The effectiveness of a blended care program for the discontinuation of benzodiazepines use for sleeping problems in primary care: a clustered randomized trial.

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TITLE PAGE

FULL/LONG TITLE OF THE TRIAL

The effectiveness of a blended care program for the discontinuation of benzodiazepines use for sleeping problems in primary care: a clustered randomized trial.

SHORT STUDY TITLE / ACRONYM

Blended care for the discontinuation of benzodiazepine use: Big Bird trial

PROTOCOL VERSION NUMBER AND DATE

Protocol version 1.7, March 2020

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " Directive 2001/20/EC",), and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Funder:	
Signature (with name and date):	
Position:	
For and on behalf of the Study Sponsor, Chief Investigator:	
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Position: M.D., prof. dr. KU Leuven	
Statistician:	
Signature (with name and date):	
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TRIAL SUMMARY

Trial Title	The effectiveness of a blended care program for the discontinuation of benzodiazepines use for sleeping problems in primary care: a clustered randomized trial.	
Short Title	Blended care for the discontinuation of benzodiazepine use: Big Bird trial	
Trial Design	Cluster randomized controlled trial	
Trial Participants	Primary care patients aged 18 and older receiving prescriptions for (z-) benzodiazepines ((z-)BZD) for daily use in the last 6 months for a primary indication of sleeping problems.	
Planned Sample Size	120 general practitioners randomised, each recruiting 10 patients, totalling 1200 patients	
Treatment duration	1-6 months	
Follow up duration	12 months	
Planned Trial Period	42 months	
	Objectives	Endpoints
Primary	To compare the long-term effect of a blended care approach (interactive learning e-tool and face-to-face contacts with general practitioner) versus usual care on the discontinuation of (z-)BZD	Proportion of patients that discontinued (z-)BZD use at 12 months assessed by toxicological screening
Secondary	To compare the short-term effect of a blended care approach (interactive learning e-tool and face-tot-face contacts with GP) versus usual care on the discontinuation of (z-)BZD	Proportion of patients that discontinued (z-)BZD use at 6 months assessed by toxicological screening
	To compare the effect of a blended care approach (interactive learning e-tool and face-tot-face contacts with GP) versus usual care on the quality of life	EQ5D-3L assessed at week 6, 12, 26 and 52

	To compare the effect of a blended care approach (interactive learning e-tool and face-tot-face contacts with GP) versus usual care on self-reported discontinuation of (z-)BZD use	Proportion of patients with self-reported discontinuation of (z-)BZD use assessed at week 6, 12, 26 and 52
	To compare the effect of a blended care approach (interactive learning e-tool and face-tot-face contacts with GP) versus usual care on the number of defined daily doses (DDD) of benzodiazepines prescribed	The number of DDD of (z-)BZD prescribed in the preceding interval assessed at week 6,12,26 and 52
Intervention(s)		
	In the **control arm**, patients will receive 'usual care' left at the discretion of the treating GP. They are expected to follow the Belgian guidelines as described in the most recent online version of "Anxiety, stress and sleeping problems A toolbook for general practitioners." or "Sleeping pills and sedatives. How to assist your patients in the search for other solutions?" which are available both in French and Dutch. The recommended approach proposed in this toolbox typically involves education of the patient about the harmful effects of chronic (z-)BZD and the alternatives, and the advice to discontinue (z-)BZD use. A stepped approach is recommended. In a first instance a minimal intervention strategy such as a discontinuation letter or a short advice is applied. In case the minimal intervention failed or in case the GP judges the chance of a successful minimal intervention to be unlikely, a brief intervention is recommended which may span one or more consults. During such intervention, the GP will –based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. A (z-)BZD tapering scheme will be developed which typically consists of a 10–20% reduction in the daily dose of the (z-)BZD every 2–4 weeks. To facilitate withdrawal a switch from a (z-)BZD with a short half-life to diazepam may be considered. In the **intervention arm** an interactive e-learning programme delivered through a secured web-based platform for patients and general practitioners (GP) is blended with face-to-face contacts between the involved GP and patient. The e-tool provides psycho-education about sleep and sleeping disorders, sleeping medication and its associated risks, non-pharmacological alternatives and tapering of (z-)BZD. Furthermore, a sleeping diary allows patients to enter information about their sleeping habits, sleep hygiene, coping techniques, triggers and facilitators. The purpose of this e- tool is to motivate patients to discontinue the use of (z-)BZD, to adapt alternative remedies	

	and to support them in this process. The e-tool features cognitive behavioural techniques enhancing the self-management of the patient. In a first contact, patients will receive access to the interactive e-learning module and be requested to pass through the educational sessions at their own pace. In the face-to-face contacts the patients' sleeping diary, insights and experiences will be discussed and the GP will assess the patients' readiness to discontinue (z-)BZD use. Participating GPs will have access to the interactive parts of the module of their patients, making it possible to discuss issues with the patients during the face-to-face consultations. In **both arms**, once the patient is willing to withdraw, a tailored gradual taper of the (z-)BZD will be agreed upon, which typically consists of a 10–20% reduction in the daily dose of the (z-)BZD every 2–4 weeks. To facilitate withdrawal a switch from a (z-)BZD with a short half-life to diazepam may be considered. Follow-up appointments will be scheduled depending on the needs of the patient until the end of dose reduction. During these follow-up visits progression and (z-)BZD withdrawal-related problems will be discussed.

ROLE OF STUDY SPONSOR AND FUNDER

The Belgian Health Care Knowledge Centre, as mentioned in KEY TRIAL CONTACT, provides funding for this trial.

UZ/KU Leuven, as mentioned in KEY TRIAL CONTACT, acts as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. **UZ/KU Leuven** shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. **UZ/KU Leuven** acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and **UZ/KU Leuven** shall make no representations whatsoever in this respect.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The TSC is composed of the following participants:

- UZ Leuven Clinical Trial Centre
- Chief Investigator: Catharina Matheï
- Academic Centre for Primary Care (ACHG), KU Leuven: Marc Van Nuland
- Department of General Practice and Primary HealthCare, UGent: An De Sutter
- Department of General Practice, U Antwerp: Sibyl Anthierens, Kris Van Den Broeck
- Department of General Practice, VUB: Dirk Devroey
- UR Soins primaires et Santé, LIEGE Université: Marc Vanmeerbeek, Gilles Henrard
- ULB: Anna-Marie Offermans
- Leuven Biostatistics and Statitical Bioinformatics Centre, KU Leuven
- Clinical Pharmacology – Department of Pharmacology, UGent: Thierry Christiaens
- Patient representatives

KCE shall have the right (but not the obligation) to be present at each TSC meeting (more details can be found in the research agreement template).

Role of TSC:

- The TSC shall oversee the performance of the study and discuss important topics in relation thereto.
- The TSC shall monitor trial progress, conduct and advise on scientific credibility.
- The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.
- The TSC shall meet regularly and send reports to the sponsor.

Meetings of TSC:

The TSC will meet on average 3 times per year or as necessary when adapted to the stage of the trial (set-up, conduct, analysis).

Trial Management Group (TMG)

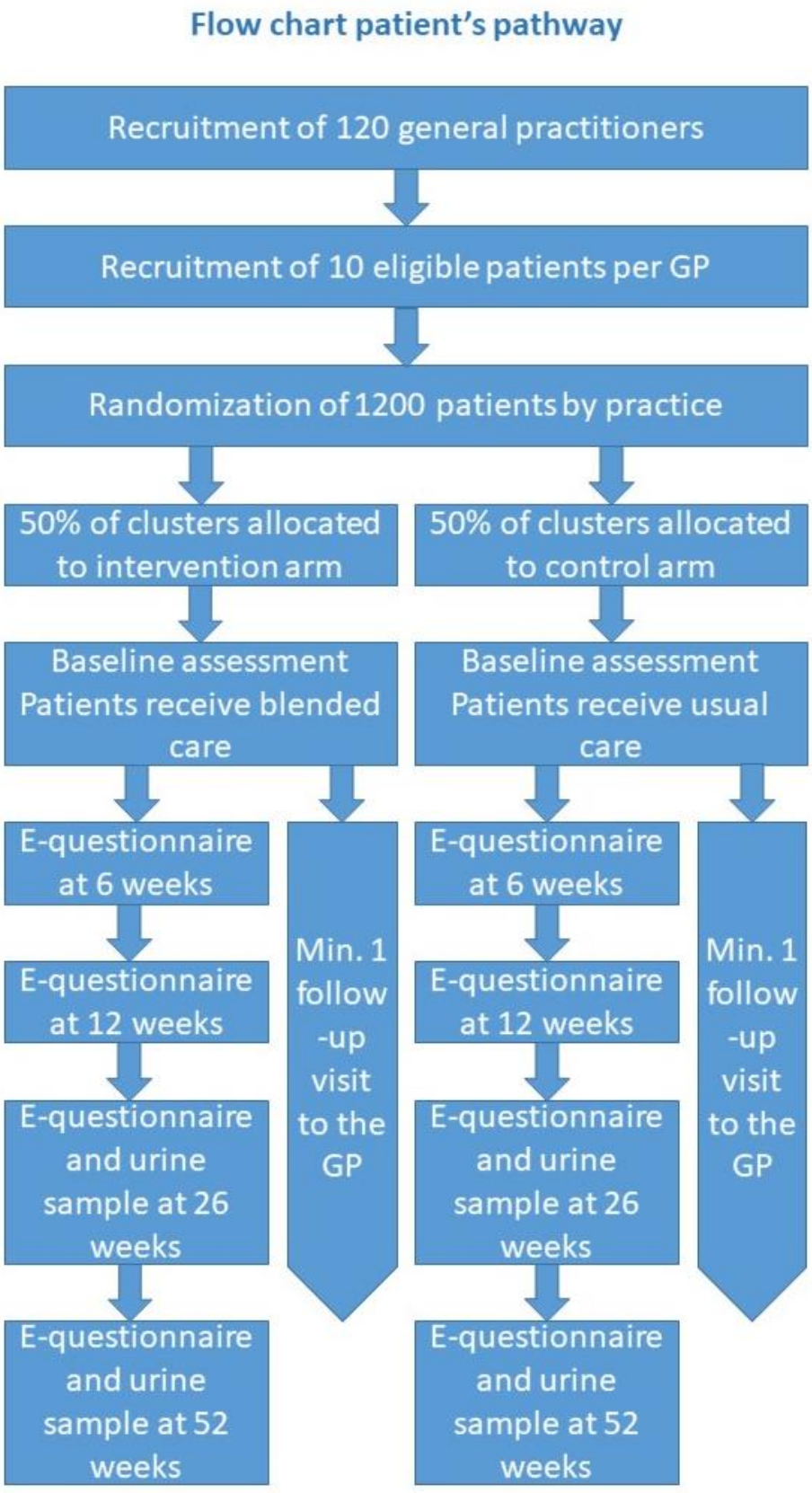
The day-to-day management of the study will be performed by the TMG which is distinct from the TSC and consists of the chief investigator and the trial coordinators.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CME	Continued medical education
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EC	Ethics Committee
EHR	Electronic Health Record
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
KCE	Belgian Healthcare Knowledge Centre
MA	Marketing Authorisation
PI	Principal Investigator
RCT	Randomised Control Trial
REC	Research Ethic Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
-(z-)BZD	Benzodiazepines and z-drugs (Zoplicon and Zolpidem)

TRIAL FLOW CHART

Figure 1: Flow chart for participant's pathway



■ STUDY PROTOCOL

1 BACKGROUND

Benzodiazepines ((z-)BZD) are prescribed worldwide extensively to treat anxiety and sleeping disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants. Although it is recommended that treatment with (z-)BZD should be limited to only a few weeks and 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. (Mugunthan 2011).

