ANDREA-LD

Community led ANti-psychotic Drug REduction for Adults with Learning Disabilities (ANDREA-LD): A Randomised Double-blind Placebo Controlled Trial

Protocol

Version 7.0

This protocol has been authorised by:			
Dr M. Robling	SEWTU Director		
Name	**Role**	**Signature**	**Date**
Prof. M. Kerr	Chief Investigator		
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General Information This protocol describes the ANDREA-LD clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but PIs identifying patients for the first time are advised to contact the South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to SEWTU.

Compliance This trial will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

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Please contact the Trial Manager for general queries and supply of trial documentation

Randomisations:

Randomisation
To be carried out by the research team at SEWTU using an automated password protected web based system.

Clinical queries:

Clinical queries
All clinical queries should be directed to the Chief Investigator. If not available, the Trial Manager will direct the query to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and faxed to the Trial Manager within 24 hours upon becoming aware of the event (See section 13 for more details).

Table of Contents

Glossary of abbreviations

ABC	Aberrant behaviour checklist
ABS	Adaptive behaviour scale
AE	Adverse Event
ASC	Antipsychotic Side-effect Checklist
CA	Competent Authority
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRF	Case Report Form
CSRI	Client service receipt inventory
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trials of Investigational Medicinal Products
CU	Cardiff University
DISCUS	Dyskinesia identification system condensed user scale
DMEC	Data Monitoring Ethics Committee
EudraCT	European Clinical Trials Database
ICH	International Conference on Harmonization
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
HTA	Health Technology Assessment
IB	Investigator Brochure
IC	Informed consent
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
ISRCTN	International Standard Randomised Controlled Trial Number
HB	Health Board
LD	Learning disabilities
MHRA	Medicine and Healthcare products Regulatory Agency
MOAS	Modified overt aggression scale
MRC	Medical Research Council
NHS	National Health Service
NISCHR	National Institute for Social Care & Health Research
NIHR	National Institute for Health Research
PAS-ADD	Psychiatric assessment schedule for adults with developmental disability
PCT	Primary Care Trust
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
PRN	Pro re nata
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
SmPC	Summary Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measure

1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	1.1	05/02/13	ER	Incorporating Sponsors comments; 1. Informed consent (section 10.3) 2. Labelling patient notes (section 12.1) 3. 24 hour unblinding (section 12.1) 4. Storage of IMPs (section 12.1) 5. GP visits and appointments (section 14)
	1.2	06/02/2013	JT	Addition of consent by carers.
	1.3	06/02/2013	ER	Addition of 9 month assessments
1	2.0	19/06/2013	ER	1. Updated participant flow diagram (section 3.2) 2. Randomisation now being carried out by a member of research team rather than pharmacist (section 10.4) 3. Update to reflect a change in pharmaceutical manufacturers and pharmacy dispensing (section 12). 4. Revised expected baseline medication doses (table 1) 5. SAE contact details updated (section 13) 6. Time taken to complete assessments updated (tables 2 and 3 – section 14) 7. Members of the DMEC finalised (section 20.2)
2	3.0	04/07/2013	ER	1. The UKU has been replaced by the ASC to measure side effects. All reference to UKU has been replaced by ASC. 2. Detail of Practice Nurse training and visits included (section 14) 3. Higher strength risperidone tablets will no longer be used. Reference to 3 and 4mg risperidone tablets has been removed. 4. TSC members' names have been updated. 5. A number of small typing errors have been corrected. 6. Specified that the storage of IMP will not be temperature monitored (section 12). 7. One if the Co-Investigators contact details has been updated.
3	4.0	27/08/2013	ER	1. Section 7 – confirmation from MHRA that site has been added is not required so reference was deleted. 2. Sections 10.4 and 12.1 – details of unblinding have been updated to remove reference to 24 hour unblinding.

				3. Section 13.3 – Pharmacovigilance reporting procedures updated to reflect MHRA approved practice. 4. Section 14 – added detail of contents of Emergency Card. 5. Section 17 – End of trial definition refined. 6. Where reference has been made to time frames, calendar or working days have been defined throughout. 7. TSC member details updated.
4	5.0	21/01/2014	ER	1. Addition of study team member and updated contact details. 2. Clarification of reduction stages has been made clearer throughout (specifically section 6). 3. Section 7 – area for pilot recruitment redefined. 4. Section 8 – eligibility criteria has been slightly refined. 5. Section 9.1 – the use of the ABS as a screening measure has been clarified. 6. Section 9.3 – ABS should not have been listed as a secondary outcome measure. 7. Section 10.3 – Consent and capacity updated. 8. Section 13 - Updated to reflect MHRA and Sponsor approved wording. 9. Section 14. – Minor changes to GP contact and qualitative follow up. 10. Section 14.3 – Refined interview content and addition of participant interviews. 11. Section 16.1 – Definition of Per Protocol population. 12. Section 16.1.1 – No interim analysis. 13. Section 16.3 – Minor changes to cost effectiveness analysis wording. 14. Section 20.1 – TSC Carer member named.
5	6.0	08/05/2014	ER	1. Section 12.1 – Use of the NOMAD system for supplying IMP to participants safely. 2. Section 13.4 – Reporting pregnancy
6	6.1	13/10/2014	ER	1. Addition of study team member and updated contact details. 2. Section 3.2 - Flow diagram updated for clarity 3. Section 10.2 – Minor amendment to participant approach method. 4. Section 14.1/14.2 – Secondary outcome assessment moved from Baseline to Screening.

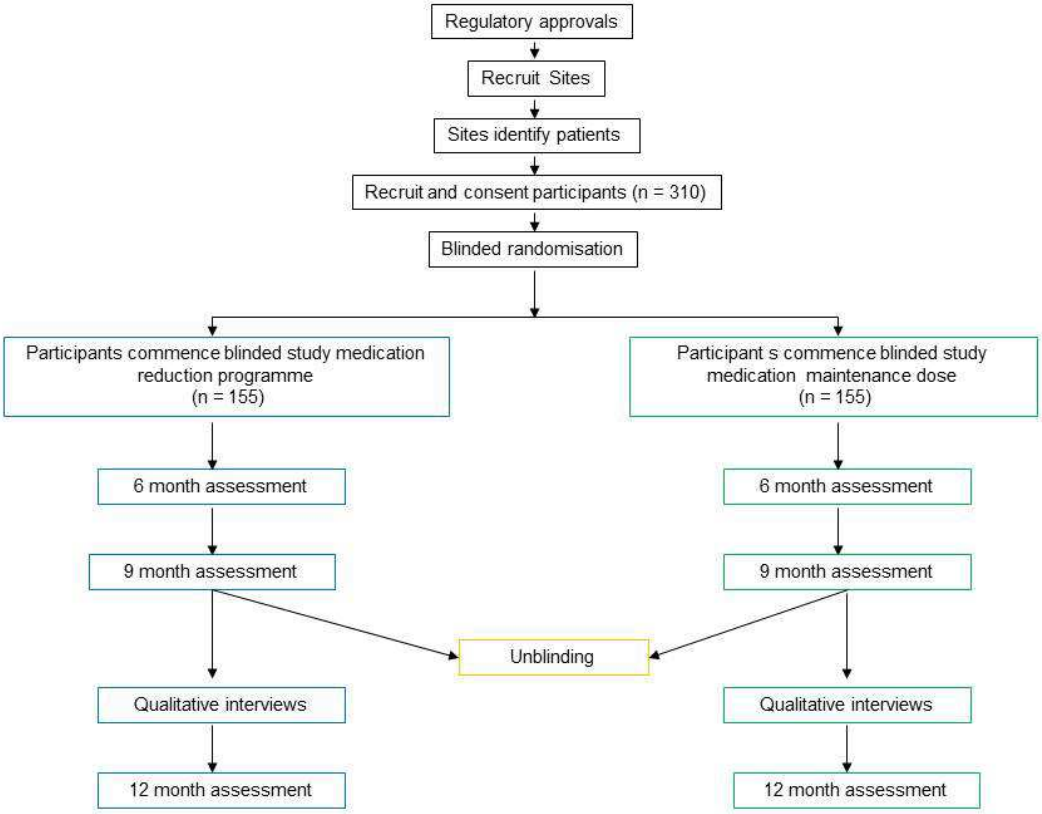
7	7.0	01/12/2014	ER	Following HTA approval: 1. Throughout, reference has been made to PIs as recruitment will now change to include community LD psychiatrists as PIs. 2. GP practices will act as PICs.

2 Synopsis

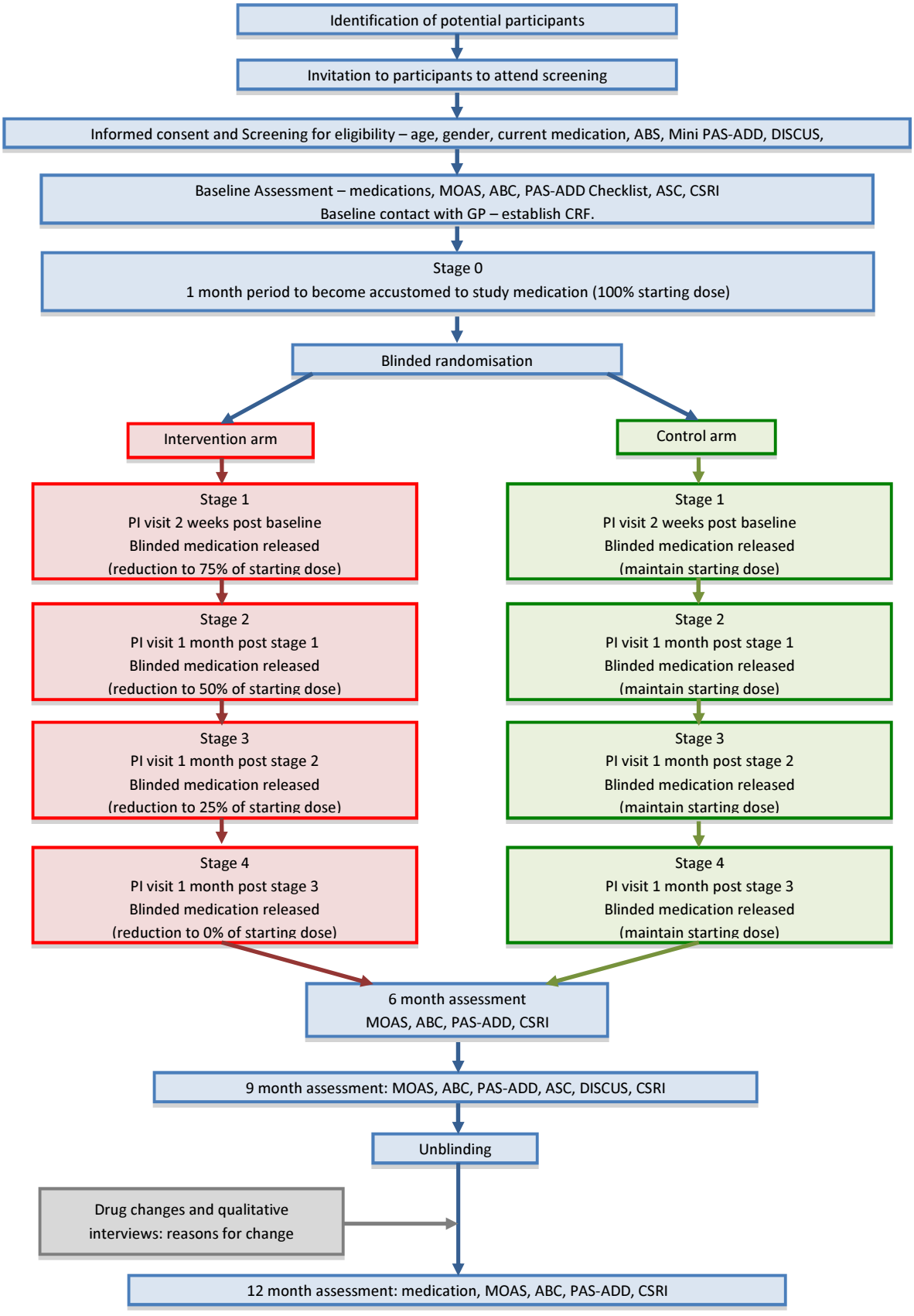
Acronym	ANDREA-LD
Trial design	Randomised double-blind placebo-controlled non-inferiority withdrawal trial
Trial participants	Adults with learning disabilities (LD) identified through LD registers prescribed one of two anti-psychotic drugs, haloperidol or risperidone, for treatment of challenging behaviour with no known current psychosis or previous recurrence of psychosis following prior drug reduction.
Planned sample size	310
Follow-up duration	12 months
Planned trial period	39 months
Primary objective	To evaluate the impact of a blinded anti-psychotic medication withdrawal programme for adults with LD without psychosis compared to treatment as usual.
Secondary objectives	Exploration of potential non-efficacy-based barriers to drug reduction in clinical practice
Primary endpoint	Scores on the MOAS nine months post-randomisation
Secondary endpoints	Other challenging behaviour, mental health, adverse effects of psychotropic medication, movement disorders, cost estimates at 9 and 12 months post-randomisation.
Investigational medicinal products	Risperidone and Haloperidol
Form	Tablet
Dose	Risperidone – 2mg, 1mg, 0.5mg Haloperidol – 5mg, 1.5mg, 0.5mg
Route	Oral

3 Trial summary & schema

3.1 Trial schema



3.2 Participant flow diagram



3.3 Trial summary

Background

Approximately 1 in 200 adults are recognised as having a learning disability. Illness in this population is high, including significant rates of challenging behaviour and mental illness. Use of psychoactive medication is high and there is particular concern over the use of anti-psychotic medication that is prescribed for reasons other than the treatment of psychosis. Control of challenging behaviour is the primary reason why such medications are prescribed despite the absence of good evidence for any therapeutic effect for this purpose. This problem is central to the intervention being evaluated in this trial.

Aim

The central research question to be addressed is whether anti-psychotic medication prescribed to adults with learning disabilities for the treatment of challenging behaviour can be withdrawn or reduced without behaviour or mental health deteriorating and treatment costs escalating.

Design

A 2 arm randomised double-blind placebo-controlled non-inferiority withdrawal trial. Treatment will be supported by a specially designed trial specific treatment and safety package. During the trial, those in the intervention arm will proceed through up to 4 monthly reduction stages within a 6 month period (although blinded, the PI has discretion to delay progression to the next step). Each reduction will be approximately 25% of the starting dose. In cases where 4 step downs are not possible, any reduction will always start at Stage 1. The control group will maintain baseline treatment. Treatment achieved at 6 months will be maintained for a further 3 months under blind conditions. At 9 months, the blinding will be broken for clinicians and participants and medication changes monitored over the 12 month period from baseline.

Population

We will recruit 310 adults with learning disabilities (LD) identified through LD registers prescribed one of two anti-psychotic drugs (risperidone or haloperidol) for treatment of challenging behaviour with no known current psychosis or previous recurrence of psychosis following prior drug reduction.

Outcome measures

The primary outcome is level of aggression as measured by the Modified Overt Aggression Scale (MOAS). Secondary outcomes are other challenging behaviour, mental health, adverse effects of psychotropic medication, movement disorders, cost estimates and percentage change in medication.

Duration and follow-up

After an initial recruitment pilot phase, assumptions will be examined to inform the next stage of recruitment..Participants will be assessed at 6, 9 and 12 months from randomisation.

4 Introduction

4.1 Background

The age-specific rate of registered learning disability in people 16 years and over in Wales is 0.47% [1] and adult users of learning disability services in England are also estimated to constitute 0.47% of the adult population[2]; making about 200,000 adults in the two countries combined. An audit of adults with learning disabilities in primary care in Wales (n=9,947) found that 29% were prescribed anti-psychotic medication[3]. An earlier and smaller primary care trial in England[4] found that 21% of 357 adults with learning disabilities were prescribed anti-psychotic medication. Applying the average of the two estimates to the number of people above suggests that there are 50,000 adults with learning disabilities in England and Wales who are prescribed anti-psychotic drugs.

The rate of prescription of anti-psychotic medication in this population far exceeds the estimated prevalence of psychosis (3-4%[5]). The discrepancy may be accounted for by the use of anti-psychotic medications for the treatment of behavioural problems, the commonest reason for their prescription[4 6 7]. Rates of prescription among samples of people with learning disabilities with challenging behaviour cluster around 50%[8 9] and may be as high as 80-95% among those in specially designated services[10 11]. Reducing the estimate above to take account of prescription of anti-psychotics for the treatment of psychosis results in about 42,000 people where these medications may be being prescribed to treat or control challenging behaviour.

Comparison of the Perry et al.[10] and Molyneux et al.[4] rates in primary care (29% & 21%) gives no reason to think that the prescription of anti-psychotics is declining. However, atypical newer generation anti-psychotics are replacing typical older medications. All of the most common medications reported by Molyneux at al.[4] were typicals. In contrast, Perry et al.[3] reported that now two of the three most common were atypicals. There were 4,714 prescriptions among the 2,891 people who were prescribed anti-psychotic medication in the latter audit, of which 2008 (43%) were for atypical medications. Romeo et al.[12] reported mean half-year medication costs for groups enrolled in a trial of risperidone and haloperidol as £127 and £8 respectively. Using these as estimates for the cost of all atypical and typical medications respectively, then full year treatment costs for the 2,891 people in the Perry et al. audit would be £553,328. Extrapolated to the 42,000 figure above gives an annual total cost of £8 million for England and Wales without including GP consultation or other NHS costs.

The effectiveness of anti-psychotic medications in treating or controlling challenging behaviour has not been demonstrated[13]. A Cochrane Collaboration review failed to find evidence to support this use[14] and a more recent review of 56 treatment trials found that the great majority lacked scientific rigour and the remainder found conflicting results[15]. A recent double-blind RCT exploring the impact on aggression of haloperidol (a typical anti-psychotic), risperidone (an atypical anti-psychotic) and placebo found that participants given placebo showed no evidence of worse response than participants assigned to either of the anti-psychotic drugs at any time point[16]. Accompanying economic evaluation concluded that the treatment of challenging behaviour among people with learning disabilities by anti-psychotic medication is not a cost-effective option[12].

Apart from a lack of therapeutic and cost-effective evidence for the treatment of challenging behaviour, concern about the high use of anti-psychotic medication for this purpose is related to the common occurrence of a range of possible adverse medication side-effects. These include possible adverse cardiovascular, including thromboembolism, central and autonomic nervous system and

endocrine function side-effects, including extrapyramidal side-effects, akathesia and other muscle or movement disorders, which may in the case of tardive dyskinesia or tardive akathesia become permanent[17]. Thus, the NHS currently commits considerable financial outlay to an unproven and expensive intervention which evidence suggests has a risk of pervasive negative impacts on the health status of the individuals concerned through cardiovascular, neurological and other serious adverse effects of medication.

4.2 Rationale for current trial

A number of drug withdrawal studies have investigated predictors of successful withdrawal from anti-psychotic medication[18 19] but are limited by being retrospective, non-random, uncontrolled or inadequately rigorous in measurement. A retrospective clinical audit investigating change from thioridazine for safety reasons among 119 adults with learning disabilities reported poor clinical outcomes: most were given alternative anti-psychotics, few withdrew, significant minorities experienced onset or deterioration in challenging behaviour or mental ill-health or adverse effects with the introduction of new drugs and costs to the specialist psychiatric service rose[20]. However, a randomised controlled withdrawal trial reported more positive results. Ahmed et al.[21] conducted a trial where 56 participants were randomised to an experimental group (n=36) and a control group (n=20). The experimental group were to receive drug reduction in four monthly stages within a six-month period between baseline and post-intervention evaluation. 33% of the former group completed full withdrawal and a further 19% had at least a 50% reduction; 48% had their medication reinstated to baseline levels after partial to full withdrawal. Drug reduction was not associated with higher challenging behaviour and drug reinstatement was not associated with either staff reported or directly observed measures of challenging behaviour. This trial prompts the need for a larger and properly blinded and controlled randomised trial of the impact of planned withdrawal on resulting drug dosage, behaviour, psychiatric symptoms, safety and the consequent costs of treatment.

The purpose of the proposed trial is to conduct a relatively large, blinded randomised controlled trial to investigate whether anti-psychotic medication prescribed to adults with learning disabilities for the treatment of challenging behaviour can be reduced or withdrawn entirely without adversely affecting their behaviour or mental health or causing a corresponding increase in financial costs. We propose to include patients receiving risperidone or haloperidol, as these are commonly-used and represent atypical and typical medications respectively. Both were evaluated by Tyrer et al.[16] as ineffective. Drug dosage will be standardized by expressing the daily dose as a percentage of the daily defined dosage. The trial will incorporate a range of outcome measures used in previous studies of this population and include an analysis of the economic consequences of the drug reduction programme. Moreover, as Ahmed et al.[21] found in an open trial that reinstatement of medication occurred for almost half of the sample but was unrelated to reported or directly observed changes in the level of challenging behaviour, this trial will compare the extent of medication change between blinded and unblinded conditions and explore the perceptions of clinicians and carers about medication usage.

5 Trial objectives

5.1 Primary objectives

The primary objective is to evaluate the impact of a blinded anti-psychotic medication withdrawal programme for adults with LD without psychosis compared to treatment as usual. We want to demonstrate that aggression, as measured at baseline, is no worse while participants are on significantly less anti-psychotics. The drug reduction programme will last six months. The primary outcome (aggression) will be assessed at 9 months (still blinded). Levels of aggression will be compared between the intervention (those with reduced medication) and control (those maintaining standard treatment) arms.

5.2 Secondary objectives

A secondary objective is to explore the potential non-efficacy-based barriers to drug reduction in clinical practice by informing all parties of the allocation (breaking the blinding) after the 9 month assessment and then track changes in medication usage for a further three months. This will be accompanied by qualitative telephone interviews with PIs and carers to gain their perceptions about medication usage and a final assessment of medication level and psychopathology at 12 months.

6 Trial design

The trial is a two arm randomised double-blind placebo-controlled non-inferiority withdrawal trial. 310 adults with learning disabilities without psychosis will be recruited and randomised to either the dose reduction arm (intervention arm, n=155) or the care as normal arm (control arm, n=155). Those in the intervention arm will proceed through four approximately equal reduction stages to full withdrawal within a six month period. The exact time to full withdrawal within that six month period will vary according to the participants' starting dose and the strengths of medication available. All in this arm will start their reduction at Stage 1 and continue until they reach 0mg. For most, each reduction will be approximately 25% of their starting dose. The control group will maintain baseline treatment, i.e continue with the medication regimen that they are receiving. All participants will undergo assessments at baseline, 6 months, 9 months and 12 months.

7 Centre and Investigator selection

A pilot trial using this design has not been conducted. Therefore, we will pilot the recruitment arrangements towards the end of the first six months in order to test the assumptions and the practicalities of the process. It will be conducted in areas where we gain R&D approval and are able to recruit Principal Investigators and sites soonest and will result in estimates of the proportion of sites that are willing to participate and the likely numbers of adults with learning disabilities who consent or have consent given on their behalf. This will allow better estimation of the total number of practices that will need to be approached and the size of the research territory required. The

intention would be to expand the territory incrementally should our initial assumptions be incorrect (e.g. if fewer than 1 in 6 agreed to participate).

A large number of GP practices in Wales (chiefly South East Wales) and England (predominantly South West) will be contacted for participation. Indicative data suggest that there will be about 1,900 adults with LD taking one of the two medications in this territory. GP practices will be recruited as either full sites or will act as patient identification centres (PICs) in order to identify patients who might be potentially eligible to take part in the trial. Community LD psychiatrists in these areas will also be contacted to act as PIs. Community LD psychiatrists will be supported to deliver IMP by hospital and community pharmacies in their area.

Before any site can begin recruitment a Principal Investigator (PI) at each site must be identified. The PI will be a General Practitioner or LD Psychiatrist and it will be their responsibility to take the lead in seeing patients as part of the trial for their site. The following documents must be in place and copies sent to the ANDREA-LD Trial Manager (see contact details above):

- The approval letter from the Centre's R&D Department, following submission of the Site Specific Information (SSI) form
- A signed Trial Agreement (PI and sponsor signature)
- Completed Signature List and Roles and Responsibilities document
- Completed contacts list of all site personnel working on the Trial
- Patient Information Sheet and covering letter (the latter to be on site headed paper)

Upon receipt of all the above documents, the ANDREA-LD Trial Manager will send a confirmation letter to the Principal Investigator detailing that the site is now ready to recruit patients into the trial. This letter must be filed in each centre's Site File. Along with this confirmation letter, the site should receive their trial pack holding all the documents required to recruit a patient into the ANDREA-LD Trial. Trial medication for a participant will be sent to their practice or pharmacy once the participant has been confirmed as eligible and their trial specific prescription has been drafted.

8 Participant selection

Adults with learning disabilities will be eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria. All queries about eligibility should be directed to the ANDREA-LD Trial Manager.

8.1 Inclusion criteria

Participants will:

i. Be adult (18 years or over).
ii. Have a learning disability as judged by administrative classification (e.g. on learning disability register, in receipt of an annual learning disability health check, in receipt of learning disability services).
iii. Currently be prescribed one of two anti-psychotic drugs, haloperidol or risperidone, for treatment of challenging behaviour.

8.2 Exclusion criteria

Other than the obverse of the inclusion criteria, participants will be excluded if:

i. They have a current diagnosis of psychosis,
ii. They have had a known recurrence of psychosis following previous drug reduction in the past 3 years,
iii. The clinician responsible for their treatment judges for any other reason that the participation in a drug reduction programme may be counter-indicated.
iv. As assessed by the research team, there is a lack of an individual to support completion of outcome assessments.

9 Outcome measures

9.1 Screening measure

Information collected will include age, gender, current medication and psychiatric history. In addition, adaptive behaviour will be assessed using the Adaptive Behaviour Scale (ABS[22]) as a means also to estimate IQ[23], as well as current mental health status which will be assessed using the Mini Psychiatric Assessment Schedule for Adults with Developmental Disability interviews (PAS-ADD interview[24]). The data gathered will be used to confirm inclusion and exclusion criteria so as to ensure that participants are adult, have an intellectual disability as defined by international criteria and do not have the psychiatric contraindications that would prevent participation. If required, clinical review will be undertaken for those exceeding thresholds for the ABS (a score that converts to an estimated IQ of above 70 using the method described by Moss and Hogg[23]) and/or the Mini PAS-ADD (a score of above 2).

9.2 Primary outcome measure

The primary outcome measure is aggression. This will be evaluated using the Modified Overt Aggression Scale (MOAS[25]). The MOAS rates four categories of aggression (verbal aggression, destruction of property, self-mutilation and physical aggression to others) each on a scale of 0-4 but then weighted by an ascending index of seriousness. The measurement here will be used in a non-inferiority comparison so a score difference of 3 or less will be taken as clinically non-significant.

9.3 Secondary outcome measures

Secondary outcome measures to be used at baseline, 6 month, 9 month and 12 month assessments:

Other challenging behaviour will be assessed using the Aberrant Behaviour Checklist (ABC[26]). This measure comprises 58 behaviours, each relating to one of five subscales.

Mental Health will be monitored using the Psychiatric Assessment Schedule for Adults with Developmental Disability Checklist (PAS-ADD[27]). The PAS-ADD is a 25 item questionnaire designed for use primarily with care staff and families. The scoring system includes threshold scores which, if exceeded, indicate the presence of a potential psychiatric problem in the scale's three diagnostic

domains (affective or neurotic disorder, possible organic condition and psychotic disorder). The proportions of people reaching threshold scores for possible mental ill-health will be compared.

Adverse effects of psychotropic medication will be assessed by the Antipsychotic Side-effect Checklist (ASC[28]) which comprises a list of the more common or clinically important side effects of antipsychotic treatment.

Movement disorders will be assessed by the Dyskinesia Identification System Condensed User Scale (DISCUS[29]). A psychometrically derived DISCUS threshold of 5 will be used.

Costs estimates of medication, health, social care and unpaid carer inputs by trial participants due to challenging behaviour or mental ill-health will be recorded using the Client Service Receipt Inventory modified for those with intellectual disability and used in a similar way (CSRI[12 30]).

The primary and secondary outcomes relating to challenging behaviour and mental health will be analysed for non-inferiority. Other secondary outcomes such as medication usage and adverse effects will be analysed for difference.

10 Recruitment and randomisation

10.1 Number of participants

A total of 310 participants will be recruited over a 15 month period. Participants' carers (where they have one) will also be recruited at the same time.

10.2 Recruitment process

Adults with learning disabilities will be identified and their treatment during the trial managed by the PI, with appropriate specialist back-up as necessary (see below).

Participating sites will be asked to identify all patients on their learning disability register currently receiving the target medications, risperidone or haloperidol. At this stage, the PIs will be asked to approach all possible participants except those with an identified psychotic illness (i.e., schizophrenia or bipolar disorder), a history of severe deterioration following drug reduction in the last three years or who are deemed unsuitable for a participation in a trial due to exceptional current circumstances (e.g. serious illness, bereavement of immediate family), providing them with an information sheet about the trial and how to indicate a willingness to be approached to participate (completion of an expression of interest form to be returned in a pre-paid envelope to the study team). The information sheet will be provided with a covering letter addressed to the patient. Should the patient be cared for by another person, it is anticipated that that person will handle any correspondences on their behalf. Patients (or their carer) may also be asked if their contact details can be passed to the study team so they can be contacted directly in order to discuss the trial.

