Antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial): an open, parallel-group, randomised controlled trial

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Summary

Background Maintenance antipsychotic medication is recommended for people with schizophrenia or recurrent psychosis, but the adverse effects are burdensome, and evidence on long-term outcomes is sparse. We aimed to assess the benefits and harms of a gradual process of antipsychotic reduction compared with maintenance treatment. Our hypothesis was that antipsychotic reduction would improve social functioning with a short-term increase in relapse.

Methods RADAR was an open, parallel-group, randomised trial done in 19 National Health Service Trusts in England. Participants were aged 18 years and older, had a diagnosis of recurrent, non-affective psychotic disorder, and were prescribed an antipsychotic. Exclusion criteria included people who had a mental health crisis or hospital admission in the past month, were considered to pose a serious risk to themselves or others by a treating clinician, or were mandated to take antipsychotic medication under the Mental Health Act. Through an independent, internet-based system, participants were randomly assigned (1:1) to gradual, flexible antipsychotic reduction, overseen by treating clinicians, or to maintenance. Participants and clinicians were aware of treatment allocations, but assessors were masked to them. Follow-up was for 2 years. Social functioning, assessed by the Social Functioning Scale, was the primary outcome. The principal secondary outcome was severe relapse, defined as requiring admission to hospital. Analysis was done blind to group identity using intention-to-treat data. The trial is completed and has been registered with ISRCTN registry (ISRCTN90298520) and with ClinicalTrials.gov (NCT03559426).

Findings 4157 people were screened, of whom 253 were randomly allocated, including 168 (66%) men, 82 (32%) women, and 3 (1%) transgender people, with a mean age of 46 years (SD 12, range 22–79). 171 (67%) participants were White, 52 (21%) were Black, 16 (6%) were Asian, and 12 (5%) were of other ethnicity. The median dose reduction at any point during the trial was 67% in the reduction group and zero in the maintenance group; at 24 months it was 33% versus zero. At the 24-month follow-up, we assessed 90 of 126 people assigned to the antipsychotic dose reduction group and 94 of 127 assigned to the maintenance group, finding no difference in the Social Functioning Scale (β 0·19, 95% CI –1·94 to 2·33; p=0·86). There were 93 serious adverse events in the reduction group affecting 49 individuals, mainly comprising admission for a mental health relapse, and 64 in the maintenance group, relating to 29 individuals.

Interpretation At 2-year follow-up, a gradual, supported process of antipsychotic dose reduction had no effect on social functioning. Our data can help to inform decisions about the use of long-term antipsychotic medication.

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Introduction

Schizophrenia and psychotic disorders are common, worldwide problems that cause considerable suffering and disability.[1] Antipsychotic drugs are the principal form of treatment. They are used to reduce acute symptoms and are recommended to be taken long term for relapse prevention. Long-term treatment recommendations are based on trials that have found continuous, maintenance antipsychotic treatment to be more effective at preventing relapse than the discontinuation of antipsychotic medication and replacement by placebo.[2–4] However, there are limitations to this evidence. Antipsychotic medication is usually discontinued abruptly in people allocated to placebo, which can produce withdrawal effects that mimic or precipitate relapse.[5] Moreover, there is little consistent

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Research in context

Evidence before this study

Meta-analyses of clinical trials have found increased rates of relapse in people who reduce or discontinue maintenance antipsychotic medication compared with people who continue. However, few such trials have assessed the effects of gradual dose reduction or long-term follow-up, or have measured outcomes other than relapse. Furthermore, the findings of a trial in people with first-episode psychosis and some naturalistic evidence suggest that gradual dose reduction and discontinuation of antipsychotic medication might be associated with improved social functioning in the long term. We used PubMed to update the search of a meta-analysis published in 2022, by searching from Nov 1, 2021, to Jan 18, 2023, using the original search terms without language restriction and new ones designed to identify trials using gradual or supported methods of antipsychotic reduction: (schizophreni* OR schizoaffective OR delusional OR psychotic) AND (stabil* OR chronic* OR long-term OR maintenance) AND ("antipsychotic*" OR "atypical antipsychotic*" OR "neuroleptic*" OR "major tranquiliser*" OR "psychotropic*" OR "depot injection*" OR "psychiatric medication*") AND (continu* OR stay OR reduc* OR lower* OR stop* OR discontinu* OR withdraw*) AND (gradual OR supported OR step* OR phase* OR slow). The review and our updated search, which retrieved 25 records, did not identify any trials of gradual reduction and discontinuation of antipsychotic medication in people with a diagnosis of schizophrenia or recurrent psychotic conditions.

