of less than 6 months.
- Incapable of judgement according to the clinical evaluation of the GP.

The minimal set of exclusion criteria is chosen in order to achieve high external validity and generalisability of the study results for ambulatory primary care. Corresponding to the higher prevalence of BSH use among women in the general population, we expect and accept to include more women into the study than men. However, should an interim analysis (time point: 50% of patients needed are recruited) reveal that 80% or more participants are female then we would introduce a selection criterion in favour of male participants.
GP = general practitioner; BSH = Benzodiazepine or other sedative hypnotics; DA = decision aid; T0 = initial consultation; T1 = 6 months after T0; T2 = 14 months after T0 of the GP’s first study patient. Appointment 1 and appointment 2 may also be merged to one appointment, if perceived as appropriate by the GP and/or patient.

Figure 1  Study flow chart.
All patients will have to provide written informed consent before definite study inclusion. To accommodate all genders, we include the option ‘diverse’ on all forms.

**GP recruitment**

In mid-2023, we will invite GPs from all German-speaking regions of Switzerland (which hosts about three quarters of all Swiss GPs) by email (if available) or postal mail to participate in the study. The invitation letter will provide basic information about the most relevant study features. Additionally, we will promote the study by directly approaching the participants of major GP conferences in German-speaking Switzerland (between June and September 2023). All invited GPs who agree to participate will receive detailed information about the study and the consent form. Undecided GPs will find an option in the invitation letter to request additional information from the study team by phone or email.

**GP allocation**

GPs who return the signed consent form will be randomised as clusters (more precisely: as cluster-defining units) to avoid contamination among their patients and in batches to avoid delays for already included GPs due to slow recruitment. A new batch of GPs will be randomised using constrained randomisation whenever the required number of participants for an even number of training sessions has been reached. The additional allocation constraint, that all GPs of the same (group) practice be allocated to the same study group (thus forming ‘super-clusters’ of clusters), will help prevent contamination between GPs.

After randomisation and completion of their online training (see section Intervention) according to their specific group allocation, GPs will start to recruit patients in their practices.

The study is planned to initiate in August 2023, with the participation of the ‘first GP in’ serving as the starting point.

**Patient recruitment**

Eligible patients will be identified by their GPs in their practices and invited to participate. Patient recruitment will be attempted during regular appointments with the GP. The GPs will ask their patients to participate and, depending on their reactions, list them either as rejecters or as participants. Both lists will remain with the respective GP until the end of the study. As GPs may tend to choose patients they perceive as more suitable or cooperative, potentially excluding those who may present greater challenges or need for intervention, we will define randomly selected working days as a recruitment window. Nevertheless, the GPs’ reluctance to select patients with a perceived poor communication climate or problematic physician–patient interactions may still lead to a selection bias.

Based on own experiences from previous similar studies in primary care,15–21 each GP can be expected to enrol 4 (and up to 8) patients without compromising feasibility and study adherence. For each practice, the maximum duration of the patient recruitment phase will be 6 months from the date the first patient is recruited.

Informed consent will be obtained from every patient, willing to discuss their sleeping behaviour, by their GP or the medical practice assistant (MPA) after explaining the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and the benefits. The GPs will further inform participants that (A) participation in the study is voluntary, (B) withdrawal from the study is allowed at any time without giving a reason and (C) withdrawal will not affect the patient’s subsequent medical assistance and treatment. Finally, GPs will also explain to the participants that by signing the consent form, they grant access to their encoded study data to the study staff, and that one designated study nurse at the study centre (the Institute of Primary Care, Zurich) will also know their identities for mailing purposes.

In addition to the verbal information, all study patients will receive a written information sheet and the consent form. The participants will have enough time to decide whether or not to participate. For patients living in a nursing home, the responsible GPs will hand out separate information sheets to the relatives, nursing care team and to the nursing home directors.

The GP (or the MPA) will sign and date the consent form at the same time as the participant. The original signed consent form will be filed as part of the study records at the study centre, and a copy will be provided to the patient.

**Patient allocation**

All patients will be allocated to their recruiting GP’s study group without further randomisation and will be part of her/his cluster.

**Blinding**

Participating GPs will need to know that this is a two-arm interventional trial for being able to consent, but they will not be informed about the respective other group’s study activities. However, based on experience from previous trials, we expect that some of the control group GPs may still suspect their allocation, resulting in not-quite-perfect blinding.