A recent systematic review summarizing current evidence-based discontinuation strategies indicate that gradual tapering of doses is an effective (z-)BZD discontinuation intervention for adult patients with long-term (z-)BZD use (CADH 2015).
Minimal interventions such as a discontinuation letter from a clinician or consultation with a general practitioner (GP) explaining both the risk of long-term (z-)BZD use and the advantages of discontinuation are effective in initiating the intervention process and achieving better (z-)BZD discontinuation outcomes when compared with usual care. Patients receiving such interventions are twice as likely to completely withdraw from (z-)BZD use (Mugunthan 2011).
Furthermore, a combination of tapering protocols with psychotherapy interventions result in superior discontinuation outcomes when compared to either individual strategy alone, and compared with alternative interventions such as medication review, consultation or education, and relaxation therapy (Paquin 2014, Gould 2014, Otto 2010).
Coupling a dose-tapering intervention with patient empowerment education improves the odds of (z-)BZD discontinuation significantly when compared with dose-tapering alone. Moreover, dose-tapering with structured education and follow-up visits, or written self-help instructions, result in higher (z-)BZD discontinuation rates than usual care (Tannenbaum 2014, Vicens 2014).
In summary, a combination of dose-tapering and non-pharmacological interventions such as psychotherapy interventions, self-help instructions and patient education produce better outcomes compared to stand-alone strategies.

Recently a small descriptive pilot study with a blended care approach combining an e-learning tool with face-to-face contacts for the discontinuation of (z-)BZD use for sleeping disorders in general practice was tested (Klaasen 2015). The results of this study suggest that a blended approach 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 but need to be confirmed by a properly powered and controlled study.

These data prompted us to design a clustered randomized trial aiming to compare a blended approach with usual care for the discontinuation of chronic benzodiazepine use for a primary indication of sleeping disorders in adult patients in a primary care setting.

2 RATIONALE

(z-)BZD use is highly prevalent in Belgium. Each day 1.260.034 daily defined doses (DDD) of (z-)BZD are dispensed in Belgium. In 2013 up to 13% of the adult Belgian population had used (z-)BZD in the two weeks preceding the health interview survey (WIV-ISP. Gezondheidsenquête 2013) Half of the (z-)BZD users did so on a daily basis for at least 6 weeks (Anthierens 2012)). Women (20%) consumed more (z-)BZD than men (10%) and consumption rates increased with age mounting up to 35% in people aged 75 years and older (WIV-ISP. Gezondheidsenquête 2013). Belgium is the world's leader in terms of global consumption of (z-)BZD. In 2011 495 million DDD were sold in Belgium as compared to 180 million in the Netherlands. This despite the fact that in the past 15 years several campaigns have been organized in Belgium by the Federal Government. These included mass media campaigns and interventions targeting pharmacists and GPs in order to educate them and to provide them with aid to assist patients with questions regarding the use or discontinuation of (z-)BZD.

This high (z-)BZD consumption rate is problematic since (chronic) (mis-)use is associated with well-known complications which are more pronounced in older adults (Thomas 1998, Leipzig 1999, Glass 2005, Barker 2004, Billioti de Gage 2012, Belleville 2010, Kripke 2012, Soyka 2017). These include increased tolerance and addiction, disturbance of the physiological sleeping pattern, pharmacological interactions and interactions with alcohol use, increased risk of motor vehicle accidents, falls and hip fractures in the elderly, memory impairment, cognitive decline, depression and emotional blunting. More recently, (z-)BZD use has been associated with dementia and increased mortality (Kripke 2012, Soyka 2017, Zhong 2015, Takada 2016). These complications are jeopardising the personal health of (z-)BZD users and come along with substantial socio-economic costs.

The SOCOST study estimated the societal costs related to the use of addictive substances including alcohol, tobacco, illicit drugs and psychoactive pharmaceuticals in Belgium in 2012 (Vander Laenen 2012)). Direct and indirect costs of addictive substances were at 4,6 billion euros in Belgium (equivalent with 419 euros per capita or 1,19% of the Gross Domestic Product (GDP)) of which 5% or 215 million euros/year could be assigned to psychoactive medication. Also, premature mortality due to psychoactive medication was mainly caused by sedative-hypnotic drugs (52,4%) and methadone (33,8%). Finally, the study indicated psychoactive medication was responsible for as much as 1% of the total loss of 3,259,200 disability-adjusted life years (DALYs) in 2012. Although the SOCOST study was not able to provide drug specific data - especially related to the use of (z-)BZDs -, it's reasonable to conclude that (z-)BZD use is related to substantial direct and indirect societal costs and to loss of DALYs.

Taking into account the high prevalence of (z-)BZD misuse together with the health-related complications, the availability of non-drug alternatives for e.g. sleep disorders (Domus Medica 2005) and anxiety disorders (Trimbos Instituut 2013), and the socio-economic costs in Belgium, the development of a programme aiming to reduce (z-)BZD use would obviously be beneficial.

GPs have a pivotal role in the management of chronic (z-)BZD use. They are highly valued and trusted by their patients. Having a long-lasting relationship with one's GP makes the GP one of the best-placed persons to counsel and motivate the (z-)BZD-using patient to cease his chronic use. (z-)BZD users are highly dependent on prescriptions from their treating physicians in order to get their sedate-hypnotic products.

Nevertheless, GP's do not feel confident in managing the tapering and discontinuation of chronic (z-)BZD use, despite the availability of guidelines and tools such as "Anxiety, stress and sleeping problems. A toolbook for general practitioners" and "Sleeping pills and sedatives. How to assist your patients in the search for other solutions?" which were developed in 2005 and 2018, respectively by order of the Belgian Federal Government as part of a federal campaign for a responsible use of (z-)BZD (FOD Volksgezondheid 2005, Christiaens 2018). Moreover, as part of this campaign by the FOD Volksgezondheid, the guidelines were translated into training sessions for GPs, which discuss implementation in daily practice. These training sessions are ideal to be included in the context of a pragmatic trial, supporting usual care for benzodiazepines withdrawal in the GP practice. Nonetheless, GPs also perceive the management of (z-)BZD withdrawal as very time-consuming and nearly impossible to integrate into their patient care practices (Anthierens 2010).

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 (Hards 2012, Wilhelmsen 2013). 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 (Kaldo 2015, Hermes 2016, Kawaguchi 2014, Ebert 2016, Andersson 2014).

A pilot study that was conducted recently in Belgium strongly suggested that blended care e.g. might also be an effective approach for the discontinuation of chronic (z-)BZD use (Klaasen 2015). In this study, the blended care intervention combined dose-tapering with (online) non-pharmacological interventions like self-help instructions and patient education, which has been shown to be more effective than a single strategy (CADH 2015). However, since patients go through the learning module on their own and at their own pace it is more feasible and less time-consuming for the GP and consequently easier to implement in general practice. Moreover, the availability of an e-tool may circumvent the lack of experience that poses an important barrier for GPs to engage in the management of (z-)BZD withdrawal. Finally, the standardised protocol-based e-tool in combination with face-to-face contact allows a tailor-made approach and is expected to enhance self-management of the patient (Wentzel 2016). Thus, a blended care approach may not only empower patients, but also facilitate and support GPs in the management of (z-)BZD withdrawal and hence result in better outcomes in terms of (z-)BZD discontinuation.

2.1 Assessment and management of risk

This clinical trial is a low risk intervention trial for the following reasons

- The use of the investigational e-tool is not associated with any risk for the patient
- The use of blended care in the treatment of mental health problems including addiction is supported by scientific evidence
- The additional diagnostic (toxicological screening) and monitoring (questionnaires) are not associated with an additional risk to the safety of the study participants and pose only a minimal burden as compared to normal clinical practice
- The prevalence and the severity of adverse events due to slow dose tapering of (z-)BZD is expected to be very low

Adverse events e.g. withdrawal symptoms are documented during the trial (see 3.6 Exploratory endpoints) and can usually be managed by the attending GP.

3 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

3.1 Primary objective

The primary aim of this trial is to compare the effect of blended care combining an interactive educational e-tool with face-to-face clinical consultations versus usual care on the proportion of subjects that has discontinued (z-)BZD use 12 months after start of the intervention in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Null hypothesis: blended care is not superior to usual care in terms of the proportion that has discontinued (z-)BZD use 12 months after start of the intervention.

Alternative hypothesis: blended care will increase the proportion of subjects that has discontinued (z-)BZD use 12 months after initiation of the intervention compared to usual care.

PICOT

Population:	Patients aged 18 and older receiving prescriptions for (z-)BZD use on a daily basis in the last 6 months for a primary indication of sleeping problems.
Intervention	Blended care combining an interactive educational e-tool with face-to-face clinical consultations with the GP.
Comparator	Care as usual for chronic (z-)BZD use left at the discretion of the GP. This may include a minimal intervention (discontinuation letter or discontinuation advice) or a more extended intervention, in combination with (z-)BZD tapering.
Outcome	The proportion of patients that discontinued (z-)BZD at 12-months assessed by toxicological screening for (z-)BZD in urine.
Time	The outcome will be assessed 12 months after initiation of the intervention.

3.2 Secondary objectives

3.1.1 Short term discontinuation

The first secondary objective is to compare the effect of blended care combining an interactive educational e-tool with face-to-face clinical consultations versus usual care on the proportion of subjects that has discontinued benzodiazepine use 6 months after the start of the intervention in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Null hypothesis: blended care is not superior to usual care in terms of the proportion that has discontinued (z-)BZD use 6 months after start of the intervention.

Alternative hypothesis: blended care will increase the proportion of subjects that has discontinued (z-)BZD use 6 months after initiation of the intervention compared to usual care.