Added value of this study

In people with recurrent psychosis or schizophrenia, we found no evidence to support our hypothesis that a gradual reduction of antipsychotic medication improved social functioning at 2-year follow-up. Antipsychotic reduction increased the risk of relapse compared with continuing maintenance treatment, although most people did not relapse; 32 (25%) people from the reduction group had a severe relapse compared with 17 (13%) from the maintenance group, which was greater than our prespecified 10% non-inferiority boundary to indicate a potentially acceptable level of increase. Time to relapse was shorter among those in the reduction group, but other outcomes were not affected. This is the first full trial to explore the outcomes of a gradual strategy of antipsychotic reduction and discontinuation in this population.

Implications of all the available evidence

Compared to continuing with maintenance treatment, gradual, monitored, reduction of antipsychotic medication over a period of months does not improve social functioning in the medium term and increases the risk of relapse in people with recurrent psychotic disorders or a first episode of psychosis. These data help to inform decision making about the use of long-term antipsychotic treatment.

evidence about outcomes other than relapse, and follow-up is usually short; in one meta-analysis,[3] only four of 48 placebo-controlled trials had followed up participants for more than a year. Therefore, conclusions about the risks and benefits of long-term maintenance treatment might not be robust.

Antipsychotic medication is recognised to result in a range of severe and disabling adverse effects, including diabetes, heart disease, tardive dyskinesia, sedation, akathisia, emotional blunting, and sexual dysfunction, and many patients find antipsychotics aversive. Therefore, interventions that reduce an individual's exposure to antipsychotics have been explored. Trials of intermittent treatment have found it to be associated with a greater risk of relapse than maintenance treatment,[6] although the discontinuation of antipsychotic medication was relatively abrupt. Meta-analyses of dose reduction studies have also reported higher rates of relapse compared with remaining on the same dose, but again reduction was frequently abrupt.[4,7] A randomised trial testing a gradual process of dose reduction and discontinuation of antipsychotic medication over 18 months in people with a first episode of psychosis found a higher rate of relapse compared with continuing treatment,[8] but at follow-up 7 years later, relapse rates were similar, and people originally randomly allocated to dose reduction and discontinuation showed a higher level of social functioning.[9]

Data from naturalistic studies are contradictory. Although uncontrolled confounding is likely to affect all such studies, some long-term prospective studies found that people with psychotic disorders who did not take continuous antipsychotic medication showed lower positive and negative symptom levels and better social functioning or recovery rates than those who did.[10] However, other studies have reported worse outcomes in those who had stopped or not taken antipsychotic medication.[11]

Research on antipsychotic reduction has mostly focused on people with first-episode psychosis, but people who have had recurrent episodes of psychosis or schizophrenia might also want more treatment options and many wish to try reducing or stopping their antipsychotic medication.[12] The current trial aimed to provide evidence about the potential risks and benefits of a gradual, supported process of antipsychotic dose reduction and discontinuation compared with maintenance treatment in people with recurrent psychotic disorders, in order to inform the collaborative treatment decisions of patients and clinicians. The hypotheses were that antipsychotic reduction might improve social functioning at follow-up compared with maintenance treatment, with a maximum increase in serious relapses of 10% in the reduction group.

Methods

Study design and participants

We have described the methods of this study in detail in a protocol paper,[13] and the protocol is available online. This was an open, parallel-group, randomised trial that lasted for 2 years, with follow-up assessments at 6, 12, and 24 months after randomisation. A lived experience advisory group advised on the design and conduct of the trial.

Participants were recruited from 19 National Health Service Trust mental health organisations across England. Potential participants were identified initially by clinical staff or recruited through advertisements placed in clinical settings and social media; those patients who expressed an interest in participating were sent further information. Participant eligibility criteria consisted of being age 18 years or older, having a clinical or ICD-10 diagnosis of schizophrenia or other non-affective psychotic disorder with multiple episodes, and being prescribed an antipsychotic. Exclusion criteria included being considered by a clinician to pose a serious risk of harm to self or others were the individual to reduce their antipsychotic medication, being mandated to take antipsychotic medication under a section of the Mental Health Act, having been admitted to hospital or treated by a crisis service for a mental disorder within the last month, lacking capacity to consent, having insufficient spoken English, pregnancy, breastfeeding, and being involved in another trial of an investigational medical product; eligibility was assessed by researchers and confirmed by the Principal Investigator for the site (appendix p 2). The OPCRIT programme,[14] which produces operationally defined diagnoses on the bases of symptom checklists, was used to verify diagnoses for all 70 participants at one site.

Written informed consent was obtained for each eligible patient, following a formal assessment of their capacity conducted by a research assistant. Consent was an ongoing process and researchers asked participants for verbal consent at each assessment.

The trial received ethical approval from Brent Research Ethics Committee (reference 16/LO/1507).

Randomisation and masking

Randomisation was conducted through Sealed Envelope—an independent, internet-based system linked with the trial database—with 1:1 allocation, using random permuted block sizes of 4, 6, and 8. The sequence was generated by members of the clinical trials unit who also assigned participants to groups. Each participant and their clinicians were aware of the treatment allocation, but the researchers who conducted assessments were masked to allocation as far as possible and analysis was also conducted masked to group identity. Researchers were instructed to record incidences when they suspected they might have been unmasked.

Procedures

We developed the antipsychotic reduction protocol after consultation with clinicians, academics, and our lived experience advisory group. Several meetings were organised for the advisory group members to discuss the protocol aims and methods with the core research team and to review drafts of the reduction protocol. The aim of the protocol was for participants to reduce their antipsychotic medication gradually and to discontinue it altogether if possible and if they agreed to do so. The antipsychotic dose reduction and maintenance protocols were administered by treating psychiatrists. For participants allocated to the reduction group, the research team devised an individualised dose reduction schedule for each participant based on their initial antipsychotic regimen. The dose was reduced incrementally every 2 months, focusing on one antipsychotic at a time if participants were prescribed more than one. The rate of reduction varied according to the dose at baseline, with most schedules aiming for discontinuation within 12 to 18 months, although some took longer when the baseline dose was high, and some were quicker when it was low. Participants were offered the option to discontinue antipsychotic medication completely if the reduction progressed well, or to reduce to a very low dose, defined as the equivalent of 2 mg of haloperidol a day or less. Guidance on the antipsychotic dose reduction strategy stressed the need for flexibility to accommodate patient preferences and included a suggested protocol for the treatment of emergent symptoms and withdrawal effects. Participants randomly assigned to maintenance treatment were requested not to make major reductions in the dose of their antipsychotic medication during the trial period, but minor reductions to address adverse effects were permitted.

Participants were monitored by their treating psychiatrist and care team according to usual practice. Clinical records were scrutinised by unblinded members of the research team every 2 months to monitor the progress of the antipsychotic dose reduction and adherence to the maintenance protocol; deviations were discussed with the treating clinician. All participants could receive other pharmacological treatment and interventions such as psychological therapies throughout the trial, as clinically indicated.

Outcomes

The primary outcome was social functioning at 24 months' follow-up, measured using the self-report Social Functioning Scale (SFS).[15] The principal secondary outcome was severe relapse, which was defined as hospital admission for psychiatric inpatient treatment. An expert endpoint committee was convened to assess the presence or absence of relapse more broadly, based on masked information from clinical case notes, using predefined criteria and guidance (appendix pp 3–5). Other secondary outcomes were mental state, measured

For the **protocol** see https://discovery.ucl.ac.uk/id/eprint/10171081/

See **Online** for appendix

For **Sealed Envelope** see https://www.sealedenvelope.com/randomisation/internet/

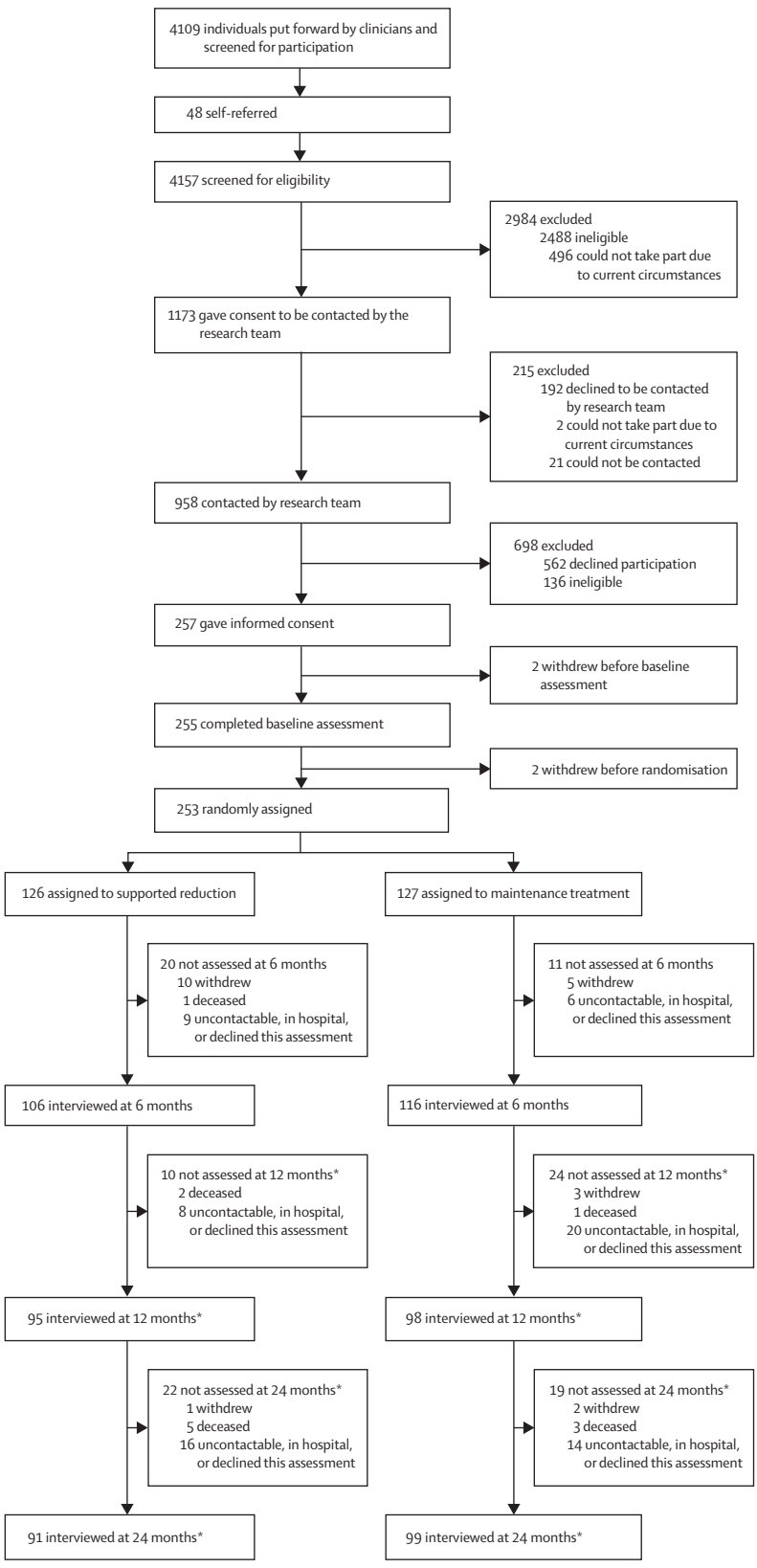

Figure 1: **CONSORT diagram**
*Continued attempts were made to follow up participants, including those who did not participate in earlier follow-up data collection, therefore numbers are not cumulative.

by the researcher-rated Positive and Negative Syndrome Scale (PANSS),[16] quality of life, measured by the self-report Manchester Short Assessment of quality of life (MANSA),[17] and the Objective Social Outcomes Index (SIX), which is derived from it.[18] Adverse effects of antipsychotics were measured using a modified version of the self-report Glasgow Antipsychotic Side-effect Scale (GASS),[19] bodyweight, and sexual dysfunction using the self-report Arizona Sexual Experiences Scale (ASEX).[20] Other assessments included the self-report Questionnaire about the Process of Recovery (QPR),[21] the self-report Client Satisfaction Questionnaire (CSQ)-8,[22] and the self-report Medication Adherence Rating Scale (MARS)-5.[23] All of these primary and secondary outcomes were measured at each of the assessments at 6, 12, and 24 months after randomisation. Cognitive function was measured at 12 and 24 months using a brief battery of tests selected designed for this trial (appendix p 6). Health economics outcome measures will be reported separately.

Data on antipsychotic use and adverse events (including hospitalisation) were collected on an ongoing basis from clinical records. These data were collected until the end of the trial, thus for participants who entered the trial early, there were data on severe relapse for longer than 24 months

Choice of primary outcome

Social functioning was chosen as the primary outcome to reflect outcomes that are important to patients and society. The Social Functioning Scale was developed in 1990 and has good reliability.[15] It is a 79-item scale made up of seven sub-scales. It is easy and quick to administer and has been widely used.[24] Scores range from 55 to 145, and people with schizophrenia typically score between 100 and 110, which is 10–20 points lower than healthy volunteers[15] and 5 points lower than people with bipolar disorder.[25] The scale is freely available and has been translated into several languages.

Statistical analysis

Our hypothesis was that antipsychotic reduction would improve social functioning with only a small increase in relapse rate. Sample size calculations, detailed in the protocol paper,[13] showed that a total sample size of 206 was required to identify a minimally clinically important difference of 4 points on the SFS with 90% power for the primary outcome. Using a non-inferiority calculation, a sample size of 372 was required for 90% power to exclude a difference of 10% between groups using a non-inferiority boundary of 10% event rates for severe relapse,