All patients will be blinded to the group allocation of their GP (and, consequently, of themselves). The study design is therefore considered to be ‘as double-blind as possible’ on the GP-patient level.

Data encoding will ensure that the study staff involved in data analysis will not know the participants’ group allocations.

**Withdrawal**

GPs: A 10% withdrawal rate among participating GPs is factored into the required minimum number of participating GPs. A reserve list will be maintained from which additional GPs can be recruited if more than 10% drop
out. All patients’ data collected until their GP’s withdrawal will be evaluated.

Patients: If patients withdraw from participation, their data collected up to that point will be evaluated and their reasons for withdrawal collected (if patients are willing to provide any).

Remuneration for GPs and patients
We will pay each participating GP a base amount of 250 Swiss Francs (CHF) plus an additional 75 CHF per patient to cover their time spent on study activities. This remuneration is not for the actual consultations, which will be covered by the patients’ healthcare insurers. In accordance with the Human Research Act (HRA), Art. 14, participating patients (who may directly benefit from the study intervention) will not be paid for their contribution.

Intervention
The intervention will take place on two levels: first, on the GP level (training on how to use the patient support tool), and second, on the patient level (in consecutive consultations).

Intervention group
The active study intervention will be a 1-hour online training of GPs on how to use the patient support tool for consultations with patients taking BSH. Additionally, the GPs and their MPAs will receive 30 min of online instructions on study procedures and data acquisition in their practices. Where appropriate, training and instructions will be open to other healthcare providers (eg, nurses in nursing homes).

Content of the training
The online training session outline will be as follows:
The patient support tool and its rationale will be introduced. GPs will then be instructed on
► How to sensitise patients for the discussion about their sleeping medication.
► How to discuss the balance of benefits and harms of BSH with patients to initiate a shared decision-making process.
► How to deal with patient resistance to deprescribing BSH, and how to apply communication strategies (elements of the ‘motivational interviewing’ technique) to overcome known barriers.
► How to propose non-pharmaceutical alternative treatments for insomnia (eg, cognitive behavioural therapy for insomnia).22 23

Content of the ‘patient support tool’
The guidelines for patient decision aids (eg, from the International Patient Decision Aid Standards Collaboration24) are considered when developing the patient support tool. This tool will be an adapted version of the Canadian Deprescribing Network toolkit for BSH deprescribing, which is a resource for GPs (decision algorithm) and patients (decision aid).3-13 Key components of our patient support tool are:
► Elicitation of the original and current reasons for BSH prescription, duration of use, current dosage and current sleep patterns.
► Compilation of a ‘pros and cons’ table for stopping/reducing BSH use.
► Discussion of the patient’s priorities on these issues.
► A BSH tapering protocol (online supplemental file 1).
► Behavioural counselling with a focus on self-efficacy and suggestions for alternative, non-BSH treatments (online supplemental file 2).
► Reassurance that BSH deprescribing can be reversed if the high burden of insomnia cannot be improved by alternatives or in case any other long-term disadvantages should occur.
A dosage schedule and a schedule of follow-up appointments with the GP to support the weaning process and to provide reassurance (online supplemental file 3).

Control group
The GPs in the control group will complete a 1-hour online course on the epidemiology of BSH use and the need for a more detailed data collection, that is, to collect more data on BSH prescriptions and related AEs (thus encouraging ‘usual care’ by the control group participants). In order to prevent unblinding of GPs, the control group’s online training will include advice on discussing general sleep hygiene with patients, which we consider a minimal sham intervention of negligible impact. Additionally, the control group GPs and their MPAs will receive 30 min of online instructions on study procedures and data collection in their practices, identical to the intervention group (except for measurements specific to the intervention). Unlike in the intervention group, GPs in the control group will not receive the ‘patient support tool’ and will not suggest the deprescribing scheme to their patients.

