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# Protocol to evaluate the feasibility of the D-PRESCRIBE intervention adapted to the Belgian community setting (END-IT CS study)

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## ABSTRACT

**Introduction** Benzodiazepine receptor agonists (BZRA) deprescribing interventions are needed to tackle high BZRA use in the older population. This study aims to assess the feasibility of the D-PRESCRIBE intervention, adapted from Canada to the Belgian community setting. This pharmacist-led intervention comprises a patient educational brochure and a pharmacist-to-prescriber communication tool.

**Methods and analysis** We will conduct a feasibility study of a cluster randomised controlled trial involving 8–10 community pharmacies (clusters) and aiming to recruit 56–80 patients (≥65 years). Intervention pharmacies will deliver the adapted D-PRESCRIBE intervention and control pharmacies, usual care. Patients will be blinded to group allocation. Quantitative data will be collected at baseline, 3 months and 6 months through patients' and pharmacists' questionnaires, aiming: (1) to test the feasibility of the intervention, (2) to test the feasibility of the study design needed for its evaluation and (3) to perform an exploratory cost-effectiveness analysis. Hence, data about implementation outcomes, mechanisms of impact (ie, mechanisms through which the intervention is supposed to be effective) and contextual factors will be gathered. Patient-centred outcomes will also be collected as they would be in a full cost-effectiveness trial. The feasibility of the study design will be assessed through participation rate, completeness of the data and a satisfaction survey, sent to participants after the 6-month data collection. Data will be analysed using descriptive statistics. To gain a deeper understanding of pharmacists and patients' experience with the intervention, interviews will be conducted after the 6-month data collection and the Theoretical Domains Framework will be used as a deductive framework for analysis.

**Ethics and dissemination** This study was approved by the Ethics Committee of CHU UCL Namur (NUB: B0392023000036). Participants will receive a summary of the results. Results will also be disseminated through the organisation of a local symposium and a peer-reviewed publication.

**Trial registration number** NCT05929417.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study evaluates the feasibility of an intervention adapted following a rigorous and transparent process.
⇒ Recommendations of the Medical Research Council framework for process evaluation and for developing and evaluating complex interventions informed this protocol.
⇒ Implementation, trial design and economic outcomes will be investigated, providing a comprehensive overview of the feasibility of the intervention.
⇒ Pharmacies will be recruited voluntarily, and this may select pharmacies with extra motivation for benzodiazepine receptor agonists deprescribing.

## INTRODUCTION

Benzodiazepine receptor agonists (BZRA) are medications frequently prescribed in the treatment of insomnia and anxiety. However, they have well-known potential side effects that comprise a higher risk of falls, hip fractures, car accidents, tolerance and dependence and cognitive decline.[1–5] Older adults are at higher risk of these side effects.[6] For these reasons, current guidelines strongly recommend avoiding their use in older adults or stopping them after 4 weeks or 2 weeks if taken for insomnia.[7 8] Despite these recommendations, BZRAs are frequently taken long-term in older adults.[9] In Belgium, 14.7% of older adults aged 65–74 years and 24.6% of older adults aged ≥85 years take a BZRA.[10] Deprescribing interventions are therefore needed. Deprescribing is defined by Farrell *et al* as 'the planned and supervised process of dose reduction or stopping medication that may be causing harm or are no longer providing benefits'[11] (p.2).

Decreasing BZRA use has been on the Belgian political agenda for many years. Several information campaigns aimed at the general public were launched by the federal

authorities to raise awareness about the risks of BZRA use and to promote alternatives. The latest was launched in 2018 and provided notably patient information through posters and pamphlets distributed in general medical practices and community pharmacies.[12] However, these awareness campaigns were not tailored for older adults particularly, whose needs may be specific compared with the general population. For example, Green *et al* showed that older adults had a strong preference for talking about side effects when discussing BZRA deprescribing,[13] while the main message of the 2018 campaign focused on non-pharmacological alternatives for sleep and anxiety.

New interventions can be developed from scratch or adapted from interventions proven effective in other contexts.[14] Among these, the EMPOWER trial tested the effectiveness of a patient educational brochure (EMPOWER) distributed by the pharmacist to community-dwelling older adults.[15] Later, the D-PRESCRIBE trial combined this EMPOWER brochure with a written pharmaceutical opinion sent by the pharmacist to the prescriber inviting them to reconsider BZRA prescribing according to currently available guidelines.[16] Both interventions demonstrated high efficacy in BZRA deprescribing, with, respectively, 27% and 43% of BZRA deprescribing at 6 months in the intervention groups versus 5% and 9% in the control groups.