	Antipsychotic dose reduction (n=126)	Antipsychotic maintenance treatment (n=127)
Sex		
Male	85 (67%)	83 (65%)
Female	40 (32%)	42 (33%)
Transgender	1 (1%)	2 (2%)
Age, years	46·6 (12·2)	46·0 (11·5)
Marital status		
Single, separated, divorced, or widowed	106 (84%)	110 (87%)
Married, cohabiting, or in civil partnership	20 (16%)	17 (13%)
Ethnicity		
White	89 (71%)	82/125 (66%)
Black	25 (20%)	27/125 (22%)
Asian	8 (6%)	8/125 (6%)
Other	4 (3%)	8/125 (6%)
First language English	107 (85%)	114 (90%)
Highest educational achievement		
Primary and secondary education to age 16 years	49/125 (39%)	36/126 (29%)
Primary and secondary education to age 18 years	22/125 (18%)	27/126 (21%)
Tertiary or further education	40/125 (32%)	56/126 (44%)
Other general education	14/125 (11%)	7/126 (6%)
Years of completed education	14 (3·3, n=121)	14 (3·9, n=125)
Employment		
Employed, voluntary work,or in education	38 (30%)	36/125 (29%)
Not working or in education	88 (70%)	89/125 (71%)
Diagnosis		
Schizophrenia	87 (69%)	87 (69%)
Other psychotic disorder	39 (31%)	40 (32%)
Length of time in contact with mental health services		
0–3 years	11 (9%)	6 (5%)
4–10 years	34 (27%)	28 (22%)
11–15 years	20 (16%)	23 (18%)
16–20 years	20 (16%)	22 (17%)
>20 years	41 (33%)	48 (38%)
Age when first referred to mental health services		
<20 years	26 (21%)	27 (21%)
20–30 years	57 (45%)	67 (53%)
31–40 years	25 (20%)	22 (17%)
≥41 years	18 (14%)	11 (9%)
Number of previous mental health admissions	3 (1–5)	3 (1–5)
Recreational drugs used in the past month	11 (9%)	14/126 (11%)
Alcohol use over the past month		
Once a month or less	80 (64%)	82/126 (65%)
Two to four times a month	24 (19%)	20/126 (16%)
Two or more times a week	22 (18%)	19/126 (19%)
Antipsychotic medication dose in chlorpromazine equivalents, mg	300 (200–450)	300 (200–400)
Outcome measures at baseline		
SFS overall	107·7 (8·6, n=123)	108·2 (10·2)
PANSS positive symptom subscale	10 (8–14, n=124)	11 (8–16)
PANSS negative symptom subscale	11 (9–15, n=124)	11 (8–15, n=124)
PANSS total	48 (41–59, n=122)	48 (40–61, n=123)
MANSA	4·7 (0·82)	4·6 (0·83)
SIX	3·4 (1·3, n=125)	3·4 (1·3)
Modified GASS	27·6 (15·2, n=105)	29·0 (17·1, n=104)
Bodyweight, kg	90·9 (20·2, n=114)	89·7 (19·1, n=116)
CSQ-8	20 (20–21, n=125)	20 (19–21, n=122)
MARS-5	24 (22–25, n=124)	25 (23–25, n=124)
QPR-15	55·7 (9·9, n=123)	56·6 (10·0, n=122)
ASEX	16·3 (6·1, n=42)	15·5 (5·0, n=39)
Cognitive tests		
Digit span	14·8 (4·5, n=124)	14·7 (4·7, n=126)
Digit symbol substitution	47·2 (17·4, n=117)	47·3 (18·2, n=121)
Rey Auditory Verbal Learning	35·7 (12·0, n=121)	36·1 (12·4, n=120)
Trail making	45 (35–62, n=121)	50 (36–64, n=121)
Verbal fluency	16·5 (4·9, n=124)	16·6 (5·2, n=126)

(Table 1 continues in next column)

(Table continued from previous column)

Data are n (%), mean (SD), or median (IQR). ASEX=Arizona Sexual Experience Scale. CSQ=Client Satisfaction Questionnaire. GASS=Glasgow Antipsychotic Side effects Scale. MANSA=Manchester Short Assessment of quality of life. MARS=Medication Adherence report Scale. PANSS=Positive and Negative Syndrome Scale. QPR Questionnaire about the Process of Recovery. SFS=Social Functioning Scale. SIX=Objective Social Outcomes Index.

Table 1: **Baseline demographic and clinical characteristics of the study participants**

which was considered to be a small and potentially acceptable level of increase. We did not manage to recruit this number, but the protocol acknowledged that the objective was to provide informative estimates of the relative hazard of severe relapse with narrow CIs.

A full statistical analysis plan was completed before database lock (May 27, 2022) and analysis of the data (appendix pp 18–30). The plan for the primary outcome was to use a mixed-effect linear model with the randomisation variable and the outcome at 24 months and baseline as fixed effects and the National Health Service Trust as a random effect. However, the model did not fit well because some Trusts did not have many participants, and we therefore reverted to multiple linear regression with robust SEs, as specified in the statistical analysis plan. Robust SEs were used to increase the SEs (and therefore 95% CIs) due to potential clustering by

Trust, which would make the data non-independent. Data from follow-up points before 24 months were not included. The model included the randomisation variable and baseline score as explanatory variables. The principal analysis was an intention-to-treat analysis using all available data at 24 months. The effect of missing data was explored by conducting sensitivity analyses including predictors of missingness of the outcome, using a threshold of $p<0·05$. Sensitivity analyses were done, including a variable reflecting the degree of COVID-19-related lockdown and a longitudinal analysis with data from 6, 12, and 24 months in the outcome, fixed effects for time, randomised group, and baseline SFS with a random effect for participant.

