Background
GHB (gamma-hydroxybutyrate) and its pro-drugs GBL (gamma-butyrolactone) 1,4-butanediol (1.4-BD) are central nervous system depressants whose street names include 'G' and 'liquid ecstasy'. They are used recreationally predominately for their stimulant and pro-sexual effects or for sedation to help with sleep and/or to "come down" after stimulant recreational drugs. Although overall population prevalence is low (0.1%), in some groups such as men who have sex with men, GHB/GBL use may reach 20%. GHB/GBL dependence may be associated with severe withdrawal with individuals presenting either acutely to Emergency Departments or to addiction services for support. Benzodiazepines are currently prescribed for GHB/GBL detoxification but do not prevent all complications such as behavioural disinhibition that may require hospitalisation or admission to a High Dependency/Intensive Care Unit. The GABAB receptor mediates most effects of GHB/GBL and the GABAB agonist, baclofen, has shown promise as an adjunct to benzodiazepines in reducing withdrawal severity when prescribed both during withdrawal and as a 2 day 'pre-load' prior to detoxification.

Methods / Design
This is a randomised, double-blind, placebo-controlled feasibility study which will recruit participants (>18 years) who are GHB/GBL dependent and wish to undergo planned GHB/GBL detoxification or are at risk of acute withdrawal and are inpatients requiring unplanned withdrawal. We aim to recruit 88 participants, 28 unplanned inpatients and 60 planned outpatients.

During detoxification we will compare baclofen 10mg three times a day with placebo as an adjunct to usual benzodiazepine regimen. In the planned outpatient arm, we will also compare a 2-day preload of baclofen 10mg three times a day with placebo. Ratings of GHB/GBL withdrawal, sleep, depression, anxiety as well as GHB/GBL use will be collected. The main data analyses will be descriptive about recruitment and characterizing the impact of adding baclofen to usual benzodiazepine regimen on measures and outcomes of GHB/GBL withdrawal to provide estimates of variability and effect size. A qualitative approach will evaluate research participant and clinician acceptability and data collected to inform cost-effectiveness.

Discussion
This feasibility study will inform a Randomised Controlled Trial to establish whether adding baclofen to a benzodiazepine regimen reduces the severity and complications of GHB/GBL withdrawal.
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Full title:  
Improving GHB withdrawal with baclofen.

Short title:  
The GHB trial

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Abstract

Background
GHB (gamma-hydroxybutyrate) and its pro-drugs GBL (gamma-butyrolactone) 1,4-butanediol (1.4-BD) are central nervous system depressants whose street names include ‘G’ and ‘liquid ecstasy’. They are used recreationally predominately for their stimulant and pro-sexual effects or for sedation to help with sleep and/or to “come down” after stimulant recreational drugs. Although overall population prevalence is low (0.1%), in some groups such as men who have sex with men, GHB/GBL use may reach 20%. GHB/GBL dependence may be associated with severe withdrawal with individuals presenting either acutely to Emergency Departments or to addiction services for support. Benzodiazepines are currently prescribed for GHB/GBL detoxification but do not prevent all complications such as behavioural disinhibition that may require hospitalisation or admission to a High Dependency/Intensive Care Unit. The GABA$_B$ receptor mediates most effects of GHB/GBL and the GABA$_B$ agonist, baclofen, has shown promise as an adjunct to benzodiazepines in reducing withdrawal severity when prescribed both during withdrawal and as a 2 day ‘pre-load’ prior to detoxification.

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Discussion
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Trial Registration
ISRCTN59911189

Protocol: v3.0; 15/2015
Keywords
GHB, gamma-hydroxybutyrate, GBL, gamma-butyrolactone, GHB/GBL withdrawal, baclofen, benzodiazepine, GABA<sub>B</sub>, GHB/GBL dependence
**Background**

