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

Summary

EudraCT number	2013-000389-12
Trial protocol	GB
Global end of trial date	30 June 2016

Results information

Result version number	v1 (current)
This version publication date	09 July 2017
First version publication date	09 July 2017
Summary attachment (see zip file)	Clean version of final report to funder (Full Final Report One Document (updated to reviewers comments) 26012017 CLEAN.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON1173-12

Additional study identifiers

ISRCTN number	ISRCTN38126962
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Ref: SPON 1173-12, REC Ref: 13/WA/0034, ISRCTN: 38126962

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Randell, Cardiff University, 44 02920687608, randelle@cardiff.ac.uk
Scientific contact	Randell, Cardiff University, 44 02920687608, randelle@cardiff.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2016
Global end of trial reached?	Yes
Global end of trial date	30 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Participants in both the intervention arm and the control arm had five appointments with the PI, four to review appropriateness of progression through the trial and finally for unblinding. Appointments were on a monthly basis at which any concerns were addressed. Contact was also made with pharmacy/nursing staff who handed out trial medication. These contacts were also monthly and offset against meetings with the PI. Along with regular reviews, participants and their carers were encouraged to contact the clinical and study team with any concerns throughout the trial.

Background therapy:

n/a

Evidence for comparator:

The rate of prescription of antipsychotic medication in this population far exceeds the estimated prevalence of psychosis (3-4%). The discrepancy may be accounted for by the use of antipsychotic medications for the treatment of behavioural problems, the commonest reason for their prescription. Rates of prescription among samples of people with learning disabilities with challenging behaviour cluster around 50% and may be as high as 80-95% among those in specially designated services.
The effectiveness of antipsychotic medications in treating or controlling challenging behaviour has not been demonstrated. Their use may therefore, in some cases, be considered mistreatment. A Cochrane Collaboration review failed to find evidence to support such treatment and a more recent review of 56 treatment trials found that the great majority lacked scientific rigour and the remainder found conflicting results. 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. Accompanying economic evaluation concluded that the treatment of challenging behaviour among people with learning disabilities by antipsychotic medication is not a cost-effective option.
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.

Actual start date of recruitment	01 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 22

Worldwide total number of subjects	22
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment opened in primary care in April 2014. Primary care sites were in four health boards in South Wales and in Bristol, North Somerset, South Gloucestershire, Derby and Wiltshire. Recruitment then extended to Community Learning Disability Teams in April 2015 in south Wales and south west England. Recruitment at all sites closed November 2015

Pre-assignment

Screening details:

Information collected: age, gender, current medication and psychiatric history. In addition, adaptive behaviour was assessed as well as current mental health status. The data gathered was used to confirm inclusion and exclusion criteria. If required, clinical review was undertaken for those exceeding thresholds for the ABS.

Pre-assignment period milestones

Number of subjects started	36[1]
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 14

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 36 participants were screened in total. However, only 22 were eventually randomised into the trial.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Arm type	Experimental
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was

dispensed monthly for nine months.
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.

Arm title	Control

Arm description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Arm type	Active comparator
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was dispensed monthly for nine months.
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.

Number of subjects in period 1	Intervention	Control
Started	11	11
Completed	11	11

Period 2	
Period 2 title	6 month assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Intervention

Arm description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Arm type	Experimental
Investigational medicinal product name	Risperidone
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Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was dispensed monthly for nine months.
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.

Arm title	Control

Arm description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Arm type	Active comparator
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was dispensed monthly for nine months.
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.

Number of subjects in period 2	Intervention	Control
Started	11	11
Completed	10	7
Not completed	1	4
Consent withdrawn by subject	1	4

Period 3

Period 3 title	9 month assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Arm type	Experimental
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was dispensed monthly for nine months.
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.

Arm title	Control

Arm description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Arm type	Active comparator

Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For blinding, medication was encapsulated. Encapsulated placebo medication identical in appearance to active medications was also produced. All participants experienced a change in the supply of their medication at the outset of the study but started on their usual dose. A run-in period was built-into the programme for all participants regardless of allocation and prior to any reduction. IMP was dispensed into Nomad Clear 2 disposable weekly trays with separate compartments for days of the week as well as times of day. Participant specific prescriptions were dispensed and dispatched directly to site. IMP was dispensed monthly for nine months.
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.