In a previous study, we adapted the Canadian D-PRESCRIBE intervention to the Belgian community setting, following recommendations from the ADAPT guidance and from the new Medical Research Council (MRC) framework on developing and evaluating complex interventions.[14 17] The rationale for adapting this intervention and the adaptation process have been described elsewhere.[18] Briefly, we first identified the 'core functions' of the D-PRESCRIBE intervention, which are 'the underlying mechanisms of change that make an intervention effective'.[19] In the frame of an adaptation, these core functions must remain unchanged to preserve the integrity of the intervention.[19] To our understanding, these core functions are: (1) to increase patients' knowledge and concerns about BZRA use; (2) to empower patients by increasing their self-efficacy; (3) to increase physicians' and pharmacists' knowledge about current guidelines regarding BZRA use in older adults; and (4) to provide tripartite communication about BZRA deprescribing and therefore limiting clinical inertia.[18] Then, we conducted interviews and group discussions with key stakeholders (patients, pharmacists and general practitioners (GP)) to assess the acceptability and needed changes in the D-PRESCRIBE components. The brochure and pharmaceutical opinion were adapted accordingly while preserving their core functions. In addition, a questionnaire survey was disseminated to GPs and pharmacists to explore at a broader scale the acceptability of the first adaptation of the pharmaceutical opinion, renamed 'pharmaceutical proposal'. This survey allowed further improvement of the pharmaceutical proposal. At the end of the adaptation process some uncertainties remained about the uptake of the pharmaceutical proposal by patients, pharmacists and GPs.[18] These were mostly related to the fact that written suggestions sent by pharmacists to GPs are not part of routine practice in Belgium. While more pharmaceutical care activities have been performed by Belgian community pharmacists in recent years (eg, medication reviews for chronic patients, influenza or COVID-19 vaccination), proactively sending a suggestion for treatment modification—including for deprescribing—would represent a significant change in the usual collaboration between pharmacists and GPs in Belgium.

The MRC framework recommends testing the feasibility of an adapted intervention and design of evaluation to identify challenges before undertaking a full effectiveness trial.[14] This article describes the protocol for a feasibility study, named the END-IT CS study. END-IT stands for bENzodiazepines Deprescribing InTerventions, and CS for Community Setting. The END-IT project encompasses the feasibility testing of two interventions, one in the community setting, described here, and one in the nursing homes setting (the END-IT NH study), described elsewhere.[20] The research objectives for the END-IT CS study are threefold:

1. To assess the feasibility of study design, especially in terms of recruitment and data collection processes needed for a full trial assessing the effectiveness and cost-effectiveness of the intervention.
2. To assess the feasibility of implementing the adapted D-PRESCRIBE intervention in Belgium.
3. If considered feasible with regards to collected data, to explore the potential cost and effectiveness of the intervention.

Results will allow us to decide (1) if the intervention needs to be further adapted and if so, how this could be done and (2) whether conducting a full implementation trial is worth considering.

## METHODS

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist recommendations for interventional trials[21] and the Consolidated Standards of Reporting Trials (CONSORT) checklist extension to randomised pilot and feasibility trials[22] guided the development of this protocol (see the SPIRIT checklist in online supplemental file 1). This protocol was informed by the protocols of the EMPOWER and D-PRESCRIBE studies.[23 24] Procedures of the original D-PRESCRIBE trial were reviewed with seven community pharmacists during a group discussion conducted in addition to the intervention adaptation process. Trial procedures were adapted according to pharmacists' real-life practice. This protocol (V.1, dated 3 April 2023) was registered on the ClinicalTrials.gov website (NCT05929417).

### Study design, setting and participants

We will conduct a feasibility study of a cluster-randomised, parallel-group, controlled trial in the community setting.