**GHB/GBL use and dependence**

GHB (gamma-hydroxybutyrate) and its related analogues GBL (gamma-butyrolactone) and 1,4-butanediol (1,4-BD) are central nervous system depressants and their street names include ‘G’ and ‘liquid ecstasy’ [1,2]. GBL and 1,4-BD are converted to GHB after ingestion and therefore all three drugs have similar pharmacological actions and profiles [1,2]. There is limited use of 1,4-BD in the UK and therefore hereafter we will use the term GHB/GBL to refer to these compounds. They are used recreationally predominately for their stimulant and pro-sexual effects, although some individuals use them for their sedative effects and/or to help “come down” after use of stimulant recreational drugs [3,4,5]. Although overall population prevalence of use is low, the Crime Survey for England and Wales reported that use significantly rose from 0.0% in 2010/11 to 0.1% in 2011/12; subsequent surveys did not collect GHB/GBL data [6]. However use of these drugs is more common in a number of sub-population groups. In particular, in populations such as clubbers and men who have sex with men (MSM), lifetime prevalence of GHB/GBL use ranges from 3.9 % to 14.3 %, with last month prevalence of use of up to 4.6 % [7]. Almost a quarter of those surveyed in “gay-friendly” South London dance clubs in July 2011 reported GHB/GBL use that night, second to mephedrone at 41% [8]. Similarly, attendees at two London sexual health clinics (December 2013 – March 2104) reported lifetime prevalence of use of GHB at 19% and GBL at 13% [9].

Reports from the UK’s Advisory Council on Misuse of Drugs [10] and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [7] have highlighted the potential for both significant acute toxicity and also dependence associated with GHB/GBL. The latest data from Public Health England reports that the numbers of people presenting to treatment services with problems with GHB/GBL continues to rise from 18 (2% of new presentations involving ‘club drug’ (methamphetamine, mephedrone, ketamine, ecstasy, GHB/GBL) those seeking treatment in 2005-06 to 249 (5%) in 2013-14 [11] and the number of deaths implicating GHB are also rising from none in 1993 to 12-20/year 2008-2012 [12]. Our clinical experience is consistent with this. Presentations with acute GHB/GBL toxicity to the Emergency Department (ED) and Clinical Toxicology Service (one of the sites in this study) at St Thomas’s Hospital (GSTT) increased from 158 in 2006 to 270 in 2010 [13]; and there has been an increase in the numbers of individuals seeking help from services such as Antidote (supporting LGBT community) and the Club Drug Clinic, Central North West London NHS Foundation Trust for GHB-related problems. Antidote has seen an increase in GHB-related problems from 1.7% (n=3) of total referrals in 2005 to 57% (n=317) in 2010 and 44% (n=334) in 2013/4.

GHB/GBL use is associated with a risk of physical dependence and a potentially life-threatening withdrawal syndrome, unlike other ‘club drugs’ such as stimulants which do not have a pronounced withdrawal syndrome [14]. Therefore, a disproportionate number of GHB/GBL dependent users compared with other club drugs require help for a potentially life-threatening withdrawal syndrome. Management of GHB/GBL withdrawal or detoxification can present challenges to clinicians and dependent users, due to rapidity of onset of the withdrawal and the severe clinical features that can occur. Regular use of GHB/GBL (typically multiple times per day every day over a period of at least a few months) can lead to
dependence with dependent users typically using the drug every 1-4 hours to prevent onset of withdrawal [15-18]. Withdrawal symptoms occur typically within hours following last use due to GHB/GBL’s rapid elimination (T1/2 ~ 27min) and may also occur during recovery from acute intoxication (overdose) [2, 11,18,19]. A proportion of the patients with GHB dependence may therefore use alcohol or other drugs such as benzodiazepines, “Z Drugs” (e.g. zopiclone) and/or baclofen to self-manage withdrawal symptoms, insomnia and craving. Typically these are used to help increase the time between dosing overnight to enable them to sleep. The clinical features of GHB withdrawal are similar to alcohol withdrawal but often with more rapid onset. GHB withdrawal can also resemble acute stimulant toxicity and co-ingestion of other drugs. Identification of GHB dependence and withdrawal can be complicated by a lack of awareness by non-specialist centres, particularly in emergency cases [20].

GHB/GBL withdrawal and its treatment

GHB/GBL withdrawal has many similar features to alcohol withdrawal, including tremor, sweating, anxiety, agitation and confusion, however it is generally more severe, has a more rapid onset and more prominent neuropsychiatric features such as delirium and psychosis [2, 15,18]. Similarly to alcohol withdrawal, benzodiazepines have been the pharmacotherapeutic mainstay for GHB/GBL withdrawal [18]. However, our clinical experience suggests that using benzodiazepines alone may be insufficient, with up to 50% of individuals presenting to our emergency department and initially 4% of those in our outpatient clinic required acute medical care [21, 22]. This latter groups had either developing significant delirium and/or worsening of their initial acute delirium on presentation that required escalation of treatment including admission to intensive care and use of additional sedatives (e.g. barbiturates or propofol) with the associated intubation and mechanical ventilation for airway support as described [15]. Acute delirium, agitation and/or psychosis results in further risks to the individual, as well as to the staff treating them due to the severity of agitation and violence.