Number of subjects in period 3	Intervention	Control
Started	10	7
Completed	10	7

Baseline characteristics

Reporting groups	
Reporting group title	Intervention

Reporting group description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Reporting group title	Control

Reporting group description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Reporting group values	Intervention	Control	Total
Number of subjects	11	11	22
Age categorical Units: Subjects			
Adult (18 years +)	11	11	22
Age continuous			
Age of participants prior to randomisation			
Units: years arithmetic mean standard deviation	 44 ± 16.1	 42 ± 10.7	 -
Gender categorical Units: Subjects			
Female	3	4	7
Male	8	7	15

End points

End points reporting groups

Reporting group title	Intervention

Reporting group description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Reporting group title	Control

Reporting group description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Reporting group title	Intervention

Reporting group description:

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 and following collection of follow-up data, the blind was broken and participants and PIs informed of treatment allocation and current dosage.

Reporting group title	Control

Reporting group description:

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Reporting group title	Intervention

Reporting group description:

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Reporting group title	Control

Reporting group description:

Those in this arm received over encapsulated risperidone but there was no change in their dose throughout the trial.

Primary: Number of participants who progressed through all stages of the intervention

End point title	Number of participants who progressed through all stages of the intervention[1]

End point description:

End point type	Primary

End point timeframe:

Eight four-week stages post-randomisation (28-weeks in total)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: We reported the proportion of participants who progressed through the different stages of the intervention. This was a pilot study and therefore no formal statistical analysis was performed on this outcome.

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Participants	6	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to 1 month after the intervention period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Randomised participants

Reporting group description: -

Serious adverse events	Randomised participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Anxiety	Additional description: There was reported deterioration in the participant's mental health. Deterioration was such that crisis intervention was required to avoid hospital admission.		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Randomised participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Behaviour disorder due to a general medical condition	Additional description: Accounts of increased challenging behaviour		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2013	1. Section 7 – confirmation from MHRA that site has been added is not required so reference was deleted. 2. Sections 10.4 and 12.1 – details of unblinding have been updated to remove reference to 24 hour unblinding. 3. Section 13.3 – Pharmacovigilance reporting procedures updated to reflect MHRA approved practice. 4. Section 14 – added detail of contents of Emergency Card. 5. Section 17 – End of trial definition refined. 6. Where reference has been made to time frames, calendar or working days have been defined throughout. 7. TSC member details updated.
21 January 2014	1. Addition of study team member and updated contact details. 2. Clarification of reduction stages has been made clearer throughout (specifically section 6). 3. Section 7 – area for pilot recruitment redefined. 4. Section 8 – eligibility criteria has been slightly refined. 5. Section 9.1 – the use of the ABS as a screening measure has been clarified. 6. Section 9.3 – ABS should not have been listed as a secondary outcome measure. 7. Section 10.3 – Consent and capacity updated. 8. Section 13 - Updated to reflect MHRA and Sponsor approved wording. 9. Section 14. – Minor changes to GP contact and qualitative follow up. 10. Section 14.3 – Refined interview content and addition of participant interviews. 11. Section 16.1 – Definition of Per Protocol population. 12. Section 16.1.1 – No interim analysis. 13. Section 16.3 – Minor changes to cost effectiveness analysis wording. 14. Section 20.1 – TSC Carer member named.
08 May 2014	1. Section 12.1 – Use of the NOMAD system for supplying IMP to participants safely.
01 December 2014	1. Throughout, reference has been made to PIs as recruitment will now change to include community LD psychiatrists as PIs. 2. GP practices will act as PICs.

01 September 2015	1. Throughout, reference to the haloperidol arm has been removed. 2. The 12 month assessment time point has been removed. This includes removal of the details: Medication changes and reasons for medication change will then be monitored for the final 3 months. 3. Reference to online randomisation has been removed and described as off-line. 4. The wording of the secondary objective has been altered to read as follows: A secondary objective is to explore the potential non-efficacy-based barriers to drug reduction in clinical practice. We will conduct qualitative telephone interviews with PIs, carers and participants to gain their perceptions about involvement in the trial and medication usage as well as a final assessment of medication level at 12 months. 5. Under the 'piloting' section, the following has been added to allow for the various 'options' as submitted to the HTA in the recovery plan. The study will then continue until full recruitment or until the point at which recruitment and/or retention rates dictate that the trial will be redefined as a feasibility trial (as confirmed by the study funder).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported