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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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ABSTRACT

Introduction Problematic benzodiazepine use is a global health issue. Although the adverse side effects of long-term use of benzodiazepines are well known, it remains difficult to implement interventions for discontinuation in primary care. Considering the success of blended care for the treatment of sleeping disorders and the support of substance use disorders, evidence suggests that a blended care approach, combining face-to-face consultations with the general practitioner with web-based self-learning by the patient, is beneficial for the discontinuation of chronic benzodiazepine use for primary insomnia in general practice. Therefore, the aim of this study is to evaluate the effectiveness of such an approach for the discontinuation of benzodiazepine and z-drugs ((z-)BZD) use in the long term and evaluate the implementation process.

Methods and analysis This study is a multicenter, pragmatic, cluster randomized controlled trial with 1200 patients, included by 120 general practitioners. Allocation to usual or blended care happens at the level of the general practice in a 1:1 ratio using a block randomization system stratified per language. The study population consists of adult primary care patients who have been using (z-)BZD for primary insomnia on a daily basis for at least six months. Primary outcome measure is the proportion of patients that discontinued (z-)BZD at 12 months assessed by toxicological screening for (z-)BZD in urine. Secondary outcomes include discontinuation of (z-)BZD at 6 months, quality of life, and the number of defined daily doses of (z-)BZD prescribed. Data will be collected using a study-specific online platform and analyzed using the intention-to-treat approach. The process of implementing blended care will be evaluated in a nested study.

Ethics and dissemination This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (ref. S61194). Study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

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Trial registration number NCT03937180; pre-results

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the authors' best knowledge, this is the first randomized controlled trial (RCT) to evaluate the effectiveness of an online intervention on benzodiazepine deprescribing in general practice.
- The use of toxicological screening of urine samples, self-report on discontinuation of (z-)BZD use, and number of defined daily doses prescribed will provide valuable insights with regard to the efficacy of the intervention and the reliability of the use of self-reporting in similar studies.
- To optimize the generalizability of the findings, this is a multicenter study with participants from both Dutch- and French-speaking parts of Belgium.
- The focus is on the effect of blended care, but the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.
- Non-e-literate patients are excluded from the study, even though this vulnerable group of patients could also benefit from more psychosocial support and counseling about medication use.

INTRODUCTION

Background

Worldwide, benzodiazepines and the related hypnotic drugs zolpidem, zopiclone and zaleplon ((z-)BZD) are prescribed extensively to treat anxiety and sleeping disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants. Recommendations state that treatment with (z-)BZD should be limited to only a few weeks. Despite the fact that long-term-use is ineffective and also associated with adverse side effects, the prevalence of long-term use, which is most common for sleeping disorders, remains widespread.[1-11] A recent systematic review summarizing current evidence-based discontinuation strategies indicates that gradual tapering of doses is an effective (z-)BZD discontinuation intervention for adult patients with long-term (z-)BZD use.[12] However, a combination of dose-tapering and non-pharmacological interventions such as psychotherapy interventions, self-help instructions and patient education produces better outcomes compared to stand-alone strategies.[13,14]

With the growing use of internet, e-based approaches are becoming more popular. Among them, blended care, defined as a combination of care by applying an interactive educational e-tool in combination with face-to-face clinical consultations with the care provider, is a new and promising approach.[15,16] Blended care has already proven to be successful in treating sleeping disorders, supporting substance use disorders, in stress management for employees, treating depression and other psychiatric and somatic conditions.[17-21]

In 2015, a small descriptive pilot study suggested that blended care for the discontinuation of (z-)BZD use for sleeping disorders may be more effective than a minimal intervention, such as a discontinuation letter or discontinuation advice, and as effective as face-to-face interventions combining tapering protocols and education. [22] Because these findings need to be confirmed by a properly powered and controlled study, a multicenter cluster randomized trial was designed, supported by the Belgian Federal Knowledge Centre for Healthcare (KCE) Trials program.

This study aims to establish an evidence-based blended care approach for the discontinuation of chronic (z-)BZD use for a primary indication of sleeping disorders in adult patients in a primary care

setting. We hypothesize that blended care will support general practitioners as it is less time-consuming and that it will empower patients to take a more active role in their discontinuation process. In that way, we think it may increase their motivation, which may result in increased discontinuation of (z-)BZD and more long-term discontinuation than currently with usual care.

Objectives

The primary objective is to compare the effect of blended care versus usual care on the proportion of subjects that has discontinued (z-)BZD use 12 months after start of the intervention as assessed by toxicological screening, in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Secondary objectives are to compare the effect of blended versus usual care on:

1. The discontinuation of (z-)BZD use 6 months after start of the intervention, as assessed by toxicological screening.
2. The quality of life, assessed by e-questionnaire at week 6, 12, 26 and 52.
3. The self-reported discontinuation of (z-)BZD use, assessed by e-questionnaire at week 6, 12, 26 and 52.
4. The number of defined daily doses (DDD) of (z-)BZD prescribed, assessed by e-questionnaire at week 6, 12, 26 and 52.

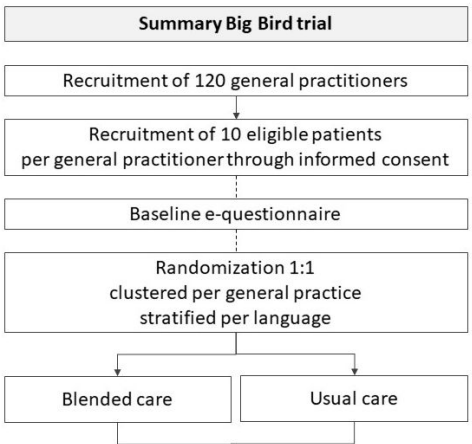

Figure 1. Flowchart of trial design summary

METHODS AND ANALYSIS

Study design and setting

This study is a multicenter, pragmatic, cluster randomized, controlled, superiority trial that will be performed in Belgian general practices. The participating general practitioners will be recruited and monitored by the academic centers for General Practice of the KU Leuven, UGent, UAntwerpen, ULiège, Université Libre de Bruxelles and Vrije Universiteit Brussel. The cluster and unit of randomization is the primary care practice. A 1:1 ratio will be used for allocation to the blended care arm and the usual care arm, as shown in figure 1.

The design of the study protocol has followed the recommendations of the SPIRIT 2013 statement.[23]

Patient and public involvement

Patients were involved in several stages of the study. During a focus group with long-term (z-)BZD users the overall feasibility of the patient activities, the lay-out and content of the e-tool, and the questionnaires and time required to complete them were discussed. Afterwards, these patients were also invited to provide written feedback on the Informed Consent Form (ICF), patient information leaflet and patient information video. Moreover, during the user acceptance testing of the tool, we involved acquaintances with different health and e-literacy profiles that were not familiar with the trial. Finally, to assure continuous involvement of patients in the study, two long-term (z-)BZD users are a member of the trial steering committee.

Eligibility criteria and recruitment

Patients' eligibility for inclusion in the study will be based on the following criteria:

1. Aged 18 years and older, capable of giving informed consent.
2. Having his/her Medical File managed by one of the participating general practitioners.
3. Receiving prescriptions of (z-)BZDs from participating general practitioner for use on a daily basis.
4. Reporting daily intake (≥ 80% of days) of (z-)BZDs in the last 6 months for a primary indication of sleeping problems.

Patients will be excluded from study participation based on the following criteria:

1. Presence of any severe psychiatric and neurologic condition that in the judgment of the treating general practitioner implies a contraindication for (z-)BZD withdrawal.
2. Presence of terminal illness.
3. Any case where stopping of (z-)BZDs might be harmful.
4. Unwillingness or inability to provide informed consent.
5. Not having e-literacy (being familiar with email and internet use).
6. Patients with a substance use disorder (other than (z-)BZD) will also be excluded from the study because in these cases there is often a sub-therapeutic (z-)BZD dependence and/or comorbid psychological/psychiatric comorbid conditions requiring specialist care.

Selection of eligible patients will be done consecutively by the general practitioner during consultations. To inform the patients about the study a patient information leaflet and video have been developed. When a patient is willing to participate, the general practitioner will obtain informed consent.

Sample size

Sample size calculation was based on a statistically significant difference in (z-)BZD discontinuation at 12 months between intervention and control group of 10%, assuming a rate of discontinuation of 15% in the control group. This assumption is based on a systematic review by Mugunthan et al[11] that shows us that usual care achieves a discontinuation rate of 10% to 17%.

To further estimate the sample size, calculations were based on findings from a similar study by Vicens et al.[14], in which the drop-out rate after 12 months was 7% and an intracluster correlation coefficient (ICC) of 0.11 was observed (personal communication).

Assuming a drop-out rate of 10% and based on an alpha of 0.05 and 80% power, a total sample size of 594 patients (297 in each group) would be required for an individually randomized study.

However, to account for clustering effects by primary care practices, we used an ICC set at 0.11 and a cluster size of 10 patients. The number of patients required was multiplied by 1.99 corresponding to the cluster design effect (DE=1+ICC (size of the cluster-1)). Thus, the final sample will minimally consist of 1182 patients. Considering each general practitioner has to recruit 10 patients, 119 general practitioners are needed. Because six academic centers for general practice are involved in the project, we aim at including 120 general practitioners in total.

Random allocation

Within the week following the enrolment of the 10th patient (or a multiple of 10, depending on the number of participating general practitioners in that practice), the general practice is randomized in one of the two study arms in a 1:1 ratio using a block randomization system stratified per language in order to guarantee that allocation to either usual care or blended care for the discontinuation of (z-)BZD is balanced between the Dutch- and French-speaking community. To guarantee that the allocation process cannot be predicted two block sizes are used, 4 and 6.

Using an electronic random numbers generator, two randomization lists have been created, one for each language. After recruitment of the required number of patients, the project manager receives an e-mail alert that indicates the practice is ready for randomization. The result of the allocation is communicated by e-mail to both the general practitioner(s) and the corresponding monitor.

Blinding

General practitioners cannot be blinded to an intervention that modifies their clinical practice. Because the researchers need to monitor the conduct of the study on site, they also cannot be blinded to the allocation of the general practitioners. Owing to study procedures, patients will neither be blinded. However, all involved parties are blinded to the allocation until after patient recruitment. Furthermore, the outcome assessors will be kept blinded to the allocation during the whole study until after data analysis.

Intervention

Patients in the usual care arm, will receive care that is left at the discretion of the treating general practitioner. They are expected to follow the Belgian guidelines, which propose education of the patient about the harmful effects of chronic (z-)BZD use, the alternatives, and the advice to discontinue (z-)BZD use. A stepped approach is recommended. First, a minimal intervention strategy such as a discontinuation letter or a short advice is applied. If unsuccessful, a brief intervention, which may span one or more consults, is recommended. During such an intervention, the general practitioner will - based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. Most likely, a tapering scheme is developed which typically consists of a 10-20% reduction in the daily dose of (z-)BZD every 2-4 weeks.

For patients in the blended care arm, usual care is supported by the use of an interactive e-tool. The e-tool provides psycho-education about sleep and sleep medication, and exercises featuring cognitive behavioral techniques to enhance the self-management of the patient. Its purpose is to motivate patients to discontinue the use of (z-)BZD, to adapt non-pharmacological remedies and to support them in this process. Patients can grant their participating general practitioner access to all their answers in the e-tool, making it possible to discuss these findings and experiences face-to-face. During consultations, the general practitioner will also assess the patients' readiness for change and match the appropriate intervention, like a tapering scheme. Follow-up appointments are scheduled depending on the needs of the patient until the end of dose reduction.

Outcome assessments

Primary outcome measure

The proportion of patients that discontinued (z-)BZD at 12-months assessed by toxicological screening for (z-)BZD in urine.

Secondary outcome measures

1. The proportion of patients that discontinued use of (z-)BZD at 6-months assessed by toxicological screening for (z-)BZD in urine.
2. Quality of life assessed by EQ-5D-3L[24].
3. Self-reported discontinuation of (z-)BZD.
4. The number of DDD of (z-)BZD prescribed.

Data will be collected either via questionnaires sent to the patient or by completion of the electronic Case Report Form (eCRF), except for the toxicological screening of urine samples, as presented in figure 2.

Data collection

E-questionnaires

At study entry, baseline data are collected using an e-questionnaire consisting of Audit-C[25], EQ-5D-3L[24], Benzodiazepine Dependence Self-Report Questionnaire[26], Insomnia Severity Index[27], and HLS-EU-Q16[28]. All together this e-questionnaire comprises less than 50 questions.

Patients will also be requested to complete an abbreviated e-questionnaire at weeks 6, 12, 26 and 52 comprising of the validated EQ-5D-3L[25], Audit-C[24] and Insomnia Severity Index. Furthermore, the e-questionnaire will register self-reported use of (z-)BZD and other psychoactive medication, self-reported falls and use of medical services in the past period.

All e-questionnaires will consist of closed questions which are answered by ticking the appropriate box. Invitations will be e-mailed to the study participants at week 5, 11, 25 and 51 with the request to complete the questionnaires online within 2 weeks. A reminder will be sent after 1 week to all participants who have not yet responded and every week after, until response or the deadline. The deadline is set at four weeks after the first reminder for the questionnaires at week 6 and 12, and eight weeks at week 26 and 52.

Assessment by general practitioner

During the baseline visit, which will take place within 12 weeks after signing the ICF, the general practitioner will start the intervention, and will collect the following data for each participating patient: demographics, comorbidities, current use of psychotropic medication, (z-)BZD prescriptions in the last 6 months (drug name(s), quantity), and a urine sample for toxicological screening.

After the baseline visit, appointments for follow-up (minimally one in the first six months) and prescription renewals will be scheduled left at the discretion of the general practitioner and depending on the needs of the patient until the end of dose reduction. This approach maximally reflects daily practice as should be in a pragmatic trial.

The general practitioners will be asked to note in the Electronic Health Record (EHR) and eCRF the (z-)BZD-related interventions delivered to the patients via standardized entry fields at each contact with the patient, during six months after baseline.

These interventions may include advice to discontinue (z-)BZD, discussion of tapering schedule, discussion of withdrawal symptoms, discussion of sleep quality, discussion of coping strategies, triggers and facilitators, decrease or increase of benzodiazepine dose.

Toxicological screening

At baseline, week 25 and 51, patients will be invited to produce a urine sample at the general practice within the next 2 weeks. For the samples of week 26 and 52, a reminder will be sent after 1 week to all participants who have not yet done so and every week after until a urine sample is obtained or the deadline is reached. The deadline is set at eight weeks after the first reminder.

The urine samples will be collected from the general practices within 5 days by the laboratory. Urine samples can be stored in a refrigerator for at least 7 days without any effect on the toxicological screening results.

All toxicological analyses will be performed at the laboratory AML in Antwerp using Liquid chromatography–tandem mass spectrometry (LC-MS/MS). This is currently the most sensitive method for the detection of (z-)BZD in urine. In contrast to the routinely used immunoassays, it is able to detect the use of low-dose (z-)BZDs which are commonly prescribed for sleeping disorders. The lower detection level for routinely used immunoassays is typically 200 ng per mL as compared to 5 ng/mL for LC-MS/MS. Other advantages of LC-MS/MS over immunoassays are that the detection of multiple components is possible in one assay, that it provides quantitative results, that the exact identification of the benzodiazepines is ensured and that it is able to detect multiple metabolites resulting in longer detection periods.

Toxicological screening of urine samples is not part of routine practice. Therefore, the general practitioners will be blinded for the results of these analyses.