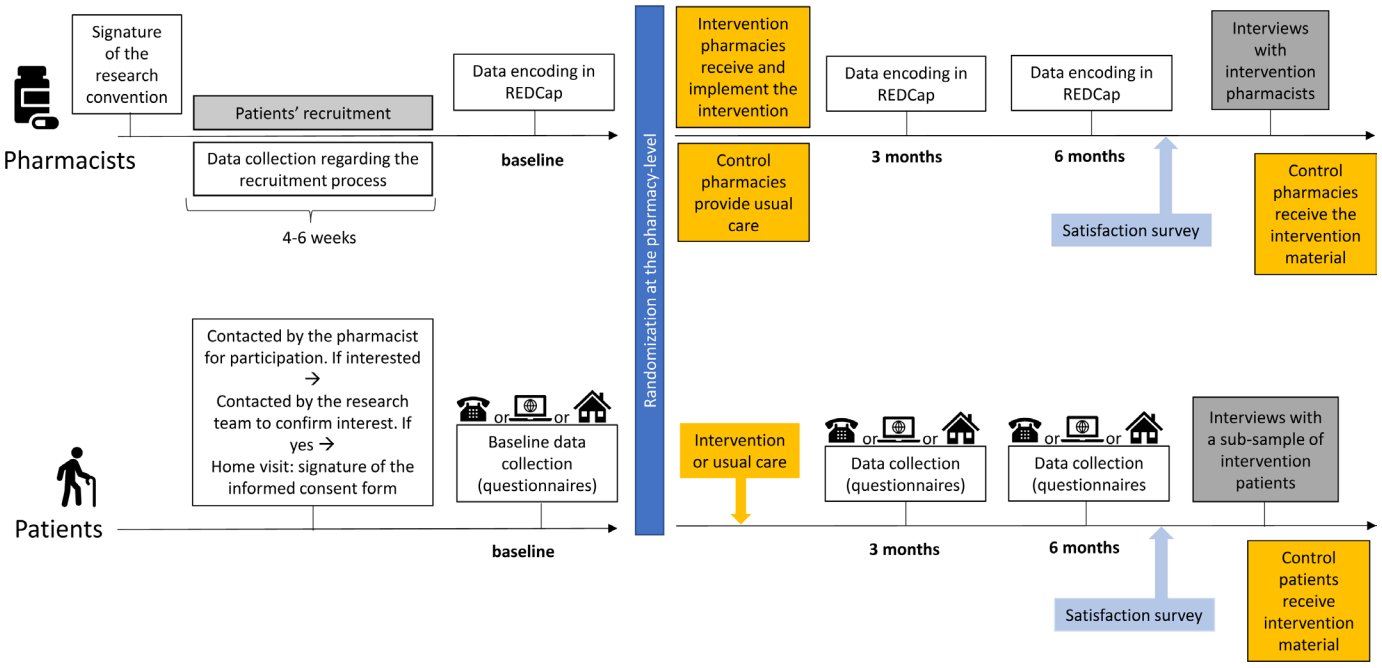


**Figure 1** Study timeline. REDCap, Research Electronic Data Capture.

Community-dwelling older adults will be recruited through French-speaking community pharmacies located in Brussels (the capital city, where people speak French and/or Dutch) and Wallonia (which is a French-speaking region, more rural, with smaller municipalities). Each pharmacy will form a cluster. Figure 1 presents the study timeline for both pharmacists and patients and the different data collection points.

## Sample size

As the sending of the pharmaceutical proposal would be new in Belgium, we chose a conservative approach and based our sample size estimation on the EMPOWER trial results (that tested the effect of the EMPOWER brochure alone) rather than on the results of the D-PRESCRIBE trial.[15] Therefore, considering a power of 80%, a statistical significance of 5%, a cluster size of 7–8 patients, and an intraclass correlation coefficient of 0.05 (lowest value) or 0.50 (highest value), we have estimated that the required sample size for a full implementation trial would be between 88 and 300 patients. For this feasibility study, we aim to recruit 56–80 participants, within 8–10 pharmacies. This sample will represent approximately 20–25% of the maximal required sample size. We expect this sample to allow us to inform sufficiently our research objectives, and we will further refine the sample size calculation for a full trial.

## Recruitment strategies

The eligibility criteria for pharmacies and older adults are described in table 1.

### Pharmacies

Pharmacies will be contacted through several channels: professional associations, social and professional networks and university networks. Information sessions will be held online to inform interested pharmacists about the details of the study. Depending on the number of interested pharmacies, we will include pharmacies with a variety of localisation (urban or rural) and type of practice (independent or cooperative pharmacy).

Financial compensation will be granted to every participating pharmacy. All pharmacies will receive €40 per included patient for recruitment and data collection. Additionally, intervention pharmacies will receive €25 per included patient for the intervention implementation. This compensation is close to the fee received for patient education for appropriate use of inhaled corticoids in the treatment of asthma in Belgium (€21.89).[25] A research convention will be signed between UCLouvain and pharmacies to formalise the collaboration during the study.

### Patients

Pharmacists will be responsible for selecting patients and establishing first contact with potential participants. To limit the burden on pharmacists, the research team will be responsible for providing comprehensive information about the study and for obtaining patients' consent. Practically, pharmacists will establish a list of all patients meeting the inclusion criteria using their dispensing software. Following this list, they will contact patients in person at the pharmacy or by phone, explaining the study in broad terms and asking for patients' oral agreement to be contacted by the research team. Patients will also be contacted by mail or email by means of a letter presenting the goal of the study and inviting patients to contact the pharmacy for more details. Within 4–6 weeks, pharmacists will continue until 10–15 patients agree to

Table 1 Eligibility criteria

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Pharmacies | ► Using a dispensing software that allows identification of eligible patients based on their age, medication and number of visits during the 12 previous months.<br>► To be located in Brussels or in a French-speaking municipality at a maximum of 1 hour to 1 hour 30 min time travel from Brussels. | ► None. |
| Patients | ► Age ≥65 years.<br>► Taking a BZRA for ≥4 weeks (ATC codes: N05BA, N05CD, N05CF and N03AE01).<br>► Being a regular patient at the community pharmacy (defined as ≥4 visits/12 previous months). | ► Severe mental illness (assessed through having an active prescription of any antipsychotic medication).<br>► Dementia or significant cognitive impairment (assessed through an active prescription or any past prescription during the last 12 months of anticholinesterase inhibitors or memantine) and/or pharmacist's judgement).<br>► Known ongoing alcohol withdrawal.<br>► Ongoing BZRA withdrawal at the time of recruitment.<br>► Patients unable to read or communicate in French. |

ATC, Anatomical Therapeutical Classification; BZRA, benzodiazepine receptor agonists.

be contacted by the research team or after the list of eligible patients is covered. From then, pharmacists will stop contacting patients, even if the target is not reached. As soon as patients agree to be contacted, the research team will phone them and ask to confirm their interest in participating in the study. If so, an appointment will be arranged at the patient's home to provide detailed information about the study and answer any questions patients may have. Patients will have to sign an informed consent form to finalise their inclusion in the study. To avoid recruiting only patients already open to BZRA deprescribing, patients will be told that the trial aims to favour BZRA reevaluation (not BZRA deprescribing). Indeed, BZRA deprescribing will only occur if the patient agrees, after shared decision-making with their GP. Patients will not receive any compensation for their participation in the study.

Keeping patients involved during the 6 months of the study is crucial; therefore, we plan a retention strategy similar to the YAWNS NB study, which is a randomised controlled trial also investigating BZRA deprescribing in older adults.[26] Patients will be contacted by phone to schedule the different research visits. If they are no longer reachable by phone, a postal reminder will be sent. If the length of the visit (phone or in-person) appears to be the reason for patients' drop-out, we will propose a shorter data collection to the participant.

## Intervention and control group

### Intervention group

Patients in the intervention group will first receive the adapted EMPOWER brochure (online supplemental file 2) during a face-to-face contact with their pharmacist, most likely on the occasion of a medication refill at the pharmacy. Then, the pharmacist will ask patients' oral consent to send the pharmaceutical proposal (online supplemental file 3) to the prescriber in a time period of maximum 2 weeks. A letter introducing the pharmaceutical proposal to the prescriber will be provided to pharmacists. Three options will be available for the pharmacist to send the document: postal mail, a phone application (SIILO, www.siilo.com) or an electronic mailbox (eHealthbox, https://www.ehealth.fgov.be/ehealthplatform/fr/service-ehealthbox), the two latter being specifically dedicated to secure information exchange between healthcare professionals.

### Control group

Patients in the control group will receive usual care. Usual care may comprise education about BZRA use (ie, providing information usually given in a day-to-day routine) but will not include proactive information on BZRA deprescribing from the pharmacist. Control pharmacies and patients will have access to the brochure and pharmaceutical proposal after the 6-month follow-up.

### Random allocation of the intervention

Similarly to the CHARMER study, an unbalanced study design will be used to prioritise the testing of the intervention feasibility.[27] Six pharmacies will be allocated to the intervention group and four pharmacies to the control group. The randomisation of each pharmacy will occur when the baseline data collection is complete. A computer-generated randomisation (using R software) will be performed by a member of the research team involved neither in the recruitment nor in the data collection.

### Blinding

In the original EMPOWER and D-PRESCRIBE trials, patients were blinded to the aims of the studies (BZRA deprescribing for the EMPOWER trial and the

deprescribing of BZRA and three other medication classes for D-PRESCRIBE) by being told they were participating in a 'medication optimization trial'.[23 24] This procedure will not be possible in our study because of the numerous topics related to BZRA use addressed in our data collection, making obvious the goal of our study. However, as in the D-PRESCRIBE trial, we will blind patients to their group allocation by telling them that the intervention could occur anytime between a few weeks and 6 months after inclusion in the study. However, pharmacists' blinding will not be possible. Pharmacists will be told about their allocation directly after the randomisation but asked not to disclose this information to the patient.

## Measures

### Feasibility of the study design

Measures assessing the feasibility of study design are reported in table 2 and comprise data regarding the recruitment process, data regarding the data collection process and a satisfaction survey. The feasibility of the recruitment process will be evaluated notably through participation rate and time needed to recruit participants. To assess the feasibility of the data collection, patient-centred data will be collected as they would be for a full cost-effectiveness trial (table 3). It will comprise socio-demographic data, data on healthcare providers, medication use, BZRA use and history of BZRA use, patient's attitude towards BZRA deprescribing (revised Patients' Attitudes towards Deprescribing questionnaire adapted to BZRA(rPATD-BZRA)[28]), quality of life (EQ-5D-5L[29]), insomnia (Insomnia Severity Index (ISI)[30]), anxiety (Geriatric Anxiety Inventory - Short Form (GAI-SF)[31]), falls, healthcare use and expenses. The feasibility of this data collection will be assessed through participants' retention in the study and the completeness of the collected data. Finally, patient and pharmacist satisfaction surveys will include questions developed by the research team and others adapted from the Research Participant Satisfaction survey.[32]

### Feasibility of the adapted D-PRESCRIBE intervention

To assess the feasibility of the adapted D-PRESCRIBE intervention, we will conduct a process evaluation that will comprise the evaluation of implementation fidelity, mechanisms of impact and contextual factors, as recommended by the MRC framework.[33]

Implementation fidelity 'refers to the degree to which an intervention or a program is delivered as intended'[34] (p.40). According to the conceptual framework developed by Carroll *et al*, two essential aspects will be measured: (1) adherence which is 'how far those responsible for delivering an intervention actually adhere to the intervention as it is outlined by the developers' and (2) participants' responsiveness to the intervention which is 'how far participants respond to, or are engaged by, an intervention' (p. 42)[34] (ie, patients, pharmacists and GPs in our intervention). Evaluating mechanisms of impact (ie, how an intervention works) is essential to highlight how the effects of an intervention occurred.[33] Several mechanisms of impact will be evaluated in relation to the core functions of the intervention described above. In addition, we will explore the effect of contextual factors on participants' responsiveness to the intervention to assess if and how they would interact with the effect of the intervention. Table 2 details quantitative data that will be collected for the process evaluation.

We will also collect qualitative data through interviews that will explore patients' and pharmacists' perceptions of the intervention aiming to have a deeper understanding of mechanisms of impact, contextual factors and implementation issues. As examples, we will investigate patients' and pharmacists' perceptions of the brochure and pharmaceutical opinion, but also patients' perceptions about benzodiazepines or support provided by the GP. All interviews will be audio-recorded and transcribed verbatim. Interview guides (translated in English) are available in online supplemental files 4 and 5.

### Exploratory cost-effectiveness analysis

Health-related quality of life will be measured with the EQ-5D-5L at each time point.[29] The combination of answers to EQ-5D will lead to a health profile of five digits that will be converted into a utility using standard Belgian tariff values.[35] Data on healthcare use and medication use will be collected (table 3) including any healthcare professional visits along with emergency room visits or hospitalisation in the past 3 months. In order to convert resource usage figures into costs, individual-level resource use will be combined with unit costs based on the average national medication cost to calculate the total health services cost for each participant. The cost of the intervention will be calculated for the D-PRESCRIBE arm. It will be based on the expenses directly related to the intervention, including printing of the brochure and pharmaceutical proposal, stamps needed to send the pharmaceutical proposal to the GP, financial compensation granted to the pharmacists per intervention delivered, average time required for pharmacists to implement the intervention and enter patients' data.

## Data collection and management

### Quantitative data

Quantitative data will be collected from both the patient and the pharmacist at three time points: at baseline, at 3 months and at 6 months (tables 2 and 3). For these data, Research Electronic Data Capture (REDCap), a secure application for encoding, managing and storing research data, will be used as an electronic case report form.[36] Two databases will be created, one for patient data and one for pharmacist data. Patients' data will be collected by both the research team and the pharmacists. The research team will collect data preferably by phone or videoconferencing. Home visits will be organised if needed. Data collected during a phone or video-conference interview will be directly encoded in REDCap. In case of a home visit, a paper questionnaire will be used and data will be

**Table 2** Feasibility evaluation: collected data and time schedule

| Measure | Collected data | Time points | | |
|---|---|---|---|---|
| | | Baseline | 3 months | 6 months |
| Feasibility of the study design | | | | |
| Recruitment process | Patients' participation rate; time to recruit patients; differences between participants and non-participants according to age and gender; means of contact between pharmacists and patients | x | | |
| | Time needed to recruit the pharmacies (in weeks); pharmacists' satisfaction with the recruitment process | | | x |
| Data collection process | Patients' retention rate (+ reasons for withdrawal) | x | x | x |
| | Completeness of patient-centred data (ie, number of variables presented in table 3 with few or no missing data) | x | x | x |
| | Pharmacists' satisfaction with the data collection process (3 items) | | | x |
| Satisfaction with the study | Patient satisfaction survey (10 items adapted from Smailes *et al*[32] and 5 items related to satisfaction with their pharmacist during the study) | | | x |
| | Pharmacist satisfaction survey (8 items adapted from Smailes *et al*,[32] 3 items related to data collection, 4 items related to intervention implementation and 4 items for global assessment) | | | x |
| Feasibility of the intervention: implementation fidelity | | | | |
| Adherence at the pharmacist level | Number of brochures given; number of pharmaceutical proposals sent to the GP; means used to send the pharmaceutical proposal to the GP; reasons for not giving the brochure; reasons for not sending the pharmaceutical proposal | | x | (x) |
| Patients responsiveness* | Number of brochures received; interest in the brochure | | x | (x) |
| | Number of patients that initiated a conversation about BZRA deprescribing with the prescriber; number of patients who tried to reduce or stop their BZRA; number of patients who successfully reduced or stopped their BZRA; reasons for not discussing BZRA deprescribing with the prescriber; reasons for not attempting BZRA deprescribing; reasons for deprescribing failure | | x | x |
| Pharmacists' responsiveness | Number of drop-out pharmacies and reasons for drop-out; satisfaction with the implementation of the intervention (4 items) | | | x |
| GPs' responsiveness | Number of physicians that answered the pharmaceutical proposal | | x | x |
| | Number of physicians that altered (or not) the prescription | | x | x |
| | Number of physicians that switched to another molecule (+ molecule involved) | | x | x |
| | If a withdrawal was undertaken: chosen tapering options (eg, specialty or capsules made by the pharmacist) | | x | x |
| Feasibility of the intervention: mechanisms of impact | | | | |
| Mechanisms of impact at the patient level | Knowledge about BZRA (five questions: true or false); self-efficacy regarding BZRA deprescription (medication reduction self-efficacy scale[49]) (1 item); intention regarding BZRA deprescription (rPATD-BZRA) (two global items of the scale) | x | x | x |
| Mechanisms of impact at the pharmacist level | Perceived knowledge regarding BZRA deprescribing (4 items); perceived skills regarding BZRA deprescribing (1 item); motivation for BZRA deprescribing (1 item); ability in BZRA deprescribing (5 items adapted from a previous study[50]); prioritisation of BZRA deprescribing (2 items) (Shapoval *et al*, in preparation) | x | x | x |
| Feasibility of the intervention: contextual factors | | | | |
| Contextual factors at the patient level | For how long patients have known their GP; for how long patients have known their pharmacist; type of GP remuneration (ie, fee-for-service or per capita); type of GP practice (ie, solo or in a group of practice); patients' trust in their GP (1 item from the Wake Forest Trust in Physician scale[51]; 1 item from the Wake Forest Trust in Physician scale[51]); patients' trust in their pharmacist (1 item adapted from the Wake Forest Trust in Physician scale[51]); patient health status (EQ-5D-5L), patients' number of previous BZRA deprescribing attempts | x | | |