PICOT

Population:	Patients aged 18 and older receiving prescriptions for (z-)BZD on a daily basis in the last 6 months for a primary indication of sleeping problems.
Intervention	Blended care combining an interactive educational e-tool with face-to-face clinical consultations with the GP.
Comparator	Care as usual for chronic (z-)BZD use left at the discretion of the GP. This may include a minimal intervention (discontinuation letter or discontinuation advice) or a more extended intervention, in combination with (z-)BZD tapering.

Outcome	The proportion of patients that discontinued of (z-)BZD at 6-months assessed by toxicological screening for (z-)BZD in urine.
Time	The outcome will be assessed 6 months after initiation of the intervention.

3.1.2 Quality of life

The second secondary objective is to compare the effect of blended care combining an interactive educational e-tool with face-to-face clinical consultations versus usual care on the quality of life in a population of adult primary care patients chronically using (z-)BZD for a primary indication of sleeping disorders.

Null hypothesis: blended care and usual care have similar effects on the quality of life.

Alternative hypothesis: blended care results in a better quality of life compared to usual care.

PICOT

Population:	Patients receiving prescriptions for (z-)BZDs on a daily basis in the last 6 months for a primary indication of sleeping problems aged 18 and older.
Intervention	Blended care combining an interactive educational e-tool with face-to-face clinical consultations with the GP.
Comparator	Care as usual for chronic (z-)BZD use left at the discretion of the GP. This may include a minimal intervention (discontinuation letter or discontinuation advice) or a more extended intervention, in combination with (z-)BZD tapering.
Outcome	Quality of life assessed by EQ5D-3L.
Time	The outcome will be assessed at week 6, 12, 26 and 52.

3.1.3 Self-reported use of benzodiazepines

The third secondary objective is to compare the effect of blended care combining an interactive educational e-tool with face-to-face clinical consultations versus usual in terms of self-reported discontinuation of (z-)BZD use in a population of adult primary care patients chronically using benzodiazepines for a primary indication of sleeping disorders.

Null hypothesis: blended care is not superior to usual care in terms self-reported discontinuation of benzodiazepine use.

Alternative hypothesis: blended care increases self-reported discontinuation compared to usual care.

PICOT

Population:	Patients receiving prescriptions for (z-)BZD on a daily basis in the last 6 months for a primary indication of sleeping problems aged 18 and older.
Intervention	Blended care combining an interactive educational e-tool with face-to-face clinical consultations with the GP.
Comparator	Care as usual for chronic (z-)BZD use left at the discretion of the GP. This may include a minimal intervention (discontinuation letter or discontinuation advice) or a more extended intervention, in combination with (z-)BZD tapering.
Outcome	Self-reported discontinuation of (z-)BZD.
Time	The outcome will be assessed at week 6, 12, 26 and 52.

3.1.4 Prescriptions for benzodiazepines

The fourth secondary objective is to compare the effect of blended care combining an interactive educational e-tool with face-to-face clinical consultations versus usual care on the number of DDD of (z-)BZD prescribed at 6, 12, 26 and 52 weeks from baseline in a population of adult primary care patients chronically using benzodiazepines for a primary indication of sleeping disorders.

Null hypothesis: blended care is not superior to usual care in terms the number of DDD of benzodiazepines prescribed at 6, 12, 26 and 52 weeks from baseline.
Alternative hypothesis: blended care will decrease the number of DDD of (z-)BZD prescribed at 6, 12, 26 and 52 weeks from baseline compared to usual care.

PICOT

Population:	Patients receiving prescriptions for (z-)BZD on a daily basis in the last 6 months for a primary indication of sleeping problems aged 18 and older.
Intervention	Blended care combining an interactive educational e-tool with face-to-face clinical consultations with the GP.
Comparator	Care as usual for chronic (z-)BZD use left at the discretion of the GP. This may include a minimal intervention (discontinuation letter or discontinuation advice) or a more extended intervention, in combination with (z-)BZD tapering.
Outcome	The number of DDD of (z-)BZD prescribed.
Time	The outcome will be assessed 6, 12, 26 and 52 weeks after initiation of the intervention.

3.3 Endpoints

The definition and operationalization of the endpoints is based on the principle that outcome measurement should not interfere with usual practice, and routinely collected outcome measures should therefore be preferred.
However, in patients abusing benzodiazepines, self-report of daily use is likely to be unreliable (Rastegar 2005). Also, patients may have access to benzodiazepines other than those prescribed by their GP (other GP or internet). Therefore, toxicological assessment was opted for as primary endpoint to assess benzodiazepine discontinuation, despite the fact that toxicological screening does not reflect real world practice. Since substance abuse is a chronic relapsing disorder the measurement time point was set at 52 weeks after randomization in order to assess the long-term effect of the discontinuation strategy in both the intervention and control group. Furthermore, it is true that a negative toxicological assessment at week 26 and 52 does not completely rule out (z-)BZD use in the follow-up period. However, with the laboratory assay that will be applied (see 7.6), the detection period in urine after use of a single DDD of (z-)BZD is about 1 week, while chronic usage of (z-)BZD extends the detection period up to 4 to 6 weeks after cessation of use. Therefore, if a patient succeeded to alter his (z-)BZD use in function of the toxicological assessments, this would rather reflect control over his/her (z-)BZD use than dependence on (z-)BZD.
The secondary endpoints, though, concern information about benzodiazepine use based on routinely collected data and patient-related outcome measures (PROMs).

3.4 Primary endpoint

The primary outcome is the proportion of subjects with a negative benzodiazepine urine test assessed 12 months after initiation of the intervention.

3.5 Secondary endpoints

- The proportion of subjects with a negative benzodiazepine urine test assessed 6 months after initiation of the intervention.
- The proportion with a better score in quality of life from baseline to 6, 12, 26 and 52 weeks.

- The proportion of subjects that self-report to have ceased benzodiazepine use at 6, 12, 26 and 52 weeks.
- The number of DDD of benzodiazepines prescribed at 6, 12, 26 and 52 weeks from baseline.

3.6 Exploratory endpoints

- Self-reported changes in alcohol intake or other psychoactive substances.
- Severity of (z-)BZD dependency .
- Quality of sleep.
- Occurrence of withdrawal symptoms, patient-reported adverse effects and falls.
- Use of medical services.
- (z-)BZD-related interventions by GP other than prescriptions
- Visits to and interactions with the e-learning module.
- Patient's satisfaction
- Physician's satisfaction

4 TRIAL DESIGN

This study is a pragmatic cluster randomised controlled superiority trial:

multi-centre:	6 academic centres of general practice will be involved in the recruitment of 120 GPs primary care practices
pragmatic:	criteria excluding patients from participation will be limited as well as procedures that do not reflect care as usual
cluster:	randomisation occurs at the level of the primary care practice while patients are the unit of analysis
randomised:	block randomization per academic centre will be performed to assign primary care practices to either the intervention or the control arm
controlled:	the intervention will be compared with usual care
superiority:	the trial is designed to show that the intervention is superior to usual care

The rationale for choosing a cluster design is to prevent contamination across the intervention and control arm. The cluster and unit of randomization is the primary care practice. There will be 2 arms – the blended care arm and the usual care arm- in 50:50 ratio.

5 STUDY SETTING

Since most (z-)BDZ are prescribed by GPs, the study will be conducted in primary care practices by 120 General Practitioners (GPs) throughout Belgium. The participating GPs will be recruited by the academic centres for General Practice of the KU Leuven, UGent, U Antwerpen, Université Liège, Université Libre Bruxelles and VUB.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

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

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

6.2 Exclusion criteria

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

- Presence of any severe psychiatric and neurologic condition that in the judgment of the treating GP implies a contraindication for (z-)BZD withdrawal
- Presence of terminal illness
- Any cases where stopping of (z-)BZDs might be harmful

- Unwillingness or inability to provide informed consent
- Not having e-literacy (being familiar with email and internet use)
- 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.

7 TRIAL PROCEDURES

7.1 Recruitment

For the recruitment of GPs, each academic centre will regionally organise training and education sessions on the management of withdrawal of (z-)BZDs and invite GPs to attend one of these. These two-hour sessions aim to refresh and train GPs' knowledge and skills on (z-)BZD discontinuation rather than to teach new information and skills.

Specifically, the training sessions will consist of an existing educational package on benzodiazepine withdrawal that was developed by the Project Group Benzodiazepines and commissioned and financed by the Federal Public Service Health. These trainings available in French and Dutch are typically delivered by a trained GP and psychologist.

The content of these sessions cover non-pharmacological minimal interventions and extended interventions and pharmacological approaches for (z-)BZD tapering and withdrawal and are based on the contents of

- "Anxiety, stress and sleeping problems. A toolbook for general practitioners" which was developed in 2005 by order of the Belgian Government as part of the fourth national campaign for a responsible use of (z-)BZD.
- The online guideline "Sleeping pill and sedatives. How to assist your patients in their search for other solutions" which was developed as part of the latest (2018) national campaign for a responsible use of (z-)BZD. Both toolboxes are available in French, Dutch.

At the end of the sessions attending GPs will be invited to participate in the study.

7.1.1 Patient identification

The participating GPs will be asked to recruit consecutively 10 patients consulting for benzodiazepine prescription renewal, during a period of maximum 6 weeks. This is feasible since assuming that 10% of the population takes (z-)BZDs on a regular basis –a conservative estimate- and assuming prescriptions are provided on a bi-monthly basis, full time working GPs see monthly between 50 and 150 patients for (z-)BZD prescription renewals (depending on the patient load varying between 1000 and 3000).

During this period of 6 weeks, the GP will keep a list of the number of eligible patients consulting for a BZD prescription renewal and will tally whether they were invited to participate in the study or not. In the latter case the GP will be asked to give the reason why he/she did not do so. Also when a patient declines participation in the study, the GP will ask for and record the reason of refusal.

Patients will be informed about the study by the GP. For that purpose, a patient information leaflet will be developed describing the aim and course of the trial and emphasizing the fact that it does not oblige patients to discontinue their (z-)BZD use but rather to investigate whether the intervention may motivate them to discontinue their (z-)BZD use.

Patients willing to participate in the study will be asked to sign an informed consent form. Since GPs often lack time they can choose to go through the leaflet together with the patient or apply a two-step approach by asking the patient to read it at home and to postpone their decision about participation in the study until the next consultation. Another option is that the GP sends the leaflet (by mail or letter) to the patient in anticipation of a scheduled consultation in the coming weeks. The GP will note the used method in the global medical file of each patient.

Especially for low literacy patients a link to a recorded video message will be provided in order to inform them about the study in a matching linguistic use.