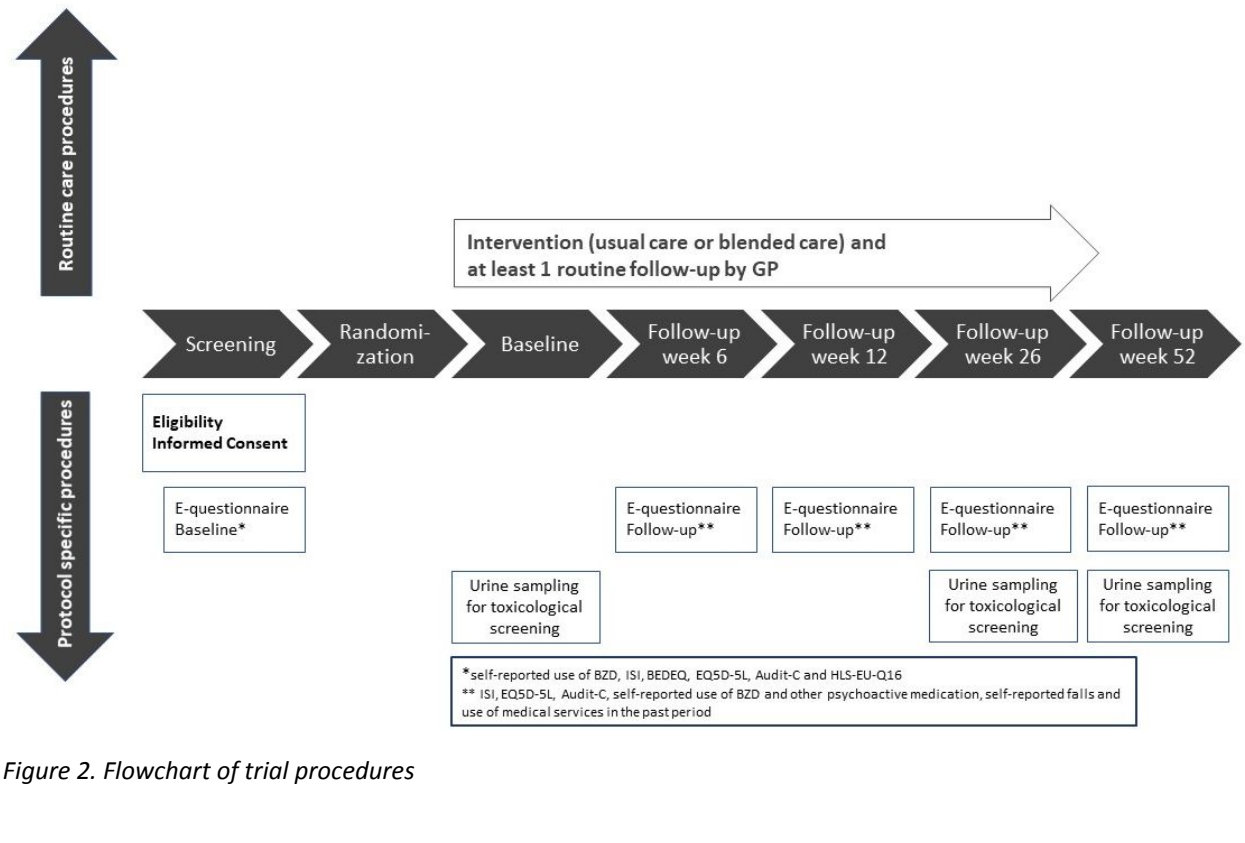

Figure 2. Flowchart of trial procedures

Data analysis

Baseline characteristics, like age, gender, relevant co-morbidities, benzodiazepine dependence score, daily dose of (z-)BZD in DDD, sleep quality and Audit-C[24] score, will be presented for the complete study population and per allocation arm.

Primary outcome analysis

The primary endpoint will be analyzed according to the intent-to-treat (ITT) approach.

Logistic regression will be used for data analysis with benzodiazepine urine test results assessed at 12 months after initiation of the intervention as a binary outcome (positive or negative) and intervention group as a factor. A random effect will be modelled to deal with clustering by general practice. The group effect will be reported as an odds ratio with 95% confidence interval.

To investigate how the primary outcome behaves in function of age, gender, (z-)BZD dose at baseline, sleep quality at baseline, benzodiazepine dependency score and use of the e-tool (only in intervention group), subgroup analysis will be performed.

Secondary outcome analysis

The proportion of subjects with a negative benzodiazepine urine test assessed 6 months after initiation of the intervention will be analyzed in the same way as the primary endpoint.

All other secondary endpoints are binary variables, measured longitudinally. Analysis will be performed using multilevel logistic regression analysis, including random intercepts for patient and for general practitioner. A random slope for time will be modelled if beneficial for model fit. The fixed effects model will include intervention group, time and the group by time interaction. In case of a significant group by time interaction, the group effect will be reported separately for each time point. In case of a non-significant group by time interaction, a group main effect will be reported. The group effects will be presented as odds ratios with 95% confidence intervals.

No correction for multiplicity is planned for the secondary analyses, as the study is not powered for these analyses, and hence, its results will be considered as hypothesis generating.

Missing data

When a patient withdraws from the study prematurely, all data collected up until the moment of withdrawal will be analyzed. In case the data for measurement of the primary endpoint was not collected, the outcome will be classified as failure or continued benzodiazepine use in the intent-to-treat analysis. After withdrawal, no further data of this patient will be collected.

Economic data evaluation

One of the goals of the KCE Trials program is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind, i.e. the necessary data to allow the conduct of a health economic evaluation will be collected. For more information on these procedures, we refer to the protocol of the trial.

Data management

Using a trial-specific online platform, data will be automatically entered in a database. These data will be generated by the general practitioners completing the eCRF and by the patients completing the e-questionnaires and using the e-tool. All collected data are stored pseudonymized, working with a

personal study code for all patients. The identity of the individual patient will be blinded to the researchers at all times.

The collected data remain in the databases of the service provider and only an excerpt of this data is transferred to the data warehouse of the researchers, where it is merged with the results of the laboratory testing.

The data entry process will be documented, creating an audit trail. The database will be stored and maintained by the service provider, who will also be responsible for the pseudonymization of patient data as Trusted Third Party, compliant with ICH-GCP regulations and the EU General Data Protection Regulation. Confidentiality of personal identifiable information will be maintained throughout the trial. Data will be stored for a period of 25 years after the study has ended, according to ICH-GCP regulations.

Nested study

A process evaluation will be nested within the pragmatic cluster randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by general practitioners and patients. It helps interpreting the results in their context. This is important for informing future implementation in practice. It will explain how general practitioners and patients experience the intervention. With this study, we aim to identify factors which influence the ability (or inability) to withdraw from (z-)BZD in order to build a framework describing the mechanisms required for successful implementation.

Individual interviews and discussion groups will be conducted with general practitioners and patients taking part in the trial. General practitioners (approximately 8) will be purposively sampled to obtain variation in gender, language, practice setting and experience. Patients (approximately 14-18) will be purposively sampled to obtain variation in age, gender, language, and how successful the withdrawal has been. Interviews will follow semi-structured topic guides exploring general practitioners' and patients' views and experiences of taking part in the trial. Topic guides will be informed by existing literature and theory of health behavior to ensure that questions elicit likely key determinants of behavior. Topic guides will be piloted with patient representatives and clinicians. Interviews and discussion groups will be carried out face to face and analyzed using thematic and framework analysis.

Participant safety and monitoring

This study is considered low-risk. Because no medication or new treatment protocols are tested, there is no additional safety reporting to the one in daily general practice. In Belgium, any adverse effects of medication can be reported to the federal agency for medicines and health products (famph) by using the yellow card. If necessary, appropriate measures will be taken in consultation with the attending general practitioner.

Close monitoring to assure proper conduct of the study is provided by all abovementioned academic centers for General Practice, in compliance with ICH-GCP regulations. Moreover, annual reports of the study progress will be sent to the Ethics Committee of the University Hospital of Leuven.

DISCUSSION

In 2008, research established that computer-assisted tailored patient education could be a useful tool in the discontinuation of chronic benzodiazepine use. Ten Wolde and colleagues performed an RCT, showing that letters, tailored to baseline characteristics of the patient, influence benzodiazepine

use positively. After the trial, the most successful intervention, being a single customized letter, was published online in a password protected environment to reach as many patients as possible.[29] No further research on the effectiveness of this online module has been published.

Currently, this is the only (English) publication on computer-assisted patient education for discontinuation of chronic benzodiazepine use. This means that our trial will be the first RCT that assesses the superiority of blended care over usual care for (z-)BZD discontinuation in primary care.

Moreover, the Big Bird trial is innovative in its methodology. In most discontinuation studies, researchers use self-reported data from patients and/or general practitioners to assess the success of an intervention. In this trial, success rate will depend on the proportion of patients that has discontinued their use of (z-)BZD as assessed by toxicological screening of urine samples at 12 months after start of the intervention. This measurement is also performed at 6 months, when access to the online platform has ended.

Some might argue that delivering urine samples will trigger patients to increase their efforts for discontinuing (z-)BZD. To limit this possibility we have taken precautionary measures by not communicating the results of the toxicological screening to the general practitioner, nor to the patient.

The toxicological analysis of urine samples will enable us to compare the concentrations of (z-)BZD with the reports of patients and general practitioners and provide insights on the reliability of self-reporting in studies on discontinuation.

Another strength of this study is the collaboration between six universities, which enables us to implement the intervention across the Belgian French and Dutch speaking population.

However, due to language and the technological character of the intervention, some vulnerable groups of patients cannot be reached. Language restrictions exclude the German community in Belgium and a number of migrant groups from participation. Also, non-e-literate patients, including elderly people that are not familiar with internet usage but who report high (z-)BZD intake, cannot take part in the trial. This is unfortunate as these patients could also benefit from more psychosocial support and counseling about medication use. If effective, we need to consider adapting the existing materials for use with these patients.

Finally, although the focus in the trial is on the effect of blended care, the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki (seventh revision). Any substantial protocol amendments will be submitted to the ethics committee.

The study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial status

Currently, recruitment of general practitioners and patients is ongoing. First patient first visit is expected in August 2019. Last patient last visit is expected in September 2020. Database lock will take place in November 2020.

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AUTHORS' CONTRIBUTIONS

CM and MVN are responsible for the original conception of the study and obtaining funding. They also drafted the study protocol, in cooperation with SA, who developed the nested study, and AL, who provided the statistical analysis plan. All authors assisted in finalizing the protocol. CM, MVN and KC obtained ethical approval. KC wrote the first draft of the manuscript, all authors contributed to further drafts. All authors read and approved the final draft.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (B322201939666) in March 2019. Reference number: S61194.

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Open access

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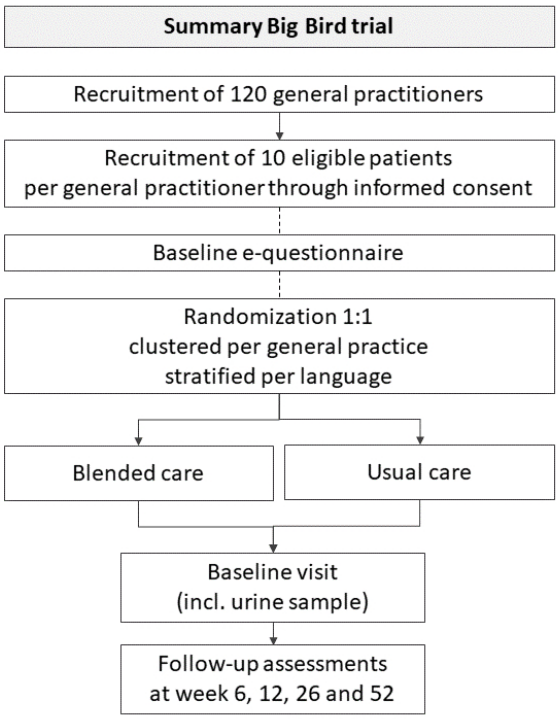

Figure 1. Flowchart trial design

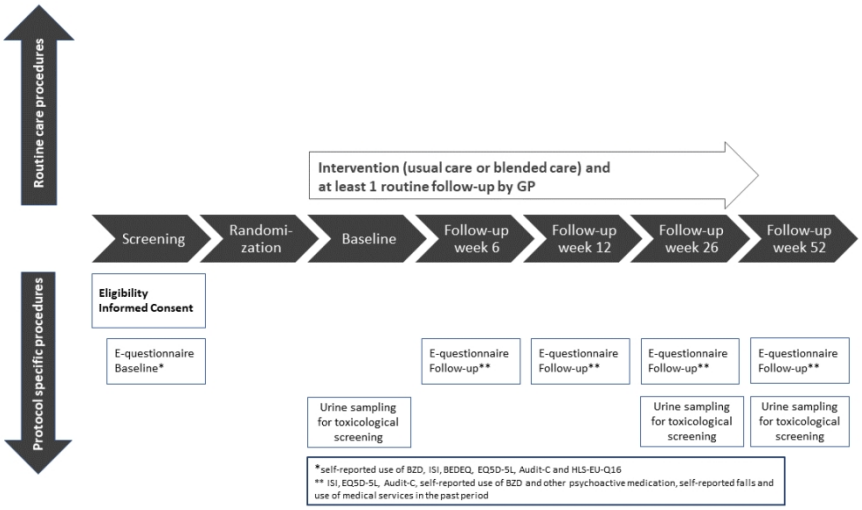

Figure 2. Flowchart trial procedures

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Status
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Ok
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Ok
	2b	All items from the World Health Organization Trial Registration Data Set	Ok
Protocol version	3	Date and version identifier	Ok
Funding	4	Sources and types of financial, material, and other support	Ok
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Ok
	5b	Name and contact information for the trial sponsor	Ok
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Ok
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Ok
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Ok
	6b	Explanation for choice of comparators	Ok
Objectives	7	Specific objectives or hypotheses	Ok

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Ok
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Ok
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Ok
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Ok
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Ok
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Ok
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Ok
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Ok
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Ok
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Ok

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Ok
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Ok
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Ok
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Ok
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Ok
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Ok
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Ok

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Ok
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Ok
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Ok
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Ok
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Ok
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ok

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ok
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Ok
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Ok
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Ok
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ok
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Ok
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ok
	31b	Authorship eligibility guidelines and any intended use of professional writers	Ok
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ok
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ok
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Ok

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the

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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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Key words MeSH: Benzodiazepines, deprescriptions, sleep initiation and maintenance disorders, cognitive behavioral therapy

ABSTRACT

Introduction Problematic benzodiazepine use is a global health issue. Although the adverse side effects of long-term use of benzodiazepines are well known, it remains difficult to implement interventions for discontinuation in primary care. Considering the success of blended care for the treatment of sleeping disorders and the support of substance use disorders, evidence suggests that a blended care approach, combining face-to-face consultations with the general practitioner with web-based self-learning by the patient, is beneficial for the discontinuation of chronic benzodiazepine use for primary insomnia in general practice. Therefore, the aim of this study is to evaluate the effectiveness of such an approach for the discontinuation of benzodiazepine and z-drugs ((z-)BZD) use in the long term and evaluate the implementation process.

Methods and analysis This study is a multicenter, pragmatic, cluster randomized controlled trial with 1200 patients, included by 120 general practitioners. Allocation to usual or blended care happens at the level of the general practice in a 1:1 ratio using a block randomization system stratified per language. The study population consists of adult primary care patients who have been using (z-)BZD for primary insomnia on a daily basis for at least six months. Primary outcome measure is the proportion of patients that discontinued (z-)BZD at 12 months assessed by toxicological screening for (z-)BZD in urine. Secondary outcomes include discontinuation of (z-)BZD at 6 months, quality of life, and the number of defined daily doses of (z-)BZD prescribed. Data will be collected using a study-specific online platform and analyzed using the intention-to-treat approach. The process of implementing blended care will be evaluated in a nested study.