There has been one death reported as a “complication of GHB/GBL withdrawal”. The individual was treated with benzodiazepines for 12 days, developed pneumonia and suffered a cardiac arrest and we feel that the significance of the GHB dependency/withdrawal in the death is unclear and it is likely that the death is not directly related to the dependence / withdrawal [23]. Despite the severity of GHB/GBL withdrawal and concerns about how to best manage unplanned and planned detoxification, at this time there is no systematic evidence base on which to base a national or international agreed treatment protocol. One review produced an algorithm based on amount of use and presence of delirium [24]. For those with severe dependence (>3 doses of GHB/GBL per 24hrs or >30g GHB/>15g/day) and “medical complications”, admission for detoxification and supportive medical care with high dose diazepam (150-200mgs / 24hours) was suggested. Pentobarbital (barbiturate) in ICU was suggested for those presenting with delirium. It was not clear how long to use pentobarbital for or what to do in those who do not respond to this treatment escalation. For those without delirium, diazepam reducing from 80-150 mgs per day over 7 days whilst an inpatient was proposed. For those using less GHB/GBL, outpatient management with diazepam reducing from 20-40mg per day over 7 days was suggested. Given the complexity, rapidity of onset of symptoms and complications of withdrawal such as acute severe delirium, it is important that daily outpatient supervision of GHB/GBL withdrawal occurs in a setting in which admission to an acute hospital is possible should complications arise [25].
Various other pharmacological approaches have been investigated. One trial compared lorazepam and pentobarbital in inpatients for GHB/GBL withdrawal; however this was not completed due to inability to recruit sufficient GHB dependent individuals [26]. Whilst pentobarbital is safe to use in hospital, due to the potential risk of coma and lethal toxicity, it is not appropriate for use in community / outpatient detoxification. A Dutch pilot uncontrolled study reported a reducing regimen of GHB/GBL successfully treated withdrawal and prevented complications such as delirium in 23 GHB/GBL-dependent inpatients [27]. GHB in the pharmaceutical preparation sodium oxybate is licenced in the UK for the treatment of narcolepsy associated with cataplexy in specialist sleep services. Current UK prescribing, storage and administration controls (due to the legal status of GHB under the UK Misuse of Drugs Act, 1971) are likely to be practical considerations that limit its usefulness in managing GHB/GBL withdrawal (due to delays in treatment administration). Anti-psychotics may lower the seizure threshold increasing the risk of GHB-withdrawal related seizures. They may also interact with GHB’s effects on the dopaminergic system increasing the risk of neuroleptic malignant syndrome [17,28].

In summary, a reducing regimen of benzodiazepines alone for GHB/GBL withdrawal is currently considered 'standard' treatment and as such is the current 'best practice'; although in a significant proportion of individuals benzodiazepines alone may be insufficient. The limited research almost always suggests benzodiazepines as the core treatment, with a range of other options having been suggested as helpful of which baclofen has strong pharmacological validity. (See next section).

GHB/GBL withdrawal and the GABA<sub>B</sub> system

In addition to activity at endogenous GHB receptors, GHB acts at GABA<sub>B</sub> receptors which play a key role in withdrawal since GABA<sub>B</sub> antagonists precipitate withdrawal in GHB dependent non-human primates [1,29] and can block GHB induced respiratory depression [30]. Benzodiazepines work through GABA<sub>A</sub> receptors however GHB has limited activity at these receptors, likely explaining their apparent incomplete clinical effectiveness in acute GHB withdrawal. The GABA<sub>B</sub> agonist baclofen has therefore been used on an unlicensed named patient basis as an adjunct to benzodiazepines to manage GHB/GBL withdrawal by the authors and others [18,31]. Baclofen is currently only licensed in the UK for the management of muscle spasticity in multiple sclerosis and other conditions.

An uncontrolled case series in 19 GHB/GBL dependent patients, all of whom except for 2 underwent outpatient treatment, reported that baclofen (10mg three times a day) in addition to high dose diazepam during the initial 4–5 days of GHB/GBL detoxification, resulted in no transfers to ICU and several patients commented that baclofen was helpful [18]. Furthermore, the experience of clinical toxicologists and addiction specialists in the UK, including those involved in this study, has been that baclofen is helpful in reducing the complications from GHB/GBL withdrawal. Consequently the recent update of the British Association for Psychopharmacology's addiction guidelines [25] suggested using baclofen (10mg three times a day) as an adjunct to benzodiazepines for GHB/GBL withdrawal.
Furthermore, our clinical experience of GHB/GBL withdrawal in outpatient settings has been that patients who slowly reduce their GHB/GBL use describe significant anxiety and cravings during the few days before commencing medically assisted detoxification. For some, this acted as a deterrent to attending for treatment and a trigger for using higher doses of GHB/GBL. Consequently, we have initially used baclofen two days prior to stopping GHB/GBL in a small number of patients. There was very positive feedback from patients regarding the benefit, particularly in terms of reduced cravings and helping to stabilise pre-detoxification GHB use. The use of baclofen in our outpatient clinical service prior to initiating medically assisted detoxification has now become more widespread. The two days of pre-detoxification ‘pre-loading’ of baclofen at a standard dose of 10mg three times a day has not resulted in any clinical incidents in relation to baclofen. This pre-loading with baclofen has previously not been formally studied to determine the usefulness of baclofen itself, and whether some of the reported benefits relate to more engagement with drug treatment services pre-detoxification.

Baclofen has been licensed in UK for many years for the treatment of spasticity (maximum, 100mg per day) and can be safely prescribed to a wide range of people [see SPC, 32]. Our clinical experience is that it is associated with few side-effects. Whilst a withdrawal state is recognised for baclofen, this is unlikely to occur with its use in acute GHB withdrawal due to the short duration (7 to 10 days) of baclofen use in this indication. We suggest that the risk of complications from baclofen withdrawal is considerably less than that of inadequately managed GHB/GBL withdrawal [15,18]. Nevertheless, whilst use of baclofen holds promise, there are potential adverse effects on cardiovascular, neurological and respiratory systems so controlled data is urgently required to determine the efficacy and safety of baclofen in GHB/GBL withdrawal. Optimising outpatient treatment to reduce the risk of complications and hospital admission is important since many individuals decline admission [17,25]. Despite this complexity and its impact on and cost to the individual and NHS, there is limited knowledge about how to best treat people in planned or unplanned GHB/GBL withdrawal.

Primary and secondary objectives

The primary objective of this study is to investigate the feasibility of recruiting GHB/GBL dependent patients and characterizing the impact of adding baclofen to a standard benzodiazepine regimen for management of GHB/GBL withdrawal in both outpatient (community) and inpatient general hospital settings.

There are several other secondary objectives. These are to examine:

- withdrawal symptoms and complications such as delirium and requirement for treatment escalation during detoxification in two populations: those presenting to an emergency department requiring immediate acute withdrawal management (unplanned) and those presenting to a specialist outpatient ‘club drug’ clinic requiring GHB/GBL detoxification (planned);
- as part of a planned detoxification whether starting baclofen 2 days prior to stopping GHB/GBL confers additional benefits in our proposed primary outcome measures (symptom severity, complications such as delirium and requirement for treatment escalation);
- and monitor recruitment rate and manage any difficulties;
- impact of GHB/GBL withdrawal on secondary outcome measures (anxiety, depression, sleep, quality of life);
- impact of study participation on GHB/GBL use up to one month post-randomisation and other alcohol/drug use;
- and to explore research participant and staff views about the acceptability of the study design;
- and gather preliminary information regarding costs of GHB/GBL withdrawal and its management to develop full economic analysis in definitive trial.

**Methods/Design**

This is a prospective, randomised, placebo controlled trial to assess the feasibility of undertaking a definitive trial investigating the efficacy of baclofen in treating GHB/GBL withdrawal, both in planned and unplanned withdrawal using both quantitative and qualitative approaches. The optimal recruitment rate and strategies and characteristics of the proposed primary outcome measures (symptom severity, complications, requirement for treatment escalation) will be assessed. Ethical approval has been obtained from National Research Ethics Service Committee London – Dulwich and the EUDRACT number is 2013-005319-28.