Data collection
Table 1 lists all time points and the corresponding measurements. The following is a brief overview.
► After signing the consent form (at T0 or in preliminary consultations shortly before T0), the patients will provide their personal basic characteristics and baseline data.
► At T0 (or in preliminary consultations shortly before T0), the T0 tests and questionnaires will be filled out. The GPs in the intervention group will suggest to the patients how to change their BSH use, using the patient support tool including the medication plan, and the GP will document the patients’ acceptance or refusal of the suggested changes. T0 is set individually for each patient and relates to the time point after the initial consultation; the consecutive time point T1 (6 months after T0) varies between patients accordingly.
► Patients in the intervention group may discuss their progress and/or readjust their BSH use in optional additional consultations with their GPs, while patients in the control group will receive usual care. Patients in both groups will be continuously monitored for
Table 1  Time points with corresponding measurements

<table>
<thead>
<tr>
<th>Time point</th>
<th>Measurements</th>
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| Tx (during GP recruitment) | 1. GP characteristics:  
  ► Age, sex  
  ► Experience as a GP (years)  
  ► Practice type (solo, group)  
  ► Region (rural/urban/suburb)  
  ► Physician drug dispensing (yes/no) |
| Tx (during GP recruitment) | 2. GP characteristics:  
  ► Age, sex  
  ► Experience as a GP (years)  
  ► Practice type (solo, group)  
  ► Region (rural/urban/suburb)  
  ► Physician drug dispensing (yes/no) |
| T0 (immediately after the initial consultation) | 1. Patient characteristics:  
  ► Age, sex  
  ► List of drugs taken (incl. “as needed” drugs)  
  ► Living situation (at home, in a nursing home)  
  2. BSH treatment (name, defined daily dose, since when)  
  ► Willing to change, that is,  
    – to stop the BSH (defined by the ATC codes N05CD and N05CF)  
    – to reduce the BSH (defined by at least 50% of the previous dosage, or by at least 50% of the DDD if switched to another BSH)  
    – to switch to a non-BSH insomnia treatment  
  ► Willing to continue with the BSH treatment  
  3. SIS  
  4. TMT-A  
  5. DIA-S  
  6. ISI  
  7. GAD-7  
  8. EQ-5D-5L |
| Between T0 and T1 (to be documented immediately and summarised at T1) | 1. Falls  
  ► No Injury  
  ► Fracture leading to  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  ► Other injury (excluding fractures), leading to  
    – no utilisation of healthcare  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  2. Other events  
  ► Onjury (not resulting from a fall)  
    – no utilisation of healthcare  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  ► Episode of anxiety (as perceived by the patient)  
    – no utilisation of healthcare  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  ► Episode of depression (as perceived by the patient)  
    – no utilisation of healthcare  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  ► Episode of confusion (as perceived by the patient)  
    – no utilisation of healthcare  
    – ambulatory care (GP visit, ED visit)  
    – hospitalisation  
  ► Hospitalisation not due to injury, fracture, anxiety or depression  
  ► Death (as a safety outcome) |

Continued
Table 1  Continued

<table>
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<tr>
<th>Time point</th>
<th>Measurements</th>
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| T1 (6 months after the patient’s initial consultation) | 1. Current BSH intake (name, defined daily dose)  
   ► Continued since study entry (no change)  
   ► Re-started with the BSH after initial change  
   2. No or reduced current BSH intake compared with T0  
   ► No current intake of BSH  
   – stopped the BSH, no alternative treatment  
   – switched to a non-BSH insomnia treatment since the initial consultation (T0)  
   ► reduced the BSH (defined by at least 50% of the previous dosage, or by at least 50% of the DDD if switched to another BSH)  
   3. SIS  
   4. TMT-A  
   5. DIA-S  
   6. ISI  
   7. GAD-7  
   8. EQ-5D-5L  
   9. Follow-up phone calls with patients to evaluate the implementation issues and assess any clinical events |
| T2 (14 months after the initial consultation of a GP’s first patient) | 1. Qualitative measurements (questionnaires) among GPs in the intervention group:  
   ► Barriers  
   ► Facilitators  
   2. Implementation measurements: GP questionnaires/no of dropouts at different time points of the study (see figure 1) and other issues according to the RE-AIM framework (see chapter 3) |

Outcome measures

Primary outcome

The percentage of patients who have stopped, reduced or switched their BSH use to a non-BSH insomnia treatment at T1 (ie, 6 months after T0) compared with T0 (initial consultation). For specific definitions, see table 2.

Clinical relevance

For the intervention group, we expect 25% of patients to have stopped, reduced or switched their BSH use to a non-BSH insomnia treatment after 6 months (T1). For the control group, we expect 10% of patients to have changed their BSH use after 6 months (T1) under usual care. With the expected difference of 15%, one out of seven patients would have changed their BSH use due to the intervention. With a successful implementation and dissemination of the intervention, a 15% reduction of patients taking BSH would translate into a corresponding reduction of AEs of high relevance to patients and healthcare systems (see the Introduction section). This would have a high impact on the individual as well as the public healthcare system. The rationale for collecting the primary outcome 6 months after the initial consultation is the issue of sustainability of the intervention’s effect.
Secondary outcomes
Except for secondary outcome number 2, all the secondary outcomes will be compared between the intervention and control group participants.

1. The percentage of patients willing to change their BSH use (ie, stop, reduce or switch to a non-BSH insomnia treatment) at the end of the initial consultation (= T0).
2. The percentage of patients not accepting the BSH de-prescribing suggestion at T0.
3. Cumulative incidence between T0 and T1 of the following clinical events including utilisation of health-care:
   a. Falls
      - No injury
      - Fracture, leading to
        o Ambulatory care (GP visit, emergency department (ED) visit)
        o Hospital stay
    - Other injury (excluding fractures), leading to
      o No utilisation of healthcare.
      o Ambulatory care (GP visit, ED visit).
      o Hospital stay
   b. Other events
      - Injury (not resulting from a fall)
        o No utilisation of healthcare.
        o Ambulatory care (GP visit, ED visit).
        o Hospital stay.
      - Episode of anxiety (as perceived by the patient)
        o No utilisation of healthcare.
        o Ambulatory care (GP visit, ED visit).
        o Hospital stay.
      - Episode of depression (as perceived by the patient)
        o No utilisation of healthcare.
        o Ambulatory care (GP visit, ED visit).
        o Hospital stay.
      - Episode of confusion (as perceived by the patient)
        o No utilisation of healthcare.
        o Ambulatory care (GP visit, ED visit).
        o Hospital stay.
      - Hospital stay not due to injury, fracture, anxiety or depression.
   - Death (as a safety outcome).

Clinical relevance
The secondary outcomes are of high clinical relevance for individuals and public health, and are associated with direct and indirect costs for avoidable events.

Measurement
At each consultation between T0 and T1, the GPs or their MPAs will ask study patients about the above events and enter all reported events directly into a REDCap database at the study centre via a dedicated online form. Additionally, at T1 (6 months after the initial consultation) a study nurse will contact the patients or, where applicable, their family members, by phone to collect data on events between T0 and T1.

4. Mean change in cognitive function level between T0 and T1.

Measurement
► Six-item screener\textsuperscript{25, 26}: measures cognitive function, orientation and attention.
► Trail Making Test Part A (TMT-A)\textsuperscript{27}: measures attention and visual-motor (cognitive) processing speed (which typically is affected by BSH consumption).
5. Mean change in depressive symptoms between T0 and T1.

Measurement
Depression in Old Age Scale\textsuperscript{28}
6. Mean change in subjective sleep quality between T0 and T1.

Measurement
Insomnia Severity Index\textsuperscript{29}
7. Mean change in anxiety symptoms between T0 and T1.

Measurement
Generalized Anxiety Disorder Scale-7 (GAD-7)\textsuperscript{30, 31} (is a part of the Patient Health Questionnaire (PHQ)\textsuperscript{32, 33}).
8. Mean change in the quality of life (QoL) between T0 and T1.
Clinical relevance

Although influenced by many factors and therefore not specific, QoL is one of the most relevant patient-related outcomes. The measurement tool chosen is an excellent instrument to monitor functions affecting QoL.

Measurement

European Quality of Life 5 Dimensions 5 Level Version: covering the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Process and implementation outcomes

According to the RE-AIM framework, see online supplemental file 4.

Data analysis

We will use descriptive and graphical methods to describe the study sample. Covariates (in particular GP and patient sex) and outcome baselines will be calculated with standardised mean differences as imbalance measures. We will use the R statistical software package in its current version for all quantitative analyses.

Primary analyses

To assess the primary outcome, we will compare raw numbers of BSH use changes in both groups by \( \chi^2 \) test and calculate BSH change rates and their unadjusted difference between groups with 95% CIs. The number needed to treat will be calculated as the inverse of the rate difference.

To adjust for patient characteristics (in particular sex), baseline imbalances and clustering (ie, a possible correlation between individuals in the same cluster), we will also analyse the primary outcome using hierarchical logistic regression using the patient as the unit of analysis and their GP as a random factor.