Ethics and dissemination This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (ref. S61194). Study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial registration number NCT03937180; pre-results

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the authors' best knowledge, this is the first randomized controlled trial (RCT) to evaluate the effectiveness of an online intervention on benzodiazepine deprescribing in general practice.
- The use of toxicological screening of urine samples, self-report on discontinuation of (z-)BZD use, and number of defined daily doses prescribed will provide valuable insights with regard to the efficacy of the intervention and the reliability of the use of self-reporting in similar studies.
- To optimize the generalizability of the findings, this is a multicenter study with participants from both Dutch- and French-speaking parts of Belgium.
- The focus is on the effect of blended care, but the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.
- Non-e-literate patients are excluded from the study, even though this vulnerable group of patients could also benefit from more psychosocial support and counseling about medication use.

INTRODUCTION

Background

Worldwide, benzodiazepines and the related hypnotic drugs zolpidem, zopiclone and zaleplon ((z-)BZD) are prescribed extensively to treat anxiety and sleeping disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants. Recommendations state that treatment with (z-)BZD should be limited to only a few weeks. Despite the fact that long-term-use is ineffective and also associated with adverse side effects, the prevalence of long-term use, which is most common for sleeping disorders, remains widespread.[1-11] A recent systematic review summarizing current evidence-based discontinuation strategies indicates that gradual tapering of doses is an effective (z-)BZD discontinuation intervention for adult patients with long-term (z-)BZD use.[12] However, a combination of dose-tapering and non-pharmacological interventions such as psychotherapy interventions, self-help instructions and patient education produces better outcomes compared to stand-alone strategies.[13,14]

With the growing use of internet, e-based approaches are becoming more popular. Among them, blended care, defined as a combination of care by applying an interactive educational e-tool in combination with face-to-face clinical consultations with the care provider, is a new and promising approach.[15,16] Blended care has already proven to be successful in treating sleeping disorders, supporting substance use disorders, in stress management for employees, treating depression and other psychiatric and somatic conditions.[17-21]

In 2015, a small descriptive pilot study suggested that blended care for the discontinuation of (z-)BZD use for sleeping disorders may be more effective than a minimal intervention, such as a discontinuation letter or discontinuation advice, and as effective as face-to-face interventions combining tapering protocols and education. [22] Because these findings need to be confirmed by a properly powered and controlled study, a multicenter cluster randomized trial was designed, supported by the Belgian Federal Knowledge Centre for Healthcare (KCE) Trials program.

This study aims to establish an evidence-based blended care approach for the discontinuation of chronic (z-)BZD use for a primary indication of sleeping disorders in adult patients in a primary care setting. We hypothesize that blended care will support general practitioners as it is less time-

consuming and that it will empower patients to take a more active role in their discontinuation process. In that way, we think it may increase their motivation, which may result in increased discontinuation of (z-)BZD and more long-term discontinuation than currently with usual care.

Objectives

The primary objective is to compare the effect of blended care versus usual care on the proportion of subjects that has discontinued (z-)BZD use 12 months after start of the intervention as assessed by toxicological screening, in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Secondary objectives are to compare the effect of blended versus usual care on:

1. The discontinuation of (z-)BZD use 6 months after start of the intervention, as assessed by toxicological screening.
2. The quality of life, assessed by e-questionnaire at week 6, 12, 26 and 52.
3. The self-reported discontinuation of (z-)BZD use, assessed by e-questionnaire at week 6, 12, 26 and 52.
4. The number of defined daily doses (DDD) of (z-)BZD prescribed, assessed by e-questionnaire at week 6, 12, 26 and 52.

METHODS AND ANALYSIS

Study design and setting

This study is a multicenter, pragmatic, cluster randomized, controlled, superiority trial that will be performed in Belgian general practices. The participating general practitioners will be recruited and monitored by the academic centers for General Practice of the KU Leuven, UGent, UAntwerpen, ULiège, Université Libre de Bruxelles and Vrije Universiteit Brussel. The cluster and unit of randomization is the primary care practice. A 1:1 ratio will be used for allocation to the blended care arm and the usual care arm, as shown in figure 1.

The design of the study protocol has followed the recommendations of the SPIRIT 2013 statement.[23]

Patient and public involvement

Patients were involved in several stages of the study. During a focus group with long-term (z-)BZD users the overall feasibility of the patient activities, the lay-out and content of the e-tool, and the questionnaires and time required to complete them were discussed. Afterwards, these patients were also invited to provide written feedback on the Informed Consent Form (ICF), patient information leaflet and patient information video. Moreover, during the user acceptance testing of the tool, we involved acquaintances with different health and e-literacy profiles that were not familiar with the trial. Finally, to assure continuous involvement of patients in the study, two long-term (z-)BZD users are a member of the trial steering committee.

Eligibility criteria and recruitment

Patients' eligibility for inclusion in the study will be based on the following criteria:

1. Aged 18 years and older, capable of giving informed consent.
2. Having his/her Medical File managed by one of the participating general practitioners.
3. Receiving prescriptions of (z-)BZDs from participating general practitioner for use on a daily basis.
4. Reporting daily intake (≥ 80% of days) of (z-)BZDs in the last 6 months for a primary indication of sleeping problems.

Patients will be excluded from study participation based on the following criteria:

1. Presence of any severe psychiatric and neurologic condition that in the judgment of the treating general practitioner implies a contraindication for (z-)BZD withdrawal.
2. Presence of terminal illness.
3. Any case where stopping of (z-)BZDs might be harmful.
4. Unwillingness or inability to provide informed consent.
5. Not having e-literacy (being familiar with email and internet use).
6. Patients with a substance use disorder (other than (z-)BZD) will also be excluded from the study because in these cases there is often a sub-therapeutic (z-)BZD dependence and/or comorbid psychological/psychiatric comorbid conditions requiring specialist care.

Selection of eligible patients will be done consecutively by the general practitioner during consultations. To inform the patients about the study a patient information leaflet and video have been developed. When a patient is willing to participate, the general practitioner will obtain informed consent. The goal is to include 10 patients within 6 to maximally 12 weeks.

Sample size

Sample size calculation was based on a statistically significant difference in (z-)BZD discontinuation at 12 months between intervention and control group of 10%, assuming a rate of discontinuation of 15% in the control group. This assumption is based on a systematic review by Mugunthan et al[11] that shows us that usual care achieves a discontinuation rate of 10% to 17%.

To further estimate the sample size, calculations were based on findings from a similar study by Vicens et al.[14], in which the drop-out rate after 12 months was 7% and an intracluster correlation coefficient (ICC) of 0.11 was observed (personal communication).

Assuming a drop-out rate of 10% and based on an alpha of 0.05 and 80% power, a total sample size of 594 patients (297 in each group) would be required for an individually randomized study. However, to account for clustering effects by primary care practices, we used an ICC set at 0.11 and a cluster size of 10 patients. The number of patients required was multiplied by 1.99 corresponding to the cluster design effect (DE=1+ICC (size of the cluster-1)). Thus, the final sample will minimally consist of 1182 patients. Considering each general practitioner has to recruit 10 patients, 119 general practitioners are needed. Because six academic centers for general practice are involved in the project, we aim at including 120 general practitioners in total.

Random allocation

Within the week following the enrolment of the 10th patient (or a multiple of 10, depending on the number of participating general practitioners in that practice), the general practice is randomized in one of the two study arms in a 1:1 ratio using a block randomization system stratified per language in order to guarantee that allocation to either usual care or blended care for the discontinuation of (z-)BZD is balanced between the Dutch- and French-speaking community. To guarantee that the allocation process cannot be predicted two block sizes are used, 4 and 6.

Using an electronic random numbers generator, two randomization lists have been created, one for each language. After recruitment of the required number of patients, the project manager receives an e-mail alert that indicates the practice is ready for randomization. The result of the allocation is communicated by e-mail to both the general practitioner(s) and the corresponding monitor.

Blinding

General practitioners cannot be blinded to an intervention that modifies their clinical practice. Because the researchers need to monitor the conduct of the study on site, they also cannot be blinded to the allocation of the general practitioners. Owing to study procedures, patients will neither be blinded. However, all involved parties are blinded to the allocation until after patient recruitment. Furthermore, the outcome assessors will be kept blinded to the allocation during the whole study until after data analysis.

Intervention

Patients in the usual care arm, will receive care that is left at the discretion of the treating general practitioner. They are expected to follow the Belgian guidelines, which propose education of the patient about the harmful effects of chronic (z-)BZD use, the alternatives, and the advice to discontinue (z-)BZD use. A stepped approach is recommended. First, a minimal intervention strategy such as a discontinuation letter or a short advice is applied. If unsuccessful, a brief intervention, which may span one or more consults, is recommended. During such an intervention, the general practitioner will - based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. Most likely, a tapering scheme is developed which typically consists of a 10-20% reduction in the daily dose of (z-)BZD every 2-4 weeks.

For patients in the blended care arm, usual care is supported by the step-by-step use of an interactive e-tool. The e-tool consists of a sleeping diary, a tapering schedule, and six modules, providing psycho-education about sleep and sleep medication, and exercises featuring cognitive behavioral techniques to enhance the self-management of the patient. Its purpose is to motivate patients to discontinue the use of (z-)BZD, to adapt non-pharmacological remedies and to support them in this process. Patients can grant their participating general practitioner access to all their answers in the e-tool, making it possible to discuss these findings and experiences face-to-face. During consultations, the general practitioner will also assess the patients' readiness for change and match the appropriate intervention, like a tapering scheme. Follow-up appointments are scheduled depending on the needs of the patient until the end of dose reduction.

At the moment, the e-tool is not publicly available since the control group cannot have access to the e-tool. It is on a secure server and password-protected so that only registered users can benefit from the content. However, the goal is to make it publicly available if our research provides positive outcomes.

Outcome assessments

Primary outcome measure

The proportion of patients that discontinued (z-)BZD at 12-months assessed by toxicological screening for (z-)BZD in urine.

Secondary outcome measures

1. The proportion of patients that discontinued use of (z-)BZD at 6-months assessed by toxicological screening for (z-)BZD in urine.
2. Quality of life assessed by EQ-5D-3L[24].
3. Self-reported discontinuation of (z-)BZD.
4. The number of DDD of (z-)BZD prescribed.

Data will be collected either via questionnaires sent to the patient or by completion of the electronic Case Report Form (eCRF), except for the toxicological screening of urine samples, as presented in figure 2.

Data collection

E-questionnaires

At study entry, baseline data are collected using an e-questionnaire consisting of Audit-C[25], EQ-5D-3L[24], Benzodiazepine Dependence Self-Report Questionnaire[26], Insomnia Severity Index[27], and HLS-EU-Q16[28]. All together this e-questionnaire comprises less than 50 questions.

Patients will also be requested to complete an abbreviated e-questionnaire at weeks 6, 12, 26 and 52 comprising of the validated EQ-5D-3L[25], Audit-C[24] and Insomnia Severity Index. Furthermore, the e-questionnaire will register self-reported use of (z-)BZD and other psychoactive medication, self-reported falls and use of medical services in the past period.

All e-questionnaires will consist of closed questions which are answered by ticking the appropriate box. Invitations will be e-mailed to the study participants at week 5, 11, 25 and 51 with the request to complete the questionnaires online within 2 weeks. A reminder will be sent after 1 week to all participants who have not yet responded and every week after, until response or the deadline. The deadline is set at four weeks after the first reminder for the questionnaires at week 6 and 12, and eight weeks at week 26 and 52.

Assessment by general practitioner

During the baseline visit, which will take place within 12 weeks after signing the ICF, the general practitioner will start the intervention, and will collect the following data for each participating patient: demographics, comorbidities, current use of psychotropic medication, (z-)BZD prescriptions in the last 6 months (drug name(s), quantity), and a urine sample for toxicological screening.

After the baseline visit, appointments for follow-up (minimally one in the first six months) and prescription renewals will be scheduled left at the discretion of the general practitioner and depending on the needs of the patient until the end of dose reduction. This approach maximally reflects daily practice as should be in a pragmatic trial.

The general practitioners will be asked to note in the Electronic Health Record (EHR) and eCRF the (z-)BZD-related interventions delivered to the patients via standardized entry fields at each contact with the patient, during six months after baseline.

These interventions may include advice to discontinue (z-)BZD, discussion of tapering schedule, discussion of withdrawal symptoms, discussion of sleep quality, discussion of coping strategies, triggers and facilitators, decrease or increase of benzodiazepine dose.

Toxicological screening

At baseline, week 25 and 51, patients will be invited to produce a urine sample at the general practice within the next 2 weeks. For the samples of week 26 and 52, a reminder will be sent after 1 week to all participants who have not yet done so and every week after until a urine sample is obtained or the deadline is reached. The deadline is set at eight weeks after the first reminder.

The urine samples will be collected from the general practices within 5 days by the laboratory. Urine samples can be stored in a refrigerator for at least 7 days without any effect on the toxicological screening results.

The detection window for (z-)BZDs in urine is dependent on multiple factors. Using Liquid chromatography–tandem mass spectrometry (LC-MS/MS) it is typically six days or longer, in case of ingestion of a single dose. However, chronic usage over a period of months or years can extend excretion times up to four to six weeks after cessation of use.

Currently, LC–MS/MS is the most sensitive method available. It is able to detect the use of low-dose (z-)BZDs, which are (z-)BZDs prescribed in low doses because of their high potency, such as flurazepam. Routinely used immunoassays typically have a detection level of 200 ng per mL as compared to 5 ng/mL for LC-MS/MS. Also, it is possible to detect multiple components in one assay, to provide quantitative results, to identify the benzodiazepines exactly and to detect multiple metabolites resulting in longer detection periods.

All toxicological analyses will be performed at the laboratory AML in Antwerp. Toxicological screening of urine samples is not part of routine practice. Therefore, the general practitioners will be blinded for the results of these analyses.

Data analysis

Baseline characteristics, like age, gender, relevant co-morbidities, benzodiazepine dependence score, daily dose of (z-)BZD in DDD, sleep quality and Audit-C[24] score, will be presented for the complete study population and per allocation arm.

Primary outcome analysis

The primary endpoint will be analyzed according to the intent-to-treat (ITT) approach.

Logistic regression will be used for data analysis with benzodiazepine urine test results assessed at 12 months after initiation of the intervention as a binary outcome (positive or negative) and intervention group as a factor. A random effect will be modelled to deal with clustering by general practice. The group effect will be reported as an odds ratio with 95% confidence interval.

To investigate how the primary outcome behaves in function of age, gender, (z-)BZD dose at baseline, sleep quality at baseline, benzodiazepine dependency score and use of the e-tool (only in intervention group), subgroup analysis will be performed.

Secondary outcome analysis

The proportion of subjects with a negative benzodiazepine urine test assessed 6 months after initiation of the intervention will be analyzed in the same way as the primary endpoint.

All other secondary endpoints are binary variables, measured longitudinally. Analysis will be performed using multilevel logistic regression analysis, including random intercepts for patient and for general practitioner. A random slope for time will be modelled if beneficial for model fit. The fixed effects model will include intervention group, time and the group by time interaction. In case of a significant group by time interaction, the group effect will be reported separately for each time point. In case of a non-significant group by time interaction, a group main effect will be reported. The group effects will be presented as odds ratios with 95% confidence intervals.

No correction for multiplicity is planned for the secondary analyses, as the study is not powered for these analyses, and hence, its results will be considered as hypothesis generating.

Missing data

When a patient withdraws from the study prematurely, all data collected up until the moment of withdrawal will be analyzed. In case the data for measurement of the primary endpoint was not collected, the outcome will be classified as failure or continued benzodiazepine use in the intent-to-treat analysis. After withdrawal, no further data of this patient will be collected.

Economic data evaluation

One of the goals of the KCE Trials program is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind, i.e. the necessary data to allow the conduct of a health economic evaluation will be collected. For more information on these procedures, we refer to the protocol of the trial.

Data management

Using a trial-specific online platform, data will be automatically entered in a database. These data will be generated by the general practitioners completing the eCRF and by the patients completing the e-questionnaires and using the e-tool. All collected data are stored pseudonymized, working with a personal study code for all patients. The identity of the individual patient will be blinded to the researchers at all times.

The collected data remain in the databases of the service provider and only an excerpt of this data is transferred to the data warehouse of the researchers, where it is merged with the results of the laboratory testing.

The data entry process will be documented, creating an audit trail. The database will be stored and maintained by the service provider, who will also be responsible for the pseudonymization of patient data as Trusted Third Party, compliant with ICH-GCP regulations and the EU General Data Protection Regulation. Confidentiality of personal identifiable information will be maintained throughout the trial. Data will be stored for a period of 25 years after the study has ended, according to ICH-GCP regulations.

Nested study

A process evaluation will be nested within the pragmatic cluster randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by general practitioners and patients. It helps interpreting the results in their context. This is important for informing future implementation in practice. It will explain how general practitioners and patients experience the intervention. With this study, we aim to identify factors which influence the ability (or inability) to withdraw from (z-)BZD in order to build a framework describing the mechanisms required for successful implementation.

Individual interviews and discussion groups will be conducted with general practitioners and patients taking part in the trial. General practitioners (approximately 8) will be purposively sampled to obtain variation in gender, language, practice setting and experience. Patients (approximately 14-18) will be purposively sampled to obtain variation in age, gender, language, and how successful the withdrawal has been. Interviews will follow semi-structured topic guides exploring general practitioners' and patients' views and experiences of taking part in the trial. Topic guides will be informed by existing literature and theory of health behavior to ensure that questions elicit likely key determinants of behavior. Topic guides will be piloted with patient representatives and clinicians. Interviews and discussion groups will be carried out face to face and analyzed using thematic and framework analysis.

Participant safety and monitoring

This study is considered low-risk. Because no medication or new treatment protocols are tested, there is no additional safety reporting to the one in daily general practice. In Belgium, any adverse effects of medication can be reported to the federal agency for medicines and health products (famph) by using the yellow card. If necessary, appropriate measures will be taken in consultation with the attending general practitioner.

Close monitoring to assure proper conduct of the study is provided by all abovementioned academic centers for General Practice, in compliance with ICH-GCP regulations. Moreover, annual reports of the study progress will be sent to the Ethics Committee of the University Hospital of Leuven.

DISCUSSION

In 2008, research established that computer-assisted tailored patient education could be a useful tool in the discontinuation of chronic benzodiazepine use. Ten Wolde and colleagues performed an RCT, showing that letters, tailored to baseline characteristics of the patient, influence benzodiazepine use positively. After the trial, the most successful intervention, being a single customized letter, was published online in a password protected environment to reach as many patients as possible.[29] No further research on the effectiveness of this online module has been published.

Currently, this is the only (English) publication on computer-assisted patient education for discontinuation of chronic benzodiazepine use. This means that our trial will be the first RCT that assesses the superiority of blended care over usual care for (z-)BZD discontinuation in primary care.

Moreover, the Big Bird trial is innovative in its methodology. In most discontinuation studies, researchers use self-reported data from patients and/or general practitioners to assess the success of an intervention. In this trial, success rate will depend on the proportion of patients that has discontinued their use of (z-)BZD as assessed by toxicological screening of urine samples at 12 months after start of the intervention. This measurement is also performed at 6 months, when access to the online platform has ended.

Some might argue that delivering urine samples will trigger patients to increase their efforts for discontinuing (z-)BZD. To limit this possibility we have taken precautionary measures by not communicating the results of the toxicological screening to the general practitioner, nor to the patient.

The toxicological analysis of urine samples will enable us to compare the concentrations of (z-)BZD with the reports of patients and general practitioners and provide insights on the reliability of self-reporting in studies on discontinuation.

Another strength of this study is the collaboration between six universities, which enables us to implement the intervention across the Belgian French and Dutch speaking population.

However, due to language and the technological character of the intervention, some vulnerable groups of patients cannot be reached. Language restrictions exclude the German community in Belgium and a number of migrant groups from participation. Also, non-e-literate patients, including elderly people that are not familiar with internet usage but who report high (z-)BZD intake, cannot take part in the trial. This is unfortunate as these patients could also benefit from more psychosocial support and counseling about medication use. If effective, we need to consider adapting the existing materials for use with these patients.

Finally, although the focus in the trial is on the effect of blended care, the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki (seventh revision). Any substantial protocol amendments will be submitted to the ethics committee.

The study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial status

Currently, recruitment of general practitioners and patients is ongoing. First patient first visit is expected in August 2019. Last patient last visit is expected in September 2020. Database lock will take place in November 2020.

FIGURES

Figure 1. Flowchart of trial design summary

Figure 2. Flowchart of trial procedures

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AUTHORS' CONTRIBUTIONS

CM and MVN are responsible for the original conception of the study and obtaining funding. They also drafted the study protocol, in cooperation with SA, who developed the nested study, and AL, who provided the statistical analysis plan. All authors assisted in finalizing the protocol. CM, MVN and KC obtained ethical approval. KC wrote the first draft of the manuscript based upon protocol version 1.6 dd. March 2019. CM, MVN, MVM, GH, SA, KVDB, ADS, HC, DD, RVO, AMO, NK and AL contributed to further drafts. All authors read and approved the final draft.

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Disclaimer

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

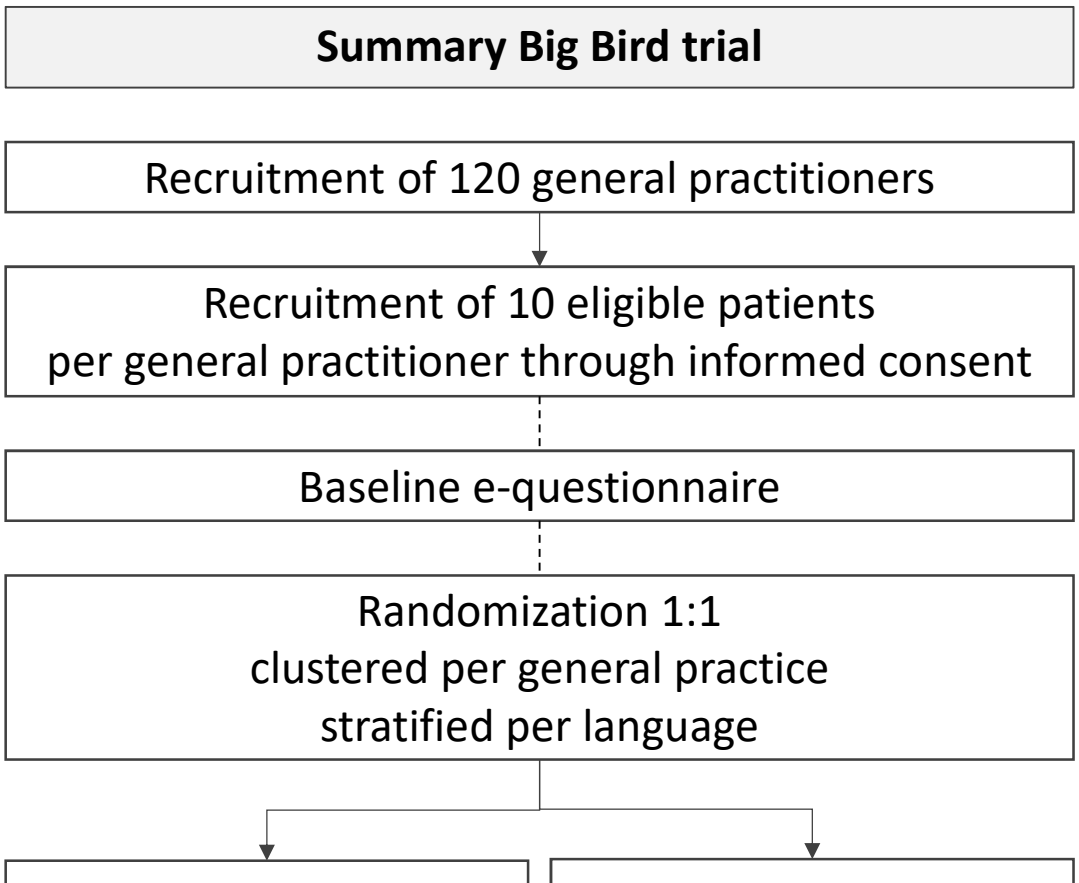
This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (B322201939666) in March 2019. Reference number: S61194.

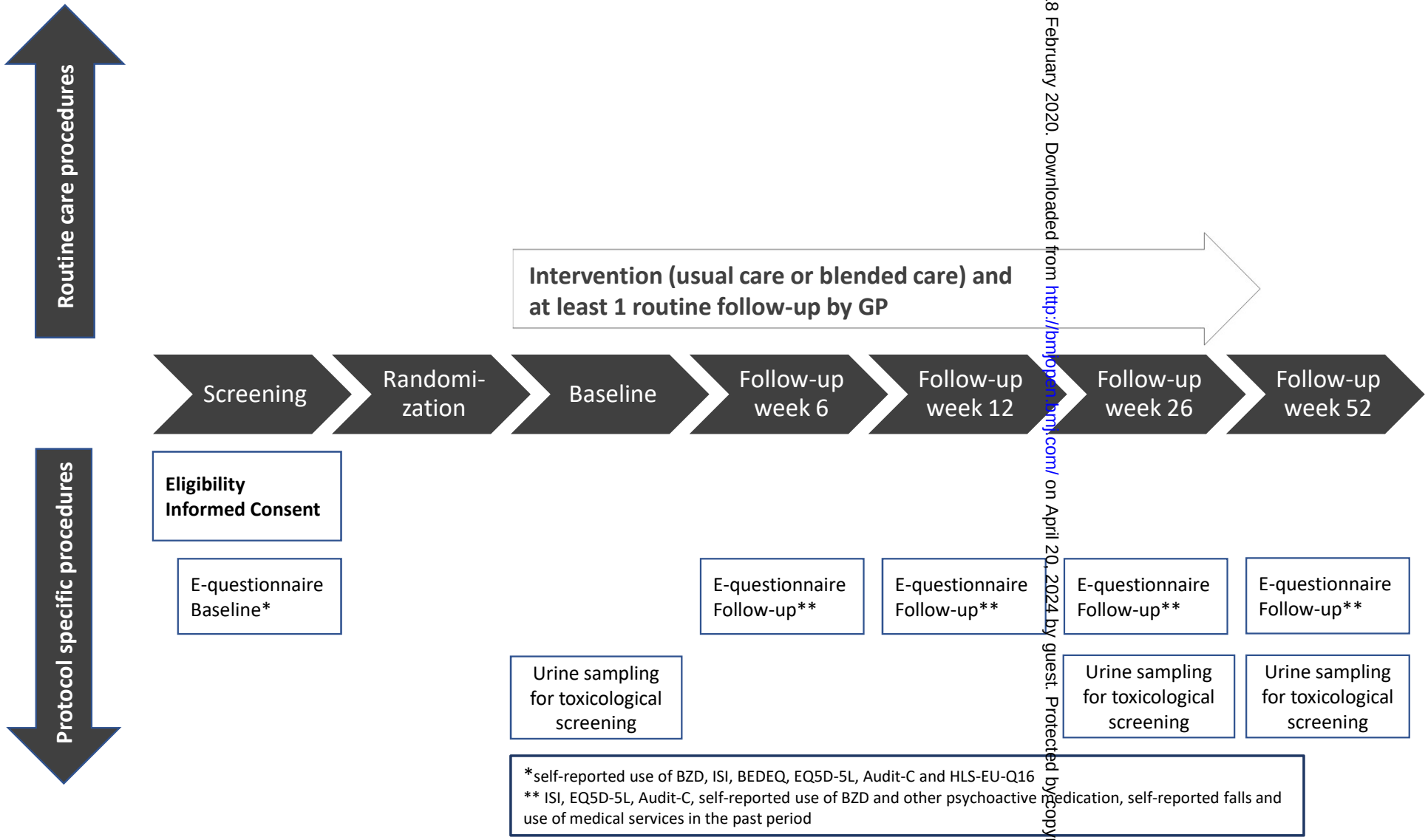
Provenance and peer review

Not commissioned, externally peer reviewed.

Open access

Protocol publication BMJ Open_final_v1.4_20191014


Summary Big Bird trial
Recruitment of 120 general practitioners
Recruitment of 10 eligible patients
per general practitioner through informed consent
Baseline e-questionnaire
Randomization 1:1
clustered per general practice
stratified per language
Blended care
Usual care
Baseline visit
(incl. urine sample)
Follow-up assessments
at week 6, 12, 26 and 52



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 1
	2b	All items from the World Health Organization Trial Registration Data Set	Clinicaltrials.gov
Protocol version	3	Date and version identifier	p. 13
Funding	4	Sources and types of financial, material, and other support	p. 13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 13
	5b	Name and contact information for the trial sponsor	Protocol p. 5 – 8
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol p. 11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol p. 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 2
	6b	Explanation for choice of comparators	p. 3
Objectives	7	Specific objectives or hypotheses	p. 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 3 – 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p. 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 5 – 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Protocol p. 23 – 24
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p. 4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p. 4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 5 – 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 7 – 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 7 – 8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p. 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p. 9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Protocol p. 40
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Protocol p. 40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 1
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol p. 40 – 41
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol p. 40 – 41
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ICF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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Key words MeSH: Benzodiazepines, deprescriptions, sleep initiation and maintenance disorders, cognitive behavioral therapy

ABSTRACT

Introduction Problematic benzodiazepine use is a global health issue. Although the adverse side effects of long-term use of benzodiazepines are well known, it remains difficult to implement interventions for discontinuation in primary care. Considering the success of blended care for the treatment of sleeping disorders and the support of substance use disorders, evidence suggests that a blended care approach, combining face-to-face consultations with the general practitioner with web-based self-learning by the patient, is beneficial for the discontinuation of chronic benzodiazepine use for primary insomnia in general practice. Therefore, the aim of this study is to evaluate the effectiveness of such an approach for the discontinuation of benzodiazepine and z-drugs ((z-)BZD) use in the long term and evaluate the implementation process.

Methods and analysis This study is a multicenter, pragmatic, cluster randomized controlled trial with 1200 patients, included by 120 general practitioners. Allocation to usual or blended care happens at the level of the general practice in a 1:1 ratio using a block randomization system stratified per language. The study population consists of adult primary care patients who have been using (z-)BZD for primary insomnia on a daily basis for at least six months. Primary outcome measure is the proportion of patients that discontinued (z-)BZD at 12 months assessed by toxicological screening for (z-)BZD in urine. Secondary outcomes include discontinuation of (z-)BZD at 6 months, quality of life, and the number of defined daily doses of (z-)BZD prescribed. Data will be collected using a study-specific online platform and analyzed using the intention-to-treat approach. The process of implementing blended care will be evaluated in a nested study.

Ethics and dissemination This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (ref. S61194). Study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial registration number NCT03937180; pre-results

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the authors' best knowledge, this is the first randomized controlled trial (RCT) to evaluate the effectiveness of an online intervention on benzodiazepine deprescribing in general practice.
- The use of toxicological screening of urine samples, self-report on discontinuation of (z-)BZD use, and number of defined daily doses prescribed will provide valuable insights with regard to the efficacy of the intervention and the reliability of the use of self-reporting in similar studies.
- To optimize the generalizability of the findings, this is a multicenter study with participants from both Dutch- and French-speaking parts of Belgium.
- The focus is on the effect of blended care, but the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.
- Non-e-literate patients are excluded from the study, even though this vulnerable group of patients could also benefit from more psychosocial support and counseling about medication use.

INTRODUCTION

Background

Worldwide, benzodiazepines and the related hypnotic drugs zolpidem, zopiclone and zaleplon ((z-)BZD) are prescribed extensively to treat anxiety and sleeping disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants. Recommendations state that treatment with (z-)BZD should be limited to only a few weeks. Despite the fact that long-term-use is ineffective and also associated with adverse side effects, the prevalence of long-term use, which is most common for sleeping disorders, remains widespread.[1-11] A recent systematic review summarizing current evidence-based discontinuation strategies indicates that gradual tapering of doses is an effective (z-)BZD discontinuation intervention for adult patients with long-term (z-)BZD use.[12] However, a combination of dose-tapering and non-pharmacological interventions such as psychotherapy interventions, self-help instructions and patient education produces better outcomes compared to stand-alone strategies.[13,14]

With the growing use of internet, e-based approaches are becoming more popular. Among them, blended care, defined as a combination of care by applying an interactive educational e-tool in combination with face-to-face clinical consultations with the care provider, is a new and promising approach.[15,16] Blended care has already proven to be successful in treating sleeping disorders, supporting substance use disorders, in stress management for employees, treating depression and other psychiatric and somatic conditions.[17-21]

In 2015, a small descriptive pilot study suggested that blended care for the discontinuation of (z-)BZD use for sleeping disorders may be more effective than a minimal intervention, such as a discontinuation letter or discontinuation advice, and as effective as face-to-face interventions combining tapering protocols and education. [22] Because these findings need to be confirmed by a properly powered and controlled study, a multicenter cluster randomized trial was designed, supported by the Belgian Federal Knowledge Centre for Healthcare (KCE) Trials program.

This study aims to establish an evidence-based blended care approach for the discontinuation of chronic (z-)BZD use for a primary indication of sleeping disorders in adult patients in a primary care setting. We hypothesize that blended care will support general practitioners as it is less time-

consuming and that it will empower patients to take a more active role in their discontinuation process. In that way, we think it may increase their motivation, which may result in increased discontinuation of (z-)BZD and more long-term discontinuation than currently with usual care.

Objectives

The primary objective is to compare the effect of blended care versus usual care on the proportion of subjects that has discontinued (z-)BZD use 12 months after start of the intervention as assessed by toxicological screening, in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Secondary objectives are to compare the effect of blended versus usual care on:

1. The discontinuation of (z-)BZD use 6 months after start of the intervention, as assessed by toxicological screening.
2. The quality of life, assessed by e-questionnaire at week 6, 12, 26 and 52.
3. The self-reported discontinuation of (z-)BZD use, assessed by e-questionnaire at week 6, 12, 26 and 52.
4. The number of defined daily doses (DDD) of (z-)BZD prescribed, assessed by e-questionnaire at week 6, 12, 26 and 52.

METHODS AND ANALYSIS

Study design and setting

This study is a multicenter, pragmatic, cluster randomized, controlled, superiority trial that will be performed in Belgian general practices. The participating general practitioners will be recruited and monitored by the academic centers for General Practice of the KU Leuven, UGent, UAntwerpen, ULiège, Université Libre de Bruxelles and Vrije Universiteit Brussel. The cluster and unit of randomization is the primary care practice. A 1:1 ratio will be used for allocation to the blended care arm and the usual care arm, as shown in figure 1.

The design of the study protocol has followed the recommendations of the SPIRIT 2013 statement.[23]

Patient and public involvement

Patients were involved in several stages of the study. During a focus group with long-term (z-)BZD users the overall feasibility of the patient activities, the lay-out and content of the e-tool, and the questionnaires and time required to complete them were discussed. Afterwards, these patients were also invited to provide written feedback on the Informed Consent Form (ICF), patient information leaflet and patient information video. Moreover, during the user acceptance testing of the tool, we involved acquaintances with different health and e-literacy profiles that were not familiar with the trial. Finally, to assure continuous involvement of patients in the study, two long-term (z-)BZD users are a member of the trial steering committee.

Eligibility criteria and recruitment

Patients' eligibility for inclusion in the study will be based on the following criteria:

1. Aged 18 years and older, capable of giving informed consent.
2. Having his/her Medical File managed by one of the participating general practitioners.
3. Receiving prescriptions of (z-)BZDs from participating general practitioner for use on a daily basis.
4. Reporting daily intake (≥ 80% of days) of (z-)BZDs in the last 6 months for a primary indication of sleeping problems.

Patients will be excluded from study participation based on the following criteria:

1. Presence of any severe psychiatric and neurologic condition that in the judgment of the treating general practitioner implies a contraindication for (z-)BZD withdrawal.
2. Presence of terminal illness.
3. Any case where stopping of (z-)BZDs might be harmful.
4. Unwillingness or inability to provide informed consent.
5. Not having e-literacy (being familiar with email and internet use).
6. Patients with a substance use disorder (other than (z-)BZD) will also be excluded from the study because in these cases there is often a sub-therapeutic (z-)BZD dependence and/or comorbid psychological/psychiatric comorbid conditions requiring specialist care.

Selection of eligible patients will be done consecutively by the general practitioner during consultations. To inform the patients about the study a patient information leaflet and video have been developed. When a patient is willing to participate, the general practitioner will obtain informed consent. The goal is to include 10 patients within 6 to maximally 12 weeks.

Sample size

Sample size calculation was based on a statistically significant difference in (z-)BZD discontinuation at 12 months between intervention and control group of 10%, assuming a rate of discontinuation of 15% in the control group. This assumption is based on a systematic review by Mugunthan et al[11] that shows us that usual care achieves a discontinuation rate of 10% to 17%.

To further estimate the sample size, calculations were first based on findings from a similar study by Vicens et al.[14], in which the drop-out rate after 12 months was 7% and an overall intracluster correlation coefficient (ICC) of 0.03 was observed. However, a range in ICCs was observed, with an ICC of 0.109 in both intervention groups. (personal communication by funder with author) Therefore, the funder requested a more conservative approach which led to the use of 0.11 in this trial.

Assuming a drop-out rate of 10% and based on an alpha of 0.05 and 80% power, a total sample size of 594 patients (297 in each group) would be required for an individually randomized study. However, to account for clustering effects by primary care practices, we used an ICC set at 0.11 and a cluster size of 10 patients. The number of patients required was multiplied by 1.99 corresponding to the cluster design effect (DE=1+ICC (size of the cluster-1)). Thus, the final sample will minimally consist of 1182 patients. Considering each general practitioner has to recruit 10 patients, 119 general practitioners are needed. Because six academic centers for general practice are involved in the project, we aim at including 120 general practitioners in total.

Random allocation

Within the week following the enrolment of the 10th patient (or a multiple of 10, depending on the number of participating general practitioners in that practice), the general practice is randomized in one of the two study arms in a 1:1 ratio using a block randomization system stratified per language in order to guarantee that allocation to either usual care or blended care for the discontinuation of (z-)BZD is balanced between the Dutch- and French-speaking community. To guarantee that the allocation process cannot be predicted two block sizes are used, 4 and 6.

Using an electronic random numbers generator, two randomization lists have been created, one for each language. After recruitment of the required number of patients, the project manager receives

an e-mail alert that indicates the practice is ready for randomization. The result of the allocation is communicated by e-mail to both the general practitioner(s) and the corresponding monitor.

Blinding

General practitioners cannot be blinded to an intervention that modifies their clinical practice. Because the researchers need to monitor the conduct of the study on site, they also cannot be blinded to the allocation of the general practitioners. Owing to study procedures, patients will neither be blinded. However, all involved parties are blinded to the allocation until after patient recruitment. Furthermore, the outcome assessors will be kept blinded to the allocation during the whole study until after data analysis.

Intervention

Patients in the usual care arm, will receive care that is left at the discretion of the treating general practitioner. They are expected to follow the Belgian guidelines, which propose education of the patient about the harmful effects of chronic (z-)BZD use, the alternatives, and the advice to discontinue (z-)BZD use. A stepped approach is recommended. First, a minimal intervention strategy such as a discontinuation letter or a short advice is applied. If unsuccessful, a brief intervention, which may span one or more consults, is recommended. During such an intervention, the general practitioner will - based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. Most likely, a tapering scheme is developed which typically consists of a 10-20% reduction in the daily dose of (z-)BZD every 2-4 weeks.

For patients in the blended care arm, usual care is supported by the step-by-step use of an interactive e-tool. The e-tool consists of a sleeping diary, a tapering schedule, and six modules, providing psycho-education about sleep and sleep medication, and exercises featuring cognitive behavioral techniques to enhance the self-management of the patient. Its purpose is to motivate patients to discontinue the use of (z-)BZD, to adapt non-pharmacological remedies and to support them in this process. Patients can grant their participating general practitioner access to all their answers in the e-tool, making it possible to discuss these findings and experiences face-to-face. During consultations, the general practitioner will also assess the patients' readiness for change and match the appropriate intervention, like a tapering scheme. Follow-up appointments are scheduled depending on the needs of the patient until the end of dose reduction.

At the moment, the e-tool is not publicly available since the control group cannot have access to the e-tool. It is on a secure server and password-protected so that only registered users can benefit from the content. However, the goal is to make it publicly available if our research provides positive outcomes.

Outcome assessments

Primary outcome measure

The proportion of patients that discontinued (z-)BZD at 12-months assessed by toxicological screening for (z-)BZD in urine.

Secondary outcome measures

1. The proportion of patients that discontinued use of (z-)BZD at 6-months assessed by toxicological screening for (z-)BZD in urine.
2. Quality of life assessed by EQ-5D-3L[24].
3. Self-reported discontinuation of (z-)BZD.

4. The number of DDD of (z-)BZD prescribed.

Data will be collected either via questionnaires sent to the patient or by completion of the electronic Case Report Form (eCRF), except for the toxicological screening of urine samples, as presented in figure 2.

Data collection

E-questionnaires

At study entry, baseline data are collected using an e-questionnaire consisting of Audit-C[25], EQ-5D-3L[24], Benzodiazepine Dependence Self-Report Questionnaire[26], Insomnia Severity Index[27], and HLS-EU-Q16[28]. All together this e-questionnaire comprises less than 50 questions.

Patients will also be requested to complete an abbreviated e-questionnaire at weeks 6, 12, 26 and 52 comprising of the validated EQ-5D-3L[25], Audit-C[24] and Insomnia Severity Index. Furthermore, the e-questionnaire will register self-reported use of (z-)BZD and other psychoactive medication, self-reported falls and use of medical services in the past period.

All e-questionnaires will consist of closed questions which are answered by ticking the appropriate box. Invitations will be e-mailed to the study participants at week 5, 11, 25 and 51 with the request to complete the questionnaires online within 2 weeks. A reminder will be sent after 1 week to all participants who have not yet responded and every week after, until response or the deadline. The deadline is set at four weeks after the first reminder for the questionnaires at week 6 and 12, and eight weeks at week 26 and 52.

Assessment by general practitioner

During the baseline visit, which will take place within 12 weeks after signing the ICF, the general practitioner will start the intervention, and will collect the following data for each participating patient: demographics, comorbidities, current use of psychotropic medication, (z-)BZD prescriptions in the last 6 months (drug name(s), quantity), and a urine sample for toxicological screening.

After the baseline visit, appointments for follow-up (minimally one in the first six months) and prescription renewals will be scheduled left at the discretion of the general practitioner and depending on the needs of the patient until the end of dose reduction. This approach maximally reflects daily practice as should be in a pragmatic trial.

The general practitioners will be asked to note in the Electronic Health Record (EHR) and eCRF the (z-)BZD-related interventions delivered to the patients via standardized entry fields at each contact with the patient, during six months after baseline.

These interventions may include advice to discontinue (z-)BZD, discussion of tapering schedule, discussion of withdrawal symptoms, discussion of sleep quality, discussion of coping strategies, triggers and facilitators, decrease or increase of benzodiazepine dose.

Toxicological screening

At baseline, week 25 and 51, patients will be invited to produce a urine sample at the general practice within the next 2 weeks. For the samples of week 26 and 52, a reminder will be sent after 1 week to all participants who have not yet done so and every week after until a urine sample is obtained or the deadline is reached. The deadline is set at eight weeks after the first reminder.

The urine samples will be collected from the general practices within 5 days by the laboratory. Urine samples can be stored in a refrigerator for at least 7 days without any effect on the toxicological screening results.

The detection window for (z-)BZDs in urine is dependent on multiple factors. Using Liquid chromatography–tandem mass spectrometry (LC-MS/MS) it is typically six days or longer, in case of ingestion of a single dose. However, chronic usage over a period of months or years can extend excretion times up to four to six weeks after cessation of use.

Currently, LC–MS/MS is the most sensitive method available. It is able to detect the use of low-dose (z-)BZDs, which are (z-)BZDs prescribed in low doses because of their high potency, such as flurazepam. Routinely used immunoassays typically have a detection level of 200 ng per mL as compared to 5 ng/mL for LC-MS/MS. Also, it is possible to detect multiple components in one assay, to provide quantitative results, to identify the benzodiazepines exactly and to detect multiple metabolites resulting in longer detection periods.

All toxicological analyses will be performed at the laboratory AML in Antwerp. Toxicological screening of urine samples is not part of routine practice. Therefore, the general practitioners will be blinded for the results of these analyses.

Data analysis

Baseline characteristics, like age, gender, relevant co-morbidities, benzodiazepine dependence score, daily dose of (z-)BZD in DDD, sleep quality and Audit-C[24] score, will be presented for the complete study population and per allocation arm.

Primary outcome analysis

The primary endpoint will be analyzed according to the intent-to-treat (ITT) approach.

Logistic regression will be used for data analysis with benzodiazepine urine test results assessed at 12 months after initiation of the intervention as a binary outcome (positive or negative) and intervention group as a factor. A random effect will be modelled to deal with clustering by general practice. The group effect will be reported as an odds ratio with 95% confidence interval.

To investigate how the primary outcome behaves in function of age, gender, (z-)BZD dose at baseline, sleep quality at baseline, benzodiazepine dependency score and use of the e-tool (only in intervention group), subgroup analysis will be performed.

Secondary outcome analysis

The proportion of subjects with a negative benzodiazepine urine test assessed 6 months after initiation of the intervention will be analyzed in the same way as the primary endpoint.

All other secondary endpoints are binary variables, measured longitudinally. Analysis will be performed using multilevel logistic regression analysis, including random intercepts for patient and for general practitioner. A random slope for time will be modelled if beneficial for model fit. The fixed effects model will include intervention group, time and the group by time interaction. In case of a significant group by time interaction, the group effect will be reported separately for each time point. In case of a non-significant group by time interaction, a group main effect will be reported. The group effects will be presented as odds ratios with 95% confidence intervals.

