A pilot randomised controlled trial of community led anti-psychotic drug reduction for adults with learning disabilities.

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Competing interests:

Prof. Kerr reports personal fees from Johnson and Johnson outside the submitted work. Dr. Deslandes and previous Cardiff and Vale University Health Board department received an honorarium from Janssen-Cilag Ltd for a speaking engagement in 2014 and funding for conference registration fees in 2015. Prof. Hood is a member of the NIHR CTU Standing Advisory Committee and a member of the HTA General Board.

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Abstract

Background

Data suggests approximately 50,000 adults with learning disabilities in England and Wales are currently prescribed antipsychotic medication. Illness in this population is high, including significant rates of challenging behaviour and mental illness but there is particular concern over the use of anti-psychotics 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.

Objectives

To assess the feasibility of recruitment and retention, and explore non-efficacy based barriers to a blinded anti-psychotic medication withdrawal programme for adults with LD without psychosis compared to treatment as usual. A secondary objective was to compare trial arms regarding clinical outcomes.

Design

A two arm individually randomised double blind placebo controlled drug reduction trial.

Setting

Recruitment was through community learning disability teams in South East Wales and South West England.

Participants

Adults with learning disabilities (LD) prescribed risperidone, for treatment of challenging behaviour with no known current psychosis or previous recurrence of psychosis following prior drug reduction.

Intervention

A blinded drug reduction programme leading to full withdrawal within six months. The control group maintained baseline treatment. Treatment achieved at six months was maintained for a further three months under blind conditions leading to breaking the blind at nine months following final data collection.

Main outcome measures

Feasibility outcomes were: (i) number and proportion of GP practices/community LD teams that progressed from initial approach to recruitment of participants (ii) number and proportion of recruited participants who progressed through the various stages of the study. Trial arms were also compared regarding clinical outcomes; Modified Overt Aggression Scale (MOAS); Aberrant Behaviour Checklist (ABC); PAS-ADD checklist; Antipsychotic Side-effect Checklist (ASC); Dyskinesia Identification System Condensed User Scale (DISCUS); Client Service Receipt Inventory (CSRI); use of other interventions to manage challenging behaviour; use of as required (PRN) medication; level of psychotropic medication use.

Results

Of the 22 participants randomised, 13 (59%) achieved progression through all four stages of reduction. Follow-up data at six and nine-months was obtained for 17 participants – 10 intervention and seven control (77% of those randomised). There were no significant changes in participants' levels of aggression or challenging behaviour at the end of the study. There were no expedited safety reports.

Limitations

Recruitment was challenging largely due to difficulty in identifying appropriate persons to consent and carer concerns regarding re-emergence of challenging behaviour. Reduced recruitment meant the full trial became an exploratory pilot study.

Conclusions

Results indicate that drug reduction is possible and safe. However concerns about taking part were likely exacerbated by limited availability of alternative (behavioural) interventions to manage behaviour therefore focused support and alternative interventions are required. The results of the qualitative study provide important insights into the experiences of people taking part in drug reduction studies that should influence future trial development.

Future work

We recommend that guidance is produced to support practitioners, carers and patients in reducing antipsychotic medication.

Study registration

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Study funding

The NIHR HTA program.

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List of Abbreviations

A&E	Accident and Emergency
ABC	Aberrant Behaviour Checklist
ABS	Adaptive Behaviour Scale
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASC	Antipsychotics Side-effects Checklist
ASD	Autism Spectrum Disorder
CACE	Complier Adjusted Causal Effect
CC	Complete Case
CCG	Clinical Commissioning Group
CEAC	Cost Effectiveness Acceptability Curves
CI	Chief Investigator
CI	Confidence Interval
CLDT	Community Learning Disabilities Team
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTIMP	Clinical Trial of an Investigational Medicinal Product
CV	Curriculum Vitae
DH	Department of Health
DISCUS	Dyskinesia Identification System Condensed User Scale
DMEC	Data Monitoring Ethics Committee
ETC	Excess Treatment Costs
EU GMP	European Union Good Manufacturing Practice
GCP	Good Clinical Practice
GP	General Practitioners
HB	Health Board
HTA	Health Technology Assessment
ICER	Incremental Cost effectiveness Ratio
IMP	Investigational Medicinal Product

IQ	Intelligence Quotient
IQR	Interquartile Range
ITT	Intention To Treat
LD	Learning Disability
LRMC	Long-Run Marginal opportunity Costs
MAR	Medication Administration Record
MCA	Mental Capacity Act
mg	milligram
MIA(IMP)	Manufacturers licence for IMP
MITT	Modified Intention To Treat
MOAS	Modified Overt Aggression Scale
NHS	National Health Service
NICE	National Institute of Care Excellence
NIHR	National Institute of Health Research
OR	Odds Ratio
PAS-ADD	Psychiatric Assessment Schedule for Adults with Developmental Disability
PCT	Primary Care Trust
PI	Principal Investigator
PIC	Participant Identification Centre
PP	Per Protocol
PRN	Pro Re Nata
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SMPU	St Mary's Pharmaceuticals Unit
SpR	Specialist Registrar
SSC	Service Support Cost

TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

Scientific Summary

Background

There are approximately 200,000 adults in England and Wales with a registered learning disability (LD). Rates of antipsychotic medication prescribing in this population are high (approximately 50,000 adults with LD), and far exceeds estimated prevalence of psychosis (3-4%). It is known however that antipsychotics are commonly prescribed for challenging behaviour and prescription rates for adults with LD cluster around 50%. There is little evidence to support the effectiveness of antipsychotic medications for this indication however, and side effects include: cardiovascular events, central/autonomic nervous system and endocrine function side-effects, akathesia and other movement disorders, weight gain and increased risk of type 2 diabetes. The recent NICE guidance acknowledges the limited evidence to support use of antipsychotic medication for management of challenging behaviour in learning disability, and states that antipsychotics should only be prescribed if psychological interventions and/or treatment for comorbid conditions have been unsuccessful, or there is significant risk to the individual or others.

There has been a recent drive from NHS England to review antipsychotic prescribing in this population, as a result of the Winterbourne Review. The Royal College of Psychiatrists has also issued a report on psychotropic drug prescribing in this population, recommending regular review of treatment response and side effects. There is some existing although limited evidence from unblinded studies that these medications can be safely reduced or withdrawn, without a corresponding increase in challenging behaviour.

Objectives

The primary objective for the trial as originally designed was to evaluate the impact of a blinded antipsychotic medication withdrawal programme for adults with LD without psychosis compared to treatment as usual. More specifically, to confirm whether withdrawal could be safely achieved without a corresponding increase in aggression, as indicated in previous non-blinded studies. The primary outcome (aggression) was to be assessed at baseline and nine months (blinded) with levels of aggression compared between arms. A secondary objective was to explore potential non-efficacy-based barriers to drug reduction in clinical practice via qualitative interviews with Principal Investigators (PIs), carers and participants. However, ANDREA-LD is reported here as an exploratory pilot trial (see

Methods below) and the primary objectives revised to assess feasibility of recruitment and retention, and explore non-efficacy based barriers to reduction. A secondary objective was to compare trial arms regarding clinical outcomes.

Methods

ANDREA-LD was designed as a large scale non-inferiority trial of an antipsychotic withdrawal programme in primary care. However, due to significant challenges (see Chapter 3), the focus of recruitment shifted to community learning disability teams. The trial closed early and is reported as an exploratory pilot study. The study population was adults (18+ years) with recognised learning disabilities without psychosis, prescribed risperidone or haloperidol for challenging behaviour. However, the number of potential participants prescribed haloperidol was much lower than anticipated and so only those taking risperidone were recruited. Follow up was reduced from 12 months to nine. Informed consent was provided by participants themselves if judged to have capacity, or by a personal (or professional if required) legal representative.

Interventions

Participants in the intervention arm progressed through up to four approximately equal reduction stages to full withdrawal within a six-month period, while the control group maintained baseline treatment. All trial medication was encapsulated to maintain the blind. Sites were supported by a detailed treatment and safety package. Treatment achieved at six months was maintained for a further three months under blind conditions. At nine months, following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Outcome measures

Screening

IQ and current psychosis were assessed at screening using The Adaptive Behaviour Scale (ABS) and the Mini Psychiatric Assessment Schedule for Adults with Developmental Disability interviews (PAS-ADD interview) respectively. Participants were eligible provided they did not score above 70 on the ABS and/or above 2 on the Mini PAS-ADD.

Main outcome measures

Feasibility outcomes were: (i) number and proportion of GP practices/community LD teams that progressed from initial approach to recruitment of participants (ii) number and proportion of recruited participants who progressed through the various stages of the study. We also compared trial arms regarding the following clinical outcomes:

- Modified Overt Aggression Scale (MOAS: primary outcome as originally designed); level of psychotropic medication use; the Aberrant Behaviour Checklist and Psychiatric Assessment Schedule for Adults with Developmental Disability Checklist (PAS-ADD) to monitor mental health, at six and nine months post-randomisation
- The Antipsychotic Side-effect Checklist (ASC) and the Dyskinesia Identification System Condensed User Scale (DISCUS) to assess movement disorders; use of other interventions to manage challenging behaviour (e.g. seclusion, physical restraint), at nine months post-randomisation
- Use of as required (PRN) medication
- The Client Service Receipt Inventory (CSRI) was modified for use in intellectual disability to collect data on services used and support received by participants.

Study visits and assessments

Participants had five appointments with the PI, four to review appropriateness of progression to the next stage and finally for unblinding. Participants/carers collected study medication from the Practice Nurse/pharmacist monthly. Eligibility data was collected at screening. All data collection was face-to-face either at site or during home visits.

Statistical methods

Randomisation and unblinding

Randomisation was based on minimisation and allocations balanced on medication dose (less than 4mg risperidone / at least 4mg risperidone) and recruitment source (General Practice/Community LD Psychiatry). Participants were randomised in a 1:1 ratio. Non-routine unblinding was performed only after authorisation from the Chief Investigator or Clinical Reviewer.

Sample size

The planned sample size was 310 participants (90% power, 95% confidence interval, non-inferiority margin of 3, effect size of 0.375) and was adjusted for 20% attrition. However, in the revised pilot study no specific sample size was set and 22 participants were recruited over 19 months until early closure of the trial.

Quantitative analysis plan

The original proposed primary analysis focused on a comparison of MOAS scores at nine month follow-up between arms. However, for the pilot study, we focused on estimating the following feasibility outcomes: number and proportion of primary care practices/community LD teams that progressed from initial approach to recruitment of participants; number and proportion of recruited participants who progressed through the various stages of the study. We also compared trial arms at six and nine months post-randomisation on; (i) MOAS (ii) level of psychotropic medication use (iii) ABC (iv) PAS-ADD, and the following outcomes at nine months only: ASC, DISCUS, and other interventions to manage challenging behaviour. Information was also collected on use of as required (PRN) medication over the study period, and costs and service utilisation at six and nine months post-randomisation.

Analysis of recruitment and retention outcomes was descriptive. Clinical outcomes were compared between arms using regression models (linear or logistic), adjusting for baseline scores and balancing variables (dose and recruitment route). MOAS score at nine months post-randomisation was fitted with a two-sided 90% confidence interval in order to reflect the planned primary analysis, and individual trajectories for MOAS scores plotted and described, with particular attention paid to individuals whose MOAS scores changed by at least four points (i.e. clinically meaningful).

The original proposed cost effectiveness analysis focused on comparison of trial arms through calculation of incremental costs effectiveness ratios (ICERs), defined as the difference between trial arms in mean costs divided by the difference in mean outcome (MOAS score) over nine months. It was proposed to conduct the main cost effectiveness analyses from health and social care agencies and a wider societal perspective to include health and social care agencies and unpaid carers. To inform the cost effectiveness analyses, it was proposed that comprehensive data on health, social care and other services used by individuals included in the study, using a tailored version of the CSRI. However, planned cost-effectiveness analyses were not carried out, given the very small sample size.

Qualitative study

We undertook qualitative interviews with a proportion of carers, PIs and participants. A key aim was to gain insight into non-efficacy based barriers to drug reduction in clinical practice, as well as attributions of behavioural changes in relation to perceived reduction of medication. Interviews were scheduled to take place during the unblinded phase of the trial between nine and 12 months. For the pilot study, these were brought forward to four to six-months post-randomisation. The purpose of the interviews was to ascertain: (a) views about participating in the study (b) reasons for partial or full reinstatement of medication after unblinding (c) views about anti-psychotic medication use to control challenging behaviour. PI interviews focused on views of the support package and how patients/carers managed during the trial. Interview topics for participants focused on (a) reasons for participating (b) how they felt they managed during the trial (c) views about taking medicines to help with behaviour. All interviews were audio-recorded, transcribed, anonymised and analysed using thematic analysis facilitated by NVivo.

Results

Recruitment and retention

Approximately 500 potential sites were approached to take part, of which 79 expressed an interest (the majority were community LD teams). Thirty-six participants were screened and 22 randomised (68.8%: 80% of those screened and 100% of those who completed a baseline assessment from primary care and 74.1%/95% from community LD teams). Participants were well balanced with respect to variables collected pre-randomisation and clinical scores were generally low at baseline. The majority of participants were on a total daily dose of risperidone less than 4mg, and were recruited from community LD teams.Arms were well balanced with respect to these key variables. Of 22 participants randomised, 13 (59.1%) achieved progression through all four stages of reduction (potential reduction in control arm). Follow-up data at six and nine-months post-randomisation was obtained for 17 participants (77.3% of those randomised) with 10 intervention and seven control participants followed up. Participants who progressed to Stage 4 tended to be older, have higher MOAS, ABC-lethargy, and ABC-hyperactivity scores at baseline, were more likely to have their challenging behaviour managed using PRN medication prior to randomisation, and were less likely to have a diagnosis of ASD.

Clinical outcomes

MOAS total scores were higher at six-months than baseline, and higher nine-months post-randomisation than at six months, remaining higher in the intervention arm in both MITT and PP populations. For most participants, change in MOAS total scores was slight. However, five participants experienced a change from baseline in MOAS total score of at least 4. Scores for secondary outcome measures were also generally slightly higher in the intervention arm at six and nine months, including other challenging behaviour (ABC subscales), mental health (PAS-ADD), movement disorders (DISCUS; nine months only), and PRN use (although diary completion rates were low). Reported side effects were higher in the control arm, and antipsychotic medication use at six and nine months was lower in the intervention arm. It is difficult to draw conclusions from the limited data on use of other interventions to manage challenging behaviour. Four adverse events (AE) and one serious adverse event (SAE) were reported.

Qualitative results

The results suggest that carers, participants, and clinicians agreed on the importance of the research question, that study procedures were acceptable, and support from the research team was good. Generally there was a feeling that the study should be supported by the learning disability community but also an awareness of the challenges involved. Issues that caused more concern included: consenting arrangements (particularly carers' concerns about acting as a personal legal representative), whether the study inclusion and exclusion criteria were appropriate (e.g. whether to include participants with autism) and the size of the over-encapsulated study medication. In addition, carers in particular reported participants experienced a number of negative behaviours during the study period. However, these behaviours were not always attributed to drug reduction, even by carers, and many behaviours were not new within the study period.

Conclusions

Recruitment of this population, within primary care in particular, is challenging. In general this is largely due to difficulty in identifying appropriate persons to consent and carer concerns regarding re-emergence of challenging behaviour. In primary care, low numbers of potentially eligible participants per practice and GP concerns relating to safety were also a significant factor. Carer and GP concerns were likely exacerbated by limited availability of alternative (behavioural) interventions to manage behaviour. It is not therefore, feasible to recruit this population to a drug reduction programme within primary care. Although recruitment in community learning disability teams was more successful, it is still unlikely that the target sample size would have been achievable in a reasonable timeframe, without provision of alternative interventions to manage behaviour.

Although it is not possible to draw firm conclusions from the small sample size in the current trial, results indicate that drug reduction is possible and likely to be safe in the majority of cases. However, low level changes were observed in behavioural and mental health measures and in the development of movement disorder in some participants, suggesting that focused support and alternative interventions are required. We therefore recommend that guidance is produced to support practitioners, carers and patients in this process. The results of the qualitative study provide important insights into the experiences of people taking part in drug reduction studies that should influence future trial development. Firstly it seems that reported barriers to recruitment did not reflect the experience of those recruited to the study. Study

procedures were acceptable and complex issues such as blinding and overwrapping of medication were not particularly problematic.

The results also provide information of value to those wishing to conduct further high quality interventional RCTs in people with a learning disability. We have shown that carers and participants coped well with fairly complex trial processes. This study suggests that whilst there is a clear need, primary care services are not currently well equipped to deliver this type of intervention. This is important for other studies which should explore the clinical competencies needed and how these apply to primary care if that is where the target population predominantly receive healthcare. We also recommend that measures are put in place to improve recruitment to studies in people with a learning disability (see Chapter 7). Despite increasing guidance on the use of antipsychotic medication, no guidance exists for reducing this medication. This pilot study has provided valuable insights into the development of such guidance for clinicians and carers,and beyond this to support improved access to trials for people with a learning disability.

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Plain English summary

Currently, approximately 50,000 adults with learning disabilities in England and Wales are prescribed antipsychotic drugs. For these individuals, there are frequent occurrences of physical and mental illness and challenging behaviour. Sometimes antipsychotics are prescribed to control challenging behaviour rather than for psychosis despite any real evidence that the drugs help with this. This study was designed to see if it was possible to take individuals off an antipsychotic called risperidone without their behaviour worsening.

Participants were randomly split into two groups and either given their normal amount of risperidone or gradually reduced amounts over six months. They were followed up for nine months. Carers, participants and their doctors were not told which group they were in until the end of the study.

Recruitment was mainly from Community Learning Disabilities Teams across South Wales and South West England. All 22 participants were adult and had carers to complete questionnaires about their behaviour before, during, and after the study to allow for detection of any changes.

Recruitment was difficult and fewer people took part than originally planned. This was largely due to difficulties in identifying appropriate persons to consent and concerns from carers about challenging behaviour re-emerging. Although there were no significant changes in levels of aggression or challenging behaviour at the end of the study we can't provide a definite answer to the main question given the small number who took part. The study has provided important insights into the experiences of people taking part which should influence future trial development.

1 Introduction

1.1 Prevalence of learning disability and antipsychotic prescribing

The age-specific rate of registered learning disability in people 16 years and over in Wales is 0.47% (Local Government Data Unit 2011) and adult users of learning disability services in England are also estimated to constitute 0.47% of the adult population;[1] 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 antipsychotic medication.[2] An earlier and smaller primary care study in England[3] found that 21% of 357 adults with learning disabilities were prescribed antipsychotic 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 antipsychotic drugs. Comparison of the Perry et al. (2010) and Molyneux et al. (1999) rates in primary care gives no reason to think that the prescription of antipsychotics is declining. Indeed, a more recent North American survey found that 45% of 4,069 individuals with a learning disability who lived in the community and received services from the New York State Office for People with Developmental Disabilities received antipsychotic medication: 39% atypical drugs and 6% typical drugs.[4]

The rate of prescription of antipsychotic medication in this population far exceeds the estimated prevalence of psychosis (3-4%).[5, 6] The discrepancy may be accounted for by the use of antipsychotic medications for the treatment of behavioural problems, the commonest reason for their prescription.[3, 7-9] Rates of prescription among samples of people with learning disabilities with challenging behaviour cluster around 50% [10, 11] and may be as high as 80-95% among those in specially designated services.[12, 13] After taking account of prescription of antipsychotics for the treatment of psychosis, about 42,000 of the estimated 50,000 above may be receiving these medications to treat or control challenging behaviour. In a recent study of primary care prescribing commissioned by Public Health England,[14] it was estimated that between 30,000 and 35,000 adults with a learning disability were being prescribed either an antipsychotic, an antidepressant or both without a recorded diagnosis of psychosis or affective disorder. This estimate equates to 16.2% of adults in England registered as having a learning disability by their GP.

1.2 Effectiveness and cost-effectiveness of antipsychotics for challenging behaviour

The effectiveness of antipsychotic medications in treating or controlling challenging behaviour has not been demonstrated.[15] Their use may therefore, in some cases, be considered mistreatment.[9] A Cochrane Collaboration review failed to find evidence to support such treatment[16] and a review of 56 treatment trials found that the great majority lacked scientific rigour and the remainder found conflicting results.[17] A more recent review found evidence to suggest a number of atypical antipsychotics are effective in treating challenging behaviour in adults with intellectual disability and autism[18] although the authors acknowledge that tolerability and the balance of benefit versus adverse effects is unclear in this population. A recent cohort study of mental illness, challenging behaviour and psychotropic drug use in intellectual disability also concluded that more evidence with regards safety and efficacy of these medications is needed, when prescribed for challenging behaviour without a corresponding diagnosis of severe mental illness. A double-blind RCT exploring the impact on aggression of haloperidol (a typical antipsychotic), risperidone (an atypical antipsychotic) and placebo found that patients given placebo showed no evidence of worse response than patients assigned to either of the antipsychotic drugs at any time point.[19] Accompanying economic evaluation concluded that the treatment of challenging behaviour among people with learning disabilities by antipsychotic medication is not a cost-effective option.[20]

Perry et al. (2010) reported that there were 4,714 prescriptions among the 2,891 people who were prescribed antipsychotic medication, of which 2008 (43%) were for atypical medications. Romeo et al. (2009) 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 prior to the start of this trial produced an estimate of the full year treatment costs for the 2,891 people in the Perry et al. audit of £553,328. Extrapolated to the 42,000 figure above gave an annual total cost of £8 million for England and Wales without including GP consultation or other NHS costs. However, medication costs are subject to change over time and that of risperidone has decreased since these calculations were made.

1.3 Known side effects of antipsychotic medications

Apart from a lack of therapeutic and cost effectiveness for the treatment of challenging behaviour, concern about the high use of antipsychotic medication for this purpose is related to the common occurrence of a range of possible adverse medication side-effects in learning disability populations.[21] 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.[22] Moreover, certain atypical medications are associated with an increased risk of obesity and diabetes.[23, 24] Mahan et al. (2010) found that individuals taking psychotropic medication had significantly higher scores on the *Matson Evaluation of Drug Side-effects* scale in four domains: Skin, Allergies, and Temperature, and Central Nervous System: General, Parkinsonism/Dyskinesia, and Behavioural/Akathesia.

These side effects are consistent with those in other populations, such as adults with schizophrenia[25] where movement disorder (typical antipsychotics in particular), weight gain (atypical antipsychotics) and sedation (typical and atypical) are commonly reported, and in dementia, where use of antipsychotics has been associated with stroke and increased mortality.[26-28]

1.4 Prescribing guidelines for the management of challenging behaviour

The recent NICE guidance (2015) acknowledges the limited and low quality evidence supporting the use of antipsychotics for management of challenging behaviour in learning disability. The guidance also states that antipsychotics should only be prescribed if: (i) psychological or other interventions have been unsuccessful in managing behaviour (ii) treatment for any comorbid conditions (physical or psychological) have not improved behaviour (iii) risk to the individual or others is significant, due to aggression, violence or self-injury. Further recommendations include use of medication only in conjunction with behavioural/other interventions; ensuring appropriate strategies are in place to review prescribing and any benefits/adverse effects; and ensuring there is a plan in place to stop medication, particularly where prescribing is transferred to community or primary care.
In 2014, NHS England commissioned the Winterbourne Medicines Programme (NHS Improving Quality 2014) to review use of antipsychotic prescribing in adults with learning

disability. The work has identified high levels of inappropriate psychotropic drug prescribing in primary care, and in adults with intellectual disability detained under the Mental Health Act, where in some instances, medication appeared to be prescribed for challenging behaviour rather than the underlying mental health condition. As a result of this work a number of recommendations have been made, including: greater involvement of people with learning disabilities, their family and carers in decision making; provision of active care pathways for behaviours that challenge; and instigating a collaborative 'call to action' (NHS England, 2015) approach, bringing together patients, families, carers, health professionals and improvement experts to agree the actions required to reduce inappropriate use of antipsychotics. This approach has been used successfully in reducing antipsychotic prescribing in dementia.[26] As a result of the work undertaken by NHS England, The Royal College of Psychiatrists (2016) have issued a recent report on psychotropic drug prescribing in this population, recommending regular (preferably 3-monthly) review of treatment response and side effects. The report also includes a foreward from Dr Paul Lelliot, Deputy Chief Inspector, Mental Health Care Quality commission, who states:

"There is compelling evidence that a significant number of people with intellectual disabilities are prescribed psychotropic medication that, at best, is not helping them. In particular, there is a risk that doctors are prescribing medication to treat behaviour that is an expression of distress or a mode of communication rather than a mental disorder."

1.5 Withdrawal of antipsychotic medication

A number of drug withdrawal studies have investigated predictors of successful withdrawal from antipsychotic medication[29, 30] but are limited by being retrospective, non-randomised, 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 antipsychotics, 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.[31] However, a randomised controlled withdrawal study reported more positive results. Ahmed et al. (2000) 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; nor was drug reinstatement associated with either staff reported or directly observed measures of challenging behaviour. A recent systematic review[32] of reduction or withdrawal of antipsychotics concluded that these drugs can be reduced in adults with ID, although the authors noted adverse effects did occur for some participants in some studies. However, the authors also note much of the evidence to date is from relatively small and biased samples, and that interventions and comparators are generally inadequately described. It is not possible from the available evidence to identify individual characteristics that could predict a poor response to withdrawal.

A large, controlled and blinded randomised trial of the impact of planned withdrawal on resulting drug dosage, behaviour, psychiatric symptoms, safety and the consequent costs of treatment is therefore required.

1.6 The ANDREA-LD trial

The initial purpose of this study was to conduct such a sufficiently large, blinded randomised controlled trial to investigate whether antipsychotic medication prescribed to adults with learning disabilities for the treatment of challenging behaviour could be reduced or withdrawn entirely, without adversely affecting their behaviour or mental health or causing a corresponding increase in financial costs. We proposed to limit recruitment to patients receiving risperidone or haloperidol in order to increase the feasibility of blinding while including within the trial both atypical and typical medications, specifically those found to be ineffective for challenging behaviour by Tyrer et al. (2008). Moreover, as Ahmed et al. (2000) had found in their open study that reinstatement of medication occurred for almost half of the sample despite being unrelated to reported or directly observed changes in the level of challenging behaviour, this study was designed to compare the extent of medication change between blinded and unblinded conditions and explore the perceptions of clinicians and carers about medication usage. However, as the next chapter describes, poor recruitment led to modified aims for the study.