Time to severe relapse was analysed with survival analysis using a Cox proportional hazards model with robust SEs. The extent to which there was a departure from constant proportional hazards was assessed statistically using Schoenfeld residuals. Logistic models with robust SEs on the occurrence of severe relapse within 24 months and the combination of severe and less severe relapse were conducted as supportive analyses.

Other secondary outcomes were analysed in the same way as the primary outcome, using multiple linear regression models with robust SEs, with the score at 24 months as the outcome and using all available data at 24 months. The number of psychiatric inpatient days was analysed using zero inflated negative binomial regression with robust SEs, controlling for number of psychiatric inpatient days in the 6 months to baseline, and the natural log of the number of days of follow-up as an offset. Employment status was analysed using logistic regression with robust SEs. All analyses were conducted using Stata (version 17.0).

The trial was registered with the International Standard Randomised Controlled Trials register, (registration number: ISRCTN90298520) and with ClinicalTrials.gov, NCT03559426.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

4157 people were screened by the research team, of whom 253 were randomly assigned, 126 to the reduction group and 127 to the maintenance group (figure 1). Reasons for non-participation could not be collected since non-participants had not provided consent. Recruitment lasted from April 5, 2017, to March 16, 2020. The last follow-up assessment was conducted on March 10, 2022. Data were collected from clinical notes beyond 24 months up until 36 months for 180 participants (80 in the reduction group, 100 in the maintenance group). Overall, the sample included 168 (66%) men, 82 (32%) women, and three (1%) transgender people (table 1). 171 (67%) were White, 52 (21%) were Black, 16 (6%) were Asian, and 12 (5%) were of other ethnicity. Mean age was 46 years (SD 12, range 22–79). 174 (69%) were diagnosed with schizophrenia and 79 (31%) with another psychotic disorder. In the more detailed diagnostic breakdown provided by the OPCRIT programme on a sub-sample of 70 participants across both groups, 56 were diagnosed with schizophrenia, ten with schizoaffective disorder, and four with other non-organic psychotic disorder.

190 participants were interviewed at the 24-month follow-up. Assessors guessed or were inadvertently unmasked to group allocation in 13 cases. There was no significant difference between the groups on the primary outcome, the Social Functioning Scale (β 0·19, –1·94 to 2·33; table 2). The sensitivity analyses, including a longitudinal analysis using data from all follow-up points, an analysis including the degree of COVID-19 lockdown, and one including predictors of missingness, did not change this finding (appendix pp 7–14).

Time to severe relapse was shorter in the reduction group compared with the maintenance group (hazard ratio 2·2; 95% CI 1·2–4·0; p=0·007; figure 2). There was no evidence that the assumption of proportional hazards was violated using Schoenfeld residuals (p=0·59; appendix p 15).

By 24 months, 32 participants (25%) in the reduction group had at least one severe relapse compared with 17 (13%) in the maintenance group (odds ratio 2·20; 95% CI 1·15–4·22; table 2). This was larger than the 10% non-inferiority boundary. By the end of data collection from clinical notes (maximum duration being 36 months), 34 participants (27%) in the reduction group had at least one severe relapse compared with 17 (13%) in the maintenance group. At 24 months, 20 (16%) people in the reduction group and 11 (9%) in the maintenance group had a non-severe relapse, and the total who had any sort of relapse within 24 months was 52 (41%) in the reduction group and 28 (22%) in the maintenance group (table 2). There was no difference in median psychiatric bed days between groups. Mean bed days were higher for those in the reduction group, but the data were highly skewed.

Other secondary outcomes showed no difference between the groups at 24 months, including measures of symptoms, quality of life, adverse effects scales, bodyweight and employment (table 2).

Participants allocated to antipsychotic dose reduction reached a median of 67% reduction (IQR –100% to –40%) of their baseline dose at some point during the trial. The median dose for the group at 24 months was 33% less than at baseline (IQR –67% to 0; table 3). The median change among maintenance participants was zero. 34 (27%) individuals randomised to reduction stopped their antipsychotic medication completely at some time during the 24-month follow-up period, and 13 (10%) of those allocated to maintenance treatment did so.