No correction for multiplicity is planned for the secondary analyses, as the study is not powered for these analyses, and hence, its results will be considered as hypothesis generating.

Missing data

When a patient withdraws from the study prematurely, all data collected up until the moment of withdrawal will be analyzed. In case the data for measurement of the primary endpoint was not collected, the outcome will be classified as failure or continued benzodiazepine use in the intent-to-treat analysis. After withdrawal, no further data of this patient will be collected.

Economic data evaluation

One of the goals of the KCE Trials program is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind, i.e. the necessary data to allow the conduct of a health economic evaluation will be collected. For more information on these procedures, we refer to the protocol of the trial.

Data management

Using a trial-specific online platform, data will be automatically entered in a database. These data will be generated by the general practitioners completing the eCRF and by the patients completing the e-questionnaires and using the e-tool. All collected data are stored pseudonymized, working with a personal study code for all patients. The identity of the individual patient will be blinded to the researchers at all times.

The collected data remain in the databases of the service provider and only an excerpt of this data is transferred to the data warehouse of the researchers, where it is merged with the results of the laboratory testing.

The data entry process will be documented, creating an audit trail. The database will be stored and maintained by the service provider, who will also be responsible for the pseudonymization of patient data as Trusted Third Party, compliant with ICH-GCP regulations and the EU General Data Protection Regulation. Confidentiality of personal identifiable information will be maintained throughout the trial. Data will be stored for a period of 25 years after the study has ended, according to ICH-GCP regulations.

Nested study

A process evaluation will be nested within the pragmatic cluster randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by general practitioners and patients. It helps interpreting the results in their context. This is important for informing future implementation in practice. It will explain how general practitioners and patients experience the intervention. With this study, we aim to identify factors which influence the ability (or inability) to withdraw from (z-)BZD in order to build a framework describing the mechanisms required for successful implementation.

Individual interviews and discussion groups will be conducted with general practitioners and patients taking part in the trial. General practitioners (approximately 8) will be purposively sampled to obtain variation in gender, language, practice setting and experience. Patients (approximately 14-18) will be purposively sampled to obtain variation in age, gender, language, and how successful the withdrawal has been. Interviews will follow semi-structured topic guides exploring general practitioners' and patients' views and experiences of taking part in the trial. Topic guides will be informed by existing literature and theory of health behavior to ensure that questions elicit likely key determinants of behavior. Topic guides will be piloted with patient representatives and clinicians. Interviews and

discussion groups will be carried out face to face and analyzed using thematic and framework analysis.

Participant safety and monitoring

This study is considered low-risk. Because no medication or new treatment protocols are tested, there is no additional safety reporting to the one in daily general practice. In Belgium, any adverse effects of medication can be reported to the federal agency for medicines and health products (famph) by using the yellow card. If necessary, appropriate measures will be taken in consultation with the attending general practitioner.

Close monitoring to assure proper conduct of the study is provided by all abovementioned academic centers for General Practice, in compliance with ICH-GCP regulations. Moreover, annual reports of the study progress will be sent to the Ethics Committee of the University Hospital of Leuven.

DISCUSSION

In 2008, research established that computer-assisted tailored patient education could be a useful tool in the discontinuation of chronic benzodiazepine use. Ten Wolde and colleagues performed an RCT, showing that letters, tailored to baseline characteristics of the patient, influence benzodiazepine use positively. After the trial, the most successful intervention, being a single customized letter, was published online in a password protected environment to reach as many patients as possible.[29] No further research on the effectiveness of this online module has been published.

Currently, this is the only (English) publication on computer-assisted patient education for discontinuation of chronic benzodiazepine use. This means that our trial will be the first RCT that assesses the superiority of blended care over usual care for (z-)BZD discontinuation in primary care.

Moreover, the Big Bird trial is innovative in its methodology. In most discontinuation studies, researchers use self-reported data from patients and/or general practitioners to assess the success of an intervention. In this trial, success rate will depend on the proportion of patients that has discontinued their use of (z-)BZD as assessed by toxicological screening of urine samples at 12 months after start of the intervention. This measurement is also performed at 6 months, when access to the online platform has ended.

Some might argue that delivering urine samples will trigger patients to increase their efforts for discontinuing (z-)BZD. To limit this possibility we have taken precautionary measures by not communicating the results of the toxicological screening to the general practitioner, nor to the patient.

The toxicological analysis of urine samples will enable us to compare the concentrations of (z-)BZD with the reports of patients and general practitioners and provide insights on the reliability of self-reporting in studies on discontinuation.

Another strength of this study is the collaboration between six universities, which enables us to implement the intervention across the Belgian French and Dutch speaking population.

However, due to language and the technological character of the intervention, some vulnerable groups of patients cannot be reached. Language restrictions exclude the German community in Belgium and a number of migrant groups from participation. Also, non-e-literate patients, including elderly people that are not familiar with internet usage but who report high (z-)BZD intake, cannot take part in the trial. This is unfortunate as these patients could also benefit from more psychosocial

support and counseling about medication use. If effective, we need to consider adapting the existing materials for use with these patients.

Finally, although the focus in the trial is on the effect of blended care, the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki (seventh revision). Any substantial protocol amendments will be submitted to the ethics committee.

The study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial status

Currently, recruitment of general practitioners and patients is ongoing. First patient first visit is expected in August 2019. Last patient last visit is expected in September 2020. Database lock will take place in November 2020.

FIGURES

Figure 1. Flowchart of trial design summary

Figure 2. Flowchart of trial procedures

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AUTHORS' CONTRIBUTIONS

CM and MVN are responsible for the original conception of the study and obtaining funding. They also drafted the study protocol, in cooperation with SA, who developed the nested study, and AL, who provided the statistical analysis plan. All authors assisted in finalizing the protocol. CM, MVN and KC obtained ethical approval. KC wrote the first draft of the manuscript based upon protocol version 1.6 dd. March 2019. CM, MVN, MVM, GH, SA, KVDB, ADS, HC, DD, RVO, AMO, NK and AL contributed to further drafts. All authors read and approved the final draft.

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Disclaimer

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

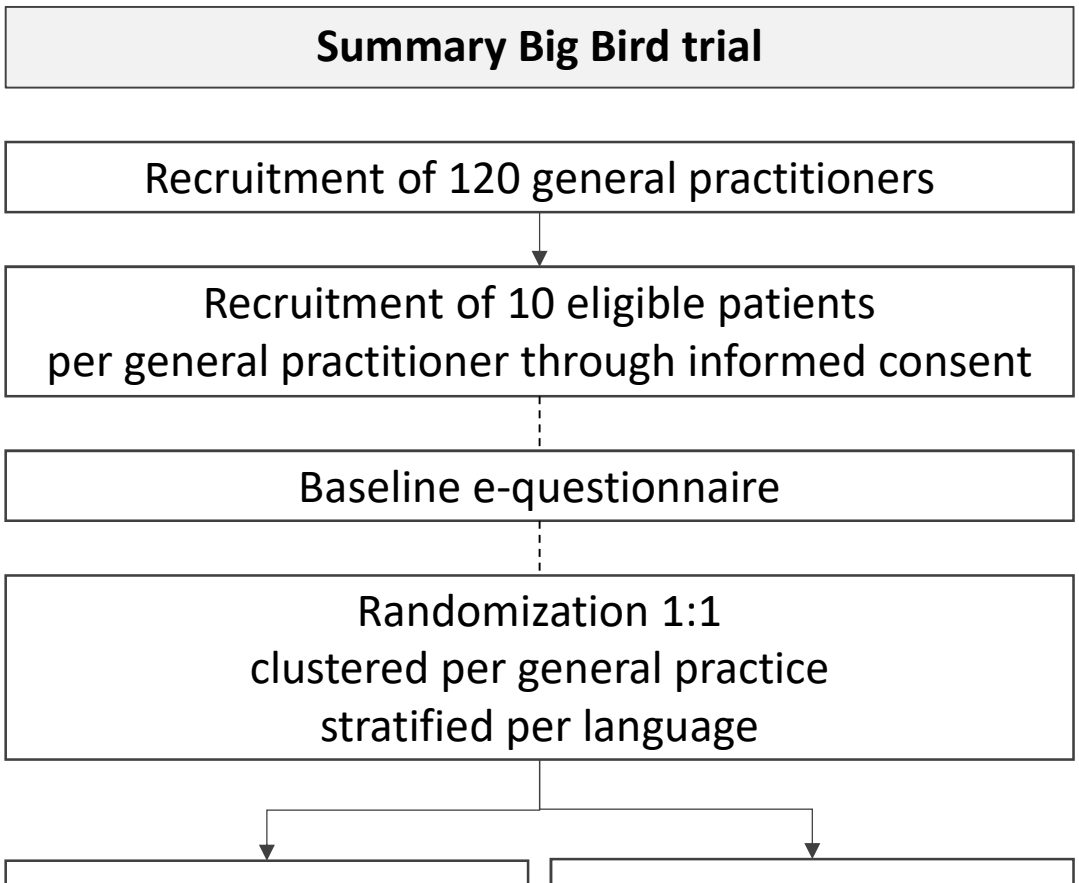
This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (B322201939666) in March 2019. Reference number: S61194.

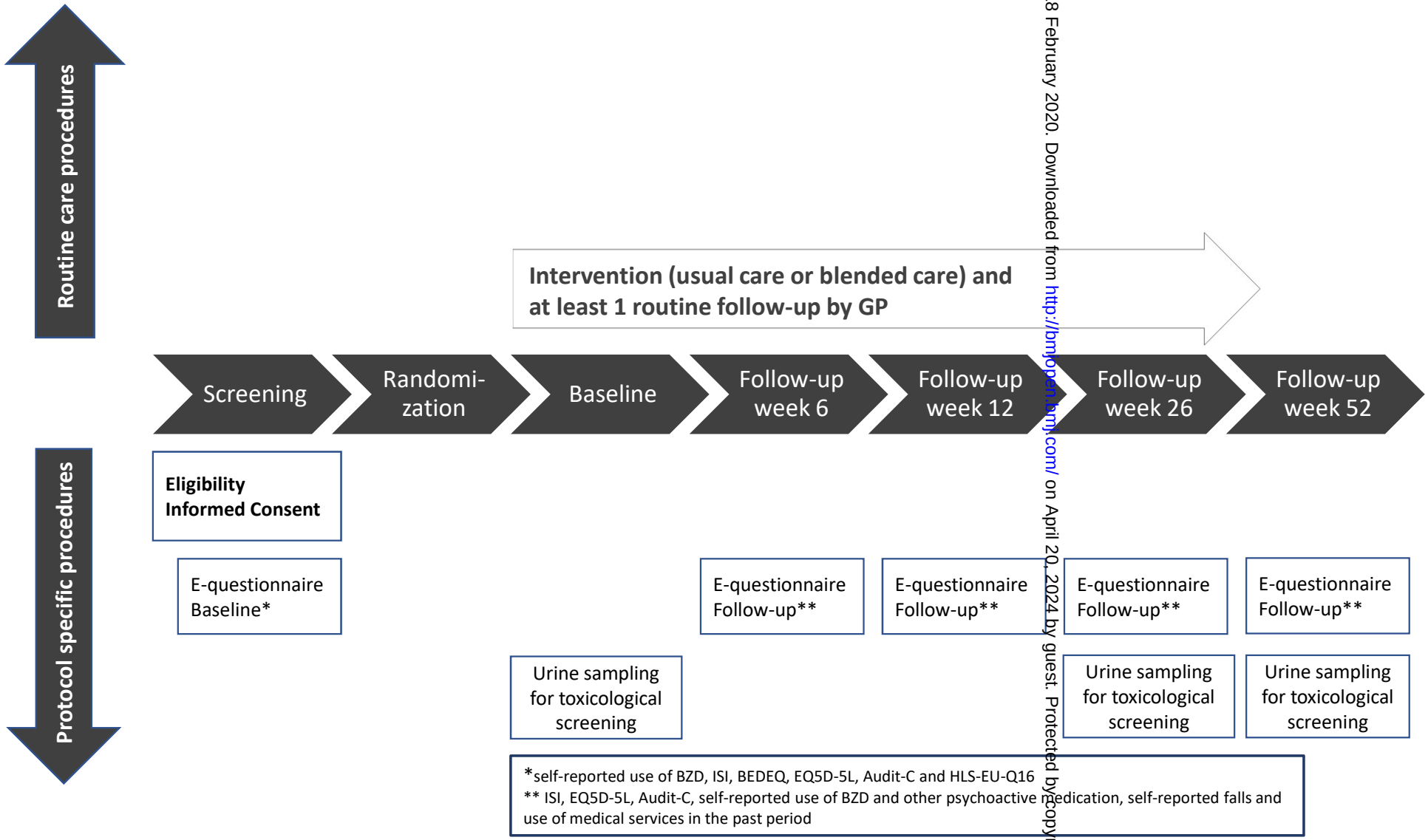
Provenance and peer review

Not commissioned, externally peer reviewed.

Open access

Protocol publication BMJ Open_final_v1.5_20191120


Summary Big Bird trial
Recruitment of 120 general practitioners
Recruitment of 10 eligible patients
per general practitioner through informed consent
Baseline e-questionnaire
Randomization 1:1
clustered per general practice
stratified per language
Blended care
Usual care
Baseline visit
(incl. urine sample)
Follow-up assessments
at week 6, 12, 26 and 52



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 1
	2b	All items from the World Health Organization Trial Registration Data Set	Clinicaltrials.gov
Protocol version	3	Date and version identifier	p. 13
Funding	4	Sources and types of financial, material, and other support	p. 13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 13
	5b	Name and contact information for the trial sponsor	Protocol p. 5 – 8
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol p. 11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol p. 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 2
	6b	Explanation for choice of comparators	p. 3
Objectives	7	Specific objectives or hypotheses	p. 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 3 – 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p. 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 5 – 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Protocol p. 23 – 24
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p. 4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p. 4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 5 – 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 7 – 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 7 – 8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p. 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p. 9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Protocol p. 40
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Protocol p. 40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 1
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol p. 40 – 41
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol p. 40 – 41
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ICF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Public health
Keywords:	PRIMARY CARE, PUBLIC HEALTH, SLEEP MEDICINE, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

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The effectiveness of a blended care program for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomized trial, the Big Bird trial.

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Key words MeSH: Benzodiazepines, deprescriptions, sleep initiation and maintenance disorders, cognitive behavioral therapy

ABSTRACT

Introduction Problematic benzodiazepine use is a global health issue. Although the adverse side effects of long-term use of benzodiazepines are well known, it remains difficult to implement interventions for discontinuation in primary care. Considering the success of blended care for the treatment of sleeping disorders and the support of substance use disorders, evidence suggests that a blended care approach, combining face-to-face consultations with the general practitioner with web-based self-learning by the patient, is beneficial for the discontinuation of chronic benzodiazepine use for primary insomnia in general practice. Therefore, the aim of this study is to evaluate the effectiveness of such an approach for the discontinuation of benzodiazepine and z-drugs ((z-)BZD) use in the long term and evaluate the implementation process.

Methods and analysis This study is a multicenter, pragmatic, cluster randomized controlled trial with 1200 patients, included by 120 general practitioners. Allocation to usual or blended care happens at the level of the general practice in a 1:1 ratio using a block randomization system stratified per language. The study population consists of adult primary care patients who have been using (z-)BZD for primary insomnia on a daily basis for at least six months. Primary outcome measure is the proportion of patients that discontinued (z-)BZD at 12 months assessed by toxicological screening for (z-)BZD in urine. Secondary outcomes include discontinuation of (z-)BZD at 6 months, quality of life, and the number of defined daily doses of (z-)BZD prescribed. Data will be collected using a study-specific online platform and analyzed using the intention-to-treat approach. The process of implementing blended care will be evaluated in a nested study.