2 Methods

ANDREA-LD was originally designed as a large scale non-inferiority trial of an antipsychotic withdrawal programme in primary care. The main outcome was level of reported aggression at 9 months post-randomisation. With slower than anticipated recruitment in primary care, the study was expanded to recruit via community learning disabilities teams. However, due to significant challenges to various elements of set-up and recruitment, the trial closed early and is therefore reported as an exploratory pilot study (as defined by the NIHR HTA programme). Sections (2.1 to 2.10) detail the trial as it was originally designed, and, section 2.11 describes the changes made in response to lower than anticipated recruitment rates. Section 2.12 details the final presentation of the trial following the decision to close early.

2.1 Design

ANDREA-LD was a two arm randomised (1:1) double-blind placebo-controlled non-inferiority withdrawal trial. Those randomised to the intervention arm progressed through a dose reduction regime while those in the control arm received their treatment as usual. After the baseline assessment, follow up assessments were planned for six, nine and 12 months. The aim was to recruit 310 adults with learning disabilities without psychosis and currently treated with one of two antipsychotics (risperidone or haloperidol) for the treatment of challenging behaviour. Ethical approval was given by Wales Research Ethics Committee (REC) 3.

2.2 Objectives

2.2.1 Primary Objectives

The primary objective was to evaluate the impact of a blinded anti-psychotic medication withdrawal programme for adults with LD without psychosis compared to treatment as usual. More specifically, we wanted to confirm whether reduction or withdrawal of antipsychotic medication prescribed for challenging behaviour without psychosis, could be safely achieved without a corresponding increase in aggression, as indicated in previous non-blinded studies. The primary outcome (aggression) was to be assessed at baseline and nine months (blinded) with levels of aggression compared between the intervention (reduced medication) and control (standard treatment) arms.

2.2.2 Secondary Objectives

A secondary objective was to explore the potential non-efficacy-based barriers to drug reduction in clinical practice. We aimed to complete qualitative telephone interviews with Principal Investigators (PIs), carers and participants to explore their perceptions about involvement in the trial and medication usage, in addition to a final assessment of medication dosage at 12 months.

2.3 Site selection

Sites were originally intended to be GP practices. Research active GP practices across four Health Boards in South Wales (Cardiff and Vale University, Cwm Taf, Abertawe Bro Morgannwg University and Aneurin Bevan Health Boards) were approached to participate in the trial. One general practitioner (GP) at each site would be recruited to act as PI and at least one practice nurse was recruited to take on the task of taking delivery of and handing out study medication to participants.

2.4 Participants

2.4.1 Inclusion criteria

Adults with a learning disability were eligible for the trial if they met all of the inclusion criteria and none of the exclusion criteria. Inclusion criteria were:

- Aged 18 years or over,
- A recognised 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),
- Currently prescribed risperidone or haloperidol, for treatment of challenging behaviour.

2.4.2 Exclusion criteria

Patients were excluded if:

- They had a current diagnosis of psychosis,
- They had had a known recurrence of psychosis following previous drug reduction in the past 3 years,

- The clinician primarily responsible for their care judged for any other reason that participation in a drug reduction programme may be contra-indicated,
- The research team, were unable to identify an appropriate individual to complete outcome assessments.

2.5 Recruitment process

Participating sites were asked to identify all patients in their records who had a learning disability and were receiving either risperidone or haloperidol. PIs then examined the list and excluded any they felt met the exclusion criteria. It was then up to the PI to approach these individuals (or their carer if appropriate) with information about the trial and details of how to indicate a willingness to be approached to participate. This could have been either via completion of an expression of interest form returned in a pre-paid envelope to the study team, or by the PI handing contact details directly to the study team, with the individual's permission.

Once an expression of interest was received, the study team made contact with the patient (or their carer), to discuss the study in more detail, identify key personnel (to provide consent if necessary and complete outcome assessments) and arrange a screening assessment. The screening assessment would be carried out in order to assess the potential participants' capacity, gain informed consent and to ensure that inclusion criteria were fully met. Approximately two weeks after the screening assessment had taken place, a baseline assessment was carried out. The participant was then randomised by a member of the study team to either experimental reduction or to control treatment as usual (i.e., maintenance of current medication level).

2.5.1 Informed consent

It was anticipated that while some participants would have capacity to give informed consent, there would also be a proportion judged by researchers to lack capacity. In such cases consent from a personal legal representative was sought instead (failing that, a professional legal representative). Assessment of capacity was made by members of the trial team or research network who were professionals with considerable experience in assessing capacity in this population. It was permitted for assessments of capacity and consent to be undertaken by the

PI at site if necessary. Criteria for consent included: presumption of capacity, an assessment of the individuals understanding of the risks/benefits of taking part in the trial and their ability to retain this information; the ability to communicate their decision making. Potential participants were given a plain language and pictorial participant information sheet at least 24 hours 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.

2.5.2 Potential participants with capacity

Upon meeting with the researcher, the trial and potential risks and benefits were explained verbally in simple terms. Checks were made frequently for understanding during the explanation. Once all questions had been answered and the individual was happy to take part, they were asked to tick or initial each statement on the consent form as a means of indicating their consent and to sign the form. This process was witnessed and signed off by a carer independent of the research team. Participants could decide to withdraw their consent at any stage. A small sample of participants with capacity was also invited to take part in a qualitative interview at the end of the study. Capacity was again assessed at this time.

2.5.3 Potential participants who lacked capacity

Where capacity was judged by an experienced researcher to be lacking, a similarly straightforward explanation of the trial and its potential risks and benefits was given verbally to a personal legal representative or failing that, a professional legal representative. Neither the personal nor professional legal representative was connected with the conduct of the trial (e.g. the PI). That individual was asked to give consent on the participant's behalf. Again, consent could be withdrawn at any stage. Legal representatives were 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.

2.5.4 Carers of potential participants /PIs

The participant's main carer was also asked to give separate consent to complete assessments designed to be completed by a third party, and to consent to taking part in the qualitative interviews at the end of the trial if selected. PIs were also asked to consent to participate in the qualitative interviews.

2.5.5 Risks and anticipated benefits

Risk was considered against the recognised risks of long term anti-psychotic medication and therefore the potential benefits of withdrawal. Benefits would include: reduction of cardiovascular risk, in particular stroke, reduction of musculoskeletal risk from tardive dyskinesia and other extra-pyramidal side effects, 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 may be associated with the following risks;

i. The emergence of tardive dyskinesia. Advice for PIs on the recognition, assessment and management approaches were included in the detailed treatment and safety package prepared by the trial team.

ii. Emergence of unrecognised psychiatric illness. There remained 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, was most likely to be an anxiety disorder. Advice for PIs on the recognition and assessment of psychiatric symptoms was included in the detailed treatment and safety package prepared by the trial team. A clinical algorithm (described in section 2.6) was developed to support the primary care team to follow the appropriate treatment and care pathways. Clear guidance was available for predicted scenarios in which unblinding may be necessary such as the emergence of psychotic symptoms.

iii. Deterioration in behaviour. A previous study[33] showed that measurable behavioural deterioration was uncommon following drug reduction but other studies have shown greater deterioration and carer concern can be high. Advice on assessing a meaningful behaviour change was provided in the PI support package. As behavioural signs and psychiatric symptoms for this population are intertwined, the clinical algorithm referred to above also dealt with behaviour change.

2.5.6 Supporting secondary care services

In the case of individuals recruited through general practice and who had involvement with learning disability services, contact was made with these teams on confirmation of eligibility.

At this time, a description was given of the study protocol, the PI support package (see section 2.6) and the procedure for accessing the code break.

It was not anticipated that the study would have a considerable impact on the current well-developed specialist learning disability services. These services would most probably already know many individuals involved in the study and we estimated the chance of severe deterioration would be small and would be distributed across at least six health boards. It was possible that the study might increase the referrals to learning disability services due to a greater awareness of the issue of anti-psychotic drug prescribing across primary care. Such referrals would be a positive outcome; learning disability teams are skilled in drug assessment and regular review is a key component of good clinical care.

2.6 Interventions

The intervention group progressed through up to four approximately equal reduction stages to full withdrawal within a six month period while the control group maintained baseline treatment. The following rules were used to decide each participants IMP regime:

- Participants in both arms stayed on the same number of tablets throughout the study where feasible;
- For those in the intervention arm,
    - Reductions from stage to stage were as equal as possible but where this was not possible, larger reductions were made first;
    - Reductions were made in such a way that there was only one tablet in each encapsulation;
    - If a participant was on multiple doses per day, preference was given to reducing the middle of the day doses, then later doses, then earlier doses respectively;
    - Schedules were reviewed by clinicians and could be changed if there is a valid clinical reason.

Drugs were supplied to ensure blinding but treatment was PI led and although blinded as to whether medication was being reduced, the PI retained discretion to delay progression to the next step (i.e. to maintain current medication level).

Sites were 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 produced this 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 started with a 'management flow chart' followed by more detail on elements such as history taking, examination, consultation with the research team, making appropriate referrals and information on the code-breaking practice. The flow chart (Figure 1) was designed as an easy access decision making tool. Each box in the flow diagram pertained to specific issues that were addressed in more detail over the following pages of the support package. PIs were given training in how to use the manual and its content at the point of site initiation and were provided with contact details of the study's Chief Investigator and clinical reviewer. As part of their training, PIs were also requested to add labels to participants' medical notes in order to flag their participation in the trial.

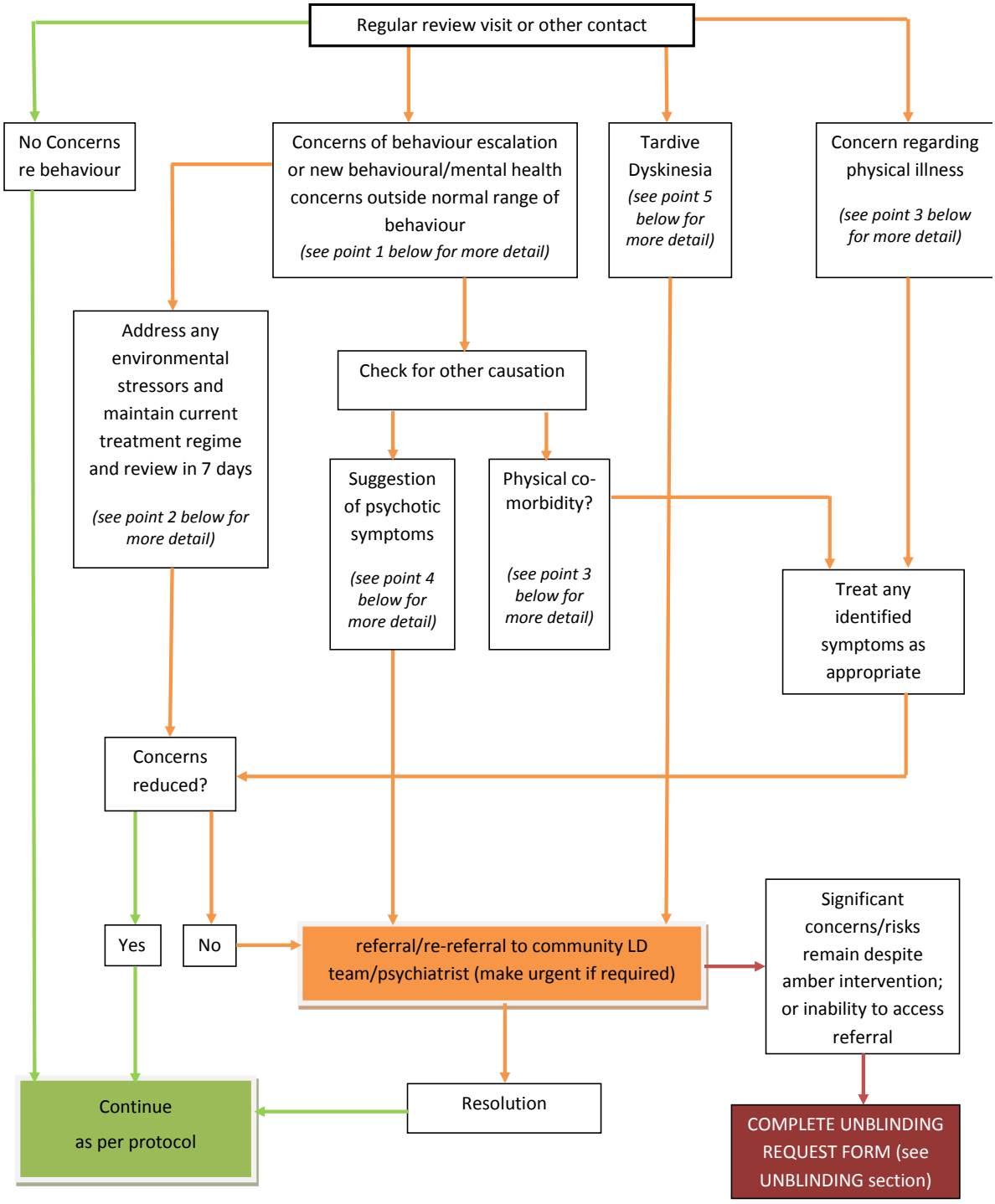


Figure 1: ANDREA-LD clinicians 'management flow diagram'.

Treatment achieved at six months was maintained for a further three months under blind conditions. At nine months following collection of follow-up data, the blinding was broken. PIs were informed of the participant's treatment allocation and current medication dosage. It

was the PIs responsibility to then reveal the allocation to the participant and their carer and to handle any further prescribing and to communicate with the participants wider care team.

2.6.1 Supply of blinded medication:

In order to achieve effective blinding, medication was encapsulated. Risperidone and haloperidol tablets of varying doses were encapsulated based on estimates of the likely numbers of participants recruited on each medication at the common doses. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their anti-psychotic medication at the outset of the study. Although individuals started the trial on their usual dose of medication, it was important to ensure the number of tablets they took daily remained constant over the blinded period and the effective dose could be reduced across dose reduction steps. In order to allow participants to familiarize themselves with their new medication, a run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction.

Manufacturing estimates assumed that all participants would achieve at least 50% reduction. In reality, the number of reduction steps achieved was likely to be much more variable, although this assumption allowed for a reasonable degree of flexibility. Manufacturing estimates included provision of medications to all participants up to nine months when the blind was lifted.

IMP were manufactured by St Mary's Pharmaceuticals Unit (SMPU) under their MIA(IMP) license and dispensed using Nomad® trays according to participant-specific prescriptions. SMPU were able to do this under section 37 of the Medicines for Human Use Regulations (2004) as 'post QP certification labelling for safety purposes'. Nomad Clear 2 are disposable weekly trays with separate compartments for days of the week as well as times of day – morning, midday, evening and bedtime. IMP was dispensed monthly for nine months. Although participants were to take 28 days of medication at each stage, enough IMP was provided for 33 days (to allow for a +5 day window around the planned 28-day timeframe between medication review visits) in case of any delays or issues in getting the prescription. Participant specific prescriptions were issued to SMPU by the research team following consent and randomisation. SMPU then dispensed and dispatched these directly to site where

they were formally received and kept secure by a practice nurse (or designated individual). Accountability documentation was completed on receipt of the IMP and returned to the study team thus evidencing the ownership of the IMP. Prescriptions were only handed out to the patient/carer/legal representative/researcher by authorised site staff. Again, accountability documentation was completed and returned to the study team at this time. This process was repeated for each new months IMP following the PIs decision to allow the participant to progress through the trial.

When any new prescriptions of study drug were collected from site, unused IMP from previous stages had to be returned by the participant or their carer. Sites were then responsible for the destruction of any unused study medication according to local procedure and following authorisation from the Trial Manager. Completion of accountability documentation at various time points allowed the study team to evidence the location of IMP throughout the trial.

Toxicity was not expected and use of all PRN (Pro Re Nata) medication was permitted and recorded in study diaries during the trial. Drug reduction was unlikely to cause interaction with other drugs however it was recommended that participants taking warfarin underwent more frequent INR tests. All concomitant medication was permitted and details of any taken were collected by the research team. IMP was stored at ambient temperatures at site therefore no temperature monitoring was undertaken.

2.7 Procedures

2.7.1 Piloting

Once the trial was open for recruitment, arrangements were piloted in primary care for six months in order to test the assumptions and practicalities of trial processes and recruitment. At the end of this period, any adjustments would be made as necessary and the study was to then continue until full recruitment.

2.7.2 PI visits/contact

Participants in both trial arms (intervention and control) had five appointments with the PI in total. The first four took place in the two weeks preceding the release of each new batch of blinded medication and were approximately 28 calendar days apart. The purpose of the

appointments was for the PI to make an assessment as to whether there were any concerns about the participant's progression to the next stage of the trial. Where face-to-face appointments could not be held, the PI could consult over the telephone. It was the participating PIs' responsibility to provide participants with details of each of these appointments, record them on an appointment card given to the participant or their carer, and to remind them of the appointment nearer the time of the visit to ensure attendance as well as communicate these to the research team. The site was also responsible for re-arranging any appointments as necessary. The appointment card contained the PI's contact details; an emergency number for participants or carers to use should they need to and a reminder of the amount of medication the participant had been taking when they started the study. It was important that the PI was the first point of contact for participants or carers if they had any concerns. The fifth PI visit took place after the nine month assessment and was for the PI to unblind the participant and their carer and reveal the treatment allocation. It was also the point at which a discussion would take place regarding participants' care from there on.

2.7.3 Practice Nurse visits

Participants (or their carer/representative) in both trial arms (intervention and control) collected their prescribed study medication from the Practice Nurse monthly until the blind was broken at nine months. At each of these visits, the Practice Nurse took receipt of any unused medication from the previous prescription before distributing any new medication. The practice nurse would then complete accountability paperwork before destroying any unused medication upon confirmation from the Trial Manager.

2.7.4 Assessments and follow-up

Eligibility data was collected at screening. Full data was to be collected at baseline and post-intervention, approximately nine months from randomisation. Data on medication and psychopathology (MOAS, ABC, PAS-ADD) and costs (CSRI) were to be obtained at six months and 12 months. All data collection was collected face-to-face either at site or during home visits.

Table 1: 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
Baseline (B)	Medication, MOAS, ABC, PAS-ADD Checklist, CSRI	Carer	1.5 hours
Baseline (B)	ASC, DISCUS	Participant/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

Details of outcomes and follow up time points can be seen in Table 2 and were the same for both experimental and control groups.

Table 2: 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 Checklist (ASC)	B, 9m	15 mins
Movement disorders	Dyskinesia Identification System Condensed User Scale (DISCUS)	B, 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.

2.8 Outcomes

2.8.1 Screening measure

Information collected included age, gender, current medication and psychiatric history. In addition, adaptive behaviour was assessed using the Adaptive Behaviour Scale (ABS)[34] as a means also to estimate IQ,[35] as well as current mental health status which was assessed using the Mini Psychiatric Assessment Schedule for Adults with Developmental Disability interviews (PAS-ADD interview).[36] The data gathered was used to confirm inclusion and exclusion criteria. If required, clinical review was 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)[35] and/or the Mini PAS-ADD (a score for section M, potentially indicative of psychotic disorder, of above 2).

2.8.2 Primary outcome measure

The primary outcome measure was aggression and was evaluated using the Modified Overt Aggression Scale (MOAS).[37] 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 to be used here was a non-inferiority comparison so a score difference of 3 or less was to be taken as clinically non-significant.

2.8.3 Secondary outcome measures

Secondary outcome measures at baseline, six month, nine month and 12 month assessments were:

The Aberrant Behaviour Checklist (ABC)[38] comprising 58 behaviours, each relating to one of five subscales to assess other challenging behaviour.

The Psychiatric Assessment Schedule for Adults with Developmental Disability Checklist (PAS-ADD)[39] to monitor mental health. 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 were to be compared.

The Antipsychotic Side-effect Checklist (ASC)[40] was used to measure adverse effects of psychotropic medication. The ASC comprises a list of the more common or clinically important side effects of antipsychotic treatment.

The Dyskinesia Identification System Condensed User Scale (DISCUS)[41] was used to assess movement disorders. A psychometrically derived DISCUS threshold of 5 was to be used.

The Client Service Receipt Inventory (CSRI) was modified for use in those with intellectual disability and has been used previously in learning disability research (CSRI).[20, 42] The CSRI was used to collect data on a comprehensive range of services used and support received by each individual in the study. The collection of these data facilitated the calculation of the cost of medication, health, social care and unpaid carer inputs incurred by trial participants due to challenging behaviour or mental ill-health.

The primary and secondary outcomes relating to challenging behaviour and mental health were to be analysed for non-inferiority with other secondary outcomes such as medication usage and adverse effects to be analysed for difference. A description of all scales, the range of their possible values, and their interpretation, is given in Appendix 4.

2.9 Statistical methods

2.9.1 Randomisation and unblinding

The off-line password protected randomisation programme was designed by the trial statistician and based on the method of minimisation. Allocations were 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%, was used alongside the minimisation procedure to increase the integrity of the minimisation process (i.e. there was an 80% chance that the allocation would minimise the imbalance with respect to the aforementioned balancing variables).

Following consent and baseline assessments, participants were randomised to either the intervention arm (gradual reduction) or control arm (treatment as usual) in a 1:1 ratio by a member of the study team. Any unblinding was performed only after authorisation from the Chief Investigator or (if not available) an authorised Clinical Reviewer who was an appropriately qualified clinician and member and the trial management team. In the event of an emergency, the treating clinician would have access to details of the participants' baseline dose (i.e. the dose at which they entered the study) and so could treat accordingly.

2.9.2 Sample size

We originally aimed to randomise 310 participants (155 per group) in total which would have provided 90% power to fit a one-sided 95% confidence interval around the difference in mean MOAS scores between groups nine month post-randomisation. A sample size of 310 assumed a non-inferiority margin of 3, a standard deviation of 8 (i.e. an effect size of 0.375) and had been adjusted to allow for 20% attrition.

2.9.3 Main analysis

The original proposed primary analysis focused on a comparison of 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, would have been 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) would be calculated. Non-inferiority would have been concluded if the limit of the confidence interval was less than 3 in all study populations (complete case (CC), full intention-to-treat (ITT) – with multiple imputation used to impute missing outcome data, and a per-protocol (PP) population – that would include participants who had outcome data available, had not

withdrawn from trial treatment, and, if they were allocated to the intervention group, had experienced at least one reduction).

A Complier Average Causal Effect (CACE) analysis would have been performed as a secondary analysis of the primary outcome, to obtain an ITT estimate in the treatment adherent. If non-inferiority was concluded, a superiority analysis of the difference in MOAS scores between trial arms was planned in the CC and ITT populations, using a two-sided 90% confidence interval.

All secondary analyses (anti-psychotic medication use, other challenging behaviour, mental health, adverse effects, movement disorders), would have been conducted using the complete case population, with those secondary outcomes assessed for non-inferiority (challenging behaviour and mental health) and adverse effects also analysed using the PP population.

Potential moderators of the effect of the intervention on MOAS score (e.g. age, gender, medication type, adherence with intervention) would have been explored in multivariable analyses using interaction terms. It was also originally proposed to model aggression levels using mixed models to explore changes over time.

2.9.4 Cost effectiveness analysis

The original proposed main cost effectiveness analysis focused on the comparison of the two trial arms 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 outcome (MOAS score) over 9 months.

It was proposed to conduct the main cost effectiveness analyses from health and social care agencies and a wider societal perspective to include health and social care agencies and unpaid carers. To inform the cost effectiveness analyses from these two perspectives, it was proposed that comprehensive data on health, social care and other services used by individuals included in the study, using a tailored version of the Client Service Receipt Inventory (CSRI). To estimate component costs, service use data were due to be combined with the unit costs for each service using long-run marginal opportunity costs (LRMC) principles. For services where national figures were not available or not suitable we proposed

to calculate best estimates of LRMC, values and time spent by friends or relatives providing support were due to be estimated using the unit costs of a local authority care worker. Three main categories of costs due to be analysed were: medication costs; 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; medication costs, aggregated health and social care costs and cost of time spent care giving by relatives and friends.

Costs were proposed to cover the period from baseline to 6 months (end of full treatment withdrawal period) and 6-9 months (three months following full treatment withdrawal period).The MOAS score was to 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 was proposed, adjusting for baseline covariates (MOAS score, baseline costs and variables balanced on / stratified by at randomisation - medication type, dosage and recruitment source).

A series of cost-effectiveness analyses were to be conducted by combining outcomes with costs from a health and social care agencies, and health and social care agencies and unpaid carers in turn. In the event that the experimental reduction group had lower costs and better outcome than its comparator, it would have been interpreted as the dominant treatment and where the experimental reduction group had higher costs and worse outcome than the comparator treatment, the experimental reduction group would have been dominated by the comparator. If the experimental reduction group was both more effective and more costly than its comparator, the nature of the tradeoffs to be made would have been made using cost effectiveness acceptability curves (CEACs). To generate the CEAC non-parametric bootstrapping of the costs and effectiveness data would have been used to generate the joint distribution of incremental mean costs and incremental effects. The CEAC 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.

We originally planned to 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).

2.9.5 Qualitative study

We undertook qualitative telephone interviews with a proportion of carers, PIs and participants who took part in the trial. One of the main purposes of these interviews was to gain insight into the non-efficacy based barriers to drug reduction in clinical practice as well as attributions of behavioural changes in relation to potential reduction of medication. The interviews were scheduled to take place during the unblinded phase of the trial between the nine and 12 month time points and were 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. PI interviews also focussed on PI views of the support package and views about how the patient and carer(s) managed during the trial period. Interviews were expected to take up to 30 minutes.

We aimed to interview up to 60 carers and the corresponding PI. It was hoped that both parties would agree to take part in these paired interviews but we accepted that this was not guaranteed. The sample was to be selected purposefully incorporating participants from both trial arms and from across the geographical recruitment areas.

We also hoped to interview a proportion of participants of the ANDREA-LD trial. Those taking part would be required to have the capacity to provide consent for a face-to-face interview. Interview topics for participants focused 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 agreed to take part in an interview were offered a £10 High Street shopping voucher to thank them for their time and considered views. PIs who participated in interviews were offered £50. With the participants' consent, all interviews were audio-recorded, transcribed and anonymised.

2.9.6 Qualitative analysis

It was proposed that data from the transcribed anonymized telephone interviews would be subject to thematic analysis as described by Braun and Clarke.[43] Thematic analysis allows researchers to take an initial inductive approach toward the dataset. Following familiarization with the data, researchers index data according to a priori and emerging themes. A priori themes are informed by the research literature on the topic of antipsychotic medication for people with learning disabilities. Analysis is facilitated by use of the computer-assisted qualitative data analysis software package, NVivo. Data from each dataset (participants, carers and PIs) would be analysed separately and then comparisons made across datasets.

2.10 Alterations to study design

2.10.1 Recruitment via community learning disabilities teams

Despite expansion of recruitment in primary care to areas in England, it was apparent that targets would not be achieved in the predicted time frames relying on this route. We gained approval from the funders to expand recruitment to community learning disability teams (CLDT) with LD psychiatrists acting as PIs and hospital based pharmacies taking on the role of the practice nurses and giving out trial medication.