**Research settings**

The study will recruit from two services where individuals present for treatment for GHB/GBL withdrawal. The CNWL Club Drug Clinic, based in Central London, UK, is an outpatient clinic where individuals are referred or self-present for treatment for GHB/GBL dependence and may undergo planned detoxification as part of their treatment package and secondly, to a specialist Clinical Toxicology Service at Guy’s and St Thomas’ NHS Foundation Trust, London, UK for those who present with unplanned withdrawal requiring immediate management.

**Participants**

**Inclusion Criteria**

Any individual who is >18 years old, is either in active GHB/GBL withdrawal or has underlying GHB/GBL dependence and wishes to undergo GHB/GBL detoxification or is thought to have underlying GHB/GBL dependence and is at risk of acute withdrawal and for outpatient arm only, who is registered with a drug treatment service will be eligible for the study.

**Exclusion Criteria**

An individual will not be eligible for inclusion in this study if they are unable to provide written informed consent and any of the following criteria apply; The clinician decides that medication is not required for management of GHB/GBL withdrawal, If medication is indicated but the patient lacks capacity to consent, is unable to take oral medication or is unable to take baclofen according to SPC due to known hypersensitivity to baclofen or any of the excipients, hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, active peptic ulceration, porphyria. In addition for those with epilepsy that is not well controlled either with or without medication or those with end stage renal failure.
(CKD stage 5, GFR <15 mL/min) (have special warnings and precautions for use, according to the SPC) will not be entered since the risk vs benefit ratio for prescribing is not in favour of prescribing baclofen. In addition, participants who are unable to follow the study protocol due to serious mental health disorder e.g. enduring psychotic illness, suicidal intent will not be eligible. Further, any participant who has taken any investigational drug within 30 days prior to drug administration or any woman refusing a pregnancy test will not be eligible.

**Randomisation**

An assessment of eligibility will be made by a medical doctor following discussion with the potential participant and review of the accessible medical records. For some participants wishing to participate in the study but where there is limited or no access to medical records, the individual will be included in the trial unless one or more of the eligibility criteria are known not to be met.

To be able to respond to the urgent needs of people at high risk of withdrawing from GHB/GBL in a timely manner, study medication will be pre-packed and pre-randomised, and will be stored at both study sites. Randomisation codes will be generated by the trial statistician. Those eligible for inclusion will be randomised to baclofen or placebo by taking the next lowest consecutively numbered pack from storage cupboards in the respective treatment centre.

If eligible, given informed consent and following baseline assessment, the participants are allocated as follows (see Figure 1A and 1B). Those in the planned arm will receive a pre-load before their detoxification proper and will be allocated to one of three groups: pre-load of placebo (one tablet three times a day) followed by benzodiazepine GHB/GBL detoxification regimen with study medication, baclofen (10mg three times a day) or placebo (one tablet three times a day) for up to 10 days or pre-load of baclofen (10 mg three times a day) followed by benzodiazepine GHB/GBL detoxification regimen with baclofen (10mg three times a day) for up to 10 days. Those in the unplanned arm will receive their benzodiazepine detoxification regimen for GHB/GBL withdrawal with study medication, baclofen (10mg three times a day) or placebo (one tablet three times a day) for up to 10 days. In both unplanned and planned GHB/GBL withdrawal, clinicians will use the benzodiazepine and dosing regimen that they consider appropriate. Study medication will be discontinued at the same time as the benzodiazepine, with the decision about when both medications are discontinued made by their clinician.

*Figure 1 about here.*

**Assessment and Outcome measures**

Data will be collected to inform the primary and secondary outcome measures in the definitive trial. The proposed primary outcome measure includes symptom severity, complications, requirement for treatment escalation and proposed secondary outcomes.
include change in anxiety, depression, sleep, quality of life as well as relapse to GHB/GBL use or change in other illicit drug or alcohol use 30 days after start of detoxification.

On the first day of GHB/GBL detoxification, ratings will be obtained from each participant of their symptoms of GHB/GBL withdrawal using a scale widely used for alcohol withdrawal - Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) which is currently used clinically by teams to monitor GHB/GBL withdrawal [33-36]. CIWA-Ar may not adequately capture all neuropsychiatric symptoms/signs [33,34] and the ‘sedation assessment tool’ will assess behavioural disturbance [37]. Depressive (PHQ-9; 38) and anxiety (GAD-7; 39) symptoms will be assessed using scales already in routine clinical use. We will also record sleep pattern using a questionnaire [40]. Any medication taken by the time of the ratings will be recorded. Blood pressure, respiratory rate, oxygen saturation and pulse will also be recorded when CIWA-Ar is completed. Since this is a pragmatic trial, we aim to minimise any extra tests or investigations and research participants will receive standard medical care as usual. If as part of this standard medical care blood and/or urine is collection for toxicological screening for recreational drugs/novel psychoactive substances, the result will be recorded but not sought solely for the purposes of this study.

During detoxification, daily assessments will record the withdrawal assessment scale (CIWA-Ar; 29), behavioural disturbance (SAT; 37), sleep pattern, any use of other drugs/novel psychoactive substances/ alcohol and nicotine (including substitution), as well as when they took any medication. On the last day of taking detoxification medication (or the next working day for outpatients where this falls on a weekend/public holiday), withdrawal, depressive and anxiety symptoms (PHQ-9: 38; GAD-7: 39) and sleep pattern will be recorded in all participants. Research participant satisfaction will be measured with the ‘client satisfaction questionnaire’ (CSQ-8; 41,42). Any information not already obtained or previously available will also be completed and will include the following: using a semi-structured questionnaire: years of GHB/GBL use, amount of GHB/GBL in week prior to detoxification and amount in a typical day/week, pattern of use, whether they are self-reported “dependent” on any of these, medication(s) that have been used to help self-treat or prevent previous withdrawal. Previous psychiatric and medical history, other drug or alcohol use including nicotine and determination of any dependence will be similarly established as well as using time-life follow-back, the alcohol screening questionnaire (AUDIT; 43) and appropriate parts of the mandatory ‘Treatment Outcome Profile’ (TOPs; 44) used in substance misuse services will be completed.

Regarding medication, the total amount of benzodiazepine prescribed, its dosing regimen and how much taken will be recorded. Use of any other medication during the detoxification will also be recorded.

Any complications arising during preload or detoxification will be recorded. These will be classified as adverse events if not one of the following predetermined events which are known to occur in acute GHB/GBL withdrawal or detoxification: agitation or aggression, hallucinations (visual, auditory and/or tactile), tachycardia, seizures, ataxia, sedation, tremor and/or sweating.
On day 30 after the start of detoxification (benzodiazepine detoxification, not preload), the researcher will contact the research participant to obtain information about any subsequent use of GHB/GBL, other recreational drugs / novel psychoactive substances / alcohol as well as any medication (prescribed or otherwise obtained) taken and psychosocial treatment / support received for their GHB/GBL dependence. In addition, any issues or events that could be related to their detoxification will be recorded.

**Sample size**

The aim is to recruit 88 research participants undergoing GHB/GBL detoxification, 60 planned outpatients and 28 unplanned inpatients.

**Qualitative Process Evaluation: Research participant and clinician acceptability**

We will undertake qualitative, semi-structured, one-to-one interviews with 12 research participants, 6 from each site. Participants will be sampled purposively to represent key case-mix variables and treatment allocation. These interviews will investigate (a) participants experience and acceptance of the study procedures (notably recruitment, randomisation and outcome assessment procedures), and (b) their treatment experience. The interviews will be conducted using a topic guide. This will be drafted on the basis of the study aims, relevant literature and clinical experience, but there will be scope for iterative development of the guide as data collection and analysis progress. Participants who have had a previous detoxification, will be asked to reflect on how the trial detoxification compared with previous ones.

In addition, two focus groups involving the clinical teams from each site will also be conducted. These will explore clinician experience of the trial and the acceptability of trial procedures. Key senior members of staff will also be offered a one-to-one semi-structured interview. All interviews and focus-groups will be audio-recorded, transcribed and analysed using a thematic framework approach and managed using NVivo (Scolari/Sage) computer software. Initial coding frameworks for both participant and staff datasets will be based on the study aims of how feasible and acceptable it is to undertake a definitive trial, but sub-themes will be further developed through analytic induction and grounded in the data. This will be revised iteratively as data collection and analysis progress.

**Cost effectiveness**

Data will be collected to inform the undertaking of a full economic evaluation in the definitive RCT by piloting the data collection methods that would be used in such a full trial. Piloting data collection instruments will show the feasibility of recording service use information from the population and identify the services and other costs to participants that would need to be included in a full, economic evaluation of a phase III trial.

**Safety monitoring plan**
An Independent Data Monitoring and Ethics Committee (IDMEC) will be established to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. It will report to the Trial Steering committee which provides overall supervision for the GHB trial on behalf of the Trial Sponsor and the Trial Funder, ensures that the trial is appropriately conducted, and provides advice, through its Chair, to the Trial Management Group. An interim analysis will be undertaken to characterise the number of adverse events in each arm once 5 individuals have been recruited to each arm at one site. In particular, treatment escalation including admission to Level 3 facility (Intensive Care Unit – ICU) for those presenting to emergency department (unplanned) arm or admission to Level 1 or above bed in a general hospital for those in club drug clinic (planned) will be closely monitored. Based on clinical experience of complications from GHB/GBL withdrawal, if 5 individuals in any one group require treatment escalation, the sponsor and IDMEC will be immediately informed and recruitment suspended until there has been a discussion and consideration of the protocol and whether the trial should continue. The end of the trial is defined as completion of follow-up of or 3 attempts to contact the last participant randomised to study medication. The trial may terminate before all (n=88) participants have been recruited if we have obtained sufficient information about recruitment, engagement/or and evaluation of outcome measures.

Data analysis

The primary focus of this study is to assess the feasibility of undertaking a definitive trial. In particular we will characterize optimal recruitment rate and strategies and characteristics of the proposed primary outcome measure (symptom severity, complications, requirement for treatment escalation). The main analyses will be descriptive and provide estimates of variability and effect size with 95% confidence intervals. This will include the rate of recruitment, the proportion of approached people who consent to randomisation, the proportion who complete detoxification and the proportion who will complete the follow up assessment. We will also describe the distribution of scores on the primary outcomes and estimate the variance of the measure in this population. Data for our proposed secondary outcomes in the definitive trial will include change in anxiety, depression, sleep, quality of life as well as relapse to GHB/GBL use or change in other illicit drug or alcohol use 30 days after start of detoxification. We will also identify appropriate criteria e.g. benzodiazepine requirement or withdrawal score for minimisation or stratification in the full RCT.

We will use ANCOVA adjusting for patients’ characteristics and relevant clinical data. Where there is follow up, methods applied to longitudinal data will be appropriate since they are able to detect significant differences between arms but they can also detect changes of the outcome measure(s) over time. We will also conduct an interim analysis to characterise the number of adverse events in each arm as described above.

Discussion

Whilst GHB/GBL may not be widely used by the general population, there is greater use in certain sub-populations such as gay and bisexual males (GBM). Regular use of GHB and its related analogues can lead to the development of physical dependency and an associated withdrawal syndrome on stopping use [1,2]. This typically is rapid in onset after last dose and
may mimic other conditions (e.g. acute stimulant toxicity, acute alcohol withdrawal) making its diagnosis and management challenging for clinicians [2, 11,14]. This is particularly of concern in areas where GHB and related analogue use is low, so there may be a lack of awareness of the potential for dependency and withdrawal. A proportion of individuals with GHB-related withdrawal may require more intensive sedation and subsequent admission to HDU/ICU to ensure not only their safety, but also that of the staff caring for them. This incurs significant costs to the individual through length of stay and potential for ICU-related complications as well as to the NHS and wider society due to the required resource utilisation.

There much anecdotal evidence that the current clinical practice of using benzodiazepines alone as initial treatment may be insufficient to adequately manage GHB/GBL withdrawal and prevent the requirement for treatment escalation. Since GHB/GBL acts as a GABA\textsubscript{B} receptor agonist, using another GABA\textsubscript{B} agonist, baclofen, to attenuate withdrawal has pharmacological validity. Our clinical experience, and that of others, is that the addition of baclofen (10mg three times a day) to benzodiazepines does indeed reduce GHB/GBL withdrawal symptoms and associated complications [11,14]. Furthermore, pre-loading with baclofen for 2 days prior to detoxification appears to provide additional benefits. When designing this trial, we were not aware that this is undertaken routinely outside our specialist clinic and is important to understand its role in improving and managing GHB/GBL withdrawal. A similar approach may be used by some clinicians for particular patients to help them to prepare for their alcohol detoxification by reducing craving and excessive consumption prior to starting their detoxification proper.