Continued

**Table 2** Continued

| Measure | Collected data | Time points | | |
|---|---|---|---|---|
| | | Baseline | 3 months | 6 months |
| Contextual factors at the pharmacist level | Pharmacist's professional experience (time since graduation); setting of the pharmacy (rural or urban); type of pharmacy (independent or chain pharmacy); pharmacists' seniority in the pharmacy (since how long he/she has worked in this pharmacy); duration of pharmacist-GP collaboration (since how many years the pharmacist has known the prescriber (GP) of each included patient); quality of collaboration with the prescriber (Attitudes Towards Collaboration Instrument for Pharmacists (interactional determinants) 10 items[52]); participation in local GP-pharmacists concertation | x | | |

*Data collected within the shortened data collection (retention strategy).
BZRA, benzodiazepine receptor agonists; GP, general practitioner; rPATD-BZRA, revised Patients' Attitudes towards Deprescribing questionnaire adapted for BZRA.

**Table 3** Additional patient-centred outcomes: collected data and time schedule

| Measure | Collected data or measure instrument | Time points | | |
|---|---|---|---|---|
| | | Baseline | 3 months | 6 months |
| Socio-demographic data* | Age, gender, education level, living arrangement | x | | |
| Medication use*†‡ | Number of chronic regular prescribed medications | x | x | x |
| BZRA use†‡ | Total number of BZRA taken, BZRA brand names, BZRA dosages, BZRA frequency of use | x | x | x |
| BZRA use history* | Duration of BZRA use, main reason for BZRA use, if the current prescriber is the initial prescriber of BZRA, if the initial prescription occurred on personal request, if the initial prescription occurred during hospitalisation, if the patient already tried to stop his BZRA, number of previous BZRA deprescribing attempts | x | | |
| Prescribed or over-the-counter sleep or anxiety medication use† | Use of melatonin, phytotherapy or complement for sleep or anxiety (number of medications, brand names, dosage, frequency of use) | x | x | x |
| Antidepressant use (ATC N06)§ | Use of antidepressant (number of medications, brand names, dosage, frequency of use) | x | x | x |
| Opioid use (ATC N02)§ | Use of opioids (number of medications, brand names, dosage, frequency of use | x | x | x |
| Patient's attitude toward BZRA deprescribing*¶ | rPATD-BZRA (13 items)[28] | x | x | x |
| Quality of life*‡¶ | EQ-5D-5L (5 items) + Visual Analogue Scale[29] | x | x | x |
| Quality of sleep*¶ | Insomnia Severity Index (7 items)[30] | x | x | x |
| Anxiety*¶ | Geriatric Anxiety Inventory-Short Form (5 items)[31] | x | x | x |
| Falls* | Fall since the last 6 months or last contact | x | x | x |
| Healthcare use* | Number of visits (related to sleep, anxiety, BZRA use) to GP, pharmacist, specialist physician, psychologist or psychotherapist, emergency room, hospitalisation since the last contact | | x | x |
| Healthcare expenses* | Amount usually spent for a GP consultation | x | | |

*Data collected by the research team.
†Data collected by both the research team and the pharmacist.
‡Data collected within the shortened data collection (retention strategy).
§Data collected by the pharmacist.
¶Copyright license and rights to use these questionnaires were obtained.
ATC, Anatomical Therapeutical Classification; BZRA, benzodiazepine receptor agonist; GP, general practitioner; rPATD-BZRA, revised Patient's Attitudes towards Deprescribing questionnaire adapted for BZRA.

encoded afterwards. Pharmacists will encode patients' data and their personal data directly in REDCap. Pharmacists will only be able to access their patients' data and forms they must complete into REDCap. Additionally, pharmacists will collect data related to the recruitment process in a separate form to return to the research team by email. Finally, the satisfaction survey will be distributed (1) to pharmacists through an anonymous link to an online questionnaire and (2) to patients through a postal questionnaire.