Twenty LD psychiatrists from six trusts in Wales and England were then recruited to act as sites in the trial. An additional 13 hospital pharmacies were recruited in order to hand out trial medication.

2.10.2 Other alterations

Evidence from screening logs showed that the number of potential participants receiving haloperidol was much lower than anticipated. For this reason, the decision was taken not to manufacture blinded haloperidol medication but continue to recruit only with those taking risperidone. With these changes in place, the randomisation programme was also altered so that allocations were stratified by recruitment source (General Practice/Community LD Psychiatry) and balanced with respect to medication dose only: low (less than 4mg for risperidone/ high (at least 4mg for risperidone).

2.11 Exploratory pilot study design.

2.11.1 Exploratory pilot study methods

In November 2015, the decision was taken to close the trial to recruitment due to the difficulties described. At this point, 22 participants had been recruited into the trial. The study team submitted a closedown plan to the funders and it was agreed that all randomised participants would continue to receive the intervention and follow up to nine months. This meant that the trial would be complete by the end of June 2016 and would be reported as an exploratory pilot study (as defined by the HTA programme). As such, there were a few key alterations to the methods previously described which were as follows.

Table 3: Summary of changes to trial design

	Study component	**Changes to design**
1.	Sample size, recruitment & retention	No specified sample size. 22 recruited.
2.	Length of follow-up	Reduced from 12 months to nine months post-randomisation.
3.	Intervention	No change
4.	Analysis of primary & secondary outcomes	Still pre-planned, but primarily focusing on outcomes related to conducting antipsychotic drug withdrawal trials in an LD population (see Section 2.11.2 for more details)
5.	Qualitative analysis	Interviews brought forward to four to six month time point. Focus shifted to feedback on involvement in the trial and sample reduced.
6.	Economic evaluation	Not reported

2.11.2 Exploratory study analysis

As the required sample size would not be achieved, we planned to focus on estimating feasibility outcomes. With a particular interest in recruitment and retention, we planned to estimate the following:

- The number and proportion of primary care practices/community LD teams that progressed through the various stages from initial approach to recruitment of participants.
- The number and proportion of recruited participants who progressed through the various stages of the study.

We also compared trial arms regarding the following clinical outcomes:

- MOAS at six and nine months post-randomisation
- Level of psychotropic medication use, assessed at the six-month and nine-month post-randomisation assessments
- ABC at six and nine months post-randomisation
- PAS-ADD at six and nine months post-randomisation
- ASC at nine months post-randomisation
- DISCUS at nine months post-randomisation
- Use of as required (PRN) medication over the study period
- Use of other interventions to manage challenging behaviour at nine months post-randomisation, including:
    - Physical intervention/restraint
    - Seclusion
    - As required medication (PRN)
- Costs and service utilisation at six and nine months post-randomisation

Analysis of recruitment and retention outcomes was descriptive, with frequencies and percentages reported both overall and split by recruitment route (primary care or community LD teams). Pre-randomisation variables, including those related to the participant, their recruitment route, and their starting medication were used to explore the association between participant characteristics and their progression through the study post-randomisation (to Stage 4 of the intervention).

Clinical outcomes were compared between arms using appropriate regression models (linear or logistic, depending on type of variable). Data transformations were made, where required, to fulfil regression assumptions. The analyses were also adjusted for the corresponding

clinical score at baseline (if measured), as well as variables that were balanced on at randomisation (dose of antipsychotic medication (< 4mg or ≥ 4mg) and recruitment route (primary care, secondary care)).

Three analysis sets were considered:

- The Intention to Treat population (ITT), which comprised all randomised participants. Where participants had either withdrawn from the study intervention (but remained in the trial for follow-up assessments), or not provided follow-up assessments at six/nine months post-randomisation, it was assumed that they returned to their original starting dose.
- The Modified ITT population (MITT), which comprised all randomised participants whose follow-up data were known.
- The Per Protocol population (PP), which comprised all randomised participants who had progressed to Stage 4 of the intervention (regardless of the trial arm to which the participant was randomised).

The analysis of the level of psychotropic medication at six and nine months was conducted in the ITT, MITT, and PP populations. The remaining clinical outcomes analyses were conducted in the MITT and PP populations only.

As it was the original primary outcome, further exploratory analyses were performed with the MOAS score:

- The MOAS score at nine months post-randomisation was fitted with a two-sided 90% confidence interval in order to reflect the original primary analysis intended for this study.
- Individual trajectories for the MOAS scores at baseline, six months, and nine months post-randomisation were plotted and described, with particular attention paid to individuals whose MOAS scores changed by at least four points (a change considered to be clinically meaningful).

2.11.3 Economic analysis

Due to the small sample size of the exploratory pilot, economic analysis was not reported as planned.

3 Setting up and delivering a drug reduction trial for adults with learning disabilities: challenges and lessons learned.

The unique nature of this trial meant that there were particular challenges faced that had not been experienced by other research in this area. These have been summarised under the following headings.

3.1 Recruitment

3.1.1 Recruitment of sites

Research active GP practices in south Wales and south west England were recruited into the study in the first instance. Initially, numbers of practices interested was quite low so we expanded to include practices not known to be research active. In total, approaches were made to 351 practices in 4 Health Boards in South Wales and 127 in 8 CCGs in South West England using a variety of methods including; email, mailshot, articles in GP magazines/circulars and follow-up phone calls. The result was active declines from 204 practices across Wales and 17 practices in England with no response from the rest.

When recruitment later moved to community LD teams, we approached 30 LD psychiatrists also in south Wales and south west England. While the decision to participate in the research could be made at a practice level by GPs, this decision required buy in from not only the whole health board or trust at secondary care level, but also from the LD services and teams. In one area, meetings were held with a member of the trial team and representatives from the whole LD directorate before a decision was made to participate. Concerns centred mainly around the buy in from wider care teams and how any escalations in behaviour would be handled and communicated between relevant parties. Of the 30 approached, 20 LD psychiatrists across six health boards/trusts agreed to take part in the trial.

In primary care, a site was considered to be the GP practice while in secondary care, a site referred to each health board or trust's LD directorate. Due to the changing nature of the NHS, establishing who the appropriate body to obtain approval from was more complex than anticipated. In one area of England, provision of LD services was provided on behalf of the NHS by a Community Interest Company. Research was not something commonly dealt with by the company so the permissions process was unclear and took time to establish. This had the knock on effect of delaying recruitment of investigators and thus participants.

Gaining permissions to use community learning disabilities services in south Wales was also challenging. Abertawe Bro Morgannwg University Health Board learning disabilities directorate acts as provider of learning disability services across Bridgend, Cardiff, Merthyr, Neath Port Talbot, Rhondda Cynon Taff and Swansea. Gaining permission to recruit participants through the LD clinics in these areas had to be dealt with separately to gaining permission to use hospital pharmacies local to those clinics which were dealt with by each individual health board.

Recruitment of participants depended on ensuring that approvals were in place for an investigator and a local hospital pharmacy at the same time. Recruitment in one health board was impacted by this as approval had been granted to recruit through an LD clinic by one health board but the health board in charge of the local hospital pharmacy delayed granting permission for some months while their board reviewed the request. Securing NHS costs added to the delay in gaining permission to recruit in certain areas as the allocation process had become more complex with this change in study recruitment.

3.1.2 Recruitment of investigators

Along with permission from R&D boards, it was necessary for investigators to have undertaken Good Clinical Practice (GCP) training before undertaking research activities. This proved to be an obstacle for many, particularly in secondary care settings where clinicians' involvement in research was less common. GCP training is specific to clinical trials and typically takes up to three hours to complete – a time commitment that was not always easy for clinicians to accommodate. Despite having 16 investigators based in primary care sites and 20 in community LD teams, only 14 of these recruited any participants into the trial – three GPs and 11 community LD psychiatrists. Low recruitment rates on the part of PIs are explored in more detail through interviews which are reported in chapter 6.

Of the 11 psychiatrists who recruited participants, three were Specialist Registrars (SpR) in learning disabilities. . The SpRs were able to provide invaluable support for the trial in that they took on the role of investigator, obtained GCP training and were able to see a number of participants on behalf of other clinicians who might not have had the time to get involved in research. SpRs worked on rotation however and if they moved to different health boards or trusts there were difficulties in maintaining care of participants as part of the trial.

Fortunately, we were able to overcome this in the current trial and arrange for other clinicians to take on the role of investigator.

3.1.3 Recruitment of participants

Details of the eligibility criteria were clearly laid out in the trial protocol, and practices and LD teams were able to identify sufficient numbers of potentially eligible patients. However, the number of potentially eligible patients actually approached with details about the trial, was fairly low, particularly among primary care clinicians.

The study team drafted an audit tool that provided search terms and read codes for GP practices to help them identify those who might be eligible to take part. Once patients had been identified, GPs appeared reluctant to directly approach these patients or their carers about the study and to invite them to take part. It is not clear what the reasons for this were as we did not gain any feedback through interviews with primary care clinicians (this is discussed in more detail in chapter 6). Anecdotal feedback suggests that it may have been in part due to the nature of the consent procedure as well as concern about taking on decisions for care that are normally the domain of secondary care LD clinicians. However, following the change in recruitment from primary care to community LD teams, primary care practices became participant identification centres, rather than full sites, in an attempt to mitigate this issue. Where clinicians had identified patients who might potentially be eligible, it was then possible to refer them to the CLDT clinicians who would be able to discuss the study in more detail. This potential was not subsequently utilized by GPs and did not result in participants coming from leads in primary care.

3.1.4 Consent procedure

There is understandable anxiety over the capacity of individuals with intellectual impairment to participate in clinical trials. Within the drafting of the Mental Capacity Act (MCA: 2005) specific provision was made relating to the care, treatment and decisions on behalf of people who lack capacity including participation in clinical trials. Further, important information is contained in the Medicines for Human Use (Clinical Trials) Regulations (2004). As a Clinical Trial of an Investigational Medicinal Product (CTIMP), the ANDREA-LD trial was required to adhere to the latter regulations (which supersede the MCA) meaning that for those who lacked capacity, consent would need to be given by a personal or professional legal

representative of the participant. While clinicians (particularly CLDT psychiatrists) were well versed in the Mental Capacity Act (MCA: 2005), a lack of experience in research meant that many were not familiar with differences in the consent procedure as specified under the Medicines for Human Use Regulations.

It was anticipated that many potential participants in the ANDREA-LD trial would likely lack capacity to give informed consent, and so clear study specific guidance explaining the Regulations was drafted. The guidance specified that the following factors needed to be taken into consideration:

- Firstly, no patient would be treated as unable to make a decision unless all practical steps to help them to do so had been taken without success;
- Secondly, even if an individual lacked capacity, their opinion would still be taken into consideration and;
- Thirdly, should they lack capacity, the research team would, in accordance with due legal process, consult with relevant parties to clarify whether their participation was in their best interest.

Even with this guidance and reassurance, it became apparent that the consent process for the trial would be more challenging than anticipated.

Not only were clinicians apprehensive with regards the consent regulations but wider care teams, carers and support staff were as well. The impact of this meant it took much longer than hoped to explain the consent procedure to individuals, and also to identify someone willing to act as a legal representative in cases where the participant lacked capacity. On average, anecdotal evidence suggests it was taking between 2 and 3 weeks just to complete phone calls and arrange a meeting in order to complete the consent procedure. This was especially the case in residential settings where carers who would be well placed to provide consent were required to defer this decision to managers and seniors whose involvement often meant that a best interests meeting was called with wider care teams. With added layers of referral, it was often difficult to identify an individual who would be willing to provide any necessary consent.

3.2 Intervention delivery

3.2.1 Dosing

After extensive discussions, the decision was made by the trial team to include patients on any dose of risperidone provided it was not being prescribed for psychosis and the participant showed no evidence of psychosis. The rationale being that if the withdrawal programme were shown to be effective and safe, it needed to work for individuals who would be on varying doses of medication. If the patient was deemed clinically eligible to enter the trial on all other criteria, their dose of risperidone should not be restricting factor. By not limiting the entry criteria in this way the pool of potentially eligible participants was also increased. We hypothesized based on clinical experience, that doses of risperidone would be relatively low in the target population given it was being prescribed for challenging behaviour as opposed to psychosis, for which larger doses are clinically indicated. The trial team therefore felt there would likely be a limited number of dose combinations to cover as part of the trial. Careful consideration was given to the practicalities of how participants would receive their individually tailored medication regime.

3.2.2 Blinding medication

Blinding clinicians, carers and participants to treatment allocation presented a practical challenge. How could varying medication strengths be potentially tapered off without revealing which arm the participant had been randomised to? The decision was made to over-encapsulate all trial medication using size 0 Swedish orange hypromellose capsules so that all strengths of risperidone and placebo looked the same. The number of pills taken each day would also need to remain the same throughout the trial. To achieve this, the trial statistician created an algorithm which was used at baseline to create a unique dosing schedule for each participant (Table 4). Based on the participants' prescription upon entering the trial, the algorithm calculated how many capsules each individual would need to take on a daily basis to ensure that the blind would remain intact. Due to manufacturing constraints, only specific tablet strengths of risperidone were used in the trial (0.5mg, 1mg, 2mg). The algorithm aimed to make the reductions as equal as possible using the minimum number of capsules as possible, based on up to four possible drug reduction stages within a six month period (N.B. it was not possible to reduce medication in four stages for participants on very low doses of risperidone e.g. 0.5mg daily). If the participant had been allocated to the reduction arm, as the dose of active medication was reduced, a placebo capsule was introduced into the treatment

regime. This allowed a constant number of capsules to be taken throughout the trial but with a variation in dose as necessary to accommodate the reducing regime.

Table 4: Example IMP reduction regime

BASELINE IMP REGIME: Total daily dose 1.5mg of Risperidone for 33 days. To be taken as follows:		
	Mg	**Number of tablets**
Morning	**1.0**	**1**
~~**Midday**~~		
Bedtime	**0.5**	**1**

STAGE 1 IMP REGIME: Total daily dose 1.0mg of Risperidone for 33 days. To be taken as follows:		
	Mg	**Number of tablets**
Morning	**1.0**	**1**
~~**Midday**~~		
Bedtime	**0.0**	**1**

STAGE 2 IMP REGIME: Total daily dose 0.5mg of Risperidone for 33 days. To be taken as follows:		
	Mg	**Number of tablets**
Morning	**0.5**	**1**
~~**Midday**~~		
Bedtime	**0.0**	**1**

STAGE 3 IMP REGIME: Total daily dose 0.0mg of Risperidone for 33 days. To be taken as follows:		
	Mg	**Number of tablets**
Morning	**0.0**	**1**
~~**Midday**~~		
Bedtime	**0.0**	**1**

STAGE 4 IMP REGIME: Total daily dose 0.0mg of Risperidone for 33 days. To be taken as follows:		
	Mg	**Number of tablets**
Morning	**0.0**	**1**
~~**Midday**~~		
Bedtime	**0.0**	**1**

Using the Nomad® trays with separate compartments for days of the week as well as times of day, meant that participant specific doses of IMP could be safely dispensed and delivered. The trial team was able to specify which tablets (and thus which strength) should be taken when whilst maintaining the blind.

Because of the change in appearance of participants' normal medication, a run in period was provided which allowed individuals to get accustomed to using the Nomad® trays and taking the slightly larger than normal capsules. For the vast majority, the change in the appearance of the medication was not a problem. Only one participant had difficulty taking the trial medication and had to be excluded. It was also important for carers to become accustomed to the new medication during this period as they would be responsible for ensuring that participants took their medication as prescribed. Written and verbal information was provided to carers on how to handle study medication and the importance of using the Nomad® trays correctly. It was important to ensure that carers fully understood how we were using the capsules and trays to blind the medication and for them to be clear on how to raise any concerns they had. Especially where a participant resided in a staffed house, it was important that everyone involved in providing that person with their medication knew about the trial. A number of individuals required more tailored IMP deliveries which included aligning IMP dispensing with that of other prescriptions the participant might be taking in order that Medication Administration Record (MAR) sheets could be completed more easily. These are sheets that serve as a record of the drugs administered to a patient at residential setting. Although Nomad® trays were used along with European Union Good Manufacturing Practice (EU GMP) Annex 13 compliant labelling; two residential settings delayed participants progression onto study medication insisting an extra label, signed off by the clinician was included. Individual requests such as these became extremely time consuming and difficult for the study team to manage.

3.2.3 Progression through the trial

Participant safety and careful monitoring of behaviour was of utmost importance in the trial design. The programme of reducing medication was devised to allow PIs to have regular contact with participants and to provide the opportunity to delay any potential reductions at any point if there was concern about the individual. This meant that trial medication could only be given out on a monthly basis once the PI had confirmed how the participant was to

progress (Figure 2.). To accommodate this, monthly prescriptions were dispensed and delivered to site within a 10 working day timeframe. PIs therefore made their monthly contact with participants two weeks from the start of a new medication stage to allow adequate time for a new batch of trial medication to be dispensed and delivered. The PI's decision regarding progression to the next study stage was translated into an IMP order by the study team and sent through to the pharmaceutical unit for dispensing. This pattern of working required investigators to be prompt in their communication with the trial team and to see participants within the specified time frame. When this was done, the system worked well however it also meant that the trial team needed to provide constant oversight to investigators on a real time basis which increased the burden on the study team's workload and monitoring.

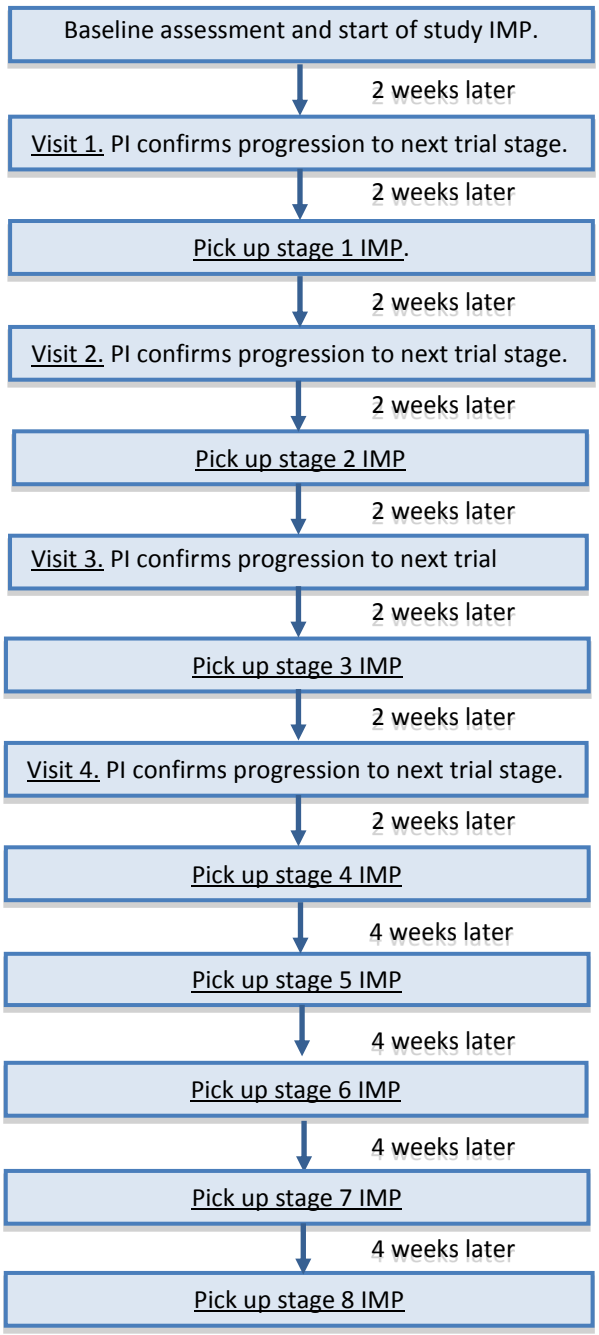


Figure 2: Flow diagram for PI visits and IMP collection

3.2.4 Dispensing medication

Another challenge was to ensure that instructions for taking medication while maintaining the blind were clear. To do this, the study team chose to deliver medication using the Nomad® dosing system. Some participants and carers would have been used to receiving medication in this type of dosing tray which is designed to make it more straightforward for individuals to know how much medication to take and when.

Once IMP had been manufactured at SMPU in Cardiff, it then had to be dispensed into the NOMAD® trays according to the participant-specific prescriptions. The trial team made extensive investigations into who would be able to carry out the dispensing and then how to get the IMP to participants in different geographical areas throughout south Wales and south west England. After discussions with various parties, the option chosen was to use SMPU not only to manufacture the IMP but to also supply to the patient-specific orders in a NOMAD® system under the process of 'post QP certification labelling for safety purposes'. SMPU were then able to dispatch IMP orders as necessary directly to specified sites or pharmacies via courier where they could be received by a designated member of staff.

When recruiting in primary care settings, each practice nurses' role was to take receipt of participants' medication and ensure that it was handed out according to the protocol. They also completed accountability records to evidence the whereabouts of the IMP Enough IMP for 33 days was delivered at each stage, which meant that there was usually unused IMP that needed to be returned and destroyed. Any unused IMP from a previous stage could have been at a higher dose for participants in the reduction arm. It was important that the correct blinded medication was used each time.

Once recruitment in community LD teams began, it was apparent the set up used in primary care would not translate as LD psychiatry clinics were not equipped to handle, store and dispose of medication as required by GCP. To resolve this, options were examined including the use of community pharmacies and delivering IMP via the post. The priority was to ensure as little disruption as possible for the participant or their carer in obtaining medication on a frequent basis. This had of course to be balanced with what would be practical for the study team to set up and maintain and what would fit with regulatory requirements. The

benefit of using community pharmacies would mean an IMP pick up location local to each participant. However, the drawback was that it was not feasible for the study team to set up and maintain a potentially very large number of pharmacies like this (we would not know which pharmacy would be most appropriate to use until the participant had been recruited). It would not be possible to ensure agreements, GCP training and initiation were all in place, prior to issuing study medication. Use of postal services to supply IMP was also not feasible due to regulatory issues and ensuring any unused IMP was returned.

The approach taken was to use hospital based pharmacies. Larger hospitals with ready GCP trained clinical trials pharmacies were used to take receipt of IMP orders from SMPU and to issue medication to participants or their carers. Participants often had reason to visit local hospitals for other health care reasons so picking up trial medication from these locations was not overly burdensome for carers. For those who did find this a challenge, the study team was able to coordinate medication delivery in person by various members of the research team and supporting research network. This was only possible for a small number of participants however. Researchers did not have the capacity to do this for all as it involved special journeys from the office to the hospital pharmacy, on to the participants home, back to the pharmacy and then back to the office.

3.3 Summary

Trial procedures as laid out in the protocol were designed to allow the study to operate efficiently and in such a way as to accommodate individual requirements where possible. There were a number of factors however that had varying impacts on the delivery of the trial which were outside the design of the trial.

The main premise of the original trial design had been that it would be possible for clinicians in primary care to implement a drug reduction programme for adults with learning disabilities being prescribed antipsychotic medication in the absence of psychosis. It became apparent fairly early on into the trial that there were a number of factors that were inhibiting this. First and foremost, the reluctance of GPs to be involved in the trial was a major stumbling block. Added to this, the requirement for investigators to have GCP training meant considerable delays in site recruitment. Secondly the consent procedure for entering participants into the

trial was new territory for many clinicians and delays were created while GPs referred to more specialist secondary care clinicians also involved in the patients care for advice. The trial then moved to recruiting participants through community learning disabilities teams with LD psychiatrists acting as PIs. Obtaining appropriate permissions to recruit from secondary care services was not always straight forward and the complexity meant it took longer than anticipated. Obtaining GCP was also a delaying factor for secondary care clinicians many of whom had little or no clinical trials experience.

While confidence over consent procedures for participants who lacked capacity seemed to be an issue for primary care clinicians, secondary care investigators appeared more comfortable with the process even though it was different from their normal practice. However when it came to carers who were asked to provide consent for a participant who lacked capacity, many only had knowledge of the MCA (2005) thus it longer than anticipated and more engagement with wider care teams to explain the procedure as outlined under Medicines for Human Use Regulations (2004). It would often take up to two to three weeks to ensure an appropriate person was able to provide consent for an individual who lacked capacity to take part in the trial.

Once the procedure for maintaining the blind and delivering IMP to participants had been established, the system ran relatively smoothly. Use of the NOMAD® system worked well and the majority of investigators and carers had no problem in completing trial procedures. There did however emerge a small number of individual tailoring requirements to certain aspects of the trial which were requested by some carers. While the trial only had a small number of recruits, the team could accommodate these however, had recruitment been higher, this would have created more of a problem for the team to keep track of. A limited number of investigators also required more closely monitoring to ensure procedures were being undertaken correctly and on time which again put a time and workload burden on the trial team.

Initially securing sites to recruit participants took considerable amount of time but of the challenges listed here, the elements that created the biggest ongoing impact on the trial team in terms of time and resource were the tailored processes requested by some individuals and the monitoring required to ensure study documentation was being completed on time by some

investigators. Study processes were very time dependent and it was crucial that all parties involved completed tasks as required. Where this didn't happen, the study team had to work quickly to ensure the participants progression in the trial.

As explained in the qualitative results, the analyst was blinded to the arm allocation for each participant during the analysis and drafting of this report. At the time of interview 9 carers were blinded to the arm allocation and 7 had been unblinded. Participants 7, 17, 36 and 58 were all on the Intervention arm of the study and all withdrawn due to concerns from carers or the participants themselves about behaviour. Whilst some of these behaviours had been on-going before the ANDREA-LD study, some of these concerns seemed to be very real for the carers. Participants 6, 35 and 53 were in the Control arm, and were withdrawn from the study. The carer of participant 6 reported that participant 6 had been withdrawn due to concerns about hallucinations. However, the carer also signals that a history of allergic reactions to medications may have also been a reason for the clinician's cautious approach in withdrawing the participant. Unfortunately interviews with carers of participants 35 and 53 were not conducted, possibly because the carer had wished to withdraw themselves and the participant from the study completely, and so we have no qualitative data on the reasons for their withdrawal. Also of note, although perhaps not surprising, is the lack of equipoise towards the study arm by the carers and (to a lesser extent) clinicians. This is seen in discussion about their reasons for participating (seen as an individual benefit in terms of supported withdrawal rather than more altruistic reasons for benefit to the learning disability population in general). This lack of equipoise may account for some expressions of hope, reported in section 9.16, that the participant had been successfully withdrawn.

4 Statistical analysis

4.1 Recruitment

Approximately 500 potential sites were contacted in total; 470 GP practices and 30 community LD teams in Wales and South West England. Of those contacted, 79 expressed an interest in taking part (16%), which comprised the majority of community LD psychiatrists contacted (67%) and a minority from primary care (13%). The majority of sites expressing interest in taking part identified potentially eligible participants (61, or 77%) and became sites to recruit participants (36, or 59%). From those sites, 18 provided a participant who was screened (37%), with a higher percentage of community LD teams providing participants for screening (50% versus 28%), and 10 provided a participant who was randomised (20%), again with a higher yield from community LD teams (30% versus 14%) (Table 5).