	6-month outcomes		12-month outcomes		24-month outcomes		
	Antipsychotic dose reduction (n=126)	Antipsychotic maintenance treatment (n=127)	Antipsychotic dose reduction (n=126)	Antipsychotic maintenance treatment (n=127)	Antipsychotic dose reduction (n=126)	Antipsychotic maintenance treatment (n=127)	Treatment effect (95% CI)
SFS (overall score)	107·2 (9·5, n=98)	107·4 (10·1, n=112)	106·1 (8·8, n=92)	106·8 (10·3, n=95)	105·7 (10·5, n=90)	106·7 (9·7, n=94)	β 0·19 (–1·94 to 2·33)*
Time to severe relapse	..	..	..	..	..	..	HR 2·23 (1·24 to 3·99)†
Severe relapse at any time during 24 months	..	..	..	..	32 (25%)	17 (13%)	OR 2·20 (1·15 to 4·22)
Severe relapse at any time to the end of the trial	..	..	..	..	34 (27%)	17 (13%)	OR 2·39 (1·25 to 4·56)
Non-severe relapse at any time during 24 months	..	..	..	..	20 (16%)	11 (9%)	OR 1·99 (0·91 to 4·35)
Any relapse at any time during 24 months	..	..	..	..	52 (41%)	28 (22%)	OR 2·48 (1·43 to 4·30)
Psychiatric bed days during 24 months	..	..	..	..	0 (0 to 31, 27 [56]; n=117)	0 (0 to 0, 11 [47]; n=121)	IRR 0·95 (0·53 to 1·70)
PANSS positive symptoms subscale	10 (8 to 13, n=102)	10 (8 to 15, n=114)	9 (8 to 13, n=89)	10 (8 to 14, n=96)	10 (8 to 14, n=82)	10 (8 to 14, n=91)	β 0·33 (–0·91 to 1·56)
PANSS negative symptoms subscale	11 (8 to 16, n= 98)	10 (8 to 13, n=108)	11 (8 to 13, n=86)	9 (8 to 14, n=93)	9 (8 to 13, n=77)	10 (8 to 14, n=88)	β –0·82 (–1·95 to 0·32)
PANSS total score	43 (37 to 57, n=81)	44 (38 to 58, n=88)	42 (36 to 53, n=65)	46 (36 to 55, n=69)	43 (36 to 54, n=52)	48 (38 to 63, n=59)	β –2·10 (–6·18 to 1·97)
MANSA	4·7 (0·8, n=100)	4·6 (1·0, n=115)	4·8 (0·9, n=88)	4·7 (0·8, n=95)	4·6 (1·0, n=86)	4·7 (0·7, n=89)	β –0·05 (–0·24 to 0·14)
SIX	3·5 (1·9, n=99)	3·3 (1·2, n=115)	3·3 (1·3, n=89)	3·4 (1·2, n=95)	3·3 (1·2, n=86)	3·3 (1·1, n=90)	β 0·01 (–0·25 to 0·26)
GASS	22·7 (15·2, n=73)	30·0 (18·4, n=89)	19·7 (13·9, n=67)	24·1 (15·7, n=65)	21·9 (15·5, n=70)	25·3 (16·0, n=68)	β –3·98 (–8·77 to 0·81)
CSQ-8	20 (19 to 21, n=98)	20 (20 to 21, n=108)	26 (24 to 29, n=84)	25 (24 to 29, n=91)	25 (19 to 28, n=83)	25 (22 to 29, n=84)	β –1·31 (–3·46 to 0·85)
MARS-5	24·5 (23 to 25, n=98)	24 (22 to 25, n=111)	24 (23 to 25, n=86)	24 (23 to 25, n=90)	25 (23 to 25, n=81)	25 (23 to 25, n=85)	β 0·47 (–0·26 to 1·21)
QPR-15	56·1 (9·7, n=98)	54·7 (10·7, n=110)	41·3 (10·6, n=83)	39·3 (10·3, n=89)	41·5 (9·5, n=78)	41·1 (9·5, n=83)	β –0·04 (–2·39 to 2·32)
ASEX	13·0 (5·2, n=23)	16·4 (4·9, n=31)	19 (6·3, n=11)	14·7 (4·9, n=24)	14·6 (4·2, n=10)	17·4 (6·7, n=18)	β –0·02 (–3·06 to 3·02)
Bodyweight (kg)	93·2 (23·4, n=83)	88·9 (18·5, n=88)	93·6 (22·0, n=66)	88·2 (18·3, n=74)	89·6 (25·0, n=63)	85·5 (18·4, n=71)	β 2·77 (–2·29 to 7·83)
Cognitive tests‡							
Digit span	..	..	15·1 (5·2, n=85)	15·1 (4·5, n=93)	14·7 (4·9, n=83)	15·4 (4·7, n=88)	β –0·89 (–2·12 to 0·34)
Digit symbol substitution	..	..	47·2 (19·5, n=65)	47·5 (16·4, n=70)	47·2 (20·8, n=62)	47·7 (20·9, n=66)	β –1·88 (–6·10 to 2·33)
Rey Auditory Verbal Learning	..	..	34·7 (14·1, n=81)	37·6 (14·0, n=90)	37·0 (16·1, n=76)	38·2 (12·6, n=85)	β –0·91 (–4·37 to 2·55)
Trail making	..	..	46 (31 to 67, n=64)	43 (33 to 59, n=71)	48 (35 to 61, n=63)	44 (34 to 67, n=69)	β 2·89 (–4·71 to 10·49)
Verbal fluency	..	..	17·1 (6·0, n=82)	16·9 (5·7, n=89)	17·4 (6·8, n=82)	17·3 (5·5, n=83)	β –0·06 (–1·73 to 1·60)
Employment							
Employed, voluntary work or in education	29 (27%, n=106)	23 (20%, n=116)	21 (22%, n=95)	24 (25%, n=98)	18 (20%, n=91)	20 (20%, n=99)	Ref (1)
Not working or in education	77 (73%, n=106)	93 (80%; n=116)	74 (78%, n=95)	74 (76% n=98)	73 (80%, n=91)	79 (80%, n=99)	OR 1·03 (0·50 to 2·10)