### Qualitative data

Semi-structured interviews will be conducted by a trained psychologist with pharmacists and a subsample of patients in the intervention group, after the 6-month quantitative data collection is ended. Interviews will take place at the patient's home or at the working place (for pharmacists). Patients will be selected purposively to ensure enough diversity in deprescription status (successful, did not try, failed), and previous BZRA deprescribing attempts (yes vs no). We plan to interview two patients from each intervention pharmacy. This predefined sample could be adapted depending on emerging results.

## Analyses

### Quantitative data

All analyses will be performed using R software.[37] Descriptive statistics will be performed on quantitative data. Categorical variables will be expressed as numbers and percentages and continuous variables as mean±SD or median (P25–P75) depending on normality assessment. Intervention and control groups will be compared regarding patients' characteristics and intervention effects on potential mechanisms of impact using Pearson's $\chi^2$ tests (or Fisher's exact tests), Student's t-test or Mann-Whitney tests.

This study does not aim to evaluate the effectiveness of the intervention and is thus not powered to do so. Therefore, we will report BZRA cessation at 6 months and BZRA dose reduction (defined as at least 25% dose reduction) at 6 months in each group using descriptive statistics only. Lost to follow-up patients or withdrawn patients will be classified with patients that would have failed BZRA deprescribing.

Missing data will inform the research team of the feasibility of data collection. Hence, the relevance of some variables that would have too many missing values will be discussed before a potential full implementation trial.

If considered feasible based on the completeness of the collected data, we will conduct an exploratory cost-effectiveness analysis on completed cases and estimate patients' quality-adjusted life years (QALYs) and associated costs following the recommendations of the Belgian Healthcare Knowledge Centre.[38] We will describe the proportion of respondents falling within each level and dimension for the EQ-5D-5L at baseline and at the 3-month and 6-month follow-ups, both overall and by intervention and control groups. Utility scores for each health-related quality of life questionnaire at baseline, 3-month and 6-month follow-up will be calculated to present the change in mean EQ-5D-5L per intervention and control groups over time. The primary analysis will involve obtaining a ratio of the differences in costs and the differences in health outcomes (QALY) to generate the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per one unit of health outcome gained.[39] Given the findings, a value of information (VoI) analysis will be conducted using a decision analysis model.[40] The VoI analysis will help to determine whether a full trial is worthwhile to assess cost-effectiveness.

### Qualitative data

Interviews will be analysed using a deductive and inductive thematic approach using QRS NVivo V.11. The Theoretical Domains Framework (TDF(v2)) will be used as a deductive framework. However, new themes or subthemes may be identified inductively from the data. The TDF(v2) describes 14 main domains that may explain behaviour change.[41] It has been widely used in the field of implementation science, notably for conducting process evaluation, which is also our purpose.[41] The two first patients' and pharmacists' interviews will be analysed by two independent coders. The two coders will meet to compare their coding. If a satisfying agreement is reached, the remaining interviews will be performed by a single coder. If not, two additional interviews will be analysed by the two coders who will compare their coding once more. This process will be repeated until reaching satisfying agreement. This qualitative part will be reported following the Consolidated criteria for Reporting Qualitative research checklist.[42]

## Patient and public involvement

In the frame of the interviews conducted during the adaptation process of the intervention, six patients were asked about what would make them accept participating in a study like this and what would be important to measure if they were participating. The results did not change what was planned by the research team. The results of the study will be discussed with an advisory board that will include patients' and carers' representatives together with healthcare professionals and policymakers. This advisory board will be involved in results dissemination and help make decisions on the opportunity of refining the intervention components and proceeding to a full implementation trial.

## ETHICS AND DISSEMINATION

This study protocol received approval by the Ethical Committee of the CHU UCLouvain Namur on 11 April 2023 (NUB: B0392023000036). Patient written consent will be obtained twice, first for participation in the trial (and the related quantitative data collection) and second for participation in the qualitative interviews after the

trial. Informed consent forms will be signed jointly by the patient and a member of the research team. Oral consent will be obtained from participating pharmacists (no written consent is legally required in Belgium for healthcare providers). The information and consent forms are available in online supplemental files 6–10 (in French).

Exclusion criteria were carefully considered to help minimise patient risk prior to enrolment. BZRA withdrawal symptoms could occur if participants decide to taper BZRA. However, both the EMPOWER and D-PRESCRIBE trials have shown that the provided tapering scheme allows safe discontinuation.[15 16] Besides, the EMPOWER brochure emphasises the need for professional follow-up if cessation is considered. Patients' prescribers will be informed through the pharmaceutical proposal so that they can also adequately support their patient in case of need. If participants report any adverse effect during a research phone interview, they will be encouraged to talk about it with their healthcare provider (pharmacist or GP).