Table 5: Summary of site flow from approach to recruiting participants

Stage	GP practices	Community LD Psychiatrists	Overall
Contacted	470	30	500
Expressed interest	59	20	79
Identified potentially eligible participants	41	20	61
Became sites to recruit participants	16	20	36
Provided a participant who was screened	8	10	18
Provided a participant who was randomised	4	6	10

Thirty-six participants were screened in total, with five participants screened in primary care and 31 from community LD teams. Of those screened, 23 went on to complete a baseline assessment (72%); three from primary care (60%) and 20 from community LD teams (74%).

In total, 22 participants were then randomised following a baseline assessment (69% of those screened), with percentages from primary care and community LD teams (80% of those screened and 100% of those who completed a baseline assessment from primary care and 74%/95% from community LD teams) (Table 6 and Figure 3).

Table 6: Summary of participant flow from screening to randomisation

Stage	Primary care	Community LD teams	Overall
Screened	5	27	32
Completed baseline	3	20	23
Randomised	3	19	22

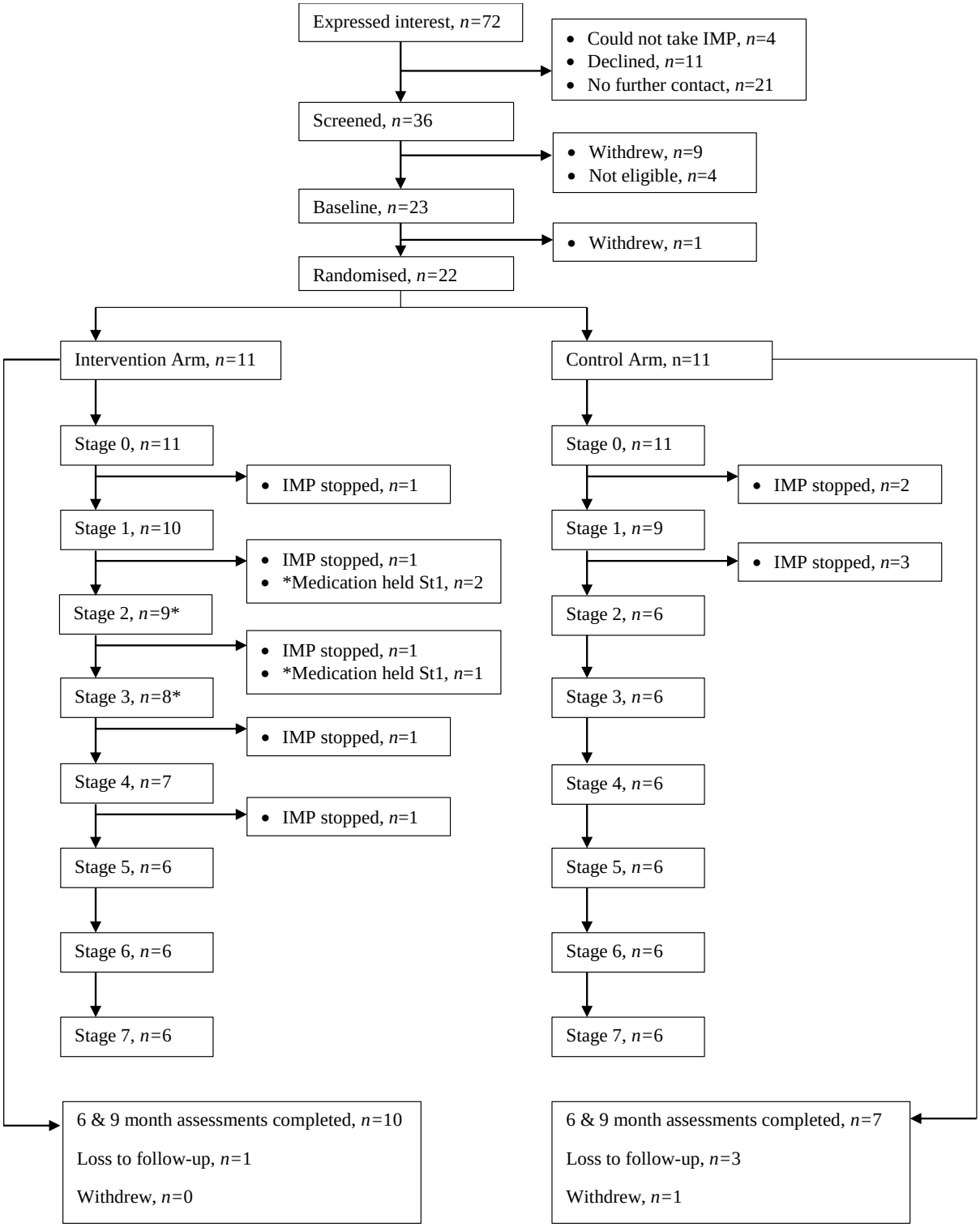


Figure 3: Consort Diagram

4.2 Baseline data

4.2.1 Pre-randomisation characteristics of study participants

Participants were well balanced with respect to variables collected pre-randomisation (including at screening and during baseline visits). Overall, 15 participants were male (68%) and the mean age was 43 years (SD = 13.4). There were no self-referrals. The majority of participants were consented into the study by a legal representative (18, or 82% of those randomised). Ten of the randomised participants had a diagnosis of autistic spectrum disorder (45%) and none had ever been diagnosed with attention deficit hyperactivity disorder (ADHD). Ten had been diagnosed with epilepsy (45%), with all ten currently on medication for epilepsy, four having had a seizure in the last year, and seven having had a seizure in the last five years.

Regarding strategies used by carers to manage challenging behaviour, three participants were managed using physical intervention (14%), six were managed using seclusion (29%), and nine using PRN medication (43%). Most participants were in regular contact with their LD team (21, or 95%), and when confidence handling challenging behaviour was self-rated (by carer) on a scale of one to ten (one being least confident and ten being most confident), the median score was 10 (IQR = 8 to 10) (Table 7).

*Table 7: Pre-randomisation characteristics of study participants**

		Control (n=11)	**Intervention (n=11)**	**Overall (n=22)**
Recruitment route	**Primary care**	2 (18)	2 (18)	4 (18)
	Community LD teams	9 (82)	9 (82)	18 (82)
Self-referral	**No**	11 (100)	11 (100)	22 (100)
	Yes	0 (0)	0 (0)	0 (0)
Gender	**Male**	7 (64)	8 (73)	15 (68)
	Female	4 (36)	3 (27)	7 (32)
Mean age (SD, min, max)		42 (10.7, 24, 61)	44 (16.1, 21, 68)	43 (13.4, 21, 68)
Consent	**Participant**	1 (9)	3 (27)	4 (18)

		Control (n=11)	Intervention (n=11)	Overall (n=22)
	Legal representative	10 (91)	8 (73)	18 (82)
Diagnosis of Autistic Spectrum Disorder	**No**	5 (45)	7 (64)	12 (55)
	Yes	6 (55)	4 (36)	10 (45)
Current diagnosis of ADHD	**No**	11 (100)	11 (100)	22 (100)
	Yes	0 (0)	0 (0)	0 (0)
Ever been diagnosed with ADHD	**No**	10 (91)	11 (100)	21 (95)
	Yes	1 (9)	0 (0)	1 (5)
Diagnosed with epilepsy	**No**	7 (64)	5 (45)	12 (55)
	Yes	4 (36)	6 (55)	10 (45)
Currently on medication for epilepsy	**No**	5 (56)	5 (45)	10 (50)
	Yes	4 (44)	6 (55)	10 (50)
Seizure in the last year	**No**	8 (80)	9 (82)	17 (81)
	Yes	2 (20)	2 (18)	4 (19)
Seizure in the last 5 years	**No**	8 (80)	6 (55)	14 (67)
	Yes	2 (20)	5 (45)	7 (33)
Use of physical intervention to manage challenging behaviour	**No**	11 (100)	8 (73)	19 (86)
	Yes	0 (0)	3 (27)	3 (14)
Training in physical interventions (if answered Yes to having used P.I.)	**No**	N/A	0 (0)	0 (0)
	Yes	N/A	3 (100)	3 (100)
Length of time since P.I. training last received (if answered Yes to having received P.I. training)	**Less than 6 months ago**	N/A	2 (67)	2 (67)
	6 months to 1 year ago	N/A	1 (33)	1 (33)
	1 to 2 years ago	N/A	0 (0)	0 (0)
	More than 2 years ago	N/A	0 (0)	0 (0)
Use of seclusion to manage	**No**	5 (50)	10 (91)	15 (71)

		Control (n=11)	Intervention (n=11)	Overall (n=22)
challenging behaviour	**Yes**	5 (50)	1 (9)	6 (29)
Use of PRN medication to manage challenging behaviour	**No**	6 (60)	6 (55)	12 (57)
	Yes	4 (40)	5 (45)	9 (43)
In regular contact with the LD team	**No**	0 (0)	1 (9)	1 (5)
	Yes	11 (100)	10 (91)	21 (95)
Median Confidence handling challenging behaviour score (IQR, min, max)		10 (8.0 to 10.0, 7, 10)	10 (8.5 to 10.0, 7, 10)	10 (8.0 to 10.0, 7, 10)

*Data are n (%) unless specified otherwise.

Participants were on a median risperidone dose of 1.5mg prior to randomisation (IQR = 1.0 to 2.0mg), with two participants on a dose 4mg or higher (9%). The majority of participants were given risperidone twice a day (17, or 77% of those randomised), and for those whose data were known/available 20 participants had been on risperidone for more than a year (Table 8).

*Table 8: Pre-randomisation risperidone medication characteristics of study participants**

		Control	Intervention	Overall
Median total daily dose in mg (IQR, min, max)		1.5 (1.0 to 2.0, 0.5, 4)	1.0 (1.0 to 2.0, 0.5, 8)	1.5 (1.0 to 2.0, 0.5, 8)
Total daily dose less than 4mg		10 (91)	10 (91)	20 (91)
Total daily dose at least 4mg		1 (9)	1 (9)	2 (9)
Frequency (times per day)	**Once**	2 (18)	3 (27)	5 (23)
	Twice	9 (82)	8 (73)	17 (77)
Length of time on risperidone	**Not known**	0 (0)	1 (9)	1 (5)
	More than a year	10 (100)	10 (91)	20 (95)

*Data are n (%) unless specified otherwise.

The mean ABS total score was 162 (SD = 61.7), with no participants having an ABS-derived IQ that was 70 or higher. Median scores were 0 on all domains of the Mini PAS-ADD interview, for both four-week and two-year recall periods, and mental health thresholds were rarely triggered. One participant triggered the threshold for having a depressive disorder in the last two-years, one for an anxiety disorder in the last two-years, and three for psychosis in the last two-years. No thresholds for triggered for disorders in the last four-weeks (Table 9.)

Table 9: Pre-randomisation adaptive behaviour and mental health

			Control	Intervention	Overall
Adaptive behaviour (ABS)		**Total raw score***	145 (54.0, 58, 237)	180 (66.8, 78, 296)	162 (61.7, 58, 296)
		Derived IQ score*	28 (9.5, 18, 44)	27 (13.7, 11, 55)	27 (11.4, 11, 55)
		IQ less than 70†	10 (100)	10 (100)	20 (100)
		IQ at least 70†	0 (0)	0 (0)	0 (0)
Mental health (Mini PAS-ADD interview)	**Depressive Disorder**	**Score in the last 4 weeks**‡	0 (0 to 2, 0, 3)	0 (0 to 1, 0, 2)	0 (0 to 1, 0, 3)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 0, 0, 0)	0 (0 to 1, 0, 12)	0 (0 to 0, 0, 12)
		Threshold in the last 2 years†	0 (0)	1 (13)	1 (7)
	Anxiety Disorder	**Score in the last 4 weeks**‡	0 (0 to 2, 0, 4)	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 4)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 13)	0 (0 to 0, 0, 13)

		Threshold in the last 2 years†	0 (0)	1 (20)	1 (13)
	Hypomania /mania (expansive mood)	**Score in the last 4 weeks**‡	0 (0 to 2, 0, 2)	0 (0 to 0, 0, 1)	0 (0 to 1, 0, 2)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 1, 0, 1)	0 (0 to 1, 0, 1)	0 (0 to 1, 0, 1)
		Threshold in the last 2 years†	0 (0)	0 (0)	0 (0)
	Obsessive Compulsive	**Score in the last 4 weeks**‡	0 (0 to 1, 0, 2)	0 (0 to 1, 0, 2)	0 (0 to 1, 0, 2)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 0)
		Threshold in the last 2 years†	0 (0)	0 (0)	0 (0)
	Psychosis	**Score in the last 4 weeks**‡	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 0)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 0, 0, 3)	0 (0 to 0, 0, 2)	0 (0 to 0, 0, 3)
		Threshold in the last 2 years†	1 (9)	2 (18)	3 (14)
	Unspecified Disorder	**Score in the last 4 weeks**‡	0 (0 to 2, 0, 2)	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 2)
		Threshold in the last 4 weeks†	0 (0)	0 (0)	0 (0)
		Score in the last 2 years‡	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 5)	0 (0 to 0, 0, 5)

		Threshold in the last 2 years†	0 (0)	0 (0)	0 (0)

*Mean (SD, min, max). †n (%). ‡Median (IQR, min, max).

Clinical scores were generally low at baseline. The median MOAS total score was 1 (IQR = 0 to 2). Median scores on the ABC were highest for the irritability (median = 4, IQR = 1 to 8) and hyperactivity subscales (median = 5, IQR = 2 to 13). The median scores on the PAS-ADD checklist were 0 and no participants met thresholds for any conditions/disorders. At least one antipsychotic side effect was reported by 16 participants (73%), with a median total number of side effects of 1 (IQR = 0 to 3). No participants met the threshold for a possible movement disorder prior to randomisation (Table 10).

*Table 10: Pre-randomisation clinical scores of study participants**

		Control	**Intervention**	**Overall**
Aggression (MOAS)	**Total score**	1 (0 to 2, 0, 34)	1 (0 to 3, 0, 9)	1 (0 to 2, 0, 34)
	Verbal aggression subscale	0 (0 to 1, 0, 30)	0 (0 to 1, 0, 7)	0 (0 to 1, 0, 30)
	Physical aggression against objects subscale	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 2)	0 (0 to 0, 0, 2)
	Physical aggression against self-subscale	0 (0 to 2, 0, 2)	0 (0 to 0, 0, 3)	0 (0 to 1, 0, 3)
	Physical aggression against others subscale	0 (0 to 0, 0, 2)	0 (0 to 0, 0, 1)	0 (0 to 0, 0, 2)
Other challenging behaviour (ABC)	**Irritability subscale**	4 (2 to 6, 0, 23)	5 (1 to 9, 0, 31)	4 (1 to 8, 0, 31)
	Lethargy subscale	2 (1 to 10, 0, 16)	1 (0 to 9, 0, 16)	2 (0 to 9, 0, 16)
	Stereotypy subscale	0 (0 to 2, 0, 12)	0 (0 to 1, 0, 8)	0 (0 to 1, 0, 12)

		Control	Intervention	Overall
	Hyperactivity / non-compliance subscale	5 (3 to 14, 0, 21)	5 (2 to 10, 0, 26)	5 (2 to 13, 0, 26)
	Inappropriate speech subscale	0 (0 to 4, 0, 8)	1 (1 to 5, 0, 11)	1 (0 to 5, 0, 11)
Mental health (PAS-ADD)	**Possible organic condition total score**	0 (0 to 0, 0, 1)	0 (0 to 0, 0, 4)	0 (0 to 0, 0, 4)
	Meets threshold for possible organic condition [n (%)]	0 (0)	0 (0)	0 (0)
	Affective or neurotic disorder total score	0 (0 to 0, 0, 1)	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 1)
	Meets threshold for affective or neurotic disorder [n (%)]	0 (0)	0 (0)	0 (0)
	Psychotic disorder total score	0 (0 to 0, 0, 0)	0 (0 to 0, 0, 1)	0 (0 to 0, 0, 1)
	Meets threshold for psychotic disorder [n (%)]	0 (0)	0 (0)	0 (0)
Adverse effects of psychotropic medication (ASC)	**No side effects present [n (%)]**	3 (27)	3 (27)	6 (27)
	At least one side effect present [n (%)]	8 (73)	8 (73)	16 (73)
	Total number of side effects present	2 (1 to 4, 0, 10)	1 (1 to 2, 0, 7)	1 (0 to 3, 0, 10)
Movement disorders (DISCUS)	**Total score**	0 (0 to 0, 0, 4)	0 (0 to 1, 0, 2)	0 (0 to 0, 0, 4)
	Threshold met [n (%)]	0 (0)	0 (0)	0 (0)

*Data are Median (IQR, min, max) unless specified otherwise.

4.2.2 Randomisation characteristics

Twenty-two participants were randomised in total, with 11 allocated to each arm. As previously described, the majority of participants were on a total daily dose of risperidone less than 4mg, and the majority were recruited from community LD teams. The arms were well balanced with respect to these key variables (Table 11).

Table 11: Characteristics of study participants at randomisation

Recruitment route	Total daily dose	Control	Intervention	Overall
Primary care	Less than 4mg	2	1	3
	At least 4mg	0	1	1
	Overall	2	2	4
Community LD teams	Less than 4mg	8	9	17
	At least 4mg	1	0	1
	Overall	9	9	18
Overall	Less than 4mg	10	10	20
	At least 4mg	1	1	2
	Overall	11	11	22

4.3 Participant retention outcomes

Of the 22 participants randomised, progression from Stage 0 (run-in Stage) to Stage 1 (first reduction Stage) was achieved by 19 (86%), with three participants withdrawing from trial medication prior to progression. Progression from Stage 1 to Stage 2 was achieved by 13 participants (59%), with a further four participants withdrawing from trial medication and two having their progression delayed. Thirteen participants continued progression through Stage 3 and Stage 4, with one participant withdrawing from trial medication prior to each progression point. Therefore, progression through all four Stages of reduction (potential reduction if allocated to the control arm) was achieved by 13 participants (59%), with six of these participants from the control arm and seven from the intervention. An additional one intervention participant withdrew from trial treatment following progression to Stage 4.

Follow-up data at six and nine-months post-randomisation was obtained for 17 participants (77% of those randomised), with ten intervention participants and seven control participants followed up (Table 12).

Participants who progressed to Stage 4 tended to be older (mean age for those who progressed was 47 years (SD = 12.3) compared to 37 years (SD = 13.2) for those who did not progress), have higher MOAS total score, ABC-lethargy, and ABC-hyperactivity scores at baseline, and were more likely to have their challenging behaviour managed using PRN medication prior to randomisation (62% for those who progressed, 13% for those who did not progress). Participants who progressed were less likely to have a diagnosis of ASD (31% for those who progressed, 67% for those who did not), and were less likely to have consented themselves (8% for those who progressed, 33% for those who did not) (Table 13).

*Table 12: Progression of participants through the study post-randomisation**

	Stage		Control	Intervention	Overall
		Total randomised	11 (100)	11 (100)	22 (100)
Intervention receipt	**Stage 0 to Stage 1**	**Withdrew before progressing to Stage 1**	2 (18)	1 (9)	3 (14)
		Progressed from Stage 0 to Stage 1	9 (82)	10 (91)	19 (86)
	Stage 1 to Stage 2	**Withdrew between Stage 1 and Stage 2**	3 (27)	1 (9)	4 (36)
		Delayed progression between Stage 1 and Stage 2	0 (0)	2 (18)	2 (9)
		Progressed from Stage 1 to Stage 2	6 (55)	7 (64)	13 (59)
	Stage 2 to Stage 3	**Withdrew between Stage 2 and Stage 3**	0 (0)	1 (9)	1 (5)
		Delayed progression between Stage 2 and Stage 3	0 (0)	1 (9)	1 (5)
		Progressed from Stage 2 to Stage 3	6 (55)	7 (64)	13 (59)
	Stage 3 to Stage 4	**Withdrew between Stage 3 and Stage 4**	0 (0)	1 (9)	1 (5)
		Progressed from Stage 3 to Stage 4	6 (55)	7 (64)	13 (59)
	Stage 4 to Stage 4 (repeat 1)	**Withdrew between Stage 4 and Stage 4 (repeat 1)**	0 (0)	1 (9)	1 (5)
		Progressed from Stage 4 to Stage 4 (repeat 1)	6 (55)	6 (55)	12 (55)
	Stage 4 to Stage 4 (repeat	**Progressed from Stage 4 to Stage 4 (repeat 2)**	6 (55)	6 (55)	12 (55)

	2)				
	Stage 4 to Stage 4 (repeat 3)	**Progressed from Stage 4 to Stage 4 (repeat 3)**	6 (55)	6 (55)	12 (55)
Participant follow-up		**Completed six-month follow-up**	7 (64)	10 (91)	17 (77)
		Completed nine-month follow-up	7 (64)	10 (91)	17 (77)

*Data are n (%).

*Table 13: Univariable comparison of pre-randomisation characteristics of those who did and did not progress to Stage 4**

Domain	Variable	Did not progress to Stage 4 (n=9)	Progressed to Stage 4 (n=13)	p-value†
Participant characteristics	Mean age (SD)	37 (13.2)	47 (12)	0.080
	Gender (male)	5 (56)	10 (77)	0.290
	Consent provided by participant	3 (33)	1 (8)	0.125
	Diagnosis of ASD	6 (67)	4 (31)	0.096
	Diagnosed with epilepsy	5 (56)	5 (39)	0.429
	Mean ABS raw score (SD)	176.9 (66.49)	152.5 (59.22)	0.401
Challenging behaviour characteristics	Median MOAS total score (IQR)	0 (0 to 1)	1 (1 to 4)	0.055
	Median ABC – irritability score (IQR)	3 (0 to 5)	5 (4 to 10)	0.213
	Median ABC – lethargy score (IQR)	0 (0 to 1)	9 (2 to 10)	0.011
	Median ABC – stereotypy score (IQR)	0 (0 to 1)	0 (0 to 3)	0.430
	Median ABC – hyperactivity score (IQR)	3 (1 to 5)	8 (5 to 14)	0.087
	Median ABC – inappropriate speech (IQR)	0 (0 to 1)	2 (0 to 5)	0.154
	ASC – presence of antipsychotic medication side-effects	6 (67)	10 (77)	0.595
	Median ASC- number of side-effects present (IQR)	1 (0 to 2)	2 (1 to 3)	0.356
	Use of physical intervention to manage CB	1 (11)	2 (15)	0.774

	Use of seclusion to manage CB	2 (25)	4 (31)	0.776
	Use of PRN medication to manage CB	1 (13)	8 (62)	0.027
	Median Confidence managing CB (IQR)	10 (9 to 10)	10 (8 to 10)	0.797
Antipsychotic medication characteristics	Median Starting dose of risperidone (IQR)	2 (1 to 2.5)	1.5 (1 to 1.5)	0.357
	Dosing frequency (once daily)	2 (22)	3 (23)	0.962
	Dosing frequency (twice daily)	7 (78)	10 (77)	

*Data are n (%) unless specified otherwise. †p-value based on independent samples t-test if means (SDs) are presented, Mann-Whitney U test if medians (IQRs) are presented, and Chi-square tests if frequencies and percentages are presented.

4.4 Clinical outcomes

4.4.1 Aggression (MOAS total score)

At six-months post-randomisation, MOAS total scores remained low, but higher in those randomised to the intervention arm, with differences more discernible for the MITT population (control mean = 3.0 (SE = 1.86), intervention mean 4.5 (SE = 4.5)) than the PP population (control mean = 3.5 (SE = 2.13), intervention mean = 3.6 (SE = 1.85)). The adjusted mean differences for both populations both indicated higher MOAS total scores for those randomised to the intervention arm, though 95% CIs were wide and included zero.

MOAS total scores were higher at nine-months post-randomisation than they were at six months, remaining higher in those randomised to the intervention arm in both MITT (control mean = 3.7 (SE = 3.55), intervention mean = 7.7 (SE = 3.51)) and PP (control mean = 4.3 (SE = 4.14), intervention mean = 9.3 (SE = 4.94)) populations. The adjusted mean differences both indicated higher MOAS total scores for those randomised to the intervention arm, though as for data at six-months, 95% CIs were wide and included zero (Table 14).

Reflecting on our originally planned primary analysis (i.e. between-group comparison of the MOAS total score at nine-month post-randomisation, with a two-sided 90% CI fitted and the

upper limit of the CI inspected for non-inferiority), Table 15 and

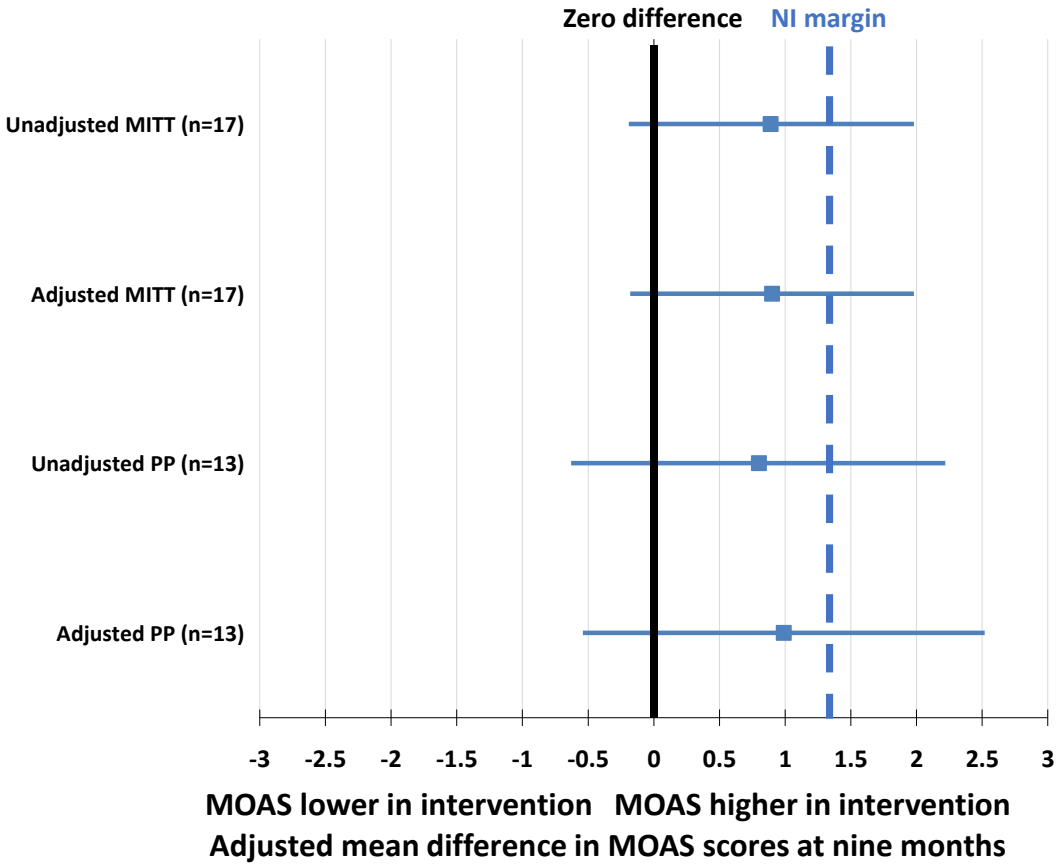


Figure 4 demonstrate that the upper limit of the CI in both the MITT and PP populations (and for unadjusted and adjusted analyses) includes the stated non-inferiority margin. Therefore, we were unable to conclude non-inferiority on the basis of this study.