Ethics and dissemination This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (ref. S61194). Study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial registration number NCT03937180; pre-results

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the authors' best knowledge, this is the first randomized controlled trial (RCT) to evaluate the effectiveness of an online intervention on benzodiazepine deprescribing in general practice.
- The use of toxicological screening of urine samples, self-report on discontinuation of (z-)BZD use, and number of defined daily doses prescribed will provide valuable insights with regard to the efficacy of the intervention and the reliability of the use of self-reporting in similar studies.
- To optimize the generalizability of the findings, this is a multicenter study with participants from both Dutch- and French-speaking parts of Belgium.
- The focus is on the effect of blended care, but the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.
- Non-e-literate patients are excluded from the study, even though this vulnerable group of patients could also benefit from more psychosocial support and counseling about medication use.

INTRODUCTION

Background

Worldwide, benzodiazepines and the related hypnotic drugs zolpidem, zopiclone and zaleplon ((z-)BZD) are prescribed extensively to treat anxiety and sleeping disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants. Recommendations state that treatment with (z-)BZD should be limited to only a few weeks. Despite the fact that long-term-use is ineffective and also associated with adverse side effects, the prevalence of long-term use, which is most common for sleeping disorders, remains widespread.[1-11] A recent systematic review summarizing current evidence-based discontinuation strategies indicates that gradual tapering of doses is an effective (z-)BZD discontinuation intervention for adult patients with long-term (z-)BZD use.[12] However, a combination of dose-tapering and non-pharmacological interventions such as psychotherapy interventions, self-help instructions and patient education produces better outcomes compared to stand-alone strategies.[13,14]

With the growing use of internet, e-based approaches are becoming more popular. Among them, blended care, defined as a combination of care by applying an interactive educational e-tool in combination with face-to-face clinical consultations with the care provider, is a new and promising approach.[15,16] Blended care has already proven to be successful in treating sleeping disorders, supporting substance use disorders, in stress management for employees, treating depression and other psychiatric and somatic conditions.[17-21]

In 2015, a small descriptive pilot study suggested that blended care for the discontinuation of (z-)BZD use for sleeping disorders may be more effective than a minimal intervention, such as a discontinuation letter or discontinuation advice, and as effective as face-to-face interventions combining tapering protocols and education. [22] Because these findings need to be confirmed by a properly powered and controlled study, a multicenter cluster randomized trial was designed, supported by the Belgian Federal Knowledge Centre for Healthcare (KCE) Trials program.

This study aims to establish an evidence-based blended care approach for the discontinuation of chronic (z-)BZD use for a primary indication of sleeping disorders in adult patients in a primary care setting. We hypothesize that blended care will support general practitioners as it is less time-

consuming and that it will empower patients to take a more active role in their discontinuation process. In that way, we think it may increase their motivation, which may result in increased discontinuation of (z-)BZD and more long-term discontinuation than currently with usual care.

Objectives

The primary objective is to compare the effect of blended care versus usual care on the proportion of subjects that has discontinued (z-)BZD use 12 months after start of the intervention as assessed by toxicological screening, in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Secondary objectives are to compare the effect of blended versus usual care on:

1. The discontinuation of (z-)BZD use 6 months after start of the intervention, as assessed by toxicological screening.
2. The quality of life, assessed by e-questionnaire at week 6, 12, 26 and 52.
3. The self-reported discontinuation of (z-)BZD use, assessed by e-questionnaire at week 6, 12, 26 and 52.
4. The number of defined daily doses (DDD) of (z-)BZD prescribed, assessed by e-questionnaire at week 6, 12, 26 and 52.

METHODS AND ANALYSIS

Study design and setting

This study is a multicenter, pragmatic, cluster randomized, controlled, superiority trial that will be performed in Belgian general practices. The participating general practitioners will be recruited voluntarily and monitored by the academic centers for General Practice of the KU Leuven, UGent, UAntwerpen, ULiège, Université Libre de Bruxelles and Vrije Universiteit Brussel. To participate, the general practice needs to be located in Belgium and treat the right patient population so it is feasible to recruit 10 eligible patients within 6 to maximally 12 weeks. The cluster and unit of randomization is the primary care practice. A 1:1 ratio will be used for allocation to the blended care arm and the usual care arm, as shown in figure 1.
The design of the study protocol has followed the recommendations of the SPIRIT 2013 statement.[23]

Patient and public involvement

Patients were involved in several stages of the study. During a focus group with long-term (z-)BZD users the overall feasibility of the patient activities, the lay-out and content of the e-tool, and the questionnaires and time required to complete them were discussed. Afterwards, these patients were also invited to provide written feedback on the Informed Consent Form (ICF), patient information leaflet and patient information video. Moreover, during the user acceptance testing of the tool, we involved acquaintances with different health and e-literacy profiles that were not familiar with the trial. Finally, to assure continuous involvement of patients in the study, two long-term (z-)BZD users are a member of the trial steering committee.

Eligibility criteria and recruitment

Patients' eligibility for inclusion in the study will be based on the following criteria:

1. Aged 18 years and older, capable of giving informed consent.
2. Having his/her Medical File managed by one of the participating general practitioners.
3. Receiving prescriptions of (z-)BZDs from participating general practitioner for use on a daily basis.

4. Reporting daily intake (≥ 80% of days) of (z-)BZDs in the last 6 months for a primary indication of sleeping problems.

Patients will be excluded from study participation based on the following criteria:

1. Presence of any severe psychiatric and neurologic condition that in the judgment of the treating general practitioner implies a contraindication for (z-)BZD withdrawal.
2. Presence of terminal illness.
3. Any case where stopping of (z-)BZDs might be harmful.
4. Unwillingness or inability to provide informed consent.
5. Not having e-literacy (being familiar with email and internet use).
6. Patients with a substance use disorder (other than (z-)BZD) will also be excluded from the study because in these cases there is often a sub-therapeutic (z-)BZD dependence and/or comorbid psychological/psychiatric comorbid conditions requiring specialist care.

Selection of eligible patients will be done consecutively by the general practitioner during consultations. To inform the patients about the study a patient information leaflet and video have been developed. When a patient is willing to participate, the general practitioner will obtain informed consent. The goal is to include 10 patients within 6 to maximally 12 weeks.

Sample size

Sample size calculation was based on a statistically significant difference in (z-)BZD discontinuation at 12 months between intervention and control group of 10%, assuming a rate of discontinuation of 15% in the control group. This assumption is based on a systematic review by Mugunthan et al[11] that shows us that usual care achieves a discontinuation rate of 10% to 17%.

To further estimate the sample size, calculations were first based on findings from a similar study by Vicens et al.[14], in which the drop-out rate after 12 months was 7% and an overall intracluster correlation coefficient (ICC) of 0.03 was observed. However, a range in ICCs was observed, with an ICC of 0.109 in both intervention groups. (personal communication by funder with author) Therefore, the funder requested a more conservative approach which led to the use of 0.11 in this trial.

Assuming a drop-out rate of 10% and based on an alpha of 0.05 and 80% power, a total sample size of 594 patients (297 in each group) would be required for an individually randomized study. However, to account for clustering effects by primary care practices, we used an ICC set at 0.11 and a cluster size of 10 patients. The number of patients required was multiplied by 1.99 corresponding to the cluster design effect (DE=1+ICC (size of the cluster-1)). Thus, the final sample will minimally consist of 1182 patients. Considering each general practitioner has to recruit 10 patients, 119 general practitioners are needed. Because six academic centers for general practice are involved in the project, we aim at including 120 general practitioners in total.

Random allocation

Within the week following the enrolment of the 10th patient (or a multiple of 10, depending on the number of participating general practitioners in that practice), the general practice is randomized in one of the two study arms in a 1:1 ratio using a block randomization system stratified per language in order to guarantee that allocation to either usual care or blended care for the discontinuation of (z-)BZD is balanced between the Dutch- and French-speaking community. To guarantee that the allocation process cannot be predicted two block sizes are used, 4 and 6.

Using an electronic random numbers generator, two randomization lists have been created, one for each language. After recruitment of the required number of patients, the project manager receives an e-mail alert that indicates the practice is ready for randomization. The result of the allocation is communicated by e-mail to both the general practitioner(s) and the corresponding monitor.

Blinding

General practitioners cannot be blinded to an intervention that modifies their clinical practice. Because the researchers need to monitor the conduct of the study on site, they also cannot be blinded to the allocation of the general practitioners. Owing to study procedures, patients will neither be blinded. However, all involved parties are blinded to the allocation until after patient recruitment. Furthermore, the outcome assessors will be kept blinded to the allocation during the whole study until after data analysis.

Intervention

Patients in the usual care arm, will receive care that is left at the discretion of the treating general practitioner. They are expected to follow the Belgian guidelines, which propose education of the patient about the harmful effects of chronic (z-)BZD use, the alternatives, and the advice to discontinue (z-)BZD use. A stepped approach is recommended. First, a minimal intervention strategy such as a discontinuation letter or a short advice is applied. If unsuccessful, a brief intervention, which may span one or more consults, is recommended. During such an intervention, the general practitioner will - based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. Most likely, a tapering scheme is developed which typically consists of a 10-20% reduction in the daily dose of (z-)BZD every 2-4 weeks.

For patients in the blended care arm, usual care is supported by the step-by-step use of an interactive e-tool. This tool consists of a sleeping diary, a tapering schedule, and six modules, providing psycho-education and medication education, which both focus on how to improve sleep. To gain access to all modules, patients have to open the sleeping diary and process module 1, where they evaluate their motivation to discontinue their (z-)BZD use. Based on the result, we offer them a customized sequence of modules to start with. However, at this time, they gain access to all modules and can freely choose which modules and how frequently they use the e-tool.

The psycho-education modules contain tips and quizzes on sleep hygiene. The medication education explains how benzodiazepines and z-drugs work, and what their impact is on sleeping patterns. Both the pro's and con's of these types of medication are explained. Moreover, the e-tool contains exercises featuring cognitive behavioral techniques to enhance the self-management of the patient. Its purpose is to motivate patients to discontinue the use of (z-)BZD, to adapt non-pharmacological remedies and to support them in this process.

The time of use will depend on the intensity of use, which is determined by the user, because certain exercises can be completed multiple times or updated, like the sleep hygiene evaluation or the sleeping diary. However, we estimate that processing all written information will take up to eight hours.

Patients can grant their participating general practitioner access to all their answers in the e-tool, making it possible to discuss these findings and experiences face-to-face. During consultations, the general practitioner will also assess the patients' readiness for change and match the appropriate intervention, like a tapering scheme. Follow-up appointments are scheduled depending on the needs of the patient until the end of dose reduction.

At the moment, the e-tool is not publicly available since the control group cannot have access to it, in order to prevent contamination bias. The e-tool is located on a secure server and password-protected so that only registered users can benefit from the content. However, the goal is to make it publicly available if our research provides positive outcomes.

Outcome assessments

Primary outcome measure

The proportion of patients that discontinued (z-)BZD at 12-months assessed by toxicological screening for (z-)BZD in urine.

Secondary outcome measures

1. The proportion of patients that discontinued use of (z-)BZD at 6-months assessed by toxicological screening for (z-)BZD in urine.
2. Quality of life assessed by EQ-5D-3L[24].
3. Self-reported discontinuation of (z-)BZD.
4. The number of DDD of (z-)BZD prescribed.

Data will be collected either via questionnaires sent to the patient or by completion of the electronic Case Report Form (eCRF) by the general practitioner, except for the toxicological screening of urine samples, as presented in figure 2.

Data collection

E-questionnaires

At study entry, baseline data are collected using an e-questionnaire consisting of Audit-C[25], EQ-5D-3L[24], Benzodiazepine Dependence Self-Report Questionnaire[26], Insomnia Severity Index[27], and HLS-EU-Q16[28]. All together this e-questionnaire comprises less than 50 questions.

Patients will also be requested to complete an abbreviated e-questionnaire at weeks 6, 12, 26 and 52 comprising of the validated EQ-5D-3L[25], Audit-C[24] and Insomnia Severity Index. Furthermore, the e-questionnaire will register self-reported use of (z-)BZD and other psychoactive medication, self-reported falls and use of medical services in the past period.

All e-questionnaires will consist of closed questions which are answered by ticking the appropriate box. Invitations will be e-mailed to the study participants at week 5, 11, 25 and 51 with the request to complete the questionnaires online within 2 weeks. A reminder will be sent after 1 week to all participants who have not yet responded and every week after, until response or the deadline. The deadline is set at four weeks after the first reminder for the questionnaires at week 6 and 12, and eight weeks at week 26 and 52.

Assessment by general practitioner

During the baseline visit, which will take place within 12 weeks after signing the ICF, the general practitioner will start the intervention, and will collect the following data for each participating patient: demographics, comorbidities, current use of psychotropic medication, (z-)BZD prescriptions in the last 6 months (drug name(s), quantity), and a urine sample for toxicological screening.

After the baseline visit, appointments for follow-up (minimally one in the first six months) and prescription renewals will be scheduled left at the discretion of the general practitioner and

depending on the needs of the patient until the end of dose reduction. This approach maximally reflects daily practice as should be in a pragmatic trial.

The general practitioners will be asked to note in the Electronic Health Record (EHR) and eCRF the (z-)BZD-related interventions delivered to the patients via standardized entry fields at each contact with the patient, during six months after baseline.

These interventions may include advice to discontinue (z-)BZD, discussion of tapering schedule, discussion of withdrawal symptoms, discussion of sleep quality, discussion of coping strategies, triggers and facilitators, decrease or increase of benzodiazepine dose.

Toxicological screening

At baseline, week 25 and 51, patients will be invited to produce a urine sample at the general practice within the next 2 weeks. For the samples of week 26 and 52, a reminder will be sent after 1 week to all participants who have not yet done so and every week after until a urine sample is obtained or the deadline is reached. The deadline is set at eight weeks after the first reminder.

The urine samples will be collected from the general practices within 5 days by the laboratory. Urine samples can be stored in a refrigerator for at least 7 days without any effect on the toxicological screening results.

The detection window for (z-)BZDs in urine is dependent on multiple factors. Using Liquid chromatography–tandem mass spectrometry (LC-MS/MS) it is typically six days or longer, in case of ingestion of a single dose. However, chronic usage over a period of months or years can extend excretion times up to four to six weeks after cessation of use.

Currently, LC–MS/MS is the most sensitive method available. It is able to detect the use of low-dose (z-)BZDs, which are (z-)BZDs prescribed in low doses because of their high potency, such as flurazepam. Routinely used immunoassays typically have a detection level of 200 ng per mL as compared to 5 ng/mL for LC-MS/MS. Also, it is possible to detect multiple components in one assay, to provide quantitative results, to identify the benzodiazepines exactly and to detect multiple metabolites resulting in longer detection periods.

All toxicological analyses will be performed at the laboratory AML in Antwerp. Toxicological screening of urine samples is not part of routine practice. Therefore, the general practitioners will be blinded for the results of these analyses.

Data analysis

Baseline characteristics, like age, gender, relevant co-morbidities, benzodiazepine dependence score, daily dose of (z-)BZD in DDD, sleep quality and Audit-C[24] score, will be presented for the complete study population and per allocation arm.

Primary outcome analysis

The primary endpoint will be analyzed according to the intent-to-treat (ITT) approach.