All data is confidential. Data will only be available to researchers involved in this study, and they will be pseudo-anonymised prior to analysis using an encrypted code assigned to each participant (patients and pharmacists). Contact details of participants and the identification key allowing them to link to their code will be stored in a different file on a computer to which access is authorised using a password. The file allowing the identification of patients will be destroyed after 7 years. De-identified data will be kept on a secure data repository (Open Science Framework (OSF)[43]). Following the FAIR Data Principles (or Findable, Accessible, Interoperable, Reusable) about data sharing,[44] de-identified data (ie, data without any name or information allowing patient's identification) will be shared on the data repository after an embargo period of 2 years.

Participants will receive a summary of the results. Results will also be disseminated through the organisation of a local symposium and a peer-review publication.

## DISCUSSION

This study will determine if the D-PRESCRIBE intervention, adapted to the Belgian context, is feasible in the Belgian community setting and if proceeding to a full-effectiveness trial could be considered. This intervention comprises two components: a patient educational brochure, specifically designed for older adults, that aims to increase patients' concerns and knowledge about BZRA long-term use and raises self-efficacy towards BZRA deprescribing. This content goes far beyond the educational material currently available in Belgium. In addition, the pharmaceutical proposal will promote interprofessional collaboration around BZRA deprescribing in an innovative way for our country. We believe testing the implementation of this intervention in Belgium is particularly timely since the Belgian National Institute of Health and Disability Insurance launched a pilot programme to promote BZRA deprescribing in the adult population (≥18 years) in February 2023.[45] Under specific conditions, the patient can benefit from a free-of-charge tapering programme using capsules containing a decreasing dosage of the compound made by the pharmacist. This programme also includes two support consultations by the pharmacist. Interprofessional collaboration is encouraged by the signing of a tripartite contract between the GP, the pharmacist and the patient. To capitalise on this new programme, information about it was included in both the adapted brochure and pharmaceutical proposal. We believe that, if found feasible, the adapted D-PRESCRIBE intervention could usefully complement tools made available by the Belgian authorities.

To our knowledge, this is the first study that will test an adapted version of the D-PRESCRIBE intervention in another country. Our study will provide new insights on the transferability of this intervention in a different context. The process evaluation conducted in this feasibility study will reveal how the intervention can be implemented in Belgian pharmacies and what will be the contextual factors playing a role in its implementation.[33] This will enable us to refine the adapted intervention and/or the study design and procedures. Procedures were kept as pragmatic as possible in order that the trial integrates easily into the pharmacy workflow. For example, pharmacists will choose how to send the pharmaceutical proposal to the prescriber. This flexibility may encourage pharmacists' satisfaction with the intervention, their retention in the study and eventual implementation of the intervention on a larger scale.

Retention of older participants in a clinical trial might be a challenge;[46] however, the participants' retention rate at 6 months was excellent in the original D-PRESCRIBE trial (89%).[16] Based on the Canadian experience, we may expect no severe attrition in our participants. Besides, participants can choose between a home visit, or a phone or video conference for data collection appointments. These will be scheduled according to participants' availability. Such strategies have been highlighted as favouring participants' retention in clinical trials.[46] The length of data collection is, however, a concern regarding the retention of participants. A reduced burden regarding data collection improves retention in clinical trials.[47] In the D-PRESCRIBE trial, follow-up calls were planned to last between 5 min and 10 min.[23] We anticipate our data collection to last 1 hour because of the need to collect implementation outcomes as well. For this reason, inspired by the study of Murphy *et al*, we will propose a shortened data collection option when needed.[26]

This study has some limitations. First, the participation of pharmacies will be on a voluntary basis, and this may select pharmacists with extra motivation for BZRA deprescribing. Moreover, our inclusion criteria regarding time travel from Brussels may limit the participation of rural pharmacies. Those two limitations could impact the generalisability of our results. Second, the nature of the intervention and topics discussed with patients during

data collection will not allow double blinding, contrary to what was done in the D-PRESCRIBE trial.[23] Finally, we did not predefine progression criteria towards a full effectiveness trial as recommended by the MRC framework.[14] In fact, the qualitative part of the process evaluation leaves room for unexpected results, which makes it difficult to set a priori criteria. Decisions will be made by the research team and will take into consideration recommendations made by the advisory board.

The recent systematic review of Omuya *et al* highlighted the need for more research about process, implementation and economic outcomes in deprescribing trials.[48] The main strength of this study is the scope of the evaluation plan that will include both these aspects and therefore contribute to addressing this gap.

## CONCLUSION

The END-IT CS study will assess the feasibility of a BZRA deprescribing intervention led by the pharmacist in the Belgian community setting. In a context where BZRA deprescribing is a political priority, our study will be a first step to assess the opportunity to strengthen pharmacists' role in this area.

## TRIAL STATUS

The quantitative data collection ended in March 2024 and the qualitative data collection in July 2024. The analyses related to the process evaluation are ongoing.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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