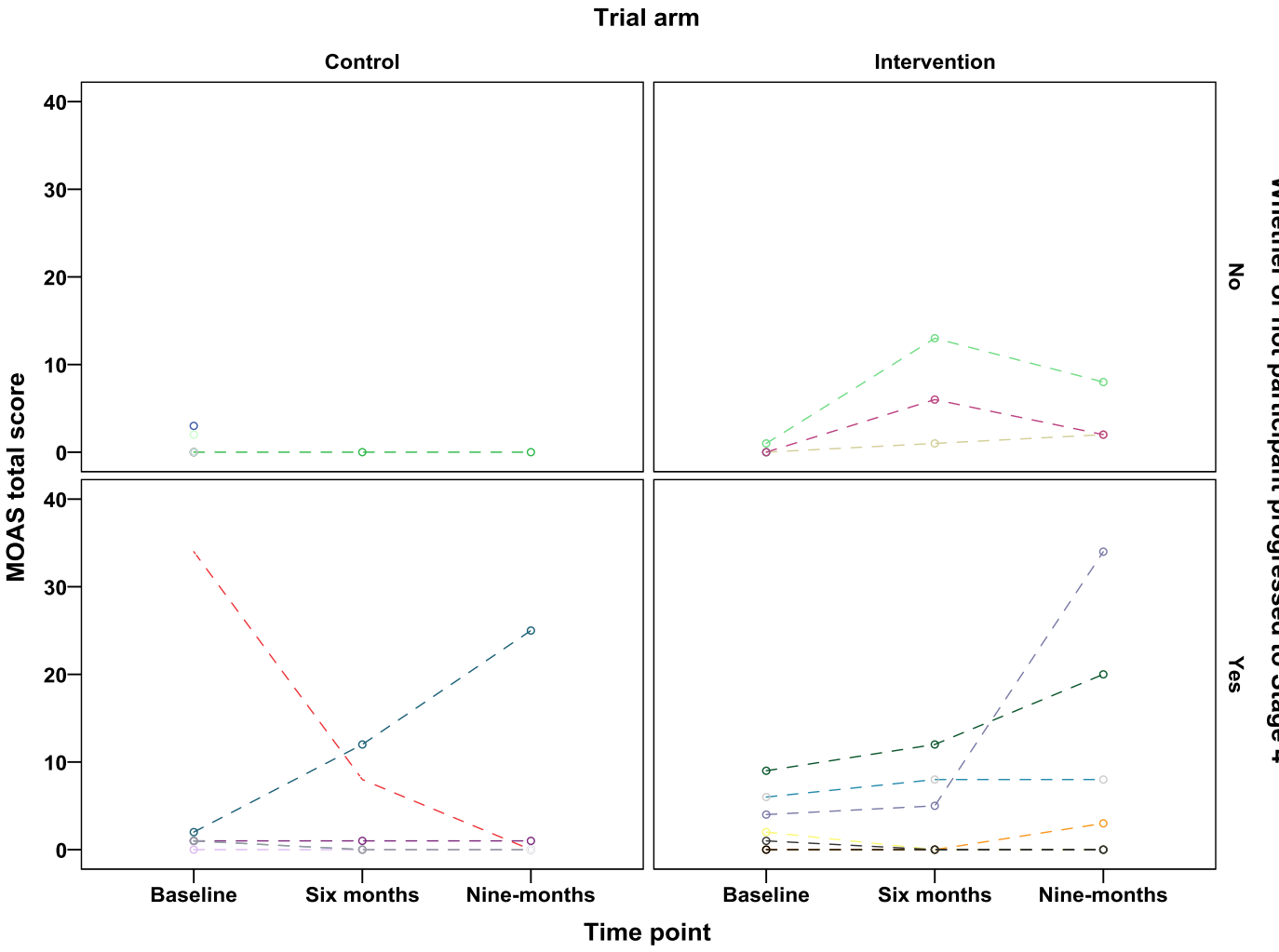


Figure 5 plots MOAS total scores for each individual at each time point, separating participants by their trial arm and whether or not they progressed onto Stage 4. A change in the MOAS total score of 4 was deemed clinically important.[19] For the majority of participants, change in MOAS total scores over time was slight. However, five participants experienced a change from baseline in MOAS total score of at least 4. Two of these participants had been allocated to the intervention arm and had progressed to Stage 4, one had been allocated to the control arm and had progressed to Stage 4, and two had been allocated to the intervention arm and had not progressed to Stage 4 (with both of these participants experiencing an increase in their MOAS total score at six months and then a decrease between six and nine months).

Table 14: Between-group comparison of MOAS scores at six and nine-months post-randomisation

Time point	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)*	Adjusted mean difference*†	95% CI of adjusted mean difference
Six months	**MITT (n=17)**	3.0 (1.86)	4.5 (1.62)	1.5 (2.49)	0.47	-0.55 to 1.48
	PP (n=13)	3.5 (2.13)	3.6 (1.85)	0.1 (2.80)	0.05	-1.03 to 1.13
Nine months	**MITT (n=17)**	3.7 (3.55)	7.7 (3.51)	4.0 (5.15)	0.90	-0.42 to 2.22
	PP (n=13)	4.3 (4.14)	9.3 (4.94)	5.0 (6.58)	0.99	-0.90 to 2.88

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and MOAS score at baseline. MOAS scores (baseline and follow-up) were transformed via the LN+1 transformation to fulfil linear regression assumptions, and adjusted mean differences are presented on the transformed scale.

Table 15: Replication of the original planned primary analysis (MOAS total score at nine-months post-randomisation)

Participant population (n)	Unadjusted / adjusted	Mean difference*	90% CI of mean difference
MITT (n=17)	**Unadjusted**	0.89	-0.19 to 1.98
	Adjusted†	0.90	-0.18 to 1.98
pp (n=13)	**Unadjusted**	0.80	-0.63 to 2.22
	Adjusted†	0.99	-0.54 to 2.52

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and MOAS score at baseline. MOAS scores (baseline and follow-up) were transformed via the LN+1 transformation to fulfil linear regression assumptions, and adjusted mean differences are presented on the transformed scale.

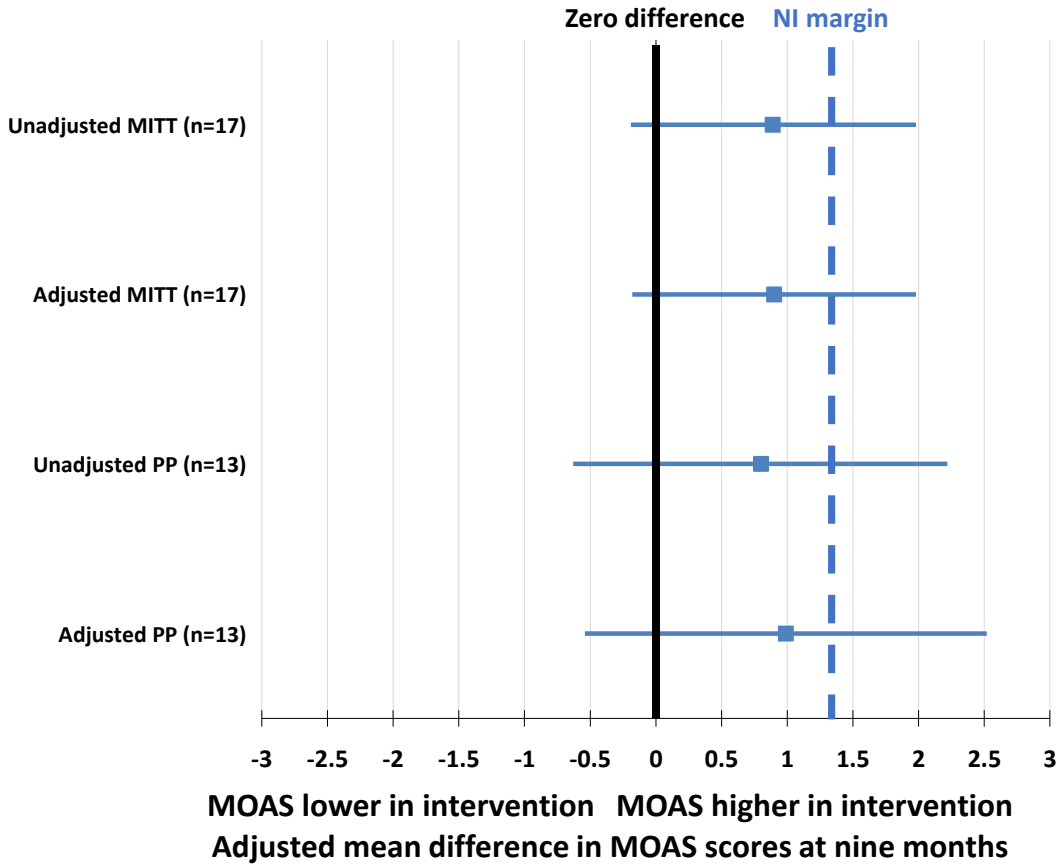


*Figure 4: Forest plot illustrating between-group mean differences on the MOAS at nine-months post-randomisation, with two-sided 90% confidence intervals**

*Estimates / confidence intervals are on the LN [x + 1] scale. Original non-inferiority margin of 3 has been translated onto this scale (1.39).

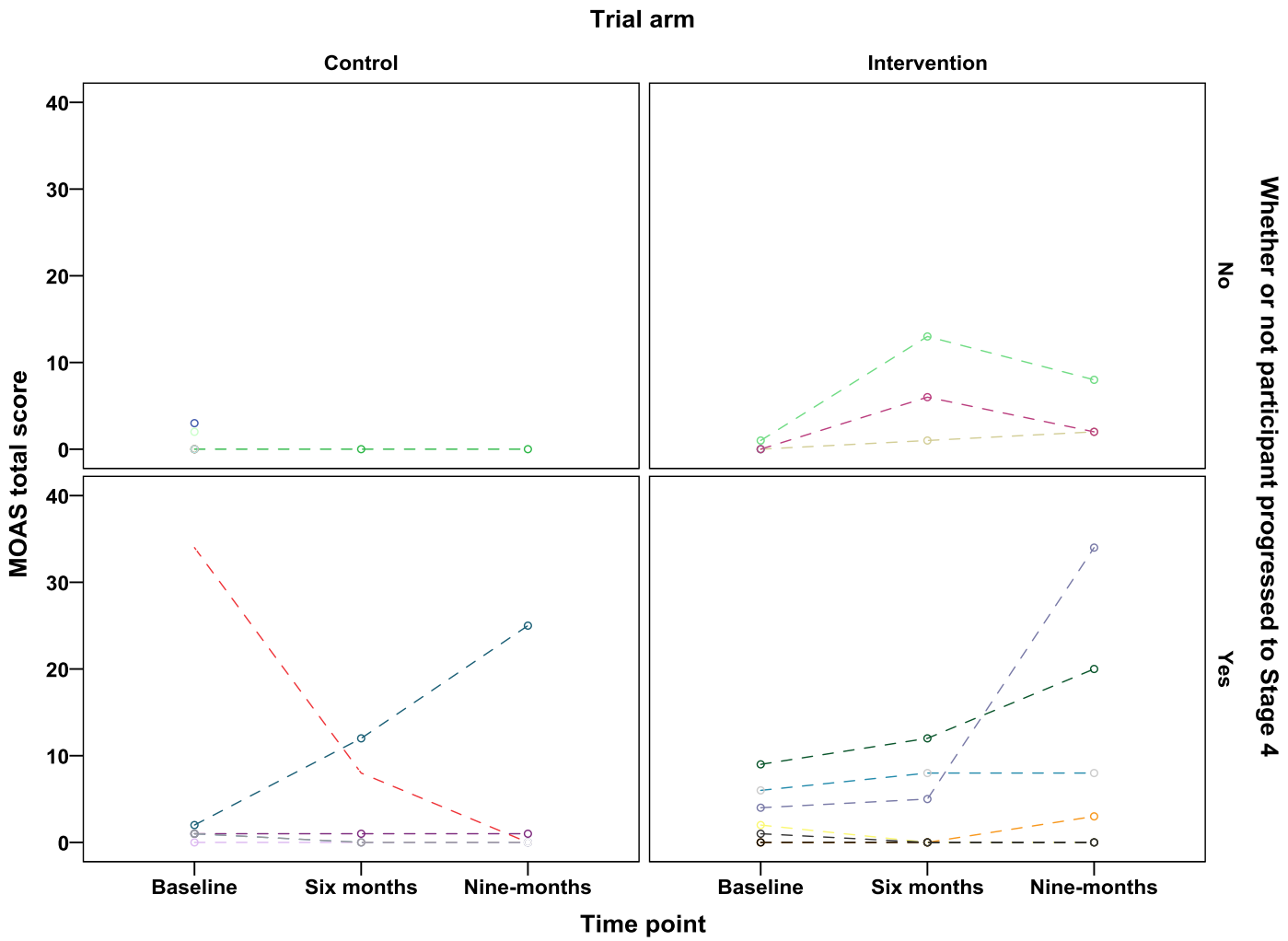


Figure 5: Individual MOAS total scores over time by trial arm and whether participant progressed onto Stage 4 of the intervention

4.4.2 Psychotropic medication use

The average total daily dose of risperidone was lower in those randomised to the intervention arm compared to those randomised to control at both six and nine-months post-randomisation, and in both ITT and MITT populations. In the MITT population (i.e. in those for whom this outcome was available), the mean was 1.6mg lower in the intervention arm (SE = 0.24), whereas in the ITT population (i.e. assuming risperidone use had returned to baseline levels in those for whom this outcome was not available) the mean was 0.6mg lower (SE = 0.78). As one participant withdrew from trial treatment soon after progressing to Stage 4 (i.e. there were no additional withdrawals before the six and nine-month time points), the differences in level of psychotropic medication use at six and nine months were identical (Table 16).

Table 16: Between-group comparison of psychotropic medication use at six and nine-months post-randomisation

Time point	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)
Six months	**ITT (n=22)**	1.7 (0.29)	1.1 (0.73)	-0.6 (0.78)
	MITT (n=12)	1.6 (0.24)	0.0 (0.00)	-1.6 (0.24)
Nine months	**ITT (n=22)**	1.7 (0.29)	1.1 (0.73)	-0.6 (0.78)
	MITT (n=12)	1.6 (0.24)	0.0 (0.00)	-1.6 (0.24)

*Difference calculated as Intervention - Control.

4.4.3 Other challenging behaviour (ABC subscales)

At six-months post-randomisation, mean ABC subscale scores were higher in those randomised to the intervention arm, with differences generally more discernible for the PP population than for the MITT population. While descriptively, the means were consistently higher for the intervention arm, the adjusted mean difference was negative (indicating a lower adjusted mean in the intervention arm) for the irritability subscale (PP population) and inappropriate speech subscale (MITT and PP populations). However, other than for the stereotypy subscale (both MITT and PP populations), all 95% CIs included zero.

While mean scores on the irritability and stereotypy subscales remained higher in the intervention arm at nine-months post-randomisation, mean lethargy, hyperactivity, and inappropriate speech scores were lower in the intervention arm. The 95% CIs of the adjusted mean differences for all ABC subscales included zero at nine-months (Table 17).

Table 17: Between-group comparison of ABC subscale scores at six and nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)*	Adjusted mean difference*†	95% CI of adjusted mean difference
Six months	Irritability	MITT (n=17)	7.1 (3.16)	11.7 (4.00)	4.6 (5.48)	0.60	-4.82 to 6.02
		PP (n=13)	7.7 (3.69)	13.1 (5.68)	5.5 (7.05)	-2.30	-9.33 to 4.74
	Lethargy	MITT (n=17)	4.6 (2.03)	7.5 (3.39)	3.0 (4.42)	4.00	-3.73 to 11.73
		PP (n=13)	5.2 (2.30)	8.4 (4.83)	3.3 (5.66)	2.77	-7.92 to 13.46
	Stereotypy	MITT (n=17)	2.1 (1.53)	4.2 (1.33)	2.1 (2.05)	2.88	0.36 to 5.34
		PP (n=13)	2.5 (1.77)	5.0 (1.77)	2.5 (2.52)	3.97	0.96 to 6.98
	Hyperactivity / non-compliance	MITT (n=17)	8.3 (2.90)	11.0 (3.23)	2.7 (4.57)	2.20	-4.52 to 8.91
		PP (n=13)	9.4 (3.19)	11.9 (4.65)	2.5 (5.84)	1.30	-8.06 to 10.66
	Inappropriate speech	MITT (n=17)	3.0 (1.07)	3.7 (1.32)	0.7 (1.82)	-0.55	-2.35 to 1.26
		PP (n=13)	3.2 (1.25)	4.9 (1.84)	1.3 (2.30)	-1.03	-3.47 to 1.42
Nine months	Irritability	MITT (n=17)	5.5 (1.65)	8.4 (3.15)	2.9 (4.04)	0.36	-5.34 to 6.05
		PP (n=13)	5.4 (2.00)	9.7 (4.34)	4.3 (5.05)	0.27	-8.47 to 9.02
	Lethargy	MITT (n=17)	4.3 (1.21)	4.0 (1.02)	-0.3 (1.59)	-0.29	-3.76 to 3.18
		PP (n=13)	4.7 (1.36)	3.7 (0.99)	-1.0 (1.65)	-0.76	-4.69 to 3.17
	Stereotypy	MITT (n=17)	2.1 (1.28)	2.5 (0.99)	0.4 (1.60)	0.95	-1.34 to 3.24
		PP (n=13)	2.5 (1.46)	2.6 (1.34)	0.1 (1.98)	0.98	-2.05 to 4.01

	Hyperactivity / non-compliance	**MITT (n=17)**	6.9 (1.84)	5.6 (1.71)	-1.3 (2.56)	-1.53	-6.24 to 3.19
		PP (n=13)	7.7 (1.96)	5.9 (2.24)	-1.8 (3.03)	-1.84	-8.51 to 4.83
	Inappropriate speech	**MITT (n=17)**	2.0 (0.66)	2.4 (0.85)	0.4 (1.12)	-0.30	-1.91 to 1.31
		PP (n=13)	2.0 (0.78)	2.7 (1.17)	0.7 (1.46)	-0.55	-2.79 to 1.70

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and corresponding ABC subscale at baseline.

4.4.4 Mental health (PAS-ADD checklist)

Mean scores on the subscales of the PAS-ADD checklist were higher in the intervention group at both six and nine-months post-randomisation, and for both MITT and PP populations. Due to a high frequency of zero scores from participants, linear regression analyses were not possible for all outcomes. Similar to the analysis of ABC subscales, while descriptively the mean scores were consistently higher for the intervention arm, for two analyses (affective/neurotic disorder at nine-months for the PP population and psychotic disorder at nine-months in the MITT population) the adjusted mean difference (where an adjustment was made for the recruitment route and corresponding score at baseline) indicated that these were lower in the intervention arm. However, all 95% CIs of the adjusted mean differences included zero (Table 18).

Table 18: Between-group comparison of PAS-ADD subscale total scores at six and nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)*	Adjusted mean difference*†	95% CI of adjusted mean difference
Six months	Possible organic disorder	MITT (n=17)	0.1 (0.14)	1.0 (0.60)	0.9 (0.73)	0.26	-0.28 to 0.79
		PP (n=13)	0.2 (0.17)	1.4 (0.81)	1.3 (0.83)		
	Affective or neurotic disorder	MITT (n=17)	0.3 (0.30)	0.8 (0.51)	0.5 (0.67)		
		PP (n=13)	0.4 (0.35)	0.9 (0.71)	0.5 (0.83)		
	Psychotic disorder	MITT (n=16)	0.0 (0.00)	0.2 (0.13)	0.2 (0.13)		
		PP (n=12)	0.0 (0.00)	0.3 (0.18)	0.3 (0.22)		
Nine	Possible organic	MITT (n=17)	0.1 (0.14)	0.9 (0.46)	0.8 (0.48)		

months	**disorder**	**PP (n=13)**	0.2 (0.17)	1.3 (0.61)	1.1 (0.63)	0.52	-0.23 to 1.26
	Affective or neurotic disorder	**MITT (n=17)**	0.3 (0.18)	0.8 (0.59)	0.5 (0.73)		
		PP (n=13)	0.2 (0.17)	1.1 (0.83)	1.0 (0.91)	-0.27	-0.70 to 0.16
	Psychotic disorder	**MITT (n=16)**	0.3 (0.33)	0.4 (0.31)	0.1 (0.47)	-0.29	-0.95 to 0.62
		PP (n=12)	0.0 (0.00)	0.6 (0.43)	0.6 (0.43)		

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and corresponding PAS-ADD subscale at baseline. PAS-ADD scores (baseline and follow-up) for the subscale *possible organic disorder* (MITT at six months and PP at nine months) were transformed via the LN+1 transformation to fulfil linear regression assumptions, and adjusted mean differences are presented on the transformed scale. Scores for the subscale *affective or neurotic disorder* (PP at nine months) were transformed via the [1/(x+1)] transformation to fulfil linear regression assumptions.

At six-months post-randomisation, the threshold for a possible organic disorder was triggered by one participant in the intervention arm. At nine-months, the threshold for an affective or neurotic disorder was triggered by one participant in the intervention arm, and the threshold for a psychotic disorder was triggered by two participants (one per arm) (Table 19).

Table 19: Between-group comparison of PAS-ADD subscale thresholds at six and nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control n (%)	Intervention n (%)
Six months	Possible organic disorder	MITT (n=17)	0 (0)	1 (10)
		PP (n=13)	0 (0)	1 (14)
	Affective or neurotic disorder	MITT (n=17)	0 (0)	0 (0)
		PP (n=13)	0 (0)	0 (0)
	Psychotic disorder	MITT (n=16)	0 (0)	0 (0)
		PP (n=12)	0 (0)	0 (0)
Nine months	Possible organic disorder	MITT (n=17)	0 (0)	0 (0)
		PP (n=13)	0 (0)	0 (0)
	Affective or neurotic disorder	MITT (n=17)	0 (0)	1 (10)
		PP (n=13)	0 (0)	1 (14)
	Psychotic disorder	MITT (n=16)	1 (17)	1 (10)
		PP (n=12)	0 (0)	1 (14)

4.4.5 Adverse effects of psychotropic medication (ASC)

In the MITT population, at least one side-effect of psychotropic medication was reported by seven control participants (100%) and eight intervention participants (80%), when asked at nine-months post-randomisation. In the PP population (i.e. in those who had progressed to Stage 4 and for whom outcome data were available), all participants reported at least one side-effect (Table 20).

The mean number of psychotropic medication side-effects reported at nine-months post-randomisation was higher in the control arm (MITT mean = 2.6 (SE = 0.72)) than the intervention arm (MITT mean = 1.4 (SE = 0.31)), with mean numbers similar for the PP population. However, the 95% CI of the adjusted mean difference included zero for both analyses (Table 21).

Table 20: Between-group comparison of ASC side-effect reporting at nine months post-randomisation

Time point	**Subscale**	**Participant population (n)**	**Control n (%)**	**Intervention n (%)**
Nine months	**At least one side-effect present**	**MITT (n=17)**	7 (100)	8 (80)
		PP (n=13)	6 (100)	7 (100)

Table 21: Between-group comparison of ASC total number of side-effects at nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)*	Adjusted mean difference*†	95% CI of adjusted mean difference
Nine months	**Total number of side-effects reported**	**MITT (n=17)**	2.6 (0.72)	1.4 (0.31)	-1.2 (0.70)	-1.04	-2.52 to 0.44
		PP (n=13)	2.7 (0.84)	1.7 (0.29)	-1.0 (0.89)	-0.74	-2.71 to 1.23

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and corresponding ASC total number of side-effects at baseline.

4.4.6 Movement disorders (DISCUS)

At nine-months post-randomisation, the mean total DISCUS score was higher for the intervention arm (MITT mean = 2.1 (SE = 1.67)) than the control arm (MITT mean = 0.0 (SE = 0.00)), while the mean for intervention participants who progressed to Stage 4 higher again (PP mean = 3.0 (SE = 2.35)) (Table 22). One participant in the intervention arm met the threshold for a possible movement disorder (Table 23).

Table 22: Between-group comparison of DISCUS total score at nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control mean (SE)	Intervention mean (SE)	Unadjusted mean difference (SE)*
Nine months	**Total DISCUS score**	**MITT (n=17)**	0.0 (0.0)	2.1 (1.67)	2.1 (1.67)
		PP (n=13)	0.0 (0.0)	3.0 (2.35)	3.0 (2.35)

*Difference calculated as Intervention - Control.

Table 23: Between-group comparison of DISCUS threshold at nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control n (%)	Intervention n (%)
Nine months	**DISCUS threshold met**	**MITT (n=17)**	0 (0)	1 (10)
		PP (n=13)	0 (0)	1 (14)

4.4.7 Managing challenging behaviour

At nine-months post-randomisation, carers reported using physical intervention to manage challenging behaviour for two participants (both allocated to the intervention arm), though only one of these had progressed through to Stage 4. They reported using seclusion for three participants (both allocated to the control arm), and PRN medication for nine participants (four allocated to control and five to the intervention arm), though for the latter only six of these participants had progressed to Stage 4 (three per arm) (Table 24).

The mean score on the scale measuring confidence handling challenging behaviour was higher for the intervention arm (MITT mean = 9.3 (SE = 0.26)) than for the control arm (MITT mean = 8.7 (SE = 0.36)), with scores similar for the PP population. However, the 95% CIs of the adjusted mean differences included zero (Table 25).