Secondary analyses

We will compare secondary outcomes between the two groups using \( \chi^2 \) tests (or Fisher’s exact tests) for binary data and t-tests (or Wilcoxon U tests) for incidence rates and metric data. Adjusted analyses will use hierarchical logistic regression models for binary outcomes, hierarchical Poisson regression for incidence rates and hierarchical linear regression models for metric scores.

Additional analyses

We will also carry out primary and secondary analyses within the subgroups of patients living at home and in nursing homes, respectively. In exploratory analyses, we will search for determinants associated with a change in BSH use and other outcomes. Confounders of such associations, for example, the duration of BSH use before study entry, will be analysed similarly. For qualitative data, we will use content analysis and thematic analysis methods. Process evaluation will follow the RE-AIM framework.

Preliminary and interim analyses

If deemed necessary, we will carry out ad hoc analyses after completion of the pilot phase with a focus on improving study instruments. The statistical methodology for such preliminary analyses will be mostly qualitative and descriptive. Interim analyses similar to the final analyses will be considered in case of delays and if requested by the sponsor.

Handling of missing data and dropouts

Both intention-to-treat (ITT) and per-protocol analyses will be performed. Patients lost to follow-up will be treated as having neither discontinued nor reduced their BSH use in ITT analyses, and other missing values will be multiply imputed. We will also analyse complete cases for comparison.

Sample size

A study in a similar setting and a similar intervention reported a BSH stop rate of 27% plus a reduction rate of 11% in the intervention group (yielding a total change rate of 38%) and corresponding rates of 5% and 6% in the control group (11% total change rate). We cautiously assume total change rates of pI=25% and pC=10%. Further assuming a cluster size of 4 (ie, 4 patients per GP), an intrachoice correlation of 0.04, a fraction of 20% of patients lost to follow-up, stipulating a power of 1–β=0.90 and a significance level of α=0.05, we calculated a minimum sample of 46 GPs and 184 patients per group, that is, 92 GPs and 368 patients overall.

To raise the power of the study for several secondary outcomes (although highly relevant), a considerably higher number of participants would be needed, which is beyond the study’s scope and budget.

AEs and notification of safety and protective measures

AEs and serious AEs (SAEs) are defined according to ClinO, Art. 63, and will be recorded continuously by the GPs over the entire duration of the study with the help of an online data mask and reported to the sponsor investigator. Both the study GP and the sponsor investigator will assess a possible causal association between the event and the study intervention.

Study timetable

The study was initiated in the mid-2022. For the study timetable see online supplemental file 5.

ETHICS AND DISSEMINATION

Local regulations

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the International Conference on Harmonisation - Good Clinical Practice (ICH-GCP), the HRA and other locally relevant legal and regulatory requirements.

Protocol amendments

Significant changes, that is, changes that affect the safety, health, rights and obligations of participants,
changes in the protocol that affect the study objective or central research topic, changes of the study site or of the sponsor investigator (ClinO, Art. 29) will be documented and reported as protocol amendments to the ethics committee as soon as possible for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may be implemented without prior approval of the ethics committee.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR. No such submission will be made in the absence of any such non-substantial changes or amendments.

Data security_disclosure of original documents
All confidential information fall under medical confidentiality rules and will be treated according to appropriate Federal Data Security Laws. All CRFs used in the study will be coded with keys as appropriate. During transcription, the data will be further encoded with an additional key specific to the person transferring the data from the CRF into the database.

All coding key lists will be managed and protected (using cryptographic encryption or physical lock and key) by one designated study nurse, who will also be the only person with access to the patients’ names and telephone numbers (for the purpose of the telephone interviews at T1). Identification of patients without key will not be possible and code breaking will only be allowed in case of patient safety concerns.

Publication policy
The study results will be published in an international peer-reviewed journal and will be presented at national medical conferences. Authorships will follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). Additionally, we will disseminate the results in national journals dedicated to primary care after the primary publication.

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Contributors
KW, GP, TG, SG and SN-J participated in the conception, design and writing of the study protocol. KW, GP and TG contributed to the revision and editing of the study protocol. KW wrote the first draft of this manuscript. GP, TG and SN-J were all involved in critical revision of the manuscript. All authors approved the final version of the manuscript.

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None declared.

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Supplemental material
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