Once an expression of interest form or contact details have been received, a member of the research team will contact the patient (or their carer if it has been sent by them on behalf of the patient), to discuss the study in more detail, identify key personnel, including legal representative for individuals where appropriate, and arrange a meeting in order to assess capacity and gain informed consent (from individuals with capacity or from legal representatives). Informed consent will also be gained

from carers for their participation in the trial. The research team will then conduct screening and baselines assessments with carers and participants

Those meeting the inclusion criteria will then be randomised to experimental reduction or control treatment as usual (i.e., maintenance of current medication level).

10.3 Informed consent

Some participants may be judged to have capacity to give informed consent but there will certainly be a proportion that will be judged to lack capacity. In such cases consent from a personal legal representative will be sought instead (failing that, a professional legal representative). All individuals will be judged individually at a screening assessment by members of the trial team who are professionals with considerable experience in assessing capacity in individuals with learning disabilities. On occasion, the assessment of capacity and consent procedure may be undertaken by the PI at site. Criteria for consent include: presumption of capacity and an assessment of understanding of the risks/benefits of the trial, the communication of results and confidentiality. Potential participants will be given a plain language and pictorial participant information sheet in advance of their meeting with the trial team in order that they might go over it with a carer or legal representative (as appropriate) in their own time and at their own speed.

Potential participants with capacity;
Upon meeting with the trial team, the trial and potential risks and benefits will be explained verbally in simple terms. Checks will be made frequently for understanding during the explanation. Once all questions have been answered and the individual is happy to take part, they will tick or initial each statement on the consent form as a means of indicating their consent and sign the form. The process will be witnessed and signed off by a carer who is independent of the research team. Participants can decide to withdraw their consent at any stage.

A small sample of participants with capacity may also be invited to take part in a qualitative interview at the end of the study (section 14.3). Capacity will again be assessed at this time.

Potential participants who lack capacity;
Where capacity is lacking, a similarly straightforward explanation of the trial and its potential risks and benefits will be given verbally to a personal legal representative or failing that, a professional legal representative. Neither the personal or professional legal representative must be connected with the conduct of the trial (e.g. the PI). That individual will be asked to give consent on the participant's behalf. Again, consent can be withdrawn at any stage. Legal representatives will be kept informed of all material changes to the trial or participant's condition so as to exercise their right of reviewing the person's participation in the trial.

Carers/PIs of potential participants;
The participant's carer will also give separate consent to completing some of the assessments designed to be completed by a third party and consent to taking part in the qualitative interviews at the end of the trial if selected.

PIs will also give consent to participate in the qualitative trial (see Section 14.3).

Risks and anticipated benefits;
Risk will be considered against the recognized risks of long term anti-psychotic medication and therefore the potential benefits of withdrawal. Benefits include: reduction of cardiovascular risk, in particular stroke, reduction of musculoskeletal risk from tardive dyskinesia, reduction in acute life threatening risk of malignant neuroleptic syndrome and a broad spectrum of psycho-social benefits from reduction of sedation, associated alertness and concentration and learning. Societal benefits would include increased contribution from adults with learning disabilities not constrained by unnecessary medication and reduced expenditure/resource use on unnecessary treatment and medical complications of long term anti-psychotic medication use. However, withdrawal has the *potential for the following dangers;*

i. *The emergence of tardive dyskinesia. Advice for PIs on the recognition, assessment and management approaches will be included in the detailed treatment and safety package prepared by the trial team.*
ii. *Emergence of unrecognised psychiatric illness. There remains a slight possibility that especially for those on very long term anti-psychotics that the drugs have masked an underlying mental illness. This, if present, is most likely to be an anxiety disorder. Advice for PIs on the recognition and assessment of psychiatric symptoms will be included in the detailed treatment and safety package prepared by the trial team. A clinical algorithm will be developed to support the primary care team to follow the appropriate treatment and care pathways. Clear guidance will be given for predicted scenarios in which unblinding may be necessary such as the emergence of psychotic symptoms.*
iii. *Deterioration in behaviour. Our previous study showed that measurable behavioural deterioration was uncommon following drug reduction but other studies have shown greater deterioration and carer concern can be high. Of course it is an understanding of this impact that is the core of this trial. Participants will be advised on assessing behaviour change by the PI support package. As behavioural signs and psychiatric symptoms for this population are intertwined, the clinical algorithm referred to above will also deal with behaviour change.*

Supporting secondary care services;
In the case of all individuals who are recruited through general practice and who have contact with learning disability services, contact will be made with their teams at the stage of initial assessment. We will describe the study protocol, explain the PI Support Pack and discuss the procedure for accessing the code break.

We do not anticipate that the study will provide a considerable impact on the current well-developed specialist learning disability services. These services will most probably already know many individuals involved in the study and we estimate that the chance of severe deterioration is small and that this small number of participants will be distributed across at least 6 health boards. It is possible that the study will raise the referrals to learning disability services as a greater awareness will be raised of the issue of anti-psychotic drug prescribing across primary care. Such referrals are a positive outcome, learning disability teams are skilled in drug assessment and regular assessment and reassessment is a key component of good clinical care.

10.4 Randomisation and unblinding

Following consent and baseline assessments, participants will be randomised to either the intervention arm (gradual reduction) or control arm (treatment as usual) on a 1:1 ratio. Randomisation will be carried out by a member of the study team using an automated password-protected web-based system. A randomisation form must be completed by the research team before initiating the automated randomisation system. Participant specific details will be entered so that randomisation may be balanced with respect to medication type and dosage. The programme will then be run and will allocate the participant to a treatment group.

This detail, along with a patient specific study prescription will then be transferred to the pharmacist responsible for dispensing the study medication. A unique trial number will be the primary identifier for all participants in the trial.

The South East Wales Trials Unit (SEWTU) will hold the master copy of randomisation (electronically). This is a double-blind trial; therefore neither the participant nor the treating clinician will know what allocation (gradual drug withdrawal or no drug withdrawal) the participant has received. The research team will have detailed records of all doses of study medication participants are currently taking for the purposes of unblinding.

Unblinding may be performed only after authorisation from the Chief Investigator or (if not available) an authorised Clinical Reviewer. In the event of an emergency, the treating clinician will have access to details of the participants' baseline dose (i.e. the dose at which they entered the study) and will be able to treat accordingly. The treating clinician will inform the PI of the emergency event. Upon knowledge of this event, the PI will complete an SAE form and send to SEWTU as detailed in section 13.2.

10.5 Screening logs

The trial team, PICs and PIs will complete approach logs detailing how many patients were provided with details of the trial. This will feed into a central screening log of all individuals who were ineligible and eligible but not consented.

11 Withdrawal & loss to follow-up

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. In all instances and in order to ascertain which aspect the participant wishes to withdraw from, withdrawal forms will be completed and sent to the trial team. Distinction will be made between:

1. Withdrawal from trial treatment
2. Withdrawal from trial follow-up
3. Withdrawal from entire trial and does not want data to be used.

If participants wish to withdraw from all aspects of the trial without giving reason, consent to use data already collected will be assumed unless otherwise specified. Care from health services will not be affected at any time by declining to participate or withdrawing from the trial. Any queries relating to potential withdrawal of a participant should be forwarded to the Trial Manager immediately.

Withdrawal from anti-psychotic medication has the potential for various dangers therefore a participant may withdraw or be withdrawn from trial treatment for the reasons listed in section 10.3

We will make every effort to reduce loss to follow-up using the methods listed below:

i. We will emphasise the importance of getting follow-up data to all participants at baseline and the different follow-up assessment points.
ii. Unless they have explicitly requested otherwise, all participants will be invited to complete follow-up questionnaires and attend follow-up appointments.
iii. We are seeing people face to face for all the assessments.
iv. We will arrange to complete follow-ups in the participants' homes or somewhere convenient if necessary.
v. We will have regular contacts in the two arms building relationships with participants. We will also send birthday cards to participants in both trial arms.
vi. We will obtain alternative contact details for participants so we can contact them or their carer directly to arrange follow-up.
vii. We will offer vouchers to thank carers, participants and PIs for taking part in the qualitative study.

12 Treatments

12.1 Treatment arms

The intervention group will proceed through up to four approximately equal reduction stages to full withdrawal within a six month period. The control group will maintain baseline treatment. Drugs will be supplied to establish blinding but treatment will remain PI led. Although blinded to whether medication is being reduced, the PI will retain discretion – in relation to participants in either arm – to delay progression to the next step (i.e. to maintain current medication level).

Sites will be supported by a detailed treatment and safety package showing clear clinical contact and decision making to support drug reduction. The Chief Investigator and Co-applicants will produce guidance focussing on how to respond to participant and carer queries, including those concerned with behavioural deterioration, emergent features of tardive dyskinesia or psychiatric symptomatology. The guidance will cover elements of history taking, examination, consultation with the research team, appropriate referral and information on the code-breaking practice. PIs will also be requested to add labels to participants' medical notes in order to flag the fact that they are taking part in this clinical trial.

Treatment achieved at 6 months will be maintained for a further 3 months under blind conditions. At 9 months, the blinding will be broken for clinicians and participants and responsibility for prescribing handed back to the PI. Medication changes and reasons for medication change will then be monitored for the final 3 months.