Table 24: Between-group comparison of approaches used to manage challenging behaviour at nine-months post-randomisation

Time point	Subscale	Participant population (n)	Control n (%)	Intervention n (%)
Nine months	**Use of physical intervention to manage challenging behaviour**	**MITT (n=17)**	0 (0)	2 (20)
		PP (n=13)	0 (0)	1 (14)
	Use of seclusion to manage challenging	**MITT (n=17)**	3 (43)	0 (0)
		PP (n=13)	3 (50)	0 (0)

	behaviour			
	Use of PRN medication to manage challenging behaviour	**MITT (n=17)**	4 (57)	5 (50)
		PP (n=13)	3 (50)	3 (43)

Table 25: Between-group comparison of confidence managing challenging behaviour at nine-months post-randomisation

Time point	**Subscale**	**Participant population (n)**	**Control mean (SE)**	**Intervention mean (SE)**	**Unadjusted mean difference (SE)***	**Adjusted mean difference*†**	**95% CI of adjusted mean difference**
Nine months	**Confidence handling challenging behaviour**	**MITT (n=17)**	8.7 (0.36)	9.3 (0.26)	0.6 (0.43)	0.59	-0.28 to 1.45
		PP (n=13)	8.8 (0.40)	9.6 (0.20)	0.7 (0.45)	0.67	-0.26 to 1.60

*Difference calculated as Intervention - Control. †Adjusted for recruitment route and corresponding confidence score at baseline.

4.4.8 Use of PRN medication

Use of PRN medication post-randomisation was captured using carer-reported diaries. However, as indicated by Table 26, the majority of participants did not return these diaries. For those who did, it would appear that PRN use was generally higher in those allocated to the intervention arm and appeared to increase over time. This is also illustrated in Figure 6.

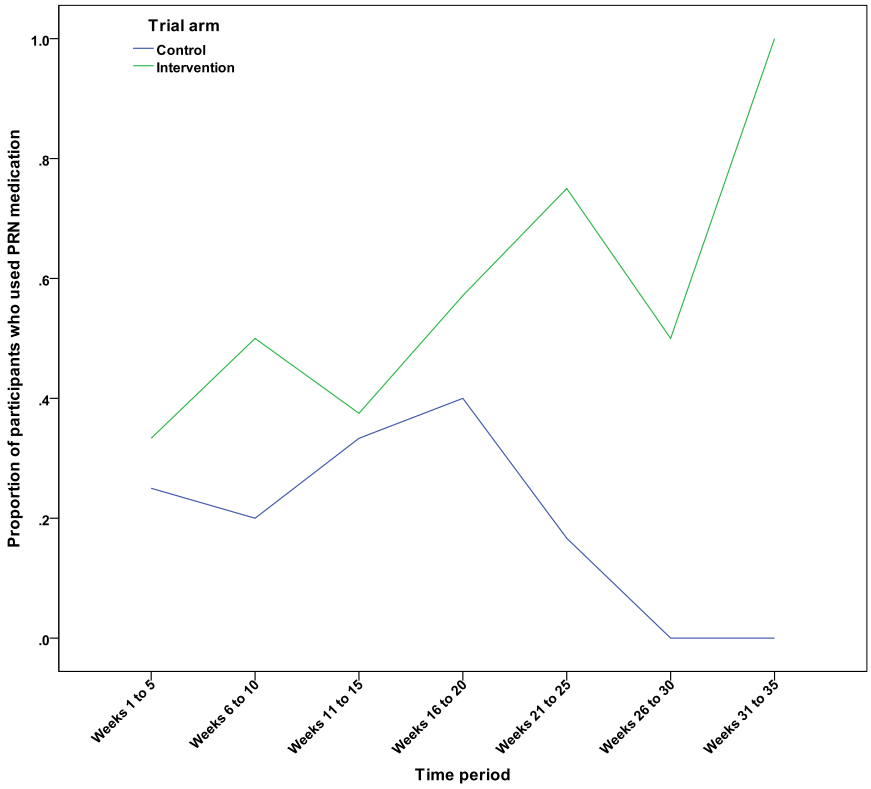
Table 26: PRN use following randomisation

Time	**n**	**Control***	**Intervention***	**Overall***
Weeks 1 to 5	10	1 (25)	2 (33)	3 (30)
Weeks 5 to 10	11	1 (20)	3 (50)	4 (36)
Weeks 11 to 15	14	2 (33)	3 (38)	5 (36)

Weeks 16 to 20	12	2 (40)	4 (57)	6 (50)
Weeks 21 to 25	10	1 (17)	3 (75)	4 (40)
Weeks 26 to 30	6	0 (0)	1 (50)	1 (17)
Weeks 31 to 35	6	0 (0)	3 (100)	3 (50)

*Data are n (%)

Figure 6: PRN use following randomisation



4.4.9 Safety reporting

During the course of the trial, there were four adverse events (AE) reported and one serious adverse event (SAE). The SAE was categorised as 'an event which required intervention to prevent outcomes such as hospitalisation'. There was reported deterioration in the participant's mental health with increased agitation, tearfulness and depressive thoughts as well as reports of hearing a voice. Deterioration was such that crisis intervention was required to avoid hospital admission. It was suspected that these that these symptoms were not a side effect of the trial medication but a recurrence of symptoms masked by the risperidone and

hence was a Serious Adverse Reaction to the withdrawal (i.e. the intervention being trialled during the study) as opposed to the medication itself. This participant withdrew from the trial intervention and the blind was broken. On entry into the trial, the participant had been taking 2.5mg of risperidone daily and progressed through 3 stages of reduction so that when the blind was broken at the time of the SAE, they were taking 0.5mg daily.

5 Qualitative Study

Exploring Carer, Participant and Clinician experiences of the ANDREA-LD trial and of medication reduction

5.1 Rationale for Qualitative Sub-Study

As specified in the original protocol, we planned to undertake qualitative telephone interviews with a proportion of carers, participants and recruiting clinicians who took part in the trial. One of the main purposes of these interviews was to gain insight on barriers to drug reduction in clinical practice as well as attributions of behavioural changes in relation to potential reduction of medication. The interviews had originally been scheduled to take place during the unblinded phase of the trial between the 9 and 12 month time points but due to the need to close trial recruitment early, and the timetable of the subsequent close-down plan, the interviews were brought forward to be conducted between 4-6 months after randomisation.

With awareness amongst the ANDREA-LD team that recruitment issues were becoming increasingly apparent, the qualitative interviews about participants' views of the trial took on greater importance. The team hypothesized that the ANDREA-LD study was challenging to clinicians, carers, and participants due to issues relating to capacity to consent, views about the necessity of anti-psychotic medication, observed changes in behaviour, and the challenges of conducting research with participants who were in residential homes.

5.2 Aim

The qualitative study was therefore set up to explore the experiences and challenges of the study with study participants, their carers, and clinicians using qualitative methods.

5.3 Objectives:

The objectives of the qualitative interviews were to ascertain:

- Views about their reasons for participating in the study and concerns about participating both before and after randomisation.
- Experiences of taking part in the study including the support received from the study team.

- Whether the participant's behaviour had changed during the trial and why those changes may have occurred, and reasons for any partial or full reinstatement to usual care medication during the study period.
- Views on the study medication (size, colour, taste etc) and study processes including consenting arrangements and completion of assessments
- Views about the use of anti-psychotic medication to treat behavioural problems for the participant in particular and also within the learning disability population in general.
- Views about what should happen to participants once the trial finished, including thoughts about whether any participants should continue to be withdrawn from anti-psychotic medication or remain on the usual dose.

5.4 Study design

We used qualitative research methods because this allowed us to explore respondents' views and experiences in-depth, including topics that we were unable to predict in advance. We thought it important to understand the views of a range of stakeholders and so our respondents included participants, carers (including family and professional carers) and recruiting clinicians. As the study had been altered to focus on recruitment in secondary care, only clinicians in these services were included in the interviews. Data were collected through a combination of face-to face interviews with participants, either face to face or telephone interviews with carers, and telephone interviews with clinicians. All data were audio recorded with the respondent's consent.

5.5 Recruitment

Our aim was to interview as many patients, carers and recruiting clinicians as feasibly possible within the time frame and from the participants of the trial.

5.5.1 Interviews with Carers

16 carers (five parents and 11 professional carers) were invited to be interviewed by ANDREA-LD research staff. Interviews were conducted either at the carer's home, in a private room within the residential care home, or by telephone.

5.5.2 Interviews with Patient Participants

With the support of residential care staff in three cases and a parent carer in the remaining case a research assistant approached ANDREA-LD patient participants who had been identified as having mental capacity to consent for themselves during the screening phase of the study. Consent to participate in the qualitative study was undertaken. Interviews were conducted in a private room (an office or lounge) within the residential setting in three cases and in an office within a day centre in the remaining case. All interviews were conducted by a research assistant. A residential carer was present during three of the interviews, a member of day service staff was present during the fourth interview. Carers were asked to support the participants, but to refrain from answering on behalf of the participants.

5.5.3 Telephone Interviews with Clinicians

Eleven secondary care clinicians were contacted to take part in a telephone interview.

5.6 Ethical Requirements

Ethical approval for the qualitative study was given as part of the main ANDREA-LD ethical application. All respondents consented to be approached with information about the qualitative study at the point of consent into the main trial. At the point at which the interviews took place, they were provided with an information sheet about the purpose of the qualitative study and what was being asked of them. All respondents signed a consent form prior to the interview and, in the case of telephone interviews, this was returned in the post. Participating clinicians received a £50 voucher as a 'thank you payment' for participating in an interview, patient participants and carers received a £10 voucher.

5.7 Data collection

An interview topic guide defined the main topics whilst allowing flexibility to pursue issues in more depth as they emerged from the interviews. The semi structured interview schedules for each of the three groups of participants are included in the appendices. All data were transcribed verbatim and anonymized on transcription.

5.8 Data analysis

Data were analysed using thematic analysis with an abductive approach (incorporating themes that had been identified in advance and themes that were derived from the data)[44].

This approach involves systematically coding data according to a thematic framework, which is developed iteratively. The thematic framework was applied to the data using the coding software package NVivo 10. Interpretations were discussed between members of the ANDREA-LD team. All quotations presented have been anonymized and respondents have been given ID numbers. In order to associate the responses from carers with the participant they care for, carer and participant interviews share a common numeric ID, so that carer 7 is the carer for participant 7. However, it was not possible to use this formula for the clinicians as some clinicians had more than one participant recruited in ANDREA-LD. The clinician IDs numbers therefore do not relate to the carer or participant ID numbers.

It is also worth noting that the analysis and report writing for this chapter were conducted blind to which arm each participant was in. It was only when the report had been drafted and commented on by other authors, that the lead analyst was then unblinded to the randomisation for participants and then this information was added to the data extracts. At this point, a further section was added to the discussion section to reflect on participants' responses in the context of their trial arm allocation.

5.9 Results

5.9.1 Interviews with Carers

All 16 (5 parents and 11 professional) carers who had been invited to participate in the study agreed to take part. The five parents interviewed had given advice as Legal Representative that their son/daughter could participate in the ANDREA-LD study. Interviews lasted between 12 and 31 minutes with an average of 19 minutes.

5.9.1.1 Reasons for participating in the study.

The majority of carers had positive reasons for participation such as a desire to reduce the participant's medication if possible. This was seen as desirable as it was felt that medication such as anti-psychotics (but also antidepressants) were modifying the participant's personality. Other staff members felt that the ANDREA-LD study presented an opportunity to review a participant's medication within a supported environment. As such reasons of personal benefit rather than population level altruism seemed to be the main motivators.

Carer 7 (staff): She wanted to try reducing her risperidone um, and she'd been talking with the psychiatrist about it, because she'd managed to come off of her citalopram

(antidepressant) which she'd been on for about 7 years and um, [participant 7] is um, highly emotionally reliant on taking things. She sees it as a fix all, doctors fix everything and pills fix everything and um, we've been trying to kind of get her to be more reliant on stabilising her *own* mood, and having, kind of, safety nets in place for her to check and balance her own mood, rather than relying on lots of medication that made her a zombie really. (Participant in Intervention arm; participant withdrawn during stage 3).

The opportunity to participate was particularly welcomed if the participant had been experiencing side effects of being on anti-psychotic medication.

Carer 17 (parent): they asked, they asked my permission, and I said "if it's going to do good" because he was putting on so much weight and when he was on this, this trial, he, he did lose a lot of weight. (Participant in Intervention arm; participant withdrawn at the end of stage 3)

Interviewer: Can you tell me your reasons for participating in the trial in the first place?

Carer 22 (parent): Yeah because [participant 22's] blood test had shown that he needed to come off the risperidone anyway. (Participant in Control arm; interview conducted at stage 7)

There was one parent who felt that their negative views about antipsychotic medication had not been taken seriously by the health care professionals to date, and that this was their chance to be proactive about medication reduction.

Carer 8 (parent): because I didn't believe that, um, that the medication was right for [participant 8], it wasn't, I didn't think it was doing anything for him really. I weighed it up I thought "well, if I don't take part, well I, I couldn't say anything could I?" (Participant in Control arm; interview conducted at stage 6).

In contrast, there were professional carers who were eager to use the ANDREA-LD study as a mechanism to persuade family members that reduction of medication could be a positive management strategy within the confines of a supported trial and gradual medication reductions without issues of bias clouding the carers' judgement about whether medication reduction was affecting behaviour.

Carer 66 (staff): [psychiatrist] though that he'd be a perfect candidate for the study. He's on risperidone um, she wanted to take him off it, and the study came up at the time and she thought that might me a quick way to reduce them. And then also it would be blind, well

double blind, so no one would really know whether he was coming off it or not. We've had some issues with his family not wanting him to come off it, because of past behaviours that they'd experienced, um so we thought that it would be a good way to, if obviously he took the reduction route, then it would be a good way for him to come off without having those um, maybe false um…
Interviewer; ok
Carer 66 (staff): what they called? Um behaviours (Participant in Intervention arm; interview conducted at stage 5).

However there was a small minority of carers who had rather passive reasons for participation. When asked why they had consented involvement with the ANDREA trial, some carers did not appear to have thought critically about their participation. Instead they had followed the lead of the clinician.

Carer 6 (parent): well um I uh suppose uh it was just that um [Dr's name] said about it
Interviewer: ok
Carer 6 (parent): then um who am I to object? You know? (Participant in Control arm; participant withdrawn at stage 0)
Interviewer: Can you tell me what the reasons were for [name] participating in the trial?
Carer 28 (staff): um, it was well, it was suggested by her psychiatrist
Interviewer: ok
Carer 28 (staff): Um. Because it was thought that she could, that she'd probably be coming off them anyway, so to do the trial first (Participant in Control arm; interview conducted at stage 5).

In some cases the carers reported that ultimately it had been the participant's decision whether or not to participate in the trial.

Carer 52 (staff): there was a discussion between [psychiatrist] and [team leader] and [participant 52] about kind of like the benefits of going ahead with it
Interviewer: ok
Carer 52 (staff): and they had an open discussion and [participant 52] ultimately decided that she'd go for it

Interviewer: ok, so the ultimate decision was left with [participant 52]?
Carer 52 (staff): yeah, yeah, yeah, she consented to it, she um, she was all positive about it the whole time, um yeah I can remember [team leader] was enthusiastic about it but ultimately it was [participant 52's] decision. (Participant in Intervention arm; interview conducted at stage 7).

5.9.1.2 Views about the trial

Concerns about the trial were surprisingly rare given that, for most carers, the ANDREA-LD study was the first large trial or CTIMP that they had experienced. For some, the uncertainty about whether the participant was in the withdrawal or treatment as normal arm was a slight cause of concern, but they understood that was necessary as part of trial procedures.
Interviewer: Were there any concerns that you, or um, maybe her father had about her participating in the trial?

Carer 28 (parent): um, only just, um, the fact that, because she was coming off the risperidone, just, well, we didn't know what, if she was going to be coming off or, or still on it, so um, but the fact that the psychiatrist was thinking of taking her off anyway it was no different.
Interviewer; ok, any concerns you have now that the, kind of, trial is going through?
Carer 28 (parent): no (Participant in Control arm; interview conducted at stage 5).

Even when carers reported that the participant in their care had not responded well to the trial in terms of changes in their behaviour, they still seemed to support the principal of the trial and were positive about the way in which it had been conducted.

Carer 7 (staff): overall I'd say it was really quite positive, you know. Fair enough, [participant 07] didn't react very well to reducing medication that rapidly but that's not to say it might not be fine for someone else. I suppose it's all dependant on how people react to a reduction really. But the support was there, you know, um everyone explained stuff really quite well, um I think yeah, I haven't got any kind of major issues with it. (Participant in Intervention arm; participant withdrawn at stage 3).

For a complex CTIMP in which many participants lived in residential homes, there were surprisingly no real issues with study procedures including the delivery of the medication.

Interviewer: Consent forms and the trial sheets and the diaries and things like that, how did you, kind of get on with all of those?
Carer 28 (staff): yeah, they were good.
Interviewer: ok, and what about the assessments, because I know there were quite a few assessments we asked, um you to do, so how did you find those?
Carer 28 (staff): yeah, they were fine as well (Participant in Control arm; interview conducted at stage 5)
Carer 9 (staff): it was very well organised basically we received delivery the day before the um new meds step box would be completed um so it was delivered in advance of at least 4 days um and yes I was able to contacted them if I needed to make rearrangements but again my concerns again at the beginning with the CRD team um [psychiatrist] and the GP gave us the constant that they're there at the end of the phone. So yes I feel that the project was very well managed and very supportive. (Participant in Intervention arm; interview conducted at stage 4).

There was also a sense from some carers that it had exposed them to research procedures and ideas that had stretched and interested them in a way that was beneficial to themselves and the people they care for.

Carer 24 (parent): I've really enjoyed it because I think it is opened up to you sort of look at other people, "should they be on this? Should they be on that? Can we reduce that?" it does, because sometime you can plod along, and yes they have their yearly review but actually do we really look at their medication? (Participant in Intervention arm; interview conducted at stage 3)

There was one notable exception to the views of carers from the mother of participant 17 who, although had no complaints of the conduct of the study, had felt the experience had been traumatic for herself and participant 17. She was clear that this was a research experience that she did not want to repeat.

Interviewer: So what was your, your general views or your experiences of being involved in the trial, so kind of, how much impact do you think that the study had on, on um you and [participant]?
Carer 17 (parent): Well [participant] was, well he was like a zombie, he was no good for anything. He wasn't eating and like I was saying about his clothes and that, and, and I was so upset
Interviewer: yes
Carer 17 (parent): you know, I wouldn't want him to do any trials like that again. (Participant in Intervention arm; participant withdrawn at stage 3).

When respondents were pressed about how the study could be done differently the main comment related to the study medication which was larger than the normal medication and, for a minority of participants, was difficult to swallow or possibly caused issues to participants who were wary of obvious (in terms of size, shape and colour) changes to their medication.

Carer 57 (staff): Maybe the tablet could be a bit smaller because it is quite a bit of a horse pill to take. (Participant in Intervention arm; interview conducted at stage 4).

Mindful of the problems ANDREA-LD had experienced in participant recruitment, respondents were also asked about how the study might be promoted more amongst professionals and the public. Suggestions were made about promoting it in professional journals, making GPs aware, newsletters, or making charities such as the National Autistic Society aware of the study.

5.9.1.3 Reasons for Withdrawal from the ANDREA study

Eight participants were withdrawn from the ANDREA study before the 9 month study completion period and unblinding of the trial arm. During interviews carers reported reasons for this were due to changes in behaviour and changes in health and wellbeing including: increases in the number of seizures, more violent behaviour, hallucinations, low mood or depression, distress, techy/irritable/grumpy, restlessness, self-harming behaviours, obsessive behaviours such as repeatedly dressing and undressing, an intensification of autistic

behaviours, memory lapses, a disinterest in personal hygiene and appearance, developing a 'zombie-like' personality, and loss of appetite.

For some carers the decision to withdraw the participant from the study was not an easy one and could sometimes cause friction or disappointment amongst team members as they debated the pros and cons of study withdrawal.

Interviewer: So what were the reasons for like, the withdrawal of medication?
Carer 36 (staff): I think it was because, I don't know whether he'd had an increase in seizures or, because he's had these episodes that were so um, like I say, with downstairs staff, you know, that they felt he, that he was becoming more violent or whatever, that maybe that was why, it was like "oh no, we're not happy, let's stick him back on the old…."
Interviewer: Ok, um, and so when he withdraw from the study, did he just go back to normal?
Carer 36 (staff): yeah, just went back straight on. It was perhaps a couple of weeks and you know "oh this isn't working as it's supposed to". Well, well we knew there was going to be, you know, pros and cons or whatever, you know to do with his behaviour. But I did think perhaps sort of try and stick at it for a little bit longer [sighs] I don't know. (Participant in Intervention arm; participant withdrawn at stage 0).

In some cases it was the relatives that had pushed with a study withdrawal while the residential carers were more willing to continue the participant on the study.

Carer 58 (staff): Well we have been having our concerns we weren't ready to jump in straight away ourselves but um [participant 58's] mum she was concerned because she had noticed quite a deterioration when she was with him because when she visited she didn't like any staff around and [participant 58] didn't either. He tended to play up a bit more. And yeah she was saying he had been pushing things a lot more um he had actually attacked the step dad. (Participant in Intervention arm; participant withdrawn at stage 2)
There was also a feeling that for some participants the withdrawal of medication had been too rapid, particularly if they had recently been experiencing other medication changes.
Carer 7 (staff): I think for [participant 7] it was too quick, I think you know, for some people its fine to go up and down a milligram or two or three but she dropped 2/3rds of her medication overnight and that had a pretty profound effect, I mean the reduction in her

citalopram was painfully slow, um but it's what [participant] needed because it was a, a very slow reduction in her security blanket, while she was figuring out what else she could rely on. (Participant in Intervention arm; participant withdrawn stage 3).

One carer reported that her daughter had been withdrawn from the study by her doctor as her daughter had been experiencing hallucinations (although there may also have been concerns about allergic reactions to medications), although withdrawing from the study did not stop her experiencing hallucinations.

Interviewer: So what were the reasons for [participant 6] withdrawal from the study?
Carer 6 (parent): Well as far as I know it was these hallucinations he thought that it that was what the cause of it was she's still having them you see. [DR'S NAME] he took her off
Interviewer: So he thought the trial medication was causing the hallucinations?
Carer 6 (parent): As I said she has a history of being allergic to medications
Interviewer; ok so when he took them off did the hallucinations stop?
Carer 6: No, no
Interviewer: ok um, so when they stopped the trial medication do you know what happened then with her medication? Did she just go back to….?
Carer (parent); yeah what she had before. (Participant in Control arm; participant withdrawn at stage 0).

5.9.1.4 Positive changes in behaviour

Whilst some carers noted a deterioration in behaviour it is worth noting that a few carers during interviews did report positive changes in behaviour during the trial study period. These included: increased energy levels/ increased motivation, less anxiety, and less self-harming behaviour. Other carers reported no notable changes in behaviour. Interestingly if this was the case, they tended to assume that the participant had been on the placebo (maintaining normal dose) arm of the study.

Interviewer: Any thoughts about um the behaviour changes for [participant]? Were they better or worse while they been on the trial?
Carer 22 (parent): We haven't seen any. That's what makes me think he's still on the same dose. (Participant in Control arm; interview conducted stage 7).

5.9.1.5 Changes in carers' behaviour as a consequence of the trial

The interviewer also raised this issue of whether the carer thought that they had changed their own attitudes and behaviour towards the participant during the trial period. This was particularly in relation to whether they might be more observant of the participants' behavioural changes. Generally the carers understood that this higher level of observation was an important part of the trial, and some appeared to be aware that this was controlled for by the randomisation process and double blinding of the study medication. There was some acknowledgement that, by necessity to complete the study forms, they were bound to be observant of behaviours.

Carer 8 (parent): Yes I am more aware, I was more aware, of [participants'] behaviour. Just extra vigilant. (Participant in Control arm; interview conducted stage 6)
Carer 9 (staff): so everyone was more aware so it could be awareness of you know if we see any anxiety building up then this is what we do to help him to calm. Possibly a different approach to managing the behaviour. (Participant in Intervention arm; interview conducted stage 4).

5.9.1.6 Speculation about the arm of the trial, the unblinding phase, and future management of the participant

Due to the necessity of closing the study early we needed to interview participants before they had been told which arm of the trial they had been randomised to. However, during interviews many carers speculated about the arm of the trial the participant had been on. For some carers who had observed no significant worsening of behaviours there was the hope (usually tinged with doubt) that the participant had been in the reduction arm of the trial.

Carer 22 (parent); It will be fantastic if he's off them but if he's not…. (Participant in Control arm; interview conducted stage 7).
For many carers there was also a sense of impending excitement about the unblinding stage.
Carer 8 (staff): So we're putting bets on whether he's taking it or not
Interviewer: Yes you've not far to go, I think you're nearly at the end
Carer 8 (staff): It will be so interesting (Participant in Control arm; interview conducted stage 6).

In relation to what happens after the trial, many carers seemed to think that this was primarily a decision for the leading clinician to make:

Interviewer: ….what happens in the future with [participant] in regards to her medication
Carer 6 (parent): well um I don't um I mean it's up to [clinician] (Participant in Control arm; interview conducted stage 0).

There was hope amongst the carers that the trial might result in some of the participants being withdrawn from the study medication after the trial. However, this only seemed to be an option for participants who had been in the medication withdrawal (intervention) arm of the trial.

Interviewer: Do you have any kind of inkling as to which arm he might have been in or, have you thought about what, what's going to happen at the end?
Carer 24 (parent): because of his behaviour change we are thinking of all scenarios, so um, I mean I, I hope that it has worked and he's no longer on it, because I think, you know, sometimes to have unnecessary medication, I think you know come off it, but I hope that, that his behaviour change hasn't been because of this and I hope he has been on the one that's been reduced off a bit and he doesn't no longer take it. Because I think, you know, yeah I do so, because I think the less tablets you take in life, the better really (Participant in Intervention arm; interview conducted stage 3).

5.9.1.7 Views about anti-psychotic medication for the participant and the learning disability population in general

Generally there was a feeling amongst most carers that anti-psychotic medication was generally not ideal for anyone with a learning disability and that non-medical therapies and interventions were generally preferable. Carers were aware of the controversy that surrounds this issue. At times words such as 'chemical restraint', 'relics of the past' were used to describe anti-psychotic medication.

Carer 47 (staff): We've a psychologist that works here and we try to be on the, kind of, forefront of kind of um, new ideas and kind of seeing if, you know, and obviously we were

quite aware there's quite a lot of controversy between, kind of like what drugs are um, um are used traditionally with LD and personality disorder that don't necessarily need to, in, in that modern age don't need to be happening so obviously we are quite forthcoming with, like, new ideas like that. (Participant in Control arm; interview conducted stage 4).

There was also acceptance that in some cases medication was necessary to address imbalances in the brain that could not be repaired by other therapeutic interventions.

Carer 52 (staff): I think obviously antipsychotic medication is to deal with chemical imbalances in the brain, whereas kind of learnt behaviours is not necessarily going to be corrected by that, so I'm, like what we was talking earlier, I'm aware that the kind of like, there's a bit of controversy on, its, you know people like you guys are trying to challenge that and try and move it forward so it's more centred around kind of, um support and talking therapies and stuff like that rather than um, medication which is not really justified. (Participant in Intervention arm; interview conducted stage 7).

Other members of staff were more accepting of the need for medication and compared it to more benign personal needs such as coffee or company.
Carer 58 (staff): I think everybody's got a threshold, as long as they stay on that plateau that if it takes antipsychotic medication to keep them on that level I don't have any issues with that whatsoever. There are certain things that I need throughout the day to keep me on an even keel, as we all do some people it's coke some people it's coffee, and other people it's just company, everybody has got their own needs when it comes to keeping a level head. (Participant in Intervention arm; interview conducted stage 2).

Parent carers were fairly pragmatic about the need for anti-psychotic medication within this population and no very strong views were expressed. Most felt that if they were needed then that was an acceptable intervention.

Carer 8 (parent): Well, I, I can't speak about other people, but if I've got to give medication, as the last resort, I will. But um, if there's any other form, you know, of anything, you know like taking him out of the situation, distracting him, I would prefer that to just pop a pill down him like. (Participant in Control arm; interview conducted stage 6).

One parent had a fairly positive view about the need for anti-psychotic medication to the point that she thought it was worth giving just to benefit from the reassurance of having a medication to rely on.

Interviewer: What are your views more generally on um, using antipsychotic medication for the treatment of challenging behaviour?

Carer 24 (parent): I think it's, I think it's good
Interviewer: you think it's good?
Carer 24 (parent): yeah because I do think it's almost like it's that satisfaction, she thinks it will help her calm down, yeah so, I think in some instances I think it's that placebo kind of effect, it's quite good and I think it works out whether you actually need that medication or not. (Participant in Intervention arm; interview conducted at stage 3).

5.9.2 Interviews with Patient Participants

Four patient participants consented to take part in an interview, all of whom had participated in the ANDREA-LD study, although two had withdrawn at some point during the study. Interviews lasted between 6 minutes and 18 minutes with an average of 11 minutes, although we had anticipated that they might be longer than this.

5.9.2.1 Reasons for participating in the study.

Of the four participants interviewed one (participant 6) could not remember the study or why she had been involved. One (participant 33) appeared happy to be on the trial but could not express why, instead re-iterating that he liked to be on the new red tablets and did not want to come off them. Participant 52 said she wanted to take part because she wanted to see if she could 'change her life' by controlling her mood swings. One participant (participant 7) was very motivated to participate in the trial, thinking that she wanted to see how would she would do without the medication and later described in the interview that she had been 'brave' to do it.

Interviewer: Ok, can you tell me then, so thinking right back, what were your reasons for taking part in the study?

Participant 7: I think one of the reasons why I decided to take part in the study, was because I wanted to see, like how, I would do, with, with um the medication and that sort of thing, um but then it went terribly wrong and I was very ill. (Participant in Intervention arm; participant withdrawn stage 3).

At least two of these participants (7 and 52) expressed that they had been actively involved in the decision making process of taking part and that their views had been sought.

Interviewer: So was it [clinician] who mentioned it to you, like just at an appointment?
Participant 52: yeah, yeah, yeah, yeah
Interviewer: And then um, so did you decide yes or no, did you speak to other people about it?
Participant 52: I decided it, yeah
Interviewer: ok, did [clinician] give you like information about the project? Like some sheets and?
Participant 52; yeah she did yeah
Interviewer: Yeah? Ok, did you have to talk to anybody about taking part or did you decide yourself?
Participant 52: I have to talk to some people about it. (Participant in Intervention arm; interview conducted stage 7).

5.9.2.2 Experience of the trial

All four participants interviewed felt that the study processes had been fine. They seemed fairly un-phased by the regularity and nature of the assessments.

Interviewer: I think there was a lady, was it [name] I think who was coming to do the assessments
Participant 52: I think she did yeah
Interviewer: How did they go?
Participant 52: They were all right
Interviewer: They were all right? No problems?
Participant 52: No, no problems. (Participant in Intervention arm; interview conducted stage 7).

The participant interviewed who had been most motivated to take part in the ANDREA-LD study was upset about how she felt during the trial period. This was not expressed as anger towards the study but rather as disappointed that the outcome was not what she had hoped for and that they study had taken a large emotional toll on her.

Interviewer: So positive or negative, please say exactly what you think, overall what do you think about taking part in the study?
Participant 7: I don't think I want to do it again
Interviewer: no? I don't blame you
Participant 7: I really don't want to do it again
Interviewer: Ok, so the study had quite a bit effect on you
Participant 7: on me mentally
Interviewer; yeah
Participant 7: and emotionally (Participant in Intervention arm; participant withdrawn stage 3)

The other three participants were more positive about their experiences on the trial.
Interviewer: So do you think that if there was another study, which was looking at changing medication again, do you think you would take part again?

Participant 33: I'd take part again
Interviewer: is there anything you think we would, you would like us to change?
Participant 33: stay on the red tablets for good (Participant in Control arm; interview conducted at stage 4).

5.9.2.3 Changes in Behaviour and Reasons for withdrawal from the trial.

Participant 6 reported that she had been experiencing sleep disturbances, possibly related to paranoia or hearing unusual talking at night. Participant 7 reported that she had been experiencing stress, had been very upset and losing her temper with staff a lot. This had resulted in her ending her participation in the trial early. Participant 33 was not able to acknowledge any changes in behaviour, but appeared to be happy continuing on his

medication. Participant 52 reported that she had felt a positive change in her behaviour since being on the study.

Participant 52: I feel quite um, I've had a bit of changes yeah
Interviewer: ok in what way?
Participant 52: um… I don't necessarily want to hurt myself so much
Interviewer: ok, so that's a good change?
Participant 52: yeah (Participant in Intervention arm; interview conducted at stage 7).

5.9.2.4 Views of antipsychotic medication

Despite the willingness to be involved in the ANDREA-LD trial all of the 4 participants felt that anti-psychotic medication was helpful to them. None were able to reflect on whether they thought medication was a suitable treatment more generally for the population of people with learning disabilities.

5.10 Interviews with Clinicians

We approached 11 clinicians, but one clinician had moved jobs with no forwarding details, one was on maternity leave and one was unavailable for interview due to other commitments. In total eight secondary care clinicians took part in a telephone interview, although the recording device did not record well enough for one interview so we are including seven interviews in our analysis. Interviews lasted between 9 and 27 minutes with an average interview length of 16 minutes.

5.10.1 Reasons for participating in the trial

Clinicians discussed both personal and professional reasons for their interest in the study. Some clinicians talked about an on-going interest in the study question of whether anti-psychotics could be safely withdrawn for some patients. Most talked about their involvement in the study with colleagues and the wider team. Some clinicians had not participated in research studies or CTIMPS before and that experience was part of the attraction of involvement. There were thought to be benefits to the wider team in terms of learning about research procedures, and awareness raising about prescribing of anti-psychotics.

Clinician 4: Research is something that has always been part of my career and I think really interesting, in fact I found that in the last maybe, probably, 8-10 years I've been a bit out of touch with proper research and this gave me a chance to just be back, even if it was from a, within the background not as a main, not as a main, one of the main researchers, but that gave me a chance to get back in touch with research which I have always been very interested

There was also the attraction of being able to contribute to an important clinical question.

Clinician 6: obviously it's a contentious area and we need a definitive answer one way or the other in terms of whether um, people with challenging behaviour do benefit from longer term use of antipsychotic medication, um I'm very aware of people becoming out on antipsychotic medication because of bad episodes, remain on it for many years later without it being adequately reviewed. I wanted to support high quality research, firm believer that we need applied research, and jobbing psychiatrists being part of research, not just um, people with, with academic roles.

5.10.2 Concerns about participating in the trial

Most concerns related to issues of recruitment and consenting arrangements. In relation to recruitment the clinicians reported that many carers had been reluctant to be involved in the study or that carers had concerns about the rapidity of the withdrawal.

Clinician 3: I guess really the uptake from some patients or their carers, yeah uh I think people generally get anxious when they think they're going to take some medication away or may take some medications away that sort of …..yeah it's challenging
Interviewer: So was there a little bit of figuring out how to manage that?
Clinician 3: yeah how to manage it and reassure people but I think that has affected the uptake.

There were also concerns about the exclusion and inclusion criteria of the study. Whilst some clinicians seemed to consider any patient of theirs either on risperidone or haloperidol were potential candidates for the study, other clinicians appeared to apply the criteria more selectively and only approached participants and carers who they thought were ready to appropriately withdraw.

Clinician 7: I didn't have any real concerns for the patients we selected either because I think they were quite carefully selected and chosen the people who were on a medication that we thought perhaps they could do without.

A couple of clinicians (clinician 6 and 7) also raised the issue that they thought people with autism were a distinct population who might not be suitable for the trial.

Clinician 7: I think the population we looked at was correct, I think the only difficulty that I saw was, we do have patients with autism and sometimes they're on small doses of antipsychotics and trying to, although it's not for a psychosis, it's for other reasons, so I think they may have been included. And when they're taken off, even a small dose of antipsychotics they had difficulties I think, so that maybe something, that they're a slightly separate population to people without autism.

In relation to capacity, there were some concerns about whether participants with some capacity really had the opportunity to make an informed choice about their participation and contribute to the study. Furthermore clinicians reported that obtaining consent from carers (personal legal representatives) had been challenging.

Clinician 3: We did spend quite a lot of time trying to find out who was the proper person to discuss informed consent and talk about informed consent, you know in the paperwork it was very clear that the carers could give full consent, but the reality was that the carers were not happy, were quite uneasy with that.

5.10.3 Experience of the study

Some clinicians who had no prior experience of being involved in CTIMPS reported that the study set up stage had been time intensive and, in their opinion, unnecessarily complicated:

Clinician 1: I think what initially before actually doing something there was a whole I think there was just so much paper work and so many versions so actually that was a bit confusing um but I think once we'd done the first one and actually walked the process so to speak um it just became clearer. But the paperwork actually didn't help, there was quite a lot.

Sometimes problems about documentation seemed to spill into the main study period:

Clinician 2; I'll tell you what was a bit of a faff was having to fax over the sheets to the study centre once they were filled in because the fax never seemed to get there
However, generally once the study was running study processes had gone relatively smoothly and clinicians were generally very grateful of the support they received from the research team.
Clinician 4: Yes once recruited the person I felt really supported and in fact I felt that, you know, in a way it was very straightforward just to do the follow ups yes that was absolutely fine, yeah there were no problems at all there
Only one clinician felt that contact with and support from the study team had been rather lacking:
Clinician 5: maybe looking back, if there had been more frequent, for example tele-contact, around the study itself. For other studies we have kind of given um, better kind of um, feedback on the study as well

5.10.4 Changes in Behaviour and Reasons for Withdrawal from the study.

Clinicians were not as forthcoming with comments about behaviour changes as the carers had been during interviews. One clinician stated that the clinicians relied on carers to report behaviour changes of study participants to them. Mainly they thought that behaviours were stable and when there had been changes these were generally explained as due to other influences within the participant's life such as an acute infection, admission to hospital or changes with other medication. As with the carer interviews, there were some positive changes in behaviour reported as well, including regaining personality.

There was also frustration expressed when some of their patients had been withdrawn from the ANDREA-LD study due to concerns about behaviour changes from carers only to find that the participant was on the full dose of medication.

Clinician 4: I did rely a lot on carers or family members to tell me about the behaviour. I always told the carers and the person "please do let me know if you see any significant changes, anything that will concern" I made a point every single time, um but sometimes

with the carers whether they could read more into something or not, because there was one person who unfortunately pulled out, they, they pulled out because they saw a change of behaviour and the person was still on there, I think it was still on their first month, therefore he wasn't yet on the active medication study, he was still just on the same dose but with the placebo tablet.

Clinicians also reported instances of where patients had withdrawn from the study, but perhaps for good reason. Even so, there was still some expressed regret that the patient had to do it before they finished the trial.

Clinician 6: the second one is the one we had to break the blind, and that's where um, in retrospect the family and the carers absolutely accurately um, guessed when he came off his final dose of medication. So they knew. They could see, and again that's a young autistic man, going back to this autism business, they could see when that last dose went, he had that background agitation returned and of course he was aggressive or whatever, um unfortunately it was, the blind was broken. (Participant on Intervention arm; interview conducted at stage 2).

There were also occasions when clinicians reported unblinding and withdrawal from the study as completely necessary, and there was no question about the fact that they wanted the participant withdrawn from the trial.

Clinician 7: [participant 17] we had to un-blind, so there were concerns about significant change in behaviour that seemed to correlate with his involvement in the trial and potential reduction of his medication. (Participant on Intervention arm; participant withdrawn at stage 3).

5.10.5 Management of participants after the completion of the study.

How participants were managed, or were expected to be managed, post-ANDREA-LD involvement differed depending on the participants and carers experience of behaviours during the study period. For some this meant continued and complete withdrawal from the study medication, but for others it meant a return to a small dose of the medication primarily

to abate concerns from family members or carers about observed changes in the participant's behaviour.

Interviewer: one of your participants has finished in the study, any changes in um, prescribing medication since they finished?
Clinician 5: No, I mean if they had been withdrawn, they have withdrawn, we have not put them back, but those who have been on the, who have not been on the placebo arm and they want back on the medication we went back on the medication for a short period to try and start again the process of withdrawing the medication
Interviewer: When the blind was broken, um for the one participant, um if you can, reflecting on how care kind of continued from there
Clinician 7: yeah, he went back on the meds
Interviewer: yeah, and that was, that was just
Clinician 7: small dose. That was at the request of his parents, well he's in supported accommodation, the staff would've hung on in there, but the parents were saying, you know, "we noticed a difference, he's less settled, he's hit us, which he hasn't done for months, um he's not how he was" and the carers said "look, you know we've noticed it as well" so it was a bit of a no brainer in that he hadn't had any side effects from the medication, we just put him on, back on the lowest possible dose and sure enough it took the edge off him again. (Participant on Intervention arm; participant withdrawn stage 3).

5.10.6 Views about the use of Anti-Psychotic Medication in the wider Learning Disability Population.

There was generally the view that anti-psychotic medication for managing challenging behaviour within this population has its uses but that it is probably over used. There was also an awareness that some patients were prescribed these medications initially for a short period, or had their dose increased initially for a short period, but that this had not been reviewed and the patient remained on the medication for unnecessary periods or at unnecessary strengths.

Clinician 4: I truly believe that when antipsychotics are prescribed for challenging behaviour, if they were prescribed on low dosages, sometime it can make a really, really important difference because that is what you see in real practice. But I think that we need to be able to evidence that really, really well and look at what are the side effects for the person,

Clinician 5: I wouldn't prescribe medication just purely for behaviour problems, I would always definitely make sure that is part of the behaviour management protocol, so there are steps in place.

There was also a feeling that the clinicians who were participating in the ANDREA-LD study were perhaps more consistent with nationally agreed standards in relation to anti-psychotic prescribing than clinicians working on the boundaries of evidence based care.

Clinician 6: We've done audit on it, you know, it is an area that's been looked at time and time again, which goes back to the fundamental problem with ascertainment, that we've primarily gone to the good services who have already been doing this and perhaps weren't able to get so rapidly that the areas where practice might not have been so um, in keeping with national standards.

There was also a sense of disappointment that, due to recruitment problems, the ANDREA-LD study would not be able to deliver an answer to the question of whether people with learning disabilities can be safely withdrawn from these medications.

Clinician 7: I think this is a really important subject, I think there has been some research in the past but obviously there has not really been a trial like this where you're looking at um, a placebo control double blind trial, because um, prospective, I think it's a really good, and I think unfortunately we didn't get that many people engaged in it which has caused a bit of an issue.

5.11 Limitations of the Qualitative study

While the qualitative study reported here incorporates views from a wide range of stakeholders, we acknowledge that our data may be biased. For example, we were only able to interview a very small proportion of participants in the ANDREA-LD trial. We found that even the participants who had been deemed to have capacity to be interviewed about their views still struggled cognitively with some of the interview content. The need for the interviewer to rephrase questions to make it more accessible to the participants may have resulted in more leading questions which leads to bias as this is a population who have a tendency to agree with statements. The interview data for the four participants should

therefore be treated with some caution. For the interviews with carers and clinicians there may be other methodological problems such as response bias. Carers who felt that the trial had been a particularly bad experience or clinicians who felt that trial procedures had been particularly tricky to handle may have been more motivated to respond to the invitation to an interview and therefore not representative of the all carers and clinicians. Due to the need to complete the interviews in a relatively short time, within the study close down period, interviews were conducted when participants were between 4-6 months post randomisation. Many participants therefore were not fully through the trial procedures and consequently some of them would not have been fully withdrawn from medication.

5.12 Conclusion

This qualitative study about stakeholders' views of the ANDREA-LD study found that carers, participants, and clinicians who took part in the ANDREA study were generally in agreement that it was an important research question, that study procedures such as delivery of medication, and assessments were acceptable, and that study support from the research team was good. Generally there was a feeling that this study should be supported by the learning disability community but also an awareness that it was a challenging study. Issues that caused more concern included: consenting arrangements (particularly carers' concerns about acting as a personal legal representative), whether the study inclusion and exclusion criteria were appropriate (particularly surrounding issues of whether to include participants with autism) and the size of the study medication. In addition, carers in particular reported that participants experienced a number of negative behaviours during the study period but these were not always attributed to drug reduction and many of the behaviors were not new within the study period. Despite the number of adverse behaviours reported in the qualitative interviews only two Serious Adverse Events (SAEs) were reported to the trial team and many behaviours were on-going regardless of the trial. It is notable though that none of the stakeholders felt that such as trial was not possible, nor that research involving people in a residential home had been a particular barrier to recruitment or retention.

6 Discussion

The purpose of this study was to conduct a blinded randomised controlled trial to investigate whether anti-psychotic medication prescribed to adults with learning disabilities for the treatment of challenging behaviour, could be reduced or withdrawn entirely without adversely affecting their behaviour or mental health, or causing a corresponding increase in financial costs. In addition, we hoped to further understand the process of drug reduction from the point view of people with a learning disability, carers and professionals and to further our knowledge of the process of running high quality RCTS in people with a learning disability.

Unfortunately recruitment was largely unsuccessful, most especially from primary care, and a revised strategy with a focus on recruiting from community psychiatric services did not demonstrate a significant improvement in the required time frame. The study therefore closed early to recruitment and is reported as a pilot study. We believe that despite the difficulties in recruitment the study has provided invaluable information in the following three domains:

- The impact of antipsychotic drug reduction on patients, carers and services.
- The nature of future studies of antipsychotic drug reduction
- The nature of future randomised controlled trials in people with a learning disability

6.1 Main findings

Before addressing these areas we will summarise the main findings from our pilot study.

- Recruitment from primary care was unsuccessful with very poor uptake and only rare successful participant completion.
- Recruitment from community psychiatric services was possible. The numbers were slow and considerable start up time was needed before recruitment built up.
- There was considerable attrition from approach to randomisation.
- Progression through the trial was independent of whether in treatment or control group.
- Reasons for participant withdrawal appear independent of trial arm.
- Participants demonstrated relatively low levels of expressed aggression at baseline.
- Participants experienced high levels of side effects at baseline.

- Prediction of successful progression (through drug withdrawal or equivalent control phases) is very tentative but the presence of a diagnosis of autism, the use of PRN medication and individuals with capacity to consent may predict poor progression.
- Clinically meaningful changes in aggression, challenging behaviour and mental health did occur for a minority of participants, although it is difficult to assess the significance of these changes given the very low overall sample size.
- Such symptomatology appears to be managed by the use of PRN medication.
- A considerable reduction in antipsychotic drug load is achieved through drug reduction.
- Those undergoing drug reduction have a reduction in side effects but previously masked movement disorder may appear.
- Participants, carers and clinicians who took part were in agreement over the need for drug reduction and found the trial process acceptable.
- Difficulties were faced in the consenting process for some people. Especially in relation to the role of legal representative.
- Carers rarely reported significant side effects, and behaviours experienced were generally in keeping with the individual's habitual behaviours.

6.2 Study challenges

The initial recruitment through primary care was chosen as future intervention was deemed most likely to occur at a primary care level. However this was wholly unsuccessful and the delay incurred, with associated use of resource, led in a large part to the overall failure of recruitment. For our chosen population numbers per practice were small, invitations to participate were often not responded to and concerns over the need for support from psychiatric services were raised, despite the inclusion of a comprehensive GP support package. Although GPs were not interviewed, there is some anecdotal evidence to suggest GPs were concerned about safety of participants, their own expertise in this area and the level of workload associated with the study (i.e. number of per-patient study specific consultations required).

Recruitment in community psychiatric services was more successful but significantly negatively impacted upon by a lack of GCP training among professionals, delays in set up

and then difficulties in identifying patients, as many were reported as having previously failed drug reduction and therefore were felt to be ineligible by the clinician. Difficulty in identifying appropriate persons to provide consent was an issue in both general practice and community learning disability teams. Carer beliefs about the efficacy of these medications to manage behaviour, and fears about the consequences of reduction were also reported as reasons for declining participation. Carer and clinician concerns about safety were also likely exacerbated by limited availability of alternative (behavioural) interventions for challenging behaviour, and in particular that no alternative to drug reduction was offered as part of the current trial. Although the rationale for this was based on previous research suggesting alternative interventions were not likely to be needed for those managed in community settings, provision of an alternative intervention may have improved recruitment. Although negative consequences of withdrawal in the current sample were infrequent and relatively minor, a low intensity behavioural alternative may offset such changes in a larger sample.

Our findings may relate to a section of the population who already receive relatively low dose antipsychotic drugs but who are not currently displaying high level challenging behaviour (on formal scales). Aggression, behaviour and psychological ill health were generally low at baseline. This needs further exploration. One suggestion would be that a proportion of people with learning disability on antipsychotics are not in fact displaying challenging behaviour. However, PRN usage and use of restraint over time in the control group suggests that behaviour is still perceived as an issue with concerns relating to behaviour raised by carers. How drug reduction applies to those on high levels of antipsychotic medication with continuing high level challenge may need further exploration.

6.3 The impact of antipsychotic drug reduction on patients, carers and services.

Our study has shown pilot data which we believe identifies that drug reduction is possible and safe. However the findings indicate a signal that reduction is not without change. Changes were observed in behavioural and mental health measures and in the development of movement disorder in some participants. 'This is important as previous open studies have reported changes, but there were concerns about biased reporting.

These changes offer an opportunity to provide focussed support and tailored behavioural interventions to patients undergoing drug reduction in the future. They will aid clinicians in advising individuals and carers on the impact of reduction predicting areas of individual need. Data from carer interviews highlighted that concerns about drug side effects and efficacy were key reasons for participation in the study. The responses reflected an ambiguity when considering the effect of antipsychotics and that people were not convinced of their efficacy. A key finding from the study was the ability of carers to identify perceived symptoms which were both positive and negative. Negative perceived symptoms such as reports of low mood or depression, distress, restlessness and intensification of autistic behaviours were reasons for discontinuation progression through the trial. It is worth noting however that these were not always attributed to drug reduction and many of the behaviours were not new within the study period. These were countered by positive perceived symptoms such as reports of increased energy levels, increased motivation, decreased anxiety and less self-harming behaviours. Some reported no notable changes in behaviour which interestingly tended to be attributed to the participant being on maintaining normal dose arm of the trial. We believe this shows the importance of a greater need for supporting carers in their understanding of the likely symptomatology during drug withdrawal.

NICE guidance on the use of antipsychotics[45] provides no detail on how to manage drug reduction. Guidance on the use of antipsychotics from the Royal College of Psychiatrists suggest that clinicians should "a taper off the drug based on its effectiveness".[46] We recommend that antipsychotic drug withdrawal is not seen as a passive process but one that has predicted needs and for this reasons guidance is needed for practitioners, carers and patients.

6.3.1 Recommendation

We recommend that the Royal College of Psychiatrists, potentially working with the Royal College of General Practitioners, establishes a working group with relevant stakeholders to provide guidance on antipsychotic drug withdrawal. This guidance should provide an auditable standard for drug withdrawal including recommendations for levels of behavioural and other service support, and accessible information for people with a learning disability and their carers. Development of guidance for carers on this issue would also be beneficial. As

Sheehan and Hassiotis note in their recent systematic review[32], a systems approach to this complex issue is required.

6.4 The nature of future studies of antipsychotic drug reduction

As discussed above the study has provided important insights into the experiences of people taking part in drug reduction studies that should influence future trial development. Firstly it seems that despite the many barriers faced in recruitment these were not reflected in the experience of carers, professionals or people with an intellectual disability.

The practical running of the study was well received and relatively complex issues such as ethics/blinding and overwrapping of medication were not particularly problematic.
The problems we faced were largely related firstly to recruitment in primary care and secondarily in the preparedness of services dealing with people with LD and antipsychotics to take part in research. In particular there is clearly no functioning network of LD specialists who can respond rapidly to research requests. We believe this is an issue with the current trial, which addressed an area of concern for carers and professionals, but not necessarily for those receiving the medication.

One of the key challenges in a drug reduction study lies within carer and professional concern that medication is being reduced and that this is causing change. If this is the case, it is something that could be relatively easily reversible. Our study showed that in fact incidents where it was necessary to remove the blind were equal between groups. It would appear that this concern is a powerful drive independent of intervention.

6.4.1 Recommendation

Future studies are needed to explore interventions that could reduce unnecessary antipsychotic drug use in people with a learning disability. They should involve interventions that, in addition to the process of reduction, address the concerns of professionals and carers by having extra support or alternative (i.e. non-pharmacological) interventions available for perceived or actual deterioration. It may be that reduction should be non-blinded but these alternative support mechanisms compared with treatment as usual.

6.5 The nature of future randomised controlled trials in people with a learning disability

This pilot study has provided information of value to those wishing to conduct further high quality interventional RCTs in people with a learning disability.

The study has shown that carers and people with a learning disability were not overly troubled by even quite complex trial processes involving over-encapsulated medication and data collection at multiple time points. Carer and participant concerns can therefore be overcome where they are adequately informed of the process.

This study suggests that whilst there is a clear need, primary care services are not currently well equipped to deliver this type of intervention. This is important for other studies which should explore the clinical competencies needed and how these apply to primary care if that is where the target population predominantly receive healthcare.

As in the case of further studies in drug withdrawal it is clear that services and professionals are not currently well prepared for recruiting into interventional pharmaceutical studies. This has also been noted in other recent studies. A recent pilot study of the use of statins to slow cognitive decline in people with Down syndrome showed similar challenges in recruitment. In this study, 21 of a target of 181 participants were recruited, 13 of whom completed the study[47]. This is a particular concern in people with a learning disability, who are often excluded from participation in RCTs and therefore the potential benefits of high quality interventions.

6.5.1 Recommendation

We recommend that measures are put in place to improve recruitment to studies in people with a learning disability and to consider how adults with LD might also be included in general population trials. These measures include a commitment from the Royal College of Psychiatrists for GCP training (including covering recruitment with reduced or no capacity) to be mandatory for its members and for CCG and other health groups; and for performance related measures linked to recruitment to be considered for learning disability studies.

6.6 Conclusion

Despite increasing guidance on the use of antipsychotic medication no guidance exists for reducing the medication. This pilot study has provided valuable insights into the development of such guidance and beyond this to support improved access to trials for people with a learning disability.

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Contributions of authors

Dr Rachel McNamara (Senior Research Fellow, Psychology) contributed to study and intervention design. She also provided oversight to trial management and led the writing of several chapters.

Elizabeth Randell (Research Associate, Psychology) contributed to study and intervention design. She also managed the trial and led the writing of several chapters.

David Gillespie (Research Associate, Statistics) contributed to study and intervention design. He conducted the quantitative analyses and led writing of that chapter as well as contributing to drafting and revising the report.

Dr Fiona Wood (Senior Lecturer, Qualitative Methods) contributed to study and intervention design. She led the qualitative analyses of the interviews and led writing of that chapter as well as contributing to drafting and revising the report.

Professor David Felce (Professor, Learning Disabilities), contributed to the design of the trial and the intervention as well as overall implementation of the study. He contributed to drafting and revising the report.

Dr Renee Romeo (Senior Lecturer, Health Economics) contributed to study and intervention design, led the health economics analyses and contributed to drafting and revising the report.

Lianna Angel (Research Assistant, Data Management), was a Data Manager and contributed to drafting and revising the report.

Aude Espinasse (Research Associate, Trial and Data Management) was a Data Manager and contributed to interpretation of the results. She also contributed to revising the report.

Professor Kerry Hood (Professor, Statistics) oversaw the quantitative analyses and was involved in the design of the trial and contributed to drafting and revising the report.

Amy Davies (Assistant Psychologist, Learning Disabilities), was a Research Assistant and contributed to data collection. She also contributed to revising the report.

Andrea Meek (Research Assistant, Learning Disabilities), was a Research Assistant and contributed to data collection and conducting qualitative interviews. She also contributed to drafting and revising the report.

Katy Addison (Research Assistant, Data Management), was a Data Manager and contributed to revising the report.

Dr Glyn Jones (Consultant Psychiatrist, Learning Disabilities), contributed to study and intervention design. He contributed to revising the report.

Dr Paul Deslandes, (Senior Lecturer, Pharmacy), contributed to study and intervention implementation and to revising the report.

Professor David Allen (Professor, Learning Disabilities), contributed to study and intervention design and to revising the report.

Professor Martin Knapp (Professor, Health Economics), contributed to study and intervention design and contributed to the Health Economics.

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Professor Michael Kerr (Professor, Learning Disabilities), led the design of the trial and the intervention as well as overall implementation of the study. He contributed to drafting and revising the report.

While we plan to retain exclusive use of data until the publication of major outputs, following these, anonymised data can be obtained by contacting the corresponding author.

All authors approved the final version of the report.

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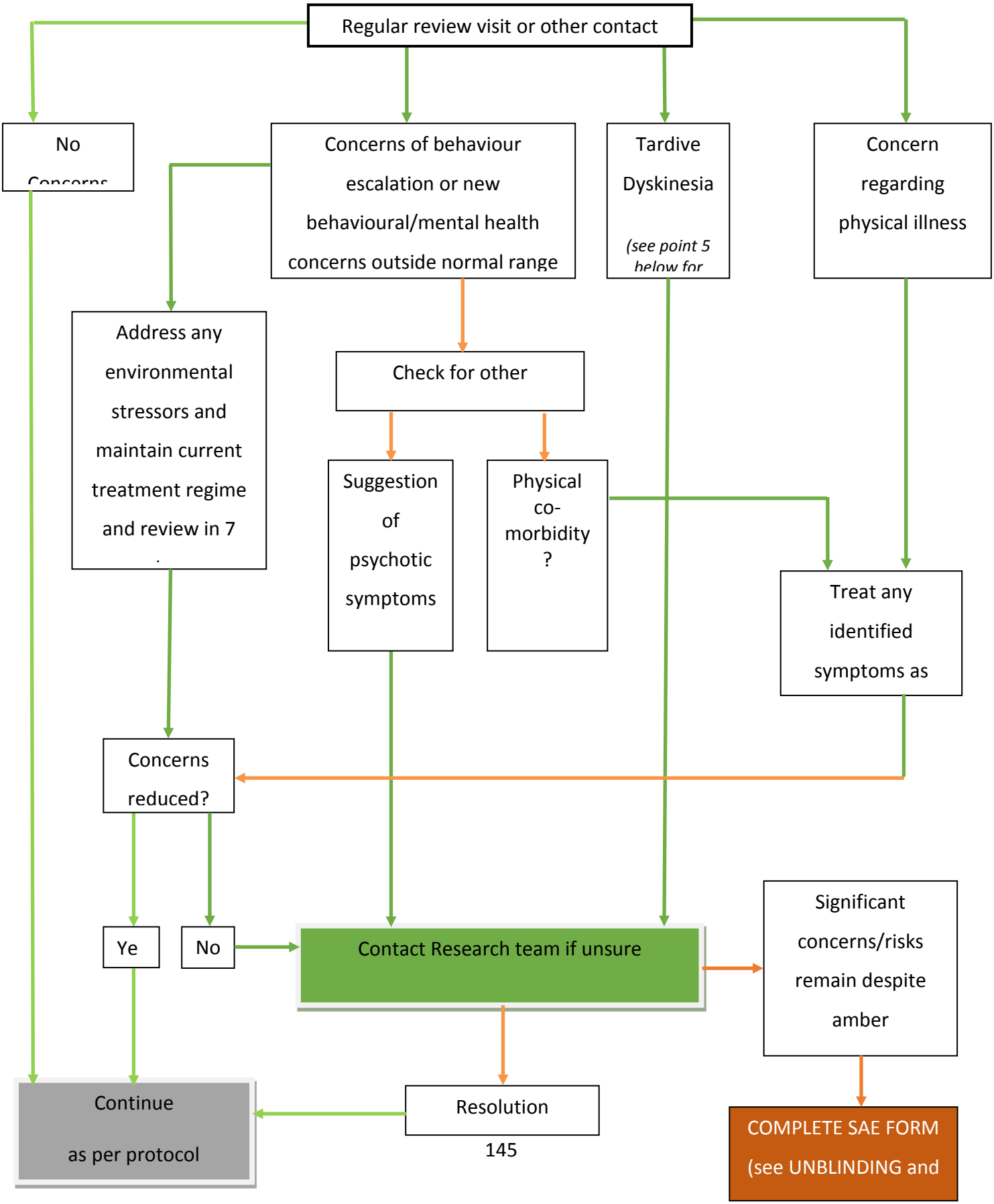
8 Appendices

8.1 Appendix 1 - ANDREA-LD PI Support Package

ANDREA-LD PI Management Flow Chart

PART 1



PART 2

1. Concerns of behaviour escalation or new behavioural/mental health concerns outside normal range of behaviour

It is quite likely that carers or families will raise concerns relating to the individual for whom they care in relation to alteration of behaviour. In this first stage of assessment you can ask a few simple questions to signpost the next step in the flow chart:

Does this seem to be a new condition rather than worsening of usual behaviour?

If it is not worsening of usual behaviour, it is worth deciding if there is an underlying physical or psychiatric condition. Completely new patterns of behaviour are unusual so detailed questioning will ensure it is definitely a new behaviour. If it does seem a new behaviour, then it is best to follow the advice on physical illness (likely to be common) or psychotic symptoms (likely to be more rare) in the flow chart. You may be directed to which step by the nature of the behaviour and other symptomatology.

If it is the usual pattern of behaviour then the next step is to assess its severity.

If this is worsening of usual behaviour -has the individual displayed behaviour as concerning as this before starting in the study?

If the answer is yes then it is likely that this is simply a fluctuation in normal patterns as people with challenging behaviour tend to have ups and downs in the normal course of their condition.

In such situations it is unlikely to be a direct result of the study. Such fluctuations are best approached by watchful waiting.

Where the behaviour is at a greater degree or the current degree causes great concern then the most likely short term reason for deterioration is environmental stressors-so please follow the advice in the environmental stressor box. If there is no such stressor then checking for a physical condition or new psychiatric symptoms would be worthwhile

2. Environmental stressors

If carers do report a change in the level of a person's challenging behaviour, it's important to try and identify what the reasons for this might be. More often than not, these will be linked with some kind of change in the person's environment rather than any change in the person themselves. Some good questions to put to carers include:

- Has there been any change in the person's routine (e.g., have they been provided with their normal pattern of day activity, been able to go out as often as they normally do, been able to see people that they normally see)?

- Has there been any change in the people working with the person (e.g., Have there been a lot of relief staff on duty who don't know the person well and not fully briefed regarding key aspects of their care?; Has a particular carer of whom the person is particularly found been away from for some reason?; Have the person's parents been away on holiday and unable to visit? Has the service manager been off on leave?)

- Are all carers currently implementing agreed support plans (particularly behavioural support plans)? How do carers check that this is the case?

- Have there been any reductions in levels of support to the person that impact on the ability to implement these plans?

- Are the reported increases well-known ones that happen at a particular time of year (Christmas and birthdays are often difficult times for people)

- Has the person been exposed to any recent triggers (for example, having to go to particular places that they don't like or asked to do things that they're not keen on; have they been left alone for lengthy periods?)

This is not an exhaustive list-but it gives you an idea of things to probe for. Carers will often not be aware that these sorts of issues may in themselves explain why the person may have been a little more difficult lately. The solution here is clearly to prompt the carers to address the environmental issues identified rather than to treat the person. Allowing some time for this to occur and the behaviour to settle is the best strategy here therefore.

Escalation of challenging behaviour and non-psychotic psychiatric symptoms

Escalation of challenging behaviour is especially linked to anxiety symptoms and may particularly be associated with environmental stressors. Addressing these stressors, as outlined above, may resolve the problem. If this does not resolve the issue please refer to the "What to do if Challenging Behaviour Escalates" section below.

3. Physical illnesses

Individuals with a learning disability are especially prone to developing physical illness but given communication difficulties, behavioural difficulties may be the presenting feature. Sources of pain (such as ear infections, headaches, abdominal pain (because of urinary tract infection, constipation)) may be especially difficult to pick up and should be actively sought out.

4. Suggestion of psychotic symptoms

The Participants in this study will have been screened for the presence of serious mental illness so, in theory, few if any should experience a relapse of psychosis or evolution of a new illness. However, the presence of mental illness in people with learning disability can be masked by a variety of factors including intellectual function and communication barriers. Therefore, some people whose medication was thought to have been originally prescribed for "Challenging Behaviours" may have in fact had an undiagnosed psychotic illness, such as Schizophrenia or a Bipolar Disorder.

If a patient in the study starts to develop an unusual pattern of speech or behaviour, it is important to remain vigilant for potential psychosis. In people with mild learning disability the presentation would usually be similar to that seen in the general population i.e. abnormal beliefs out of keeping with their social situation which are not amenable to reason or abnormal perceptions, which are not explained by obvious environmental stimuli. However, when the person lacks a level of intellectual function or emotional development commensurate with a chronological age, their ability to express their symptoms coherently may be severely diminished. Here a carer's account of unusual behaviours or communication which is out of keeping with their pre-morbid presentation may be critical in highlighting the evolution of serious mental illness.

In these circumstances it is appropriate to contact your local community Learning Disability Team to ask for an urgent psychiatric assessment. They may be able to reassure you, or could, if necessary, ask for the medication code to be broken to identify the current prescription and withdrawal of the patient from the study.

5. Tardive Dyskinesia

Tardive Dyskinesia is characterised by chewing or sucking movements, grimacing and choreoathetoid movements particularly affecting the face, but also potentially the limbs and most importantly muscles responsible for swallowing and respiration. While this syndrome can occasionally be seen in drug naive patients, it is more common in those who have taken anti psychotic medication for many years. However, neither dose nor duration of treatment is the sole determinant, and it is also more common in women, the elderly and patients with diffuse brain pathology. Almost half of the cases arise when drugs are being reduced or discontinued.

The cause is uncertain but could be super sensitivity to dopamine, resulting from prolonged dopaminergic blockade, and arises with many anti psychotic agents. Many treatments have been tried, but none is universally effective, hence the need to avoid prolonged unnecessary prescription of anti psychotic medication, especially at higher doses.

Should any patient develop symptoms suggestive of Tardive Dyskinesia during the study, it is recommended that you contact your local Learning Disability Team for further psychiatric evaluation, including, if necessary a breaking of the code to identify the current prescription and withdrawal of the patient from the study. This advice does not preclude you from seeking other expert opinion, such as a consultant neurologist if you feel this to be a more appropriate course of action.

WHAT TO DO IF CHALLENGING BEHAVIOUR ESCALATES

If a patient's challenging behaviour escalates during the study there are a number of options. Firstly, it is important to rule out any treatable physical or remediable environmental causes. It is unlikely, but not impossible, that an escalation in challenging behaviour may be related to some previously unrecognised psychosis in which case referral to your local Psychiatric or Learning Disability Service is warranted.

By far the most likely scenario is that this is a simple fluctuation in the patient's normal pattern of challenging behaviour which should be addressed through the usual range of support strategies. However, if you feel that adjustment in medication is necessary you may wish to prescribe a short course of Benzodiazepine (agent and dose will be dependent upon individual patient characteristics) or, if appropriate, an "as required" option to be administered as necessary when alternative calming strategies have proved unsuccessful.

You may, if simple interventions prove unsuccessful, contact the Study Team with a view to delaying the next incremental reduction in medication or in an extreme situation withdraw from the study.

ADVERSE EVENTS

Definitions and reporting procedures.

It is the responsibility of the Investigator to report all adverse events to SEWTU within 24 hours of becoming aware of it. Any queries concerning adverse event reporting should be directed to the Trial Manager in the first instance.

HOW TO REPORT

Complete an ANDREA-LD SAE form as follows and fax to SEWTU on 02920 687612

1. The first report should be marked as 'Initial'. Any other types of report ('follow up' or 'final' will be prompted by the study team.

2. Complete the 'report date' and 'Details of subject affected by Event'

3. Complete 'Details of Event'. Note, an adverse event is considered serious if it:

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

4. Complete 'Details of Investigational Medicinal Product(s)' section with as much detail as possible. Note, for the question 'Is the SAE related to the IMP?', consider the following:

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 using the definitions in the table below.

Relationship	Description
Unrelated	no evidence of any causal relationship with the trial/intervention
Unlikely	little evidence to suggest 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 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 evidence to suggest a causal relationship. The influence of other factors is unlikely.

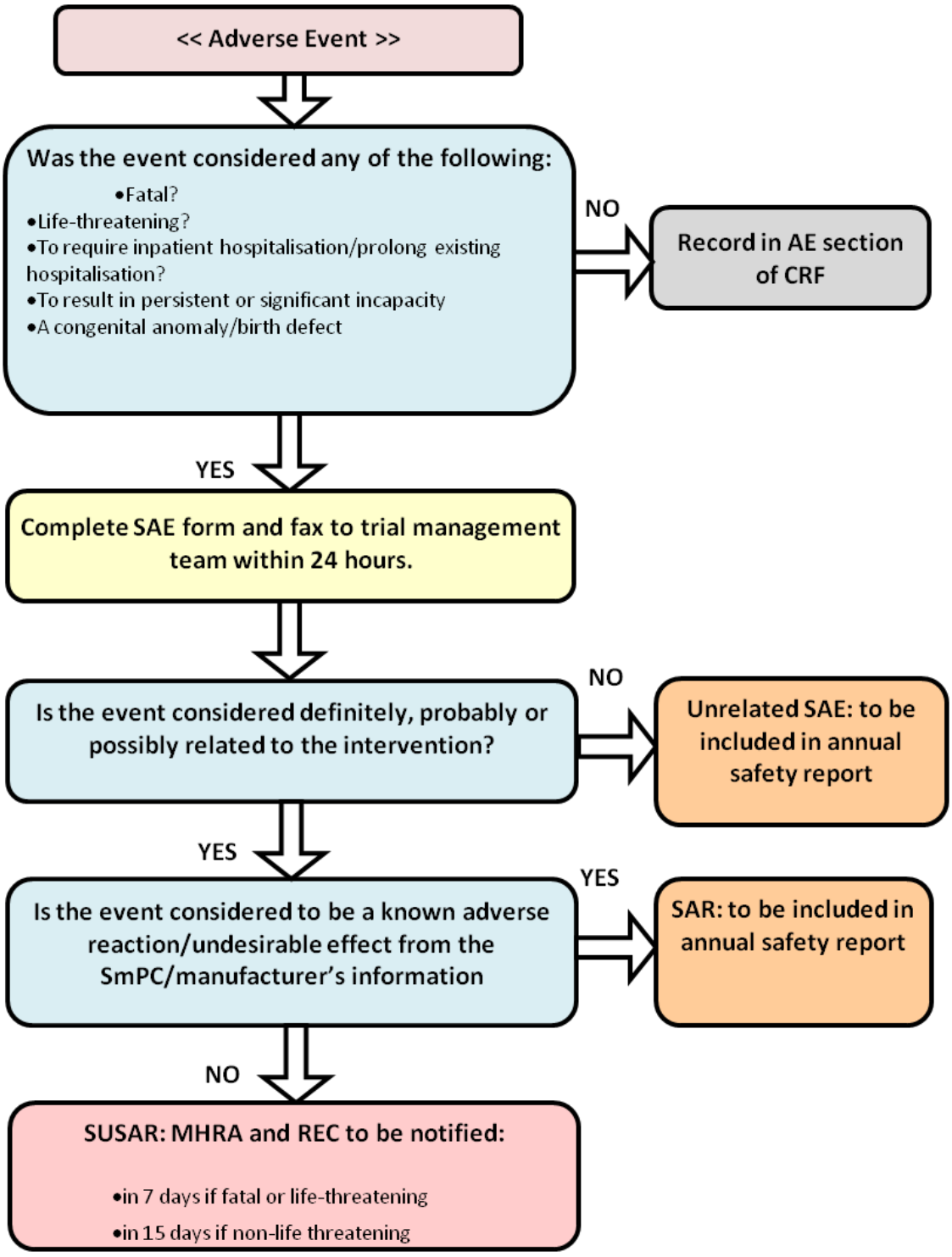
Definite clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

5. Complete 'Details of other treatment' and 'Further information relevant to assessment' sections with as much detail as possible.

6. Sign the form and send a copy as described at the end of the form. Place the original in the Trial Site File and add a copy to the patient's medical notes.

REPORTING SUMMARY



UNBLINDING

EMERGENCY

If, having worked through the management flow chart above, you still have significant concerns or feel that risks remain despite amber intervention or there was an inability to access referral, you may feel it appropriate to request emergency unblinding of treatment allocation.

In such a situation, you must report an adverse event as described above by completing a Serious Adverse Event (SAE) Form (this can be found in your Site File) and submitting it to the Trial Manager. The Chief Investigator or Clinical Reviewer will then contact you to discuss the issues surrounding the situation and, if necessary, confirm that the participants treatment allocation needs to be unblinded

ROUTINE

Breaking the code (blind) at the 9 month visit.

When each patient reaches their 9 month visit, it will be time for the blind to be broken thus revealing whether they were in the reduction arm or were receiving treatment as normal.

The ANDREA-LD team will reveal the allocation to you along with details of the dose of medication the patient is currently taking. It will be your responsibility to have a discussion with the patient and their carer (or representative) in order to relay this information.

For those still receiving medication, any on-going treatment and dosage could be based on the dose the patient finished on depending on the clinical judgment of their clinician and the patient's needs at the time.

Once the blind has been broken and the patient’s treatment allocation and drug dosage is known, we would like you to share this information with any secondary services involved in their care. Knowledge of how the patient progressed in the trial could be of importance in future decision making regarding treatment.

Contact Details

ADDRESS

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8.2 Appendix 2 - ANDREA-LD Interview schedules

ANDREA Qualitative Study

Interview schedules

Carer interviews

Q1. Reasons for participating in the trial

Can you tell me about why you were interested in [the person you care for] participating in the study?

(prompts: where they heard about it from?, who they discussed it with? Have they been involved in other research projects? who was involved in the decision?)

Q2. Concerns about participating in the trial

Did you have any concerns about participating in the trial?

(prompts: did you have any best interest meetings?, who did you discuss it with? What were your concerns? Are you still concerned?)

Q3. Views about why others might or might not want to participate in the trial.

Do you think that other participants or other carers might have concerns about participating in the trial?

(prompts: what might those concerns be?)

Q4. Thoughts about any behaviour changes of person with LD (for better, for worse, or just different) whilst they have been on the trial and their ideas for why behaviour might have changed.

How do you think you (the person you care for) has been generally whilst they have been in the trial?

(prompts: has their physical or mental health improved or declined? Behaviour changes?)

Q5. Thoughts about carers own behaviour during the trial.

Do you think you respond or behave differently to [the person in the study]

Q6. Views on the study medication

Do you think the medication was difficult for [the participant] to take?

(prompts: size, colour, texture etc)

Q7. General experiences of being involved in the trial.

Overall what was your experience of the trial? How much impact did the study have on you?

(prompts: trial procedures eg consent forms info sheets, trial questionnaires and measures, being present at the assessments, appointment times, arrangements for collecting the medication, difficulties taking the medication, possible side effects?)

Q8. Views about the use of anti-psychotic medication to treat or control challenging behaviour for the participant and for people with LD in general

Have you had any thoughts about how anti-psychotic medication is used to treat or control challenging behaviour for people with LD?

(prompts: read anything in newspapers or magazines or websites, talked to people about this?)

Q9. Reasons for any partial or full reinstatement of medication after unblinding or reasons for withdrawal from the study.

(If the participant withdrew) what were your reasons for coming off the study and do you know what medication [the participant] went back to after you withdrew?

Q10. Thoughts about how the trial could be promoted should it run again as a full RCT.

Can you think how we might raise awareness of the study should it be repeated?

Q11. Thoughts about what might happen after the trial.

The ANDREA study was about seeing if we can safely reduce anti-psychotic medication for people with LD. When the trial has finished, what do you think should happen to your [the participant's] medication?

(prompts: do they have concerns about this?)

Secondary care clinician interviews:

Q1. Can you tell me about why you were interested in participating in the study?

(prompts: where they heard about it from? who they discussed it with? Have they been involved in other research projects? who was involved in the decision? Are there any benefits?)

Q2. Do you or your team have any concerns about participating in the trial (for themselves and for the patient population)

(prompts: time involved, risk to patients and their carers).

Q3. Do you think the trial is suitable for certain types of patients? (prompts: those with milder disabilities, those who live at home or those who live in a home)

how did you decide which participants to approach for the study?

Q4. Can you tell me what you thought about some of the study processes (screening, support package, consent processes, patient follow-up).

Q5. Do you have any views about how [the participant's] behaviour may have changed (for better, for worse, or just different) whilst they have been on the trial and their ideas for why behaviour might have changed.

Q6. How do you think the patient and their carer managed whilst during the trial period.

(prompts: were they more anxious, were you more anxious about them?)

Q7. You may be aware of the debate about the value of prescribing antipsychotic medication to people with LD to treat or control challenging behaviour. Do you have any views about this? What kind of evidence would you like to see that you think would be useful to help psychiatrists make good prescribing decisions?

Q8. What would be your solution to the problem of over-prescribing anti-psychotic medication to this patient population? (prompts: substitute with other drugs (benzodiazepams), substitute with other (non-pharmacological) intervention.)

Q9. What were your reasons for any partial or full reinstatement of medication after unblinding or reasons for withdrawal from the study?

(prompts: concerns about the patients behaviour, carers or patients concerns about their behaviour, other general health problems or life events?).

Participant interviews:

The schedule will loosely follow the carer schedule, but with changes between interviews depending on what the participants could cope with, their level of language, capacity etc.

8.3 Appendix 3 - ANDREA-LD PPI Involvement

Patient and public involvement in the ANDREA-LD trial

The co-applicants for this trial have experience of involving people with learning disabilities in the inception, conduct and dissemination of research. An experienced member of All Wales People First (Mr Jonathan Richards) and Mrs Pauline Young, a parent whose child has a learning disability, joined the Trial Steering Committee (TSC). They were able to provide feedback on the trial protocol and study information as well as advice on the best ways available to introduce the research to potential participants.

8.4 Appendix 4 - Description of the scales used during the ANDREA-LD study

Scale	Scale range	Interpretation
Modified Overt Aggression Scale (MOAS)	0 to 120	Higher scores imply higher levels of aggression
Aberrant Behaviour Checklist (ABC) – Irritability subscale	0 to 45	Higher scores imply higher levels of irritability
ABC – Lethargy subscale	0 to 48	Higher scores imply higher levels of lethargy
ABC – Stereotypy subscale	0 to 21	Higher scores imply higher levels of stereotypy
ABC – Hyperactivity / non-compliance subscale	0 to 48	Higher scores imply higher levels of hyperactivity / non-compliance
ABC – Inappropriate speech subscale	0 to 12	Higher scores imply higher levels of inappropriate speech
Psychiatric Assessment Schedule for Adults with Developmental Disability checklist (PAS-ADD checklist) – possible organic disorder subscale	0 to 8	Higher scores imply higher severity of a possible organic disorder
PAS-ADD checklist – affective or neurotic disorder subscale	0 to 25	Higher scores imply higher severity of an affective or neurotic disorder
PAS-ADD checklist – psychotic disorder subscale	0 to 4	Higher scores imply higher severity of a psychotic disorder
Mini Psychiatric Assessment Schedule for Adults with Developmental Disability interview (Mini PAS-ADD interview) – depressive disorder subscale	0 to 30	Higher scores imply higher severity of a depressive disorder
Mini PAS-ADD interview – anxiety disorder subscale	0 to 22	Higher scores imply higher severity of an anxiety disorder
Mini PAS-ADD interview – hypomania / mania (expansive mood) subscale	0 to 19	Higher scores imply higher severity of an hypomania / mania
Mini PAS-ADD interview – obsessive compulsive subscale	0 to 10	Higher scores imply higher severity of an obsessive compulsive disorder
Mini PAS-ADD interview – psychosis subscale	0 to 13	Higher scores imply higher severity of psychosis
Mini PAS-ADD interview – unspecified disorder subscale	0 to 11	Higher scores imply higher severity of an unspecified disorder
Dyskinesia Identification System Condensed User Scale	0 to 60	Higher scores imply more severe movement disorders

(DISCUS) - total score		
Confidence handling challenging behaviour	0 to 10	Higher scores imply more confidence handling challenging behaviour