7.1.2 Screening

The GP will assess eligibility and willingness to participate in the study. No additional procedures are required.

The reasons for patient non-eligibility and non-participation – if provided – will be recorded in the designated form (see Patient indentification).

7.2 Consent

Eligible patients will be informed by their GP about the study. Apart from a clear oral explanation, the patient will receive a comprehensive information leaflet and a link to a video recording presenting the same information.
All the information essential to the decision-making process of the participant will be provided including:

a. a brief, clear presentation of the rights of the participant (voluntary participation and confidentiality)
b. a clear description of the research project (context, objectives, inclusion/exclusion criteria, methodology & course) highlighting the constraints (toxicological screening) in addition to the standard treatment
c. descriptions of the risks & benefits
d. the right to withdraw from the study at any given point
e. the approval of the ethical committee
f. the researchers' contacts

Patients will have the opportunity to ask questions about the study and sufficient time to make their decision. Patients will be informed that they will still receive all the usual care, whether they choose to participate or not. Thereafter, patients will be asked officially to participate in the study and those who consent will be requested to sign an informed consent form. If patients request more time to contemplate participation, they can take the informed consent form home with a stamped envelope, to send it to the GPs office afterwards, signed if they are willing to participate, and unsigned if they are not willing to participate. In the informed consent form, a reference to the nested study is included, explaining that there is a possibility they will be invited for an interview and they can refuse or accept as they choose. Separate informed consent will be obtained if they participate in the nested study.

7.3 The randomisation scheme

In order to avoid contamination between GPs working in the same practice randomization will happen at the level of general practice.

General practices will be randomized in one of the 2 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 communities.

7.3.1 Method of implementing the allocation sequence

Stratified block randomization will be done using an electronic random numbers generator in blocks of 4 and 6 GPs. Since GPs are only blinded to their allocation until after recruitment of all patients, two block sizes are used to guarantee that the allocation process cannot be predicted. Randomisation and concealment will be centralised at the KU Leuven and conducted by a staff member not involved in data collection or delivering the intervention. Generating the randomisation list will happen in cooperation with a statistician from Leuven Biostatistics and Statistical Bioinformatics Centre.
To avoid cluster heterogeneity and post- randomization selection bias, randomization to either the control arm or intervention arm will be performed only after all 10 patients are enrolled in the general practice. At this time, the study coordinator monitoring the GP's practice will contact the staff member so allocation can take place. The staff member informs the study coordinator and GP as soon as possible of the result.

7.4 Blinding

Owing to study procedures, patients and GPs will not be masked to their random allocation but GPs will be kept blinded to their allocation until after patient recruitment. The outcome assessors will be kept blinded to the allocation during the whole study until after data analysis.

7.5 Unblinding

Conditions and procedures for unblinding are not required as the participating GPs will be aware of their allocation.

7.6 Baseline data

At study entry, the following baseline data will be collected for each participating patient:

- Demographics, comorbidities and medication
- Toxicological screening of urine
- Self-reported use of (z-)BZD (drug name(s), quantity)
- (z-)BZD prescriptions in last 6 months (drug name(s), quantity)
- Audit-C
- EQ5D-3L
- Benzodiazepine Dependence Self-Report Questionnaire
- Insomnia Severity Index
- HLS-EU-Q16

Except for the toxicological screening for which the procedure is explained in 7.7, data will be collected either by completion of the eCRF or via questionnaires sent to the patient.

The invitation to complete the first questionnaire will be sent after signature of the Informed Consent Form (ICF) and registration of the patient in the online platform Slaapzorgeloos/Dormir Sereinement. This first (baseline) questionnaire should thus be completed before the baseline visit takes place. By doing so, we would like to prevent that the patients' answers are influenced by the outcome of the randomisation (see section *7.3.1 method of implementing the allocation sequence)*.

7.7 Trial assessments

Within the week following the enrolment of the 10th patient by the GP(s), the general practice will be allocated to either the blended care or usual care arm.
During the baseline visit, which will take place within 12 weeks after the screening visit, the GP will start the intervention, which will be either usual care or blended care for the discontinuation of benzodiazepines.

Assessment by GP
After the baseline visit, appointments –minimal 1- for follow-up and prescription renewals will be scheduled left at the discretion of the GP and depending on the needs of the patient until the end of dose reduction. In addition to these scheduled appointments, patients will be allowed to request an extra appointment with their GP when needed. This approach maximally reflects daily practice as should be in a pragmatic trial.
The GPs will be asked to note in the Electronic Health Record (EHR) at each contact with the patient the (z-)BZD-related interventions delivered to the patients via standardized entry fields, and to document this data in the eCRF.
These interventions may include:

- Advise to discontinue (z-)benzodiazepines
- Discussion of tapering schedule
- Discussion of withdrawal symptoms
- Discussion of sleep quality

- Discussion of coping strategies, triggers and facilitators
- Decrease of benzodiazepine dose
- Increase of benzodiazepine dose

In the exceptional circumstances of COVID-19, EC Research allows the PI or his delegate to use telemedicine visits. This means that the GP can perform a consultation by telephone or video conference. As with regular consultations, all (z-)BZD interventions need to be documented in the EHR and eCRF of the patient.

E-questionnaires

Patients will be requested to complete the following e-questionnaires at weeks 6, 12, 26 and 52 comprising of the validated EQ5D-3L, Audit-C and Insomnia Severity Index. Furthermore, the e-questionnaire will include questions about self-reported use of (z-)BZD and other psychoactive medication, self-reported falls and use of medical services in the past period.

The questionnaires will be e-mailed to the study participants at week 5, 11, 25 and 51 with the request to complete them within 2 weeks. A reminder will be sent after 1 week to all participants who have not responded yet and every week after until response or the deadline

The deadline for questionnaires at week 6 and 12 is four weeks later, and for week 26 and 52, it is eight weeks later. If the data cannot be collected in this time frame, this will result in missing data.

The e-questionnaires at baseline will all together comprise of less than 50 questions and the follow-up e-questionnaires will be even shorter. All questionnaires will consist of closed questions which are answered by ticking the appropriate box, except the self-report questionnaire.

Toxicological screening

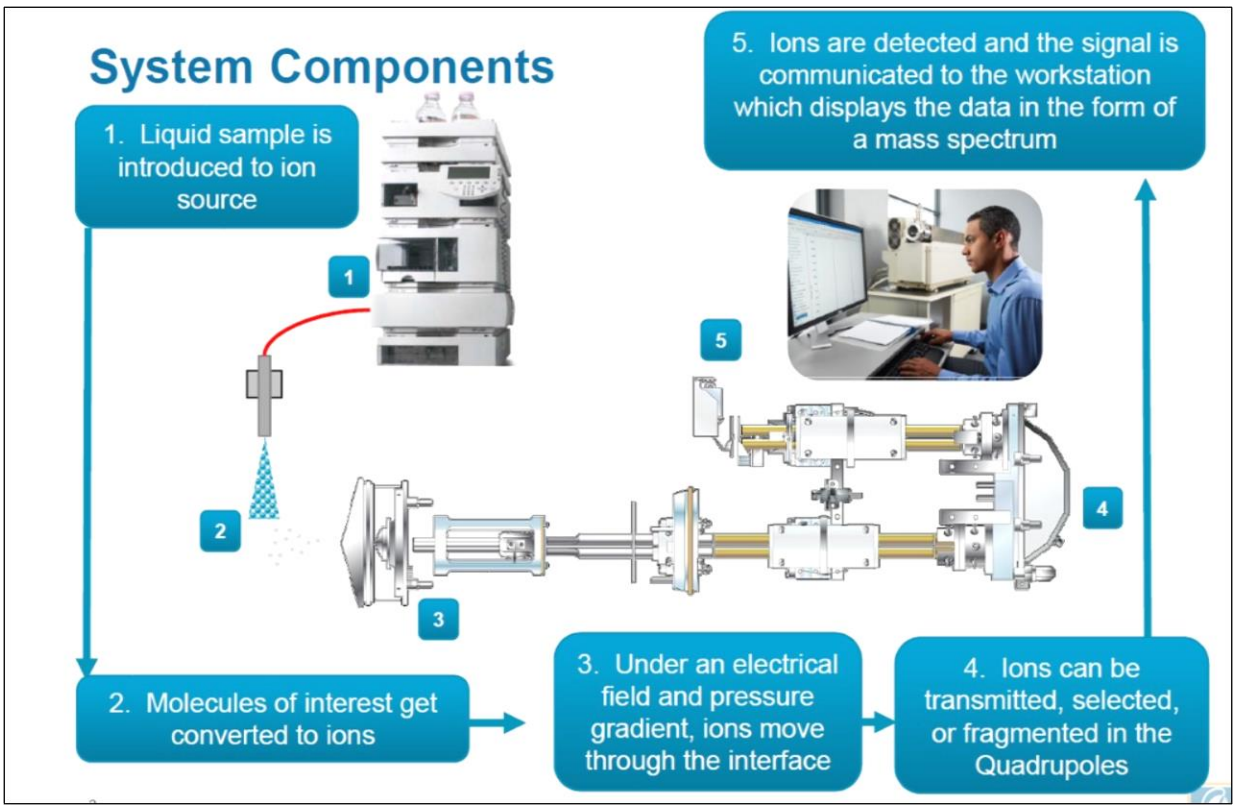
The baseline urine sample is collected during the baseline visit at the general practice.
At week 25 and 51 patients will be invited to produce another urine sample at the general practice within the next 2 weeks. A reminder will be sent after 1 week to all participants who have not yet done so and every week after until a urine sample is obtained or the deadline. The deadline is set at eight weeks later than week 26 and 52.

Depending on the workflow in the general practice, it is not necessary to schedule a consultation with the general practitioner when collecting the urine samples of week 26 and 52. However, the patient needs to come in to produce the urine sample at the general practice. Therefore, we offer them an expense allowance in the form of a voucher, worth 10 euros. Patients need to sign the urine sample log, where the unique identifiable number of the voucher is documented, to declare they have received this voucher.

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 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 ((z-)BZDs prescribed in low doses because of their high potency such as flurazepam) 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.

Figure 2: Liquid chromatography-tandem mass spectrometry



The detection window for (z-)BZDs in urine is dependent on multiple factors but is using LC–MS/MS typically 6 days or longer in case of ingestion of a single dose while chronic usage over a period of months or years can extend excretion times up to 4-6 weeks after cessation of use.

Table 1 shows the detection durations using liquid chromatography-tandem mass spectrometry after ingestion of a single therapeutic dose of 2.5 mg lorazepam, 6 mg bromazepam 1 mg flunitrazepam, 2 mg clonazepam, 10 mg zolpidem and 7.5 mg zopiclone. Unfortunately, data about detection windows for other commonly prescribed (z-)BZD such as alprazolam and flurazepam are not available. However, there is no reason to expect them to be substantially different from the ones listed in table 1.