Supply of blinded medication:
In order to achieve effective blinding, both medications (risperidone and haloperidol) will be encapsulated. A range of tablets at different doses (haloperidol: 5mg, 1.5mg, 0.5mg; risperidone: 2mg, 1mg, 0.5mg) will be encapsulated based on estimates of the likely numbers of participants recruited on each medication at the common doses (see table 1). Encapsulated placebo medications identical in appearance to active medications will also be produced. All participants will experience a

change in supplied anti-psychotic medication at the outset of the study to ensure the number of tablets they take daily remains constant over the blinded period and the effective dose can be reduced across dose reduction steps.

Reflecting previous findings[3], manufacturing estimates are based on recruitment of 110 participants on haloperidol and 250 on risperidone (n=360; required sample size n=310), assuming that all participants achieve at least 50% reduction. In reality, the number of reduction steps achieved is likely to be much more variable, although this assumption allows for a reasonable degree of flexibility. Manufacturing estimates include provision of medications to all participants up to 9 months when the blinding is lifted.

Table 1 Estimated range of approximate starting doses

Risperidone	6-8mg	4-6mg	2-4mg	0.5-2mg
	Approx. 5%	Approx. 10%	Approx. 35%	Approx. 50%
Haloperidol	5-8mg	4-5mg	2-4mg	0.5-2mg
	Approx. 20%	Approx. 40%	Approx. 20%	Approx. 20%

The manufacturer, St Mary's Pharmaceuticals Unit (SMPU), will manufacture under their MIA(IMP) licence 35929 and supply to a patient specific order in a NOMAD system under the process of 'post QP certification labelling for safety purposes'. Patient specific orders will be issued by the research team following participants consent and randomisation. SMPU will keep detailed records of doses supplied and will then dispatch orders to site. It will be the responsibility of SEWTU to hold unblinding information and to perform the code break on approval from the Chief Investigator or authorised Clinical Reviewer.

Storage of blinded medication:

IMPs stored at sites will be kept separate from other non-study medicines. The storage area for study products must have limited access and be locked when not in use. Prescriptions will only be handed out to the patient/carer/legal representative by authorised site staff who will be listed in the site delegation log.

The IMP is to be stored at ambient temperatures at site therefore no temperature monitoring will be undertaken.

Sites will be responsible for the destruction of any unused study medication according to local procedure and only with the approval of the Trial Manager.

12.2 Dose modification for toxicity

Toxicity is not expected in this dose reduction trial.

12.3 Pre-medication

Use of all PRN (Pro Re Nata) medication will be permitted during this trial.

12.4 Interaction with other drugs

Drug reduction is unlikely to cause interaction however it will be recommended that participants taking warfarin undergo more frequent INR tests.

12.5 Permitted concomitant medications

All medication is permitted. Information on all concomitant medication will be collected by the research team.

13 Pharmacovigilance

13.1 Definitions

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and the subsequent amendment regulations (SI2006/1938) and ICH-GCP:

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease. Expected adverse events in this trial are reports of aggression and challenging behaviour.

Adverse Reaction (AR): Any noxious and unintended response in a clinical trial participant to whom an IMP has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Expected adverse reactions in this trial are motor disturbances and stereotypy.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* 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.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned

hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. A Serious Adverse Event for this trial is the occurrence of a psychotic episode.

Serious Adverse Reactions (SARs): Any Serious Adverse Event occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR): These are **SARs** which are classified as 'unexpected' i.e. an adverse reaction, the nature and severity of which is not consistent with the applicable product information (SmPC) for risperidone and haloperidol.

13.2 Causality

Most adverse events and drug reactions that occur in this trial, whether they are serious or not, may be due to drug reduction. They will not be toxicity related effects. The assignment of the causality should be made by the Principal Investigator responsible for the care of the participant using the definitions in the table below. The Chief Investigator (or Clinical Reviewer Delegate) will also be responsible for making an assessment of causality.

In the case of discrepant views on causality between the site and the clinical reviewer, the event will be handled at the highest event categorisation.

Table 2. Description of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial/intervention
Unlikely	There is little evidence to suggest there is a casual relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

13.3 Expectedness

The assessment of whether or not an Adverse Reaction is an expected reaction from the administration of the IMP will be provided by the Chief Investigator (or Clinical Reviewer Delegate), it will not be provided by the Investigator responsible for the care of the participant.

This assessment will be based on the approved Reference Safety Information for the IMP indicated.

13.4 Reporting procedures

All adverse events and pregnancies that occur during the 12 months that the participant is in the trial must be reported. Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning adverse event reporting should be directed to the trial coordination centre in the first instance. A separate Standard Operating Procedure will detail the process for reporting any adverse event. It is the responsibility of the PI to report all adverse events to SEWTU as delegated by the Sponsor. Upon receipt of a completed SAE form, the trial coordination centre (SEWTU) will send it for clinical review which will be completed as soon as possible and within 2 working days. Those authorised to carry out the clinical review on behalf of the Sponsor will include the Chief Investigator and appropriately qualified co-applicants (who shall be listed on the delegation log).

Participants and their carers will also be advised to contact either their treating clinician or the research team directly in the case of an adverse event.

Any exposure of a foetus to the IMP that occurs during the trial will be followed to termination or to term. In such situations, a new PIS and consent form must be used to re-consent the patient or partner for follow-up of pregnancy until term or termination. These must be kept in the TMF.

13.4.1 Non serious Adverse Reactions/Adverse Events (AR/AEs)

An adverse event consistent with the information set out in the SmPC (for risperidone or haloperidol as appropriate) will be considered expected.

Those events which are not expected, should be recorded on the relevant case report form and sent to the trial coordination centre as per the reporting timeframes laid out for SAE's (below).

13.4.2 Serious Adverse Events/Adverse Reactions (SAE/SAR)

All SAEs and SARs should be reported to the ANDREA-LD Trial Manager at SEWTU within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcomes and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. No assessment of expectedness will be provided by the Investigator responsible for the care of the participant.

Additional information should be sent within 5 calendar days if the reaction has not resolved at the time of reporting. All events should be followed up through to resolution.

Additionally, SEWTU may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. Information relating to them should instead be captured on the relevant CRF.

13.4.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the Sponsor's responsibility (which will be delegated to the Chief Investigator or named Clinical Reviewer) to make the determination of expectedness of an SAE based on the referenced safety information (RSI), and thus whether it is a SUSAR making the event subject to expedited reporting to the MHRA.

For all SAEs regardless of event categorisation, the staff at the site should:

Complete the SAE case report form and send it immediately (within 24 hours, preferably by fax), signed and dated to SEWTU together with relevant treatment forms and anonymised copies of all relevant investigations.

OR

Contact the ANDREA-LD Trial Manager by phone and then send the completed SAE form to the trial coordination centre, SEWTU by fax within the following 24 hours as above.

SEWTU will notify the MHRA and main Research Ethics Committee (REC) of all SUSARs occurring during the trial according to the following timelines, where day zero is defined as the date the SAE form is initially received at SEWTU:

- SUSARs which are fatal or life-threatening must be reported not later than 7 calendar days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 calendar days.
- SUSARs that are not fatal or life-threatening must be reported within 15 calendar days of the sponsor first becoming aware of the reaction.

All Investigators will be informed of all SUSARs occurring throughout the trial. Principal Investigators will report any SUSARs and/or SAEs as required by their Local Research Committee and/or Research and Development Office.

SEWTU will also produce a DSUR annually detailing SARs/SUSARs/other safety information reported in the trial for each year the trial is open.

13.5 Urgent Safety Measures (USMs)

An urgent safety measure is an immediate change in a trial procedure or temporary halt to a trial procedure, put in place prior to authorisation by the MHRA, main REC and Sponsor in order to protect participants from any immediate hazard to health and safety following new safety information (SAE or other information received from an external source). Under the Medicines for Human Use (Clinical Trials) Regulations the Sponsor, Chief Investigator or Principal Investigator may

carry out USMs to protect participants from immediate harm. Any urgent safety measure relating to this trial must be notified to the Sponsor, ethics committee and MHRA within 3 days of the action being taken in the form of a substantial amendment.

Contact details for reporting SAEs

Fax: 02920 687612 attention ANDREA-LD Trial Manager

Tel: 02920 687608 (Mon to Fri 09.00 – 17.00)

14 Trial procedures

Recruitment and follow-up:

PIs and PICs will identify adults on their practice LD register or by opportunistic consultation/specialist referral. They will then refine this search to patients being prescribed Risperidone or Haloperidol and remove those with active psychosis (current symptoms of psychosis other than challenging behaviour) or who have had a recurrence of psychosis following drug reduction in the last 3 years. Patients will also be removed from the list if the PI deems that they would be unsuitable for a trial due to exceptional current circumstances (e.g., serious illness, bereavement in immediate family).

PICs will then pass details of any identified patients to the local community LD psychiatrist who is acting as PI for the trial.

PIs will then see those patients and provide details of the study or alternatively, will send them a letter inviting them to participate in the study. They will provide an information leaflet and response form which can be returned to the study team in a pre-paid envelope. The response form will indicate that the individual/carer agrees to be contacted and gives contact details.

Piloting:

The recruitment arrangements will be piloted towards the end of the first six months in order to test the assumptions and the practicalities of the process. This pilot will be conducted in areas where R&D approval for specific sites is gained soonest and will result in estimates of the proportion of general practices that are willing to participate and the likely numbers of adults with learning disabilities who consent or have consent given on their behalf. This will allow better estimation of the total number of sites that will need to be approached and the size of the research territory required. The end of this period will mark the beginning of another 6 month phase where recruitment from community learning disabilities psychiatry will be initiated in addition to the use of PICs and the already open GP sites. This phase will also be a pilot of this new method of recruitment and will end with a review of the assumptions being tested.

PI training:

PIs will be given full training in how to identify potential participants and all aspects of their involvement in the trial. They will be trained in the trials support package. Once a patient has consented to take part in this trial, the PI will ensure that this is made clear on the patients' medical notes should any other clinician at the practice see the patient at any other time.

PI visits/contact:

Participants in both trial arms (intervention and control) will have 5 appointments with the PI in total. The first 4 will take place in the two weeks preceding the release of each new batch of blinded medication and will be approximately 28 calendar days apart. Where face to face appointments cannot be held, the PI may consult over the telephone. It will be the participating PIs responsibility to provide participants with details of each of these appointments at the first visit, record them on and appointment card which is to be given to the participant or their carer and to remind them of the appointment nearer the time of the visit to ensure attendance. The site will also be responsible for re-arranging any appointments as necessary. The appointment card will also contain PI contact details, an emergency number for participants or carers to use should they need to and a reminder of the amount of medication (risperidone or haloperidol) the participant was on when they started the study. It is important that the PI is the first point of contact for participants or carers should there be any concern. The fifth PI visit will be when the PI unblinds the participant as to which treatment arm they had been allocated at 9 months post baseline.

Practice Nurse/Pharmacy training:

Practice Nurses and pharmacies will be given full training in all aspects of their involvement in the trial. This includes taking receipt of study IMP, ensuring it's correctly stored, distributing it to patients, taking receipt of any unused IMP and ensuring its safe destruction according to local procedure.

Practice Nurse/Pharmacy visits:

Participants (or their carer/representative) in both trial arms (intervention and control) will collect their prescribed study medication from the Practice Nurse/pharmacy monthly until the blind is broken at 9 months. At each of these visits, the Practice Nurse/pharmacy will take receipt of any unused medication from the previous prescription before distributing any new medication.

14.1 Data collection/assessment

Eligibility data will be collected at screening. Full data will be collected at baseline and post-intervention which will fall approximately 9 months from randomisation. Data on medication and psychopathology (MOAS, ABC, PAS-ADD) and costs (CSRI) will also be obtained at 6 months. Final assessment of medication and psychopathology (MOAS, ABC, PAS-ADD) and costs (CSRI) will be taken at 12 months. Drug changes after unblinding and a qualitative follow-up of reasons for drug change will be undertaken after 12 months. All data collection will be done face to face at site. Home visits may be made if the participant is not able to make it to site. The SEWTU Lone Working Policy will be adhered to at all times.

Table 3. Assessment timings and participant involvement.

Assessment Time Points	Measures and data collection	Participant involved	Estimated time to complete appointment
Screening (S)	Age, gender, current medication, ABS, Mini PAS-ADD	Carer	1.5 hours
	DISCUS	Participant	
Baseline (B)	Medication, MOAS, ABC, PAS-ADD Checklist, CSRI	Carer	1.5 hours

	ASC	Carer	
6 month (6m)	MOAS, ABC, PAS-ADD, CSRI	Carer	1.5 hours
9 month (9m)	MOAS, ABC, PAS-ADD, DISCUS, ASC, CSRI	Carer	1.5 hours
12 month (12m)	Medication, MOAS, ABC, PAS-ADD, CSRI	Carer	1.5 hours

14.2 Follow-up

Details of outcomes and follow up time points can be seen in Table 4 and are the same for both experimental and control groups.

Table 4. Outcome measures

Outcomes	Measure	When	Estimated time to complete assessment
Adaptive Behaviour	Adaptive Behaviour Scale (ABS)	S	40 mins
Mental Health	Psychiatric Assessment Schedule for Adults with Developmental Disability Checklist (PAS-ADD)	S*, B, 6m, 9m, 12m	30 mins
Adverse effects of psychotropic medication	Antipsychotics Side-effects Cheklist (ASC)	B, 9m	15 mins
Movement disorders	Dyskinesia Identification System Condensed User Scale (DISCUS)	S, 9m	7 mins
Aggression	Modified Overt Aggression Scale (MOAS).	B, 6m, 9m, 12m	5 mins
Other challenging behaviour	Aberrant Behaviour Checklist (ABC)	B, 6m, 9m, 12m	10 mins
Costs	Client Service Receipt Inventory [modified] (CSRI)	B, 6m, 9m, 12m	10 mins

S* The PAS-ADD used at this time point is the 'mini' version rather than the 'checklist' version.

14.3 Qualitative study

We propose to undertake qualitative telephone interviews with a proportion of carers, PIs and participants who have taken part in the trial. One of the main purposes of these interviews is to establish reasons for medication changes in the unblinded phase of the trial. This will help to establish how carers or PIs attribute behavioural changes to the reduction of medication. The interviews will therefore take place at the end of the unblinded stage of the trial. The interviews will be designed to ascertain: (a) views about participating in the study, (b) reasons for any partial or full reinstatement of medication after unblinding, (c) views about anti-psychotic medication use to treat or control challenging behaviour for the participant in particular, and the patient group in general.

We will aim to interview 60 of the 310 carers and the corresponding PI. It is hoped that both parties will agree to take part in these paired interviews but accept that this is not guaranteed. The sample will be selected purposefully incorporating participants that have been on both the withdrawal and maintaining current prescription arms of the trial, and participants that have had their medication changed after unblinding and those who have not had their medication changed after unblinding following the illustrated sample strategy (Table 5).

Table 5: Qualitative interview sampling strategy

	Intervention arm: withdrawal of medication	Placebo arm: no withdrawal of medication
Carers of participants who have their medication changed after unblinding	15	15
Carers of participants who do not have their medication changed after unblinding	15	15

Within these categories, primary carers will be selected from those participating in the trial to ensure a representation from geographical area (LHB/CCG). Carers selected will be reminded at the 12 month assessment that they had consented at baseline to participate in the interview and asked if they are still happy to take part. If they do still agree to take part in the interview, they will be informed that they will be contacted by telephone to arrange a suitable time for the interview to take place. If a carer declines an interview, another carer from within that category will be selected.

The participant's PI will be sent a letter of invitation to a telephone interview and an information sheet. Interviews are expected to take up to 30 minutes. PI interviews will focus on a) PI views of the support package; b) views about how the patient and carer(s) managed during the trial period; c) reasons for any partial or full reinstatement of anti-psychotic medication used to treat or control challenging behaviour for their patient in particular, and the patient group in general.

We also hope to interview a proportion of participants of the ANDREA-LD trial. Those taking part will be required to have the capacity to provide consent for a face-to-face interview. Interview topics will focus on a) participants reasons for participating in the trial; b) how they felt they managed during the trial period; c) their views about taking medicines to help with their behaviour.

Carers and participants who agree to take part in an interview will be offered a £10 High Street shopping voucher to thank them for their time and considered views. PIs who participate in interviews will be offered £50. With the participants' consent, all interviews will be audio-recorded, transcribed and anonymised.

15 Statistical considerations

15.1 Randomisation

The web-based randomisation system will be designed by a database programmer and the trial statistician and will be based on the method of minimisation. Allocations will be stratified by recruitment source (General Practice/Community LD Psychistry) and balanced with respect to medication type (risperidone/haloperidol) and dose: low (less than 4mg for risperidone, less than 5mg for haloperidol) / high (at least 4mg for risperidone, at least 5mg for haloperidol). A random component, set at 80%, will be used alongside the minimisation procedure to increase the integrity of the minimisation process.

15.2 Sample size

We will aim to randomise 310 participants (155 per group) in total. This will provide 90% power to fit a one-sided 95% confidence interval around the difference in mean MOAS scores between groups nine month post-randomisation. This sample size assumes a non-inferiority margin of 3, a standard deviation of 8 (i.e. an effect size of 0.375) and is adjusted to allow for 20% attrition.

16 Analysis

16.1 Main analysis

Study populations:
Three different study populations will be considered, with all three confirming non-inferiority before non-inferiority is concluded:

Complete Case Population (CC): All randomised participants whose 9 month follow-up MOAS score (primary outcome) is known.

Intention-to-Treat Population (ITT): All randomised participants. For those with missing MOAS scores at 9 month follow-up, multiple imputation will be used to impute missing responses.

Per Protocol Population (PP): For the purposes of our primary analysis, a per-protocol population must be defined a priori. This population will consist of participants:

1. With complete outcome data (i.e. a response to the MOAS at 9 month follow-up)
2. Who have not withdrawn from study treatment
3. That were either:
    a. Allocated to the control group and have not experienced any reduction in their study medication (this would be deemed a protocol violation, as the control group are meant to maintain their starting dose)
    b. Allocated to the intervention group and have reduced their study medication at least once (i.e. have, at the very least, progressed from the Stage 0 baseline run-in period to the Stage 1 first reduction period)

Statistical analysis:

The primary analysis will compare MOAS scores at 9 month follow-up between the two trial arms. An Analysis of Covariance (ANCOVA) model, with baseline MOAS score and variables balanced on / stratified by at randomisation (medication type, dosage and recruitment source) controlled for as covariates, will be fitted. Using the estimates from this model, a one-sided 95% confidence interval of the adjusted mean difference in MOAS scores at 9 month follow-up (Intervention-Control) will be calculated. Non-inferiority will be concluded if the limit of the confidence interval is less than 3 in all study populations. If necessary, MOAS scores will be transformed prior to analysis to fulfil assumptions of normality.

A Complier Average Causal Effect (CACE) analysis will be performed as a secondary analysis of the primary outcome, to obtain an ITT estimate in the treatment adherent. Adherence will be discussed, with definitions agreed, before analysis takes place.

If non-inferiority is concluded, a superiority analysis of the difference in MOAS scores between trial arms will be performed in the CC and ITT populations. A two-sided 90% confidence interval will be calculated using the estimates obtained from the ANCOVA (specified above).

All secondary analyses (anti-psychotic medication use, other challenging behaviour, mental health, adverse effects, movement disorders), will be performed using the CC population, with those secondary outcomes assessed for non-inferiority (challenging behaviour and mental health) and adverse effects also analysed using the PP population. Non-inferiority margins for secondary analysis will be agreed in the trial's statistical analysis plan prior to any analysis taking place. Variables will be transformed to fulfil the assumption of normality prior to analysis if necessary. All analyses will control for variables balanced on / stratified by at randomisation.

Potential moderators of the effect of the intervention on MOAS score (e.g. age, gender, medication type, adherence with intervention) will be explored in multivariable analyses using interaction terms. Aggression levels will be modelled using the repeated measures methods to explore changes over time.

16.1.1 Sub-group & interim analysis

There is no planned interim analysis.

16.2 Qualitative analysis

Data from the transcribed telephone interviews will be subject to thematic analysis. Thematic analysis is a useful approach for answering questions about the salient issues for particular groups of respondents or identifying typical responses. It is essentially a comparative process, by which the various accounts are coded into themes and sub-themes and then compared with each other to classify those themes that recur or are common in the dataset. The thematic framework will be derived both from themes from the interview schedule and themes that emerge from the interviews. The thematic framework will be developed and agreed by members of the research team. We will use NVIVO (qualitative data analysis software) to assist with the management and analysis of the data. A proportion of the interviews (25%) will be double coded by a second researcher to ensure reliability of the coding.

16.3 Cost effectiveness analysis

The main economic evaluation will be cost-effectiveness analysis conducted from two viewpoints: (1) health and social care agencies (2) health and social care agencies and unpaid carers. Three main categories of costs will be analysed:

i. medication costs;
ii. medication costs, aggregated health and social care costs, consisting of inpatient admissions, outpatient appointments and A&E contacts and community-based health and social care contacts;
iii. medication costs, aggregated health and social care costs and cost of time spent care giving by relatives and friends in the case of the latter viewpoint.

We will collect comprehensive data on all health, social care and other services used by individuals included in the study using a tailored version of the Client Service Receipt Inventory. Services will be costed as long-run marginal opportunity costs (LRMC) using national figures[31]. For services where national figures are not available or not suitable we will calculate best estimates of LRMC values. The

National Health Service Schedule of Reference Costs[32] will be used to estimate cost of outpatient attendances. The unit cost of medications will be obtained from the British National Formulary. We will also collect data on time inputs of care by family and other unpaid carers. Costs associated with time spent by friends or relatives providing support will be estimated using the unit costs of a local authority care worker[31].

Costs will cover the period from baseline to 6 months (end of full treatment withdrawal period), 6-9 months (three months following full treatment withdrawal period) and 9-12 months (three months following unblinding). Cost per individual over 9 months and 12 months in both treatment groups will then be derived. The MOAS score will be used as the primary measures of effectiveness in a series of cost-effectiveness analyses.

As cost data are likely to be skewed and to explore if unobserved difference in service use at baseline between the allocation groups may result in differences in cost between treatment groups, regression analysis using bootstrapping will be conducted, adjusting for baseline covariates (MOAS score, baseline costs and variables balanced on / stratified by at randomisation - medication type, dosage and recruitment source). We will use one-way sensitivity analyses to examine robustness of the findings to (a) changes in the unit costs of informal support, (b) analyses based on all randomised participants whose 9 month follow up MOAS score is known (CC population) and (c) analyses based on all randomised participants (ITT population).

The cost-effectiveness of the treatment groups will be compared through the calculation of incremental costs effectiveness ratios (ICERs), defined as the difference between trial arms in mean costs divided by the difference in mean effects. In the event that the experimental reduction group has lower costs and better outcome than its comparator it will be interpreted as the dominant treatment and where the experimental reduction group has higher costs and worse outcome than the comparator treatment, the experimental reduction group will be dominated by the comparator.

If one treatment group is both more effective and more costly than its comparator, tradeoffs will need to be considered. The approach that will be employed to reveal the nature of these trade-offs will be to plot a cost-effectiveness acceptability curve (CEAC) for each cost-outcome combination[33 34]. Non-parametric bootstrapping for the costs and effectiveness data will be used to generate the joint distribution of incremental mean costs and incremental effects. It shows the likelihood of one treatment arm being seen as cost-effective relative to another treatment arm given different (implicit monetary) values placed on incremental outcome improvements.

16.4 Data storage & retention

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network. Files will only be accessible to researchers responsible for the running of the trial and the Chief Investigator (CI). All procedures for data storage, processing and management will comply with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to researchers and the Chief Investigator. The Trial Statistician will carry out the analyses. All essential documents generated by the trial will be kept in the Trial Master File. Archiving and access to archive will be managed in accordance with the Standard Operating Procedures of the South East Wales Trials Unit (SEWTU).

17 Trial closure

The end of the trial will be considered as the date on which the completion of any follow-up monitoring and data collection occurs.

18 Regulatory issues

18.1 CTA

This trial has Clinical Trials Authorisation from the UK Competent Authority: MHRA. Reference 21323/0040/001-0001.

18.2 Ethical and governance approval

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

The study protocol has been submitted to a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority for review and approval. A favourable multi-centre ethical opinion for this trial was given by the REC for Wales prior to commencement of any trial procedures. Site specific assessments were conducted by Trust/CCG/HB R&D Departments in line with current permissions systems in the UK.

Research governance approval will be granted by Research and Commercial Division Cardiff University. All substantial protocol amendments will be approved by the REC responsible for the trial, in addition to approval by NHS R&D (and MHRA approval if applicable to the amendment). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events, it will not be recommenced without reference to the REC responsible for the trial.

The outcome of the trial (e.g. completed) will be reported to the REC responsible for the trial within 90 calendar days of completion of the last participant's final study procedures. In the event of the trial being prematurely terminated a report will be submitted to the REC responsible for the trial within 15 calendar days.

A summary of the Clinical Trial report will be submitted to the REC responsible for the trial within 1 year of completion of the last participant's final study procedure.

18.3 Ethical conduct of the trial

The Chief Investigator and Co-Investigators shall be responsible for ensuring that the clinical trial is performed in accordance with the following:

- Declaration of Helsinki (Seoul, 2008: Appendix 1).
- ICH Harmonised Tripartite Guidance for Good Clinical Practice.

- The Medicines for Human Use (Clinical Trials) Regulations 2004 [26] (Statutory Instrument 2004 No. 1031) as amended by the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (Statutory Instrument 2006 No. 1928 and No. 2984) and Amended Regulations 2008 (Statutory Instrument 2008 No. 941).
- Research Governance Framework of Health and Social Care (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005)

18.4 Consent

PIs will make initial contact with potential trial participants or their carers. This may be through a routine appointment or through an audit of their records. Potential trial participants or their carers will complete an expression of interest form to indicate their agreement to be approached by a member of the research team or they will contact SEWTU directly to express an interest in the trial. SEWTU will make an appointment for them to meet with the research team and send an information sheet in advance. During the appointment the researcher will assess capacity and seek informed consent (if they are eligible) after they have had time to read and understand the information sheet and had adequate time to ask questions about the trial. Participation in the trial will involve consent to be randomised to one of the two arms of the trial and to data collection (assessments, medical history etc). Informed consent will also be sought from the carer for their participation in the assessments. Separate consent will be sought from those taking part in interviews. Withdrawal of consent will have no detrimental impact on current and future treatment.

18.5 Confidentiality

The Chief Investigator and the research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998.

18.6 Indemnity

Cardiff University will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the trial design and/or in respect of the protocol authors/research team. Cardiff University does not provide compensation for non-negligent harm.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

18.7 Trial sponsorship

Cardiff University will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS local Health Boards in Wales and the Clinical Commissioning Groups in England that are taking part in this trial. All responsibilities delegated by the Sponsor to SEWTU will be detailed in the Memorandum of Understanding.

18.8 Funding

The trial is funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA). As an offer of thanks for their time, carers who agree to take part in a telephone interview will be offered a £10 High Street shopping voucher while PIs who participate will be offered £50.

18.9 Audits & inspections

The trial is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor. As this study is classified as a Clinical Trial of an Investigational Medicinal Product (CTIMP), it may also be participant to inspection by the MHRA.

19 Trial management

19.1 Project Team (PT)

The PT will consist of the co-ordinating team within SEWTU and WCLD and will meet weekly to discuss the day-to-day issues that arise from the study. All important discussions will be relayed to the Trial Management Group for final decision.

19.2 Trial Management Group (TMG)

The TMG will consist of the Chief Investigator, Co-applicants, Trial Manager, Trial Statistician, Trial Administrator and Sponsor representative. The role of the TMG is to help set up the trial by providing specialist advice, input to and comments on the trial procedures and documents (information sheets, protocol etc). They will also advise on the promotion and running of the trial and deal with any issues that arise. The TMG will meet either face-to-face or using audio-conferencing facilities, monthly throughout the course of the study. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

20 Data monitoring & quality assurance

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

20.1 TSC (Trial Steering Committee)

The TSC will be established and will meet annually consisting of an independent chair and 7 other independent members. All appropriate disciplines have been covered in choosing the TSC members. The TSC will be chaired by Professor Anna Cooper (Professor of Learning Disabilities, Glasgow University) who is a specialist learning disabilities psychiatrist and has conducted research in the prescription and reducing of anti-psychotic medication among this population. She is trained in 'good clinical practice' and has experience as Principal Investigator on MHRA approved trials. Members will be a Consultant Clinical Psychologist (Professor Eric Emerson, Professor of Disability & Health Research, Centre for Disability Research, Lancaster University) who has also conducted research in the prescription and reduction of anti-psychotic medication among this population, a statistician (Dr Alan Montgomery, Professor of Medical Statistics and Clinical Trials, University of Nottingham), a general practitioner (Prof Irwin Nazareth, Dept of Primary Care & Population Health, University College London), an officer of a parent and service user representative organisation (Mr Wayne Crocker, Mencap Cymru), carer (Pauline Young) and two service users (Mr Jonathan Richards and Mr Joe Powell) who are both leading members of the All Wales People First. The first meeting will be before the trial commences to review the protocol and arrange timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TSC will provide overall supervision of the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

20.2 DMEC (Data Monitoring Ethics Committee)

A separate Data Monitoring Ethics Committee (DMEC) will be convened which will review unblinded data and make recommendations to the TSC about safety. This committee will consist of three independent members, including at least one clinician and a statistician. DMEC members will be required to sign up to the remit and conditions as set out in the DMEC Charter.

(1) Dr Angela Hassiotis – Chair (Reader & Hon Consultant Psychiatrist)

(2) Dr Umesh Chauhan (Independent GP)

(3) Dr Alan Watkins (Statistician)

21 Publication policy

All publications and presentations relating to the trial will be detailed in the publication policy which will be drafted and authorised by the Trial Management Group. It will state principles for publication, describe a process for developing output, contain a map of intended outputs and specify a timeline for delivery. The publication policy will respect the rights of all contributors to be adequately represented in outputs (e.g. authorship and acknowledgments) and the trial to be appropriately acknowledged. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Trial Coordination Centre.

22 Milestones

6 months prior up to start:	Initial preparation - including information leaflets, collation of measures, MHRA and ethical approval, application for R&D approvals, staff job descriptions and initial recruitment processes.
Months 1-4:	Preparation of intervention - including support package and specialist learning disability service support arrangements and preparation of blinded medication (NB manufacture can continue into month 8).
Months 1-6:	Preparation for data collection including CRF and database design.
Months 7-14:	Recruitment pilot. Testing assumptions of recruiting via GP sites only.
Months 14-16:	Continued recruitment and set up of next pilot phase.
Months 16-21	Recruitment pilot II. Inclusion of recruitment via community learning disability psychiatry and use of GP practices as PICs.
Months 21-32:	Continued recruitment - with adjustment of strategy if necessary as indicated by pilot.
Months 10-32:	Baseline assessments - completed in month 21.
Months 11-33:	Intervention – drug reduction programme completed for all in experimental arm by month 33.
Months 19-41:	Post-intervention assessments – completed in month 30.
Months 22-44:	Qualitative follow-up study and final assessments – completed in month 44.
Month 44:	Completed data collection.
Month 46:	Completed data analysis.
Month 46:	Completed reporting and dissemination.

23 References

1. Unit LGD. Learning disability minimum dataset, 2011.
2. Emerson E, Hatton C. People with learning disabilities in England. Lancaster: Centre for Disability Research, Lancaster University, 2008.
3. Perry JL, Kerr M, Felce D, Bartley S, Tomlinson J. Monitoring the public health impact of health checks for adults with a learning disability in Wales. Cardiff: Public Health Wales, 2010.
4. Molyneux P, Emerson E, Caine A. Prescription of psychotropic medication to people with intellectual disabilities in primary health-care settings. J Appl Res Intellect 1999;**12**(1):46-57
5. Cooper SA, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. Brit J Psychiat 2007;**190**:27-35 doi: DOI 10.1192/bjp.bp.106.022483[published Online First: Epub Date]|.

6. Clarke DJ, Kelley S, Thinn K, Corbett JA. Psychotropic-Drugs and Mental-Retardation .1. Disabilities and the Prescription of Drugs for Behavior and for Epilepsy in 3 Residential Settings. J Ment Defic Res 1990;**34**:385-95
7. Robertson J, Emerson E, Gregory N, Hatton C, Kessissoglou S, Hallam A. Receipt of psychotropic medication by people with intellectual disability in residential settings. J Intell Disabil Res 2000;**44**:666-76 doi: DOI 10.1046/j.1365-2788.2000.00307.x[published Online First: Epub Date]|.
8. Emerson E, Alborz A, Kiernan C, et al. The HARC challenging behaviour project report 5: Treatment, management and service utilisation. Manchester: Heston Adrian Research Centre, University of Manchester, 1997.
9. Kiernan C, Reeves D, Alborz A. The Use of Antipsychotic-Drugs with Adults with Learning-Disabilities and Challenging Behavior. J Intell Disabil Res 1995;**39**:263-74
10. Perry J, Felce D, Allen D, Meek A. Resettlement Outcomes for People with Severe Challenging Behaviour Moving from Institutional to Community Living. J Appl Res Intellect 2011;**24**(1):1-17 doi: DOI 10.1111/j.1468-3148.2010.00567.x[published Online First: Epub Date]|.
11. Robertson J, Emerson E, Pinkney L, et al. Treatment and management of challenging behaviours in congregate and noncongregate community-based supported accommodation. J Intell Disabil Res 2005;**49**:63-72 doi: DOI 10.1111/j.1365-2788.2005.00663.x[published Online First: Epub Date]|.
12. Romeo R, Knapp M, Tyrer P, Crawford M, Oliver-Africano P. The treatment of challenging behaviour in intellectual disabilities: cost-effectiveness analysis. J Intell Disabil Res 2009;**53**:633-43 doi: DOI 10.1111/j.1365-2788.2009.01180.x[published Online First: Epub Date]|.
13. Scheifes A, Stolker JJ, Egberts ACG, Nijman HLI, Heerdink ER. Representation of people with intellectual disabilities in randomised controlled trials on antipsychotic treatment for behavioural problems. J Intell Disabil Res 2011;**55**:650-64 doi: DOI 10.1111/j.1365-2788.2010.01353.x[published Online First: Epub Date]|.
14. Brylewski J, Duggan L. Antipsychotic medication for challenging behaviour in people with intellectual disability: a systematic review of randomized controlled trials. J Intell Disabil Res 1999;**43**:360-71 doi: DOI 10.1046/j.1365-2788.1999.043005360.x[published Online First: Epub Date]|.
15. Matson JL, Neal D. Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: An overview. Res Dev Disabil 2009;**30**(3):572-86 doi: DOI 10.1016/j.ridd.2008.08.007[published Online First: Epub Date]|.
16. Tyrer P, Oliver-Africano PC, Ahmed Z, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. Lancet 2008;**371**(9606):57-63 doi: Doi 10.1016/S0140-6736(08)60072-0[published Online First: Epub Date]|.
17. Baumeister AA, Sevin JA, King BH. Neuroleptics. In: Reiss S, Aman MG, eds. Psychotropic medication and developmental disabilities: The internatinal consensus handbook. Columbus, Ohio: Ohio State University, 1998:133-50.
18. Branford D. Factors associated with the successful or unsuccessful withdrawal of antipsychotic drug therapy prescribed for people with learning disabilities. J Intell Disabil Res 1996;**40**:322-29 doi: DOI 10.1111/j.1365-2788.1996.tb00637.x[published Online First: Epub Date]|.
19. Luchins DJ, Dojka DM, Hanrahan P. Factors Associated with Reduction in Antipsychotic Medication Dosage in Adults with Mental-Retardation. American Journal on Mental Retardation 1993;**98**(1):165-72
20. Stevenson CJ, Rajan L, Reid G, Melville C, McGilp R, Cooper S-A. Withdrawal of antipsychotic drugs from adults with intellectual disabilities. Irish Journal of Psychological Medicine 2004;**21**(3):85-90
21. Ahmed Z, Fraser W, Kerr MP, et al. Reducing antipsychotic medication in people with a learning disability. Br J Psychiatry 2000;**176**:42-6

22. Nihira K, Leland H, Lambert N. *Adaptive Behaviour Scale - Residential and Community*. Second ed. Austin, Texas: Pro-ed, 1993.
23. Moss S, Hogg J. Estimating IQ from adaptive behaviour information in people with moderate or severe intellectual disability. J Appl Res Intellect 1997;**10**(1):61-66
24. Prosser H, Moss S, Costello H, Simpson N, Patel P, Rowe S. Reliability and validity of the Mini PAS-ADD for assessing psychiatric disorders in adults with intellectual disability. J Intell Disabil Res 1998;**42**:264-72 doi: DOI 10.1046/j.1365-2788.1998.00146.x[published Online First: Epub Date]|.
25. Oliver PC, Crawford MJ, Rao B, Reece B, Tyrer P. Modified Overt Aggression Scale (MOAS) for people with intellectual disability and aggressive challenging behaviour: A reliability study. J Appl Res Intellect 2007;**20**(4):368-72 doi: DOI 10.1111/j.1468-3148.2006.00346.x[published Online First: Epub Date]|.
26. Aman MG, Singh NN. *The Aberrant Behaviour Checklist*. New York: Slosson Educational Publications, 1986.
27. Moss S, Prosser H, Costello H, et al. Reliability and validity of the PAS-ADD checklist for detecting psychiatric disorders in adults with intellectual disability. J Intell Disabil Res 1998;**42**:173-83 doi: DOI 10.1046/j.1365-2788.1998.00116.x[published Online First: Epub Date]|.
28. Dott SG, Weiden P, Hopwood P, et al. An innovative approach to clinical communication in schizophrenia: the approaches to schizophrenia communication checklists. CNS spectrums 2001;**6**(4):333-8
29. Kalachnik JE, Sprague RL. The Dyskinesia Identification System Condensed User Scale (Discus) - Reliability, Validity, and a Total Score Cutoff for Mentally-Ill and Mentally-Retarded Populations. J Clin Psychol 1993;**49**(2):177-89
30. Beecham J, Knapp MRJ. Costing psychiatric interventins. In: Thornicroft GJ, Brewin CR, Wing JK, eds. Measuring Mential Health Needs. London: Gaskell, 1992:200-44.
31. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: PSSRU, 2010.
32. Health Do. National Health Service schedule of reference costs 2010. Secondary National Health Service schedule of reference costs 2010 2010. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140.
33. Vanhout BA, Al MJ, Gordon GS, Ruten FFH. Costs, Effects and C/E-Ratios Alongside a Clinical-Trial. Health Econ 1994;**3**(5):309-19 doi: DOI 10.1002/hec.4730030505[published Online First: Epub Date]|.
34. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Brit J Psychiat 2005;**187**:106-08 doi: DOI 10.1192/bjp.187.2.106[published Online First: Epub Date]|.