Due to its use in particular communities, specific addiction services have evolved with expertise in managing GHB/GBL withdrawal. Similarly presentations to Emergency Departments vary depending on local clubs and nightlife, since individuals who frequent these tend to also live in the local area. The two services in this study have such local communities and have developed their services to meet the local needs. They are therefore well-placed to conduct this study due to their experience and regular presentations of those with GHB/GBL withdrawal. There is local support and much user interest in this study.

In order to determine whether baclofen is a useful adjunct and to meet thresholds required by national guidelines e.g. NICE, a trial is still required and without such a trial, the use of baclofen will remain based on anecdotal evidence. We are not aware of any other trial using baclofen in GHB withdrawal nor has any other pharmacological approach been shown to be robustly effective or appropriate for community detoxification. Importantly this trial also seeks to establish whether the use of baclofen prior to starting detoxification i.e a preload improves symptom control and reduces complications during GHB detoxification. This is a novel aspect of the study and addresses a critical question.

**Trial status**

The study has received favourable opinions from the MHRA (Medicine and Healthcare products Regulatory Agency) and REC (Research Ethics Committee). The aim is to start recruitment by Spring 2016.
List of Abbreviations

GHB: gamma-hydroxybutyrate;
GBL: gamma-butyrolactone;
GSTT: St. Thomas’s Hospital, London;
ED: emergency department;
CNWL: Central and North West London NHS Foundation Trust;
ICU: Intensive Care Unit;
RCT: Randomised controlled trial;
GMP: Good Manufacturing Practice;
SPC: Summary of product characteristics;
GCP: Good Clinical Practice;
EMCDDA: European Monitoring Centre for Drugs and Drug Addiction;
IDMEC: Independent Data Monitoring and Ethics Committee;
CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol;
AUDIT: Alcohol Use Disorders Identification Test.

Authors’ contributions
ALH is Professor of Addiction Biology at Imperial College London and Consultant Psychiatrist at Central North West London NHS Foundation Trust (CNWL). YP is the project manager for the trial. OBJ is Consultant Psychiatrist at CNWL and lead at its Club Drug Clinic and is Honorary Senior Lecturer at Imperial College London. MJC is Professor of Psychiatry at Imperial College London. FG is Senior Statistical Consultant. Statistical Advisory Service, School of Public Health, Imperial College London and leads on statistical advice. SP is Reader in Health Economics, Department of Health Sciences, The University of York and leads on economic evaluation. TW is Associate Professor of Mental Health Research, Middlesex University and leads on qualitative process. PID and DMW are Consultant Physicians and Clinical Toxicologists Guy’s and St Thomas NHS Foundation Trust (GSTT), PID is Director for Clinical Toxicology, GSTT and Professor of Clinical Toxicology, Faculty of Life Sciences and Medicine, King’s College, London, DMW is Service (clinical) Lead for Medicine, GSTT and Honorary Senior Lecturer, Faculty of Life Sciences and Medicine, King’s College, London.

Declaration of Interests.
None of the authors have any competing interests to declare.

Funding
The “Improving GHB withdrawal with baclofen” is funded by the National Institute for Health Research’s Research for Patient Funding programme: PB-PG-0212-27068.

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DMEC: Chair: Dr Louise Sell with Dr Sally Bradberry and members of the study team.

Trials management team: Anne Lingford-Hughes, Paul Dargan, David Wood, Fabiana Gordon, Owen Bowden-Jones, Steve Parrott, Tim Weaver, Project manager (Yash Patel) and other staff as required/appropriate.

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Figure 1

A.

- Planned withdrawal
  - n=60
    - 2 days prior to GHB withdrawal
      - Baclofen
        - Benzodiazepine + Baclofen
          - n=20
    - 2 days prior to withdrawal
      - Placebo
        - Benzodiazepine + Placebo
          - n=20

B.

- Unplanned withdrawal
  - N=28
    - Benzodiazepine + Baclofen
      - n=14
    - Benzodiazepine + Placebo
      - n=14

A: CNWL Club drug clinic – PLANNED (outpatient) withdrawal. N=60 (3 groups); B: GSTT clinical toxicology service- UNPLANNED (inpatient) withdrawal. N=28 (2 groups).
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