Table 1: Detection windows for 6 benzodiazepines by liquid chromatography–tandem mass spectrometry

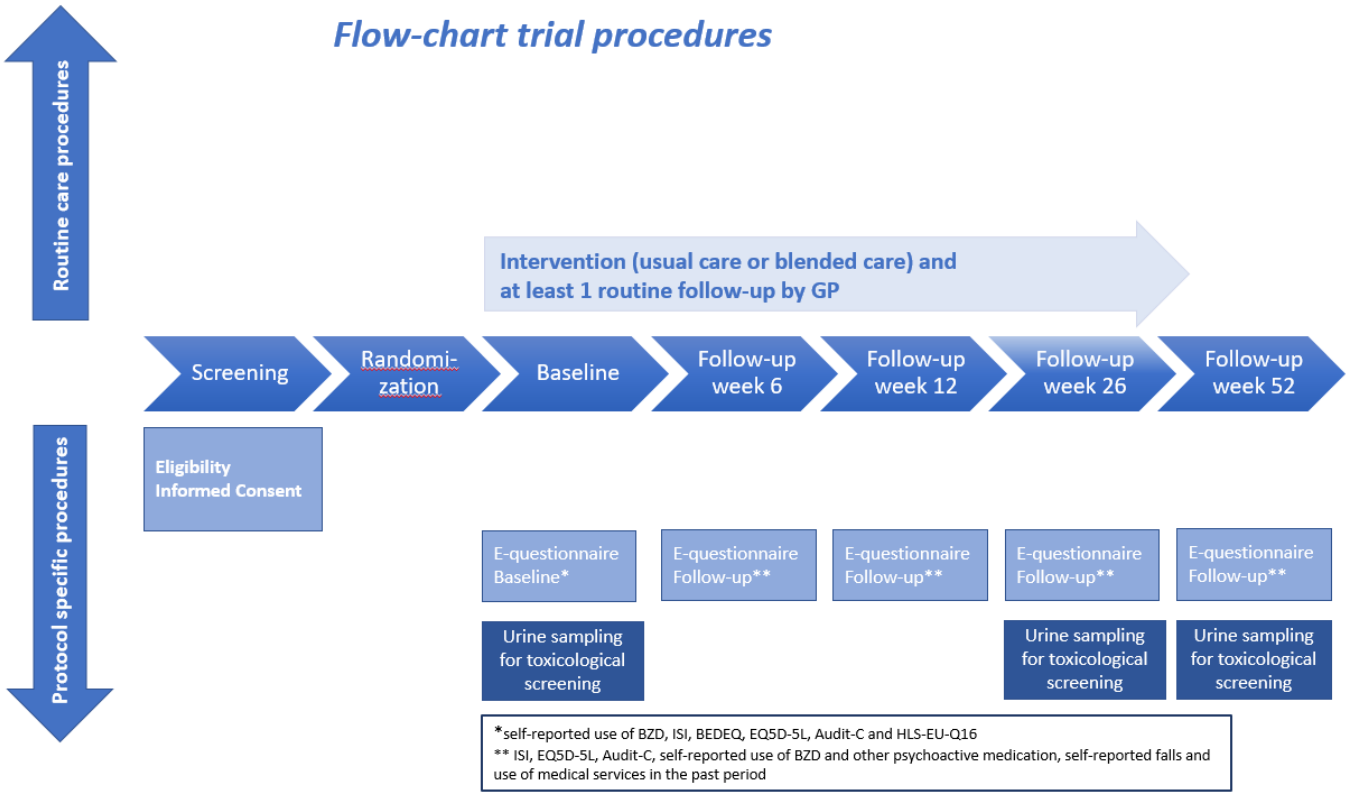
Benzodiazepine	Half-life in hours	Detection window in hours
Lorazepam	12-16	≥144
Bromazepam	15-35	≥144
Flunitrazepam	10-30	≥144
Clonazepam	1-30	≥144
Zolpidem	1-4	144
Zoplicone	2-6	≥144

Table adapted from Deveaux et al. The Role of Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) to Test Blood and Urine Samples for the Toxicological Investigation of Drug-Facilitated Crimes. Ther Drug Monit 2008; 30: 225-228

As was explained in 3.2, toxicological screening is not part of routine practice. Therefore, the GPs will be blinded for the results of these analyses.

7.8 Flow-chart of trial procedures

Figure 3: flow chart trial procedures



7.9 Long term follow-up assessments

Not applicable

7.10 Qualitative assessments – Nested studies

A process evaluation will be nested within the pragmatic clustered randomized trial. The process evaluation will capture data to understand how the intervention is used and viewed by GP and patients. This is important for informing implementation in practice. It will explain how GPs and patients experience the intervention. We aim to identify factors within each arm which influence the ability (or inability) to withdraw from benzodiazepines whilst taking part in the blended care program or whilst receiving usual care in order to build a framework describing the mechanisms required for successful implementation.

Individual interviews will be conducted with GPs and patients taking part in the trial. Interviews will be carried out to capture perceived barriers and facilitators to using the blended care approach or with the usual care approach. GPs (approximately 8) will be purposively sampled to obtain variation in gender, practice setting and experience. Patients (approximately 14-18) will be purposively sampled to obtain variation in age, gender, and how successful the withdrawal has been. Interviews will follow semi-structured topic guides exploring GPs' and patients' views and experiences of taking part in the trial. Topic guides will be informed by existing literature and theory of health behaviour to ensure that questions elicit likely key determinants of behaviour. Topic guides will be piloted with patient representatives and clinicians. Interviews will be carried out face to face and analysed using thematic and Framework analysis.

7.11 Withdrawal criteria

Withdrawal from the study can be initiated either by the patient or by the general practitioner.

As stated in the Informed Consent patients have the right to end her/his participation in the trial at any point in time and for any reason. In case a patient wishes to end her/his participation, she/he can do so either by notifying her/his GP or by ticking the box that will be provided in each e-questionnaire allowing patients to communicate their wish to withdrawal.

The treating GP can also consider a patient for withdrawal from the study. However, the GP will have to discuss this option with the study coordinator and to receive the consent of the latter before the final decision of withdrawal can be made.

In all instances, the reason for withdrawal will be asked for and notified.

Withdrawn patients will not be replaced. For statistical handling of withdrawn patients see section 10.3.4.

7.12 End of trial

Where necessary, end of trial documents and notifications will be drafted and presented.

8 TRIAL INTERVENTION / MEDICATION

8.1 Name and description of intervention(s)

Care as usual
In the control arm, patients will receive 'usual care' left at the discretion of the treating GP.
Apart from the general training session for all participating GPs they have attended prior to recruitment and randomization, GPs in the control arm will not receive additional tools.
They are expected (but not forced) to follow the Belgian guidelines (as described in "Anxiety, stress and sleeping problems. A toolbook for general practitioners" and "Sleeping pills and sedatives. How can you assist your patients in the search for other solutions?"), which recommend a stepped approach.
In first instance a minimal intervention strategy is applied which may consist of a discontinuation letter or a single discontinuation advice during a consult. In both instances information about the consequences of (z-)BZDs is given aiming at encouraging the patient to discontinue (z-)BZD use along with a (z-)BZD tapering scheme. In case the minimal intervention failed or in case the GP judges the chance of a successful minimal intervention to be unlikely, a brief intervention is recommended which may span one or more consults. During this intervention, the GP will -based on the principles of motivational interviewing- assess the patient's readiness for change and match the appropriate intervention. Once the patient is ready for withdrawal a patient-tailored (z-)BZD tapering scheme will be developed which typically consists of a 10–20% reduction in the daily dose of the (z-)BZD every 2–4 weeks. To facilitate withdrawal a switch from a (z-)BZD with a short half-life to diazepam may be considered.

Blended care

In the intervention arm an interactive e-learning program is blended with direct contacts face-to-face with the treating GP.

The GPs will provide patients participating in the study access to an interactive e-learning module delivered through a web-based platform, which patients and GPs can access securely with a personal login account. The e-tool used in this trial will be a newly designed tool, inspired by the program of slaapzorgeloos.be that was developed for a pilot trial described in section 2, and which was based on evidence resulting from a review of the literature, and other websites such as www.benzodebaas.nl and www.sleepio.com, which also focus on sleeping problems and/or benzodiazepine use.

During the preparatory phase of the trial the program of slaapzorgeloos.be was adapted including improvement of lay-out, user friendliness and content using the think-aloud method and MoSCoW analysis. During think-aloud interviews, patients and GPs are observed using the e-tool and asked to comment on their reactions to every aspect of e-tool (Bradbury 2014). This enables researchers to identify problems people might experience when using the e-tool and modify it accordingly. They are effective in highlighting navigational difficulties and can reveal useful information relating to the content of an e-tool which needs to be modified (Bradbury 2014). MoSCoW, a prioritisation model used by digital service developers, is a simple tool that can be usefully employed to prioritise the content of an e-tool. Each of the capital letters represents a priority:

- M: Must have this for the intervention to be effective, acceptable and feasible,
- S: Should have (if possible) for the intervention to be a success, but may be able to be delivered in a different way, or is in some way less critical than a Must have,
- C: Could have this as it would be useful, but only if time and resources are available,
- W: Would like for classifying a feature which would be nice, but is not essential now and can be put on hold.

This method ensures efficient development of successful interventions and aids effective communication between team members, who might otherwise perceive different priorities

The adaptation process led to a learning module that consists of 8 informational chapters, a sleeping diary, two conclusive modules and a referral to other informational materials. The learning module aims to empower patients by improving their knowledge, self-efficacy and confidence, enabling them to successfully discontinue their (z-)BZD use.
In the 8 informational chapters, the topics sleep and sleeping disorders, sleeping medication and its associated risks, non-pharmacological alternatives and tapering of (z-)BZDs are addressed.

The sleeping tips, non-medicinal alternatives and coping strategies provided in this module are based on the principles of cognitive behavioural therapy(CBT) which have been proven to be effective in the management of sleeping problems (Ye 2015). CBT is a psychological treatment designed to break the patterns of maladaptive thinking and behaviour that serve to maintain insomnia. CBT comprises a range of techniques including a behavioural component combined with a cognitive and an educational component. In order to encourage active involvement of the patient, interactive components were built in allowing patients to enter information about their sleeping habits, sleep hygiene, coping techniques, triggers and facilitators etc.