Logistic regression will be used for data analysis with benzodiazepine urine test results assessed at 12 months after initiation of the intervention as a binary outcome (positive or negative) and intervention group as a factor. A random effect will be modelled to deal with clustering by general practice. The group effect will be reported as an odds ratio with 95% confidence interval.

To investigate how the primary outcome behaves in function of age, gender, (z-)BZD dose at baseline, sleep quality at baseline, benzodiazepine dependency score and use of the e-tool (only in intervention group), subgroup analysis will be performed.

Secondary outcome analysis

The proportion of subjects with a negative benzodiazepine urine test assessed 6 months after initiation of the intervention will be analyzed in the same way as the primary endpoint.

All other secondary endpoints are binary variables, measured longitudinally. Analysis will be performed using multilevel logistic regression analysis, including random intercepts for patient and for general practitioner. A random slope for time will be modelled if beneficial for model fit. The fixed effects model will include intervention group, time and the group by time interaction. In case of a significant group by time interaction, the group effect will be reported separately for each time point. In case of a non-significant group by time interaction, a group main effect will be reported. The group effects will be presented as odds ratios with 95% confidence intervals.

No correction for multiplicity is planned for the secondary analyses, as the study is not powered for these analyses, and hence, its results will be considered as hypothesis generating.

Missing data

When a patient withdraws from the study prematurely, all data collected up until the moment of withdrawal will be analyzed. In case the data for measurement of the primary endpoint was not collected, the outcome will be classified as failure or continued benzodiazepine use in the intent-to-treat analysis. After withdrawal, no further data of this patient will be collected.

Economic data evaluation

One of the goals of the KCE Trials program is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind, i.e. the necessary data to allow the conduct of a health economic evaluation will be collected. For more information on these procedures, we refer to the protocol of the trial.

Data management

Using a trial-specific online platform, data will be automatically entered in a database. These data will be generated by the general practitioners completing the eCRF and by the patients completing the e-questionnaires and using the e-tool. All collected data are stored pseudonymized, working with a personal study code for all patients. The identity of the individual patient will be blinded to the researchers at all times.

The collected data remain in the databases of the service provider and only an excerpt of this data is transferred to the data warehouse of the researchers, where it is merged with the results of the laboratory testing.

The data entry process will be documented, creating an audit trail. The database will be stored and maintained by the service provider, who will also be responsible for the pseudonymization of patient data as Trusted Third Party, compliant with ICH-GCP regulations and the EU General Data Protection Regulation. Confidentiality of personal identifiable information will be maintained throughout the trial. Data will be stored for a period of 25 years after the study has ended, according to ICH-GCP regulations.

Nested study

A process evaluation will be nested within the pragmatic cluster randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by general practitioners and patients. It helps interpreting the results in their context. This is important for informing future implementation in practice. It will explain how general practitioners and patients experience the intervention. With this study, we aim to identify factors which influence the ability (or inability) to withdraw from (z-)BZD in order to build a framework describing the mechanisms required for successful implementation.

Individual interviews and discussion groups will be conducted with general practitioners and patients taking part in the trial. General practitioners (approximately 8) will be purposively sampled to obtain variation in gender, language, practice setting and experience. Patients (approximately 14-18) will be purposively sampled to obtain variation in age, gender, language, and how successful the withdrawal has been. Interviews will follow semi-structured topic guides exploring general practitioners' and patients' views and experiences of taking part in the trial. Topic guides will be informed by existing literature and theory of health behavior to ensure that questions elicit likely key determinants of behavior. Topic guides will be piloted with patient representatives and clinicians. Interviews and discussion groups will be carried out face to face and analyzed using thematic and framework analysis.

Participant safety and monitoring

This study is considered low-risk. Because no medication or new treatment protocols are tested, there is no additional safety reporting to the one in daily general practice. In Belgium, any adverse effects of medication can be reported to the federal agency for medicines and health products (famph) by using the yellow card. If necessary, appropriate measures will be taken in consultation with the attending general practitioner.

Close monitoring to assure proper conduct of the study is provided by all abovementioned academic centers for General Practice, in compliance with ICH-GCP regulations. Moreover, annual reports of the study progress will be sent to the Ethics Committee of the University Hospital of Leuven.

DISCUSSION

In 2008, research established that computer-assisted tailored patient education could be a useful tool in the discontinuation of chronic benzodiazepine use. Ten Wolde and colleagues performed an RCT, showing that letters, tailored to baseline characteristics of the patient, influence benzodiazepine use positively. After the trial, the most successful intervention, being a single customized letter, was published online in a password protected environment to reach as many patients as possible.[29] No further research on the effectiveness of this online module has been published.

Currently, this is the only (English) publication on computer-assisted patient education for discontinuation of chronic benzodiazepine use. This means that our trial will be the first RCT that assesses the superiority of blended care over usual care for (z-)BZD discontinuation in primary care.

Moreover, the Big Bird trial is innovative in its methodology. In most discontinuation studies, researchers use self-reported data from patients and/or general practitioners to assess the success of an intervention. In this trial, success rate will depend on the proportion of patients that has discontinued their use of (z-)BZD as assessed by toxicological screening of urine samples at 12 months after start of the intervention. This measurement is also performed at 6 months, when access to the online platform has just ended.

Some might argue that delivering urine samples will trigger patients to increase their efforts for discontinuing (z-)BZD. To limit this possibility we have taken precautionary measures by not communicating the results of the toxicological screening to the general practitioner, nor to the patient.

The toxicological analysis of urine samples will enable us to compare the concentrations of (z-)BZD with the reports of patients and general practitioners and provide insights on the reliability of self-reporting in studies on discontinuation. So, although the prescription information is not extracted automatically, the report of prescribed (z-)BZD use by the general practitioner in the eCRF contains valuable information to establish a proxy of the (z-)BZD intake per patient.Another strength of this study is the collaboration between six universities, which enables us to implement the intervention across the Belgian French and Dutch speaking population.

However, due to language and the technological character of the intervention, some vulnerable groups of patients cannot be reached. Language restrictions exclude the German community in Belgium and a number of migrant groups from participation. Also, non-e-literate patients, including elderly people that are not familiar with internet usage but who report high (z-)BZD intake, cannot take part in the trial. This is unfortunate as these patients could also benefit from more psychosocial support and counseling about medication use. If effective, we need to consider adapting the existing materials for use with these patients.

Finally, although the focus in the trial is on the effect of blended care, the implementation of such an approach is also evaluated, which will provide valuable knowledge for further eHealth developments in primary care.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki (seventh revision). Any substantial protocol amendments will be submitted to the ethics committee.

The study results will be disseminated via open-access, peer-reviewed publications and conference presentations.

Trial status

Currently, recruitment of general practitioners and patients is ongoing. First patient first visit is expected in August 2019. Last patient last visit is expected in September 2020. Database lock will take place in November 2020.

FIGURES

Figure 1. Flowchart of trial design summary

Figure 2. Flowchart of trial procedures

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AUTHORS' CONTRIBUTIONS

CM and MVN are responsible for the original conception of the study and obtaining funding. They also drafted the study protocol, in cooperation with SA, who developed the nested study, and AL, who provided the statistical analysis plan. All authors assisted in finalizing the protocol. CM, MVN and KC obtained ethical approval. KC wrote the first draft of the manuscript based upon protocol version 1.6 dd. March 2019. CM, MVN, MVM, GH, SA, KVDB, ADS, HC, DD, RVO, AMO, NK and AL contributed to further drafts. All authors read and approved the final draft.

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Disclaimer

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

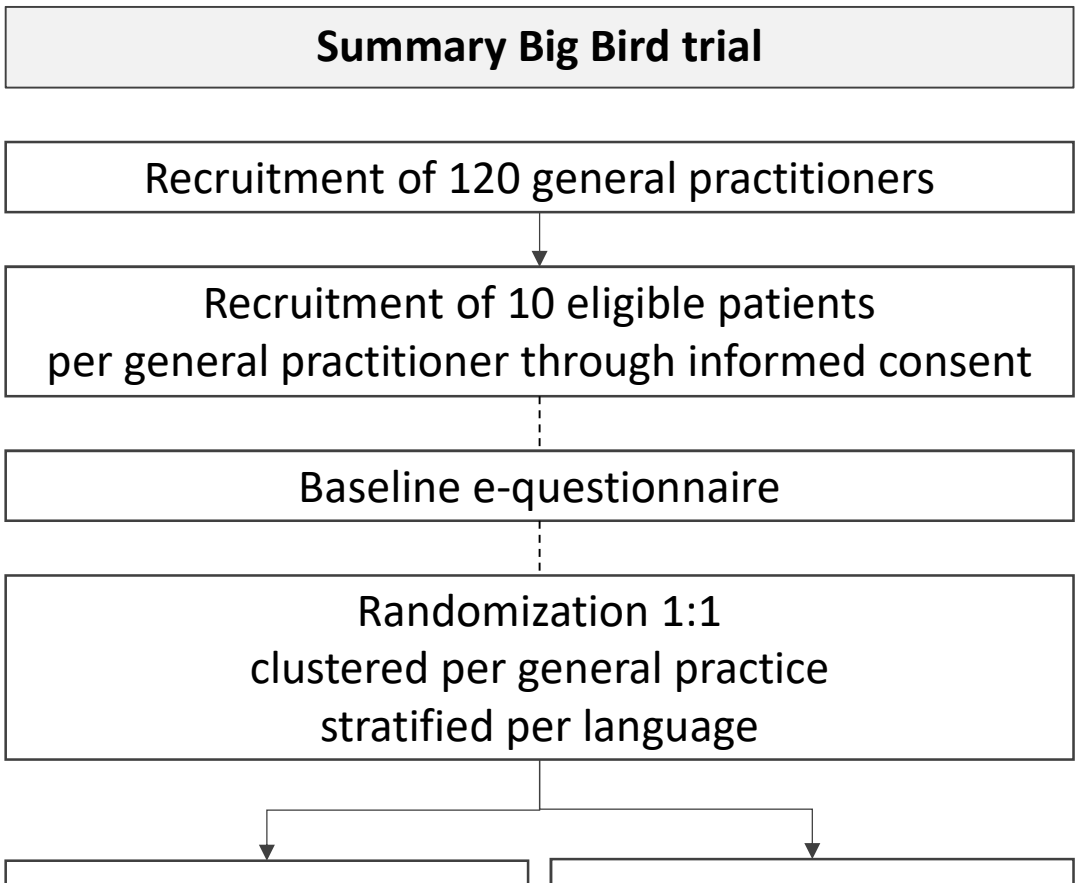
This trial was approved by the Ethics Committee for Research of UZ/KU Leuven (B322201939666) in March 2019. Reference number: S61194.

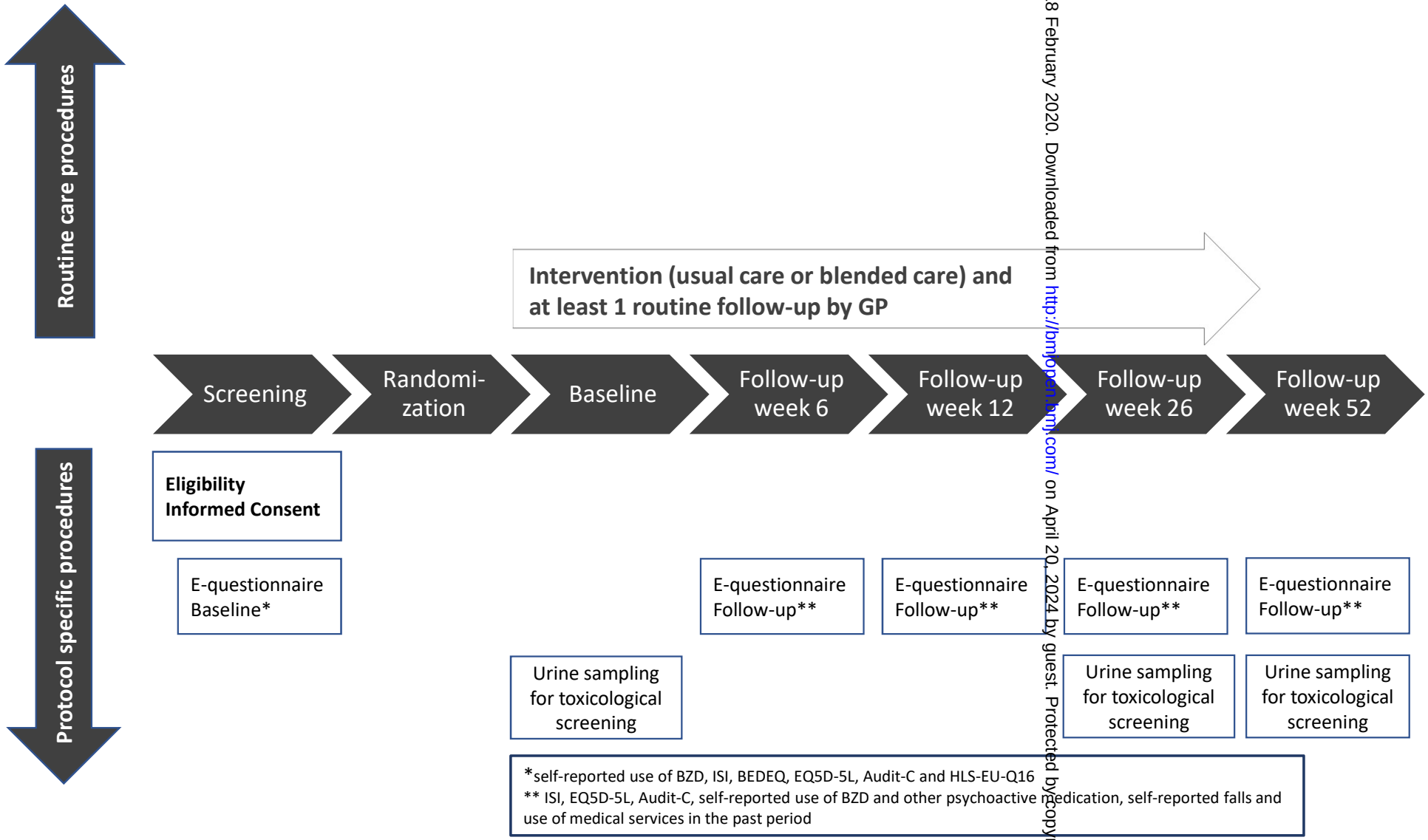
Provenance and peer review

Not commissioned, externally peer reviewed.

Open access

Protocol publication BMJ Open_final_v1.6_2020105


Summary Big Bird trial
Recruitment of 120 general practitioners
Recruitment of 10 eligible patients
per general practitioner through informed consent
Baseline e-questionnaire
Randomization 1:1
clustered per general practice
stratified per language
Blended care
Usual care
Baseline visit
(incl. urine sample)
Follow-up assessments
at week 6, 12, 26 and 52



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 1
	2b	All items from the World Health Organization Trial Registration Data Set	Clinicaltrials.gov
Protocol version	3	Date and version identifier	p. 13
Funding	4	Sources and types of financial, material, and other support	p. 13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 13
	5b	Name and contact information for the trial sponsor	Protocol p. 5 – 8
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Protocol p. 11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol p. 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 2
	6b	Explanation for choice of comparators	p. 3
Objectives	7	Specific objectives or hypotheses	p. 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 3 – 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p. 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p. 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 5 – 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Protocol p. 23 – 24
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p. 4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p. 4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 5 – 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 7 – 8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 7 – 8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p. 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p. 9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Protocol p. 40
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Protocol p. 40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 1
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol p. 40 – 41
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol p. 40 – 41
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ICF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.