During the face-to-face contacts, the treating GP will log in to his panel of the platform, where he will be able to consult the information of each patient separately. Per patient, the GP will see their name, token, the completed eCRFs, and the information from the interventions within the e-tool that was shared by the patient. This facilitates discussing the experiences of the patient and addressing questions the patient may have concerning the contents of the e-tool.

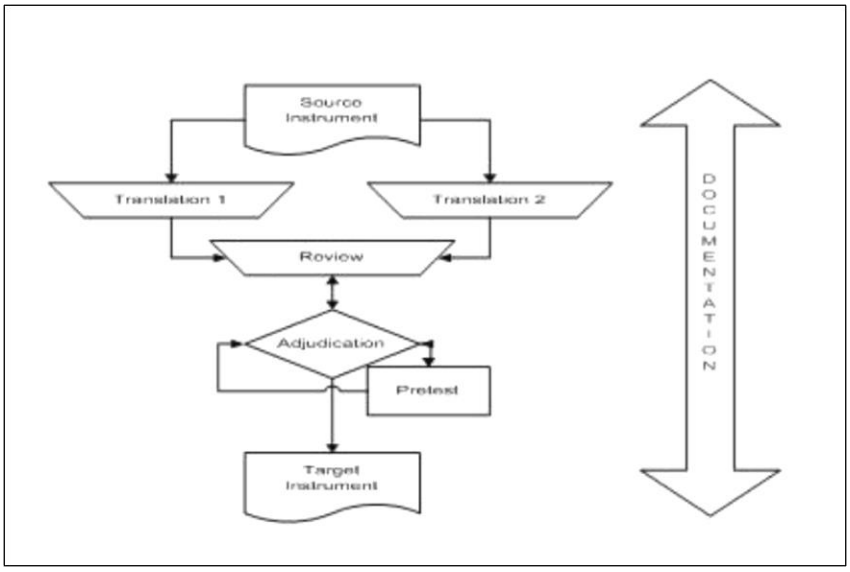
Because the learning module will be implemented in Belgium, a Dutch and French version are necessary. For translation, the TRAPD Team Translation Model will be used. A successful translation process is expected to keep the content semantically similar. In case of interactive content as surveys or web based tools, it is also expected to keep the question format similar within the bounds of the target language; retain measurement properties, including the range of response options offered; and maintain the same stimulus (Harkness 2010). Based on growing evidence, a team translation approach is now recommended to design cross-culturally comparable surveys or tools (Harkness 2008, Harkness 2010, Pan 2005 and Willis 2010). The TRAPD Team Translation Model fulfils the criteria for successful translation.

Its procedures are partially iterative. The successive steps are as follow (fig. 4):

- **T – Translation:** two (or more) independent draft translations are produced;
- **R – Review:** the translators and a reviewer compare the draft translations and decide the final translation;
- **A – Adjudication:** an adjudicator (often, the reviewer) compares the reviewed translation with the Master Questionnaire and approves the translation for the pretest or for the fieldwork;
- **P – Pretest:** the adjudicated questionnaire is tested at a small scale. The translation is corrected on the basis of the feedback from the pretest;
- **D – Documentation:** the whole process (draft translations, exchange of comments between the translators, the reviewer and the adjudicator, feedback from the pretest, final translation) is documented.

In this project, translators of the research teams of ULB and ULiege will make the translation of the material from Dutch to French in collaboration. The reviewer will be a staff member of Uliege, and the final adjudication will happen by staff members of ULiege and KULeuven.

Figure 4: The TRAPD translation model



8.2 Assessment of compliance

A built-in system will be developed for the learning module allowing to track users as they visit, leave and return to the e-learning module. Furthermore, each time the user performs specific actions (such as filling in the sleeping diary, answering questions etc.) this will be recorded.

9 SAFETY REPORTING

The risk of adverse events occurring as a consequence of the intervention in this trial is unlikely therefore safety reporting will be limited to the safety reporting that is necessary in routine care (https://www.fagg-afmps.be/nl/notification_effets/humane_geneesmiddelenbewaking/melding_gezondheidszorgbeoefenaars).

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The primary research question driving the sample size calculation is whether chronic benzodiazepine users who receive the blended learning intervention are more likely to discontinue (z-)BZD use at 12 months follow-up compared to chronic benzodiazepine users who receive usual care.
The rate of discontinuation by usual care is expected, based on a literature review of RCTs to achieve a rate ranging between 10 and 17%. (Mugunthan K, McGuire T and Glasziou P. Minimal interventions to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. Br J Gen Pract 2011; 61 (590): e573-e578.)

The study will be powered to detect 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
Based on an alpha of 0.05 and 80% power and assuming 10% patients lost to follow-up (In the study by Vicens et al the drop-out rate after 12 months was 7%) an individually randomized study would require a total sample size of 594 participants (297 in each group).
To account for clustering effects from randomized GPs with an intracluster correlation coefficient (ICC) set at 0.11 based on a study by Vicens et al. (C. Vicens, F. Bejarano, E. Sempere, et al. Comparative efficacy of two interventions to discontinue long-term (z-)BZD use: cluster randomized controlled trial in primary care. The British Journal of Psychiatry (2014) 204, 471–479.) 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 consist of 1182 patients. Because each general practitioner has to recruit 10 patients, 119 general practitioners are needed.

10.2 Planned recruitment rate

The centres for general practice of KU Leuven, U Ghent, U Antwerp, ULB, VUB and U Liège will each recruit 20 GPs for participation in the trial within a period of 6 months. In case one of the academic centres for general practice fails to reach this goal another centre will be requested to recruit more general practices.

After 3 months, all GPs will have enrolled 10 patients. Taking the high prevalence of BZD use into account there will not be any difficulty in finding enough eligible patients in GP practices included in the study (see 7.1.1 Patient identification).

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

Presentation of baseline characteristics of the study population and comparability of the 2 arms will be based on the following variables:

- Age (mean and standard deviation or median and 25-75 percentiles)
- Gender (percentage)
- Relevant co-morbidities (percentage)
- Benzodiazepine dependence score (means and standard deviation or median and 25-75 percentiles)
- Daily dose of (z)BZD in DDD (means and standard deviation or median and 25-75 percentiles)
- Sleep quality
- Audit-C score

10.3.2 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 negative benzodiazepine urine test assessed 12 months after initiation of the intervention as a binary outcome and intervention group as a factor. A random effect will be modelled to deal with clustering by general practitioner. The group effect will be reported as an odds ratio with 95% confidence interval.

Subgroup analysis will be performed in order to investigate how the primary outcome behaves in function of:

- age categories
- gender
- (z)BZD dose at baseline in DDD
- Sleep quality at baseline
- Benzodiazepine dependency score
- For the intervention group only: use of e-tool

10.3.3 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.

The EQ-5D-3L data will be summarized based on the principles of a Pareto improvement in Welfare Economics - the Pareto Classification of Health Change (PCHC) (Devlin 2010). According to this principle an EQ-5D-3L health state is deemed to be 'better' than another if it is better on at least one dimension, and is no worse in any other dimension. And an EQ-5D-3L health state is deemed to be 'worse' than another if it is worse in at least one dimension, and is no better in any other dimension. Using that principle to compare a patient's EQ-5D-3L health states between any 2 time periods, there are only 4 possibilities:

- Their health state is better
- Their heath state is worse
- Their health state is exactly the same
- The changes in health are 'mixed': better on one dimension, but worse on another.

The EQ-5D-3L scores will be analyzed as (1) better versus other, and (2) worse versus other.

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.

10.3.4 Procedure(s) to account for missing or spurious data

See section 7.7 for strategies to maximise follow-up and to prevent missing data.

When a patient withdraws from the study prematurely, all data collected up until the moment of withdrawal will be analysed (using the intent-to-treat approach). 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.

10.4 Data collection for economic evaluation

One of the goals of the KCE Trials programme is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind, e.g. the necessary data to allow the conduct of a health economic evaluation will be collected. The planned economic analysis is briefly described below, together with the variables collected in this protocol for this purpose. For the sake of clarity, the economic analysis is not a part of this trial. The decision to conduct such economic analysis will depend on the effectiveness results of this trial.

OVERVIEW
The first part is a cost study with the aim to identify significant cost drivers. A cost driver is a component in the health service significantly associated with the costs. The potential subcategories of costs considered are (Carreras et al, 2016): acute outpatient, acute inpatient, primary care, residential care, pharmacy prescriptions, chronic prescriptions, diagnostic tests, accident & emergencies, intervention costs and total costs at 6 and 12 months. A health care payer perspective is adopted and includes payments out of the federal government's and the communities' health care budget as well as patients' co-payments.
The second part on the economic evaluation concerns cost-utility (CUA), comparing costs and consequences between participants in the 'blended care' study group (intervention group) and those in the 'leaflet information' study group (control group).

ANALYSES
Part I: cost estimations
In both study groups, the subcategory costs and total costs are calculated. In addition, between-group differences are calculated for each subcategory and total costs. First, descriptive statistics will provide unadjusted information on the magnitude and distribution of the 'blended care' costs for each of the subcategories compared to the 'leaflet information' group. Secondly, a generalized linear modelling (GLM) will be applied to evaluate the total costs between both groups adjusted for the other independent factors (patient characteristics, cluster, cost drivers etc).

Part II: health economic evaluation (CUA)
Bottom-up approach:
In this phase, an analysis of the costs and health effects alongside the clinical trial will be conducted. The costs include (1) the direct medical costs for which a nomenclature code exist, and (2) costs associated with the intervention (e.g. monetary valuation of caregiver time spent on the program, administrative costs). The effects will be expressed as 'utilities' (i.e. a health-related quality of life weight, range from 0 [dead] to 1 [perfect health]).
For both study groups, resource use data and health-related quality of life (HRQOL) data will be collected using information from the patients' medical records and using a questionnaire (self-reported) for those resources not captured by the medical records. Subsequently, information from the RIZIV nomenclature

database will be used to attach costs to the different resource use data. In the intervention group, the costs associated with the intervention will be collected using a pre-printed form that has to be filled out by the participating GPs. The HRQOL data will be collected using the EQ-5D-3L questionnaire (filled out by the participating patients).
Resource use data and health-related quality of life data will be collected at regular time points: at baseline, at six weeks, at 12 weeks, at 26 weeks, and at one year. Information related to the intervention costs will be collected during the intervention period. The latter costs will be recalculated at patient level.
The ratio of the incremental costs to the incremental utilities is called the incremental cost-effectiveness ratio (ICER) calculated as : ($Cost_N$ – $Cost_C$)/(Health $effect_N$ – Health $effect_C$)a. This measures reflects the difference in costs per unit of effect (in this example: utility).
A well-known issue is the presence of missing data related to the different outcome variables (cost data, utility data). Different methods exist to handle this. In the current research project, single imputation methods will be used. In this method, the missing data are replaced with a single predicted value (e.g. the adjusted mean value) (Diaz-Ordaz et al. 2014). Sensitivity analyses will be conducted to determine how different input values will impact the outcome (Diaz-Ordaz et al. 2014).

Markov decision-analytic modelling:
A Markov decision-analytic model will be used to predict longer term patient outcomes and complications for patients in the 'blended care' arm versus the 'information leaflet' arm. The outcome considered as input for the Markov model will be the occurrence of falls. This kind of model allows us to simulate transitions in various health states beyond the duration of the intervention. Each health state is associated with costs and utilities. The health effects will be expressed as quality-adjusted life years (QALYs). QALYs are calculated by multiplying the utility level (information obtained in phase 1) with the number of years and individual lives with the condition. Input data for the Markov model will be obtained from phase 1 and from published literature.
Health economic evaluation studies are frequently characterized by some degree of uncertainty or methodological considerations. In the current study, one-way sensitivity analyses and probabilistic sensitivity analyses (non-parametric bootstrapping) will be conducted to handle this uncertainty.

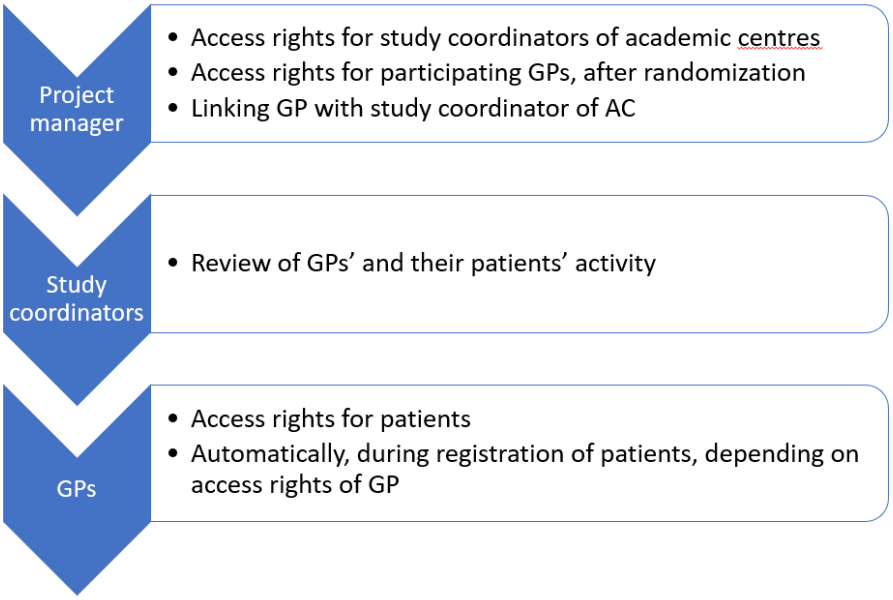
11 DATA HANDLING

11.1 Data collection tools

Data collection will be performed through the online platform developed by Viavario in cooperation with onlinehulpverlening.be. This platform will consist of administrative user panels on the one hand, and content-related tools for data collection, like the interactive learning content, questionnaires and eCRFs, on the other hand. There will be multiple administrative user panels to assure secure access to the platform, as illustrated in figure 5. In one panel, the project manager will have access to the tool to grant personal access rights to the study coordinators of each academic centre, and access rights to the GPs, depending on their allocation after randomization. Each GP will be linked to a study coordinator from an academic centre. From another panel, the study coordinator will be able to review the GP's records and the compliance by his or her patients. This means the study coordinator will have an overview of all GPs assigned to him or her, and an overview of their patients' activity, with only personal study codes as identifiers. Through the administrative user panel of the GPs, they will be able to register patients. The access rights of the patients will automatically be determined by the rights that were granted to the GP.

[a] N= new strategy (blended care); C= current strategy (information leaflet)

Figure 5: administrative user panels and securely providing access rights on each level



Data collection via the online platform will happen on 2 levels: the GPs completing the eCRF and the patients completing the questionnaires, and the interventions in the tool (only for blended care group). All information will be encrypted as much as possible. Besides this data collection, the laboratory will provide the results of the toxicological screening of the urine samples. All these data will be pseudonymised, using a personal study code, to allow integration of data from a single patient from multiple sources. The identity of the individual patient will be blinded to the research facility at all times. This is ensured by storing the Personal Identifiable Information for the Identity Provider, the program and exercise data from the online patient platform, and the e-CRF data in physically and logically separated databases. Confidentiality is ensured because the research facility will not have access to the database for the Identity Provider. This is guaranteed by technical and organisational measures, meaning only the service provider will control the access keys for the database of the Identity Provider, and the original research data from the online platform. These access keys will be secured at a high level by ensuring that each of the access keys are controlled by another member of the service provider. The research facility will only control the access to the database of encrypted and pseudonymised research data. Figure 6 illustrates these data flows. The landing zone refers to the server where all data from the online platform will arrive and be stored in the, as mentioned, three separate databases.

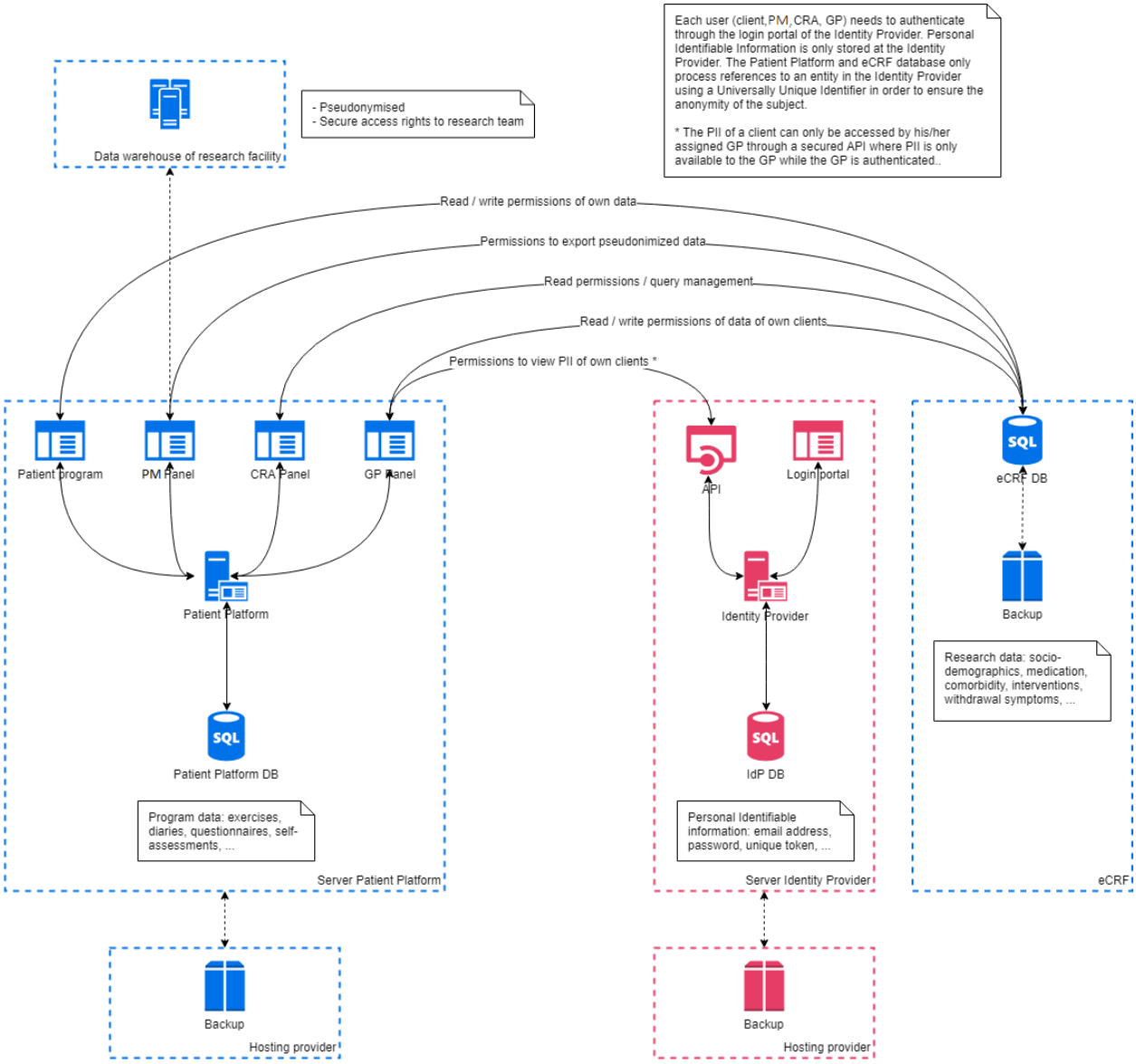
As illustrated in figure 6, data are encrypted and transferred pseudonymised into the data warehouse through secure extraction via the administrative panel of the project manager. Data from a single patient can be collected through this system from more than one source while still ensuring anonymity.

The collected data remains in the databases of the service provider and only an excerpt of this data is transferred to the data warehouse of the research facility. Data is collected continuously throughout the duration of the trial. All data is transferred through encrypted channels, using highly secured encryption algorithms.

The collection and processing of data (from patients enrolled in this study) will be limited to those data that are necessary to fulfil the objectives of the study. These data will be collected using secure communication tools and processed with the necessary precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be guaranteed by the service provider, who will be responsible for collected data storage in the landing zone. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Data collection is the responsibility of the research facility under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. Source documentation will be reviewed by the clinical team to ensure that data collection is accurate and complete.

Figure 6: Data flow using the Viavario platform



As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes….)

11.2 Data handling and record keeping

The procedure for data handling conforms with the General Data Protection Regulation (GDPR) requirements. GDPR in the context of clinical research means that access to the patient file can only be allowed for legitimate reasons, meaning:

1. For diagnosis or providing therapy,
2. With consent of the patient,
3. If necessary, for scientific research, provided that “adequate measures” are being taken, and the regulations for scientific research in the law of July 30, 2018 concerning the protection of natural persons with regard to processing personal data are complied with.

Adequate measures imply anonymising or pseudonymising data. Anonymising is irreversible. After this, the collected data are no longer personal data. Pseudonymising is a procedure that replaces identifying data with encrypted data (the pseudonym) through a certain algorithm. This algorithm can define the same

pseudonym for each person, which allows collecting and combining information on one person from different sources.

The research facility will only maintain the data warehouse of encrypted and pseudonomysed data. The service provider will maintain all collected data until database lock, being the end of the trial, or until the end of the principal agreement, whichever comes first. The data warehouse is highly secured and access to the data warehouse is only possible through a personal extranet connection.

All data transfer is organised through highly secured information channels, using end-to-end encryption. The service provider will also be responsible for the pseudonymisation of patient data as Trusted Third Party.

11.3 Access to Data

Access to the trial data is guaranteed through the dedicated servers of this trial. Only authorized researchers or monitors will be granted access to this specific server space. The service provider shall ensure that any personal data shall be treated as confidential at all times including during collection, handling and use, and that such information shall be stored securely with all technical and organizational measures necessary for compliance with applicable data protection legislation. The service provider shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto, disclosure thereof, loss or destruction while in its custody by applying the technical measures as described in the OWASP Application Security Verification Standard v3 Level 2 and ensure the confidentiality, integrity and availability of the data by implementing the technical security requirements described by the sponsor per article 5.5.3 of the ICH GCP.

11.4 Archiving

The Sponsor is responsible for archiving study specific documentation (such as but not limited to protocol, potential amendments and final report) for at least twenty years. The data warehouse will be stored in a register at the research facility. Destruction of essential documents will require authorization from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

The investigator will permit trial-related monitoring, audits, EC review and regulatory inspection, providing access to all related source data / documents. The Trial will be monitored to ensure that the Trial is being conducted in compliance with GCP and current legislation, verify, among other procedures, that written informed consent has been obtained correctly, that the Trial procedures have been followed up as shown in this protocol, and that the data have been recorded, for which the Source Data will be compared with the data recorded in the (e)CRF.

Electronic CRFs and all source documents, must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FAMPH). The accuracy of the data will be verified by review of the source documents.

In each academic center, a study coordinator will be appointed to perform monitoring visits for this trial, among other tasks.

More details about the monitoring strategy for this Trial are described in the Trial specific Monitoring Plan, which is available upon request.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethics Committee (EC) review & reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. Before the start of the study, this protocol, the informed consent forms and other related documents e.g. advertisements and GP information letters, will be submitted for review to the Research Ethics Committee (REC) and to the Sector Committee for Social Security and Health of the Privacy Commission. The study shall not commence until such approvals have been obtained.

Any subsequent protocol amendments will be submitted to the REC and Sector Committee for approval. No substantial amendment that requires review by REC will be implemented until the REC grants a favourable opinion for the study. After approval, all substantial amendments will be communicated as soon as possible to other relevant parties, like investigators, trial participants, and trial registries.

The study can and will be conducted only on the basis of prior informed consent by the study participants, or their legal representatives, to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients and/or their families. The participating physician shall obtain a signed informed consent form for all study participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The research facility shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

All correspondence with the REC shall be retained in the Trial Master File/Investigator Site File.

The Chief Investigator acknowledges that it is his responsibility to produce annual progress reports (APR) and he will do so by submitting to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

The Chief Investigator shall notify the REC of the end of the study. Should the study be ended prematurely, the Chief Investigator will notify the REC and include the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

Peer review will be conducted by expert referees to the professional and scientific standards expected for clinical studies

13.3 Public and Patient Involvement

In this study patients will actively be involved in the entire research process.
We consulted in the course of the development of this protocol patients with a history of (z-)BZD use about the design of the trial by means of a focus group discussion. Their comments were taken into account in the finalization of the protocol together with the patients' opinions that were collected during the pilot study.

In the preparatory phase of the study, patients will take part in the development of the educational e-tool, informed consent and e-questionnaires to ensure that these materials are clear and accessible. All patient related documents, questionnaires and video's that are used in the trial will be reviewed by patient representatives for their user-friendliness and their intelligibility.

We will also make sure patients are represented in the Steering Committee. This will allow their involvement in the trial development, trial conduct and trial evaluation.

After the study participants will be informed about the results of the study

13.4 Regulatory Compliance

This study protocol and the conduct of the study in general is in compliance with applicable law, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

13.5 Protocol compliance

The Chief Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Protocol deviations which are found to frequently recur, will require immediate action. Chief Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation (as defined under section 13.6).

13.6 Notification of Serious Breaches to GCP and/or the protocol

It is understood that “a serious violation” is likely to effect to a significant degree

- the safety or physical or mental integrity of the participants of the study; or
- the scientific value of the study

The Sponsor shall be notified immediately upon becoming aware of a serious violation during the study conduct phase.

13.7 Data protection and patient confidentiality

The study will be conducted in compliance with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Data Protection Act. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws.

Any personal data shall be treated as confidential at all times including during collection, handling and use, and that the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant’s initials. Such coded personal data can only be traced or linked back by said study team members, and said study team members shall treat these codes as strictly confidential.

Only anonymized personal data will be disclosed to KCE or, where specifically requested by KCE, coded personal data. In no event shall any of the reports, documents, information disclosed to KCE include data that may be linked to the specific identity of a study participant. The Sponsor shall make sure that the key to personal identities of all persons to whom the data relates is kept in a separate and secure place in compliance with applicable data privacy legislation and shall not be disclosed to KCE or unauthorized persons.

All study related data and documents will be stored for twenty (20) years, in accordance with Belgian legislation.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator hereby declares having no financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; not having received any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, ownership interest that may be related to products, services or interventions considered for use in the study, or that may be significantly affected by the study; having no commercial ties with any pharmaceutical, behaviour modification, and/or technology company; nor having any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

In consideration of participation in the study, the nominated payee will receive the sums set out in the payment schedule attached to the clinical trial agreement.

13.9 Indemnity

The Sponsor has foreseen an insurance policy for this trial as set out in the Law of 2004 through Amlin Europe NV, in collaboration with Vanbreda Risks & Benefits NV, with contract number 299.053.700. The Sponsor shall throughout the duration of the study effect and maintain this insurance policy providing an adequate level of cover in respect of all risks which may be incurred by the Sponsor arising out of the Sponsor's performance of the study.

The terms or the amount of cover of any insurance shall not relieve the Sponsor of any liabilities under the clinical trial agreement.

13.10 Access to the final trial dataset

The study results will be owned by the party who generates them. The Sponsor will have access to the study data. At the end of the study, KCE will receive from Sponsor specific study data. This will only be anonymous study data or, where requested by KCE, coded personal data are made available to KCE.

The study data shall not be provided to a third party without the prior written approval of KCE, which approval KCE shall not unreasonably withhold or delay and which KCE may subject to specific conditions in order to ensure that the provision of said study data does not have a negative impact on the further performance of the study, the rights granted to KCE under the research agreement and/or the benefit of the Study for the patients and/or the public payers.

14 DISSEMINATION POLICY

14.1 Dissemination policy

The results of the study shall be owned by the party who generates them.

The results of the study owned by Sponsor and/or (where applicable) any collaborator shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium). Sponsor shall inform and discuss its dissemination strategy with KCE in advance.

The final Study report should be made available for review by KCE before the results are disseminated. KCE shall be notified prior to any dissemination (including publication) (whether in oral, written or other form) of the foreground IP or results or study data or of matters arising from the study. The Chief Investigator shall send one draft copy of the proposed dissemination to KCE at least ten (10) days for an abstract and

thirty (30) days for a manuscript before the date intended for dissemination. For the avoidance of doubt, this obligation continues after the end of the study. KCE may object within thirty (30) days of receiving notification, if, in its reasonable opinion, the dissemination (or the timing thereof) is not in the public interests. In the event Chief Investigator or (where applicable) any collaborator intends not to protect the results of the study it needs to formally notify KCE thereof before the dissemination takes place, Sponsor shall ensure that any dissemination is scientifically correct, objective and unbiased (taking into consideration the primary endpoint(s)).

In the event of a multicentre study, Sponsor nor its collaborators shall independently publish or otherwise disclose any findings resulting from the study before publication of the main multicentre publication.

Any dissemination shall acknowledge KCE's financial support and carry a disclaimer as KCE may require in accordance with the clinical trial agreement.

Open access will be ensured (free of charge, online access for any user) to all peer-reviewed scientific publications relating to the results of the study owned by it and/or the collaborators. In particular, Sponsor shall: (i) As soon as possible and at the latest on publication, deposit a machine readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications; moreover Sponsor must aim to deposit at the same time the research data needed to validate the results of the study presented in the deposited scientific publications; and; (ii) Ensure open access to the deposited publication, via the repository at the latest on publication (if an electronic version is available for free via the publisher) or, within six (6) months of publication in any other case.

We will ensure that the findings of the study will be disseminated to relevant stakeholders others than the scientific world including the general public, health care providers and policy makers. Therefore, information about the study will be spread through websites (news sites of the universities, medical and health information sites such as gezondheid.be), newsletters and press releases. Next, we will inform agencies such as Farmaka, insurance companies and patient representative groups (Vlaams Patiënten Platform, LUSS) and encourage them to further circulate the information through their own communication channels. Furthermore, the results will be presented to various government bodies and policy makers and on conferences and on local seminars for general practitioners (LOKs, GLEMs). Finally, the study findings will be published in national journals (for example HANU, Revue de la Médicine Générale).

In case this study proves blended care to be more effective than usual care for the discontinuation of (z-)BZD, the next challenge will be to translate this evidence into routine practice. For depressive disorders, for example, evidence-based internet interventions are widely available but they fail to enter routine mental healthcare delivery at a large scale.
Though the development of an implementation strategy is clearly beyond the scope of this study, we would like to formulate some general recommendations/considerations.

- First, the implementation intervention strategy should be developed based upon a theoretical framework applying a systematic approach (Vis 2015). Multiple theories and frameworks exist but one common ingredient comprises an in-depth analysis of the perceptions, barriers and facilitators as experienced by all stakeholders. The process evaluation that is part of this trial will be informative in respect to this and hence provide a basis for an implementation strategy.
- Second, it will be essential to educate GPs about introducing blended care in general and this e-tool in particular, in their daily practice. This will require training which should be delivered through accredited Continued Medical Education (CME) but should also be part of the basic medical curriculum for GPs. The engagement of the majority of the Belgian Academic centres for general practices in this trial will undoubtedly facilitate the integration of education about blended care for the discontinuation of (z-)BZD –in combination with (z-)BZD prescribing guidelines- in the medical curriculum.
- Finally, implementation of blended care for the discontinuation of (z-)BZD will require the e-tool to have a sustainable platform and to be freely available and easily accessible. With respect to the latter, coupling with the HER should be considered.

14.2 Authorship eligibility guidelines and any intended use of professional writers

All reports will be written by researches directly involved in the study and supervised by the Steering Committee. Only researchers or participants actively involved in parts of the study will be eligible for authorship.

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■ APPENDICES

APPENDIX 1. SAFETY REPORTING DEFINITIONS

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

	• in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question