Data are n (%), mean (SD), or median (IQR), unless otherwise indicated. Number of people for whom data were available at each time point are given where different from the total for the group. ASEX=Arizona Sexual Experience Scale. CSQ=Client Satisfaction Questionnaire. GASS=Glasgow Antipsychotic Side effects Scale. MANSA=Manchester Short Assessment of quality of life. MARS=Medication Adherence report Scale. PANSS=Positive and Negative Syndrome Scale. QPR Questionnaire about the Process of Recovery. SFS=Social Functioning Scale. SIX=Objective Social Outcomes Index. *Two-sided p=0·859. †Two sided p=0·007. ‡Cognitive tests were not conducted at 6 months.

Table 2: **24-month outcomes**

88 (70%) participants in the reduction group reduced their antipsychotic dose by 50% or more, compared with 21 (17%) of the maintenance participants.

Nine (26%) of the 34 participants in the antipsychotic reduction group who stopped their antipsychotics had a severe relapse requiring hospital admission, compared

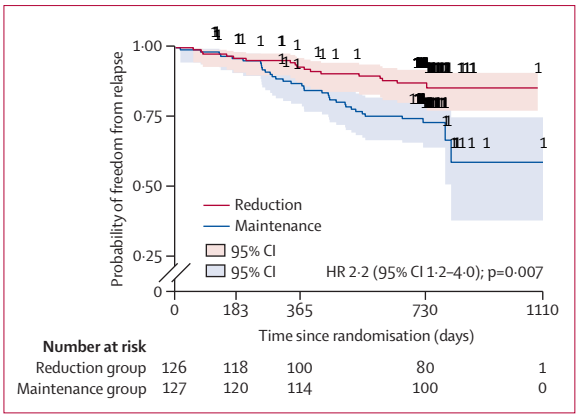

Figure 2: **Kaplan Meier plot for severe relapse**

	Antipsychotic dose reduction* (n=126)	Antipsychotic maintenance treatment* (n=127)
Medication dose at baseline: chlorpromazine equivalents†, mg	300 (200 to 450)	300 (200 to 400)
Medication dose at 24 months: chlorpromazine equivalents, mg	200 (75 to 400)	300 (150 to 425)
Maximum change in dose during the course of the study: chlorpromazine equivalents, mg	−200 (−300 to −100)	0 (−67 to 0)
Change in dose by 24-month follow-up: chlorpromazine equivalents, mg	−100 (−200 to 0)	0 (−25 to 0)
Maximum change in dose during the course of the study: percentage of baseline dose	−67% (−100% to −40%)	0 (−22% to 0)
Change in dose at 24 months: percentage of baseline dose	−33% (−67% to 0)	0 (−15% to 0)
Antipsychotic medication stopped at some point during 24-month follow-up	34 (27%)	13 (10%)
Antipsychotic dose reduced by more than 50% at some point during 24-month follow-up	88 (70%)	21 (17%)

Data are median (IQR) or n (%). *Median doses and percentage change in dose relate to the total sample of people for whom data were available. †The chlorpromazine equivalents used are provided in the appendix (pp 27–28).

Table 3: **Antipsychotic medication changes during the trial**

	Antipsychotic dose reduction (n=126)			Antipsychotic maintenance treatment (n=127)		
	Male	Female	Trans	Male	Female	Trans
Number of serious adverse events	60	33	0	56	8	0
Death	6	2	0	4	0	0
Life threatening	1	0	0	1	0	0
Mental health admission	28	21	0	21	6	0
Physical health admission	8	8	0	15	2	0
Other	17	2	0	15	0	0
Participants experiencing a serious adverse event	32	17	0	23	6	0
Number of non-serious adverse events	430	254	7	305	163	8
Participants experiencing any non-serious adverse event	58	29	1	61	34	2

Table 4: **Adverse events**

with four (31%) of the 13 who stopped in the maintenance group (appendix p 16). 25 (28%) of 88 participants in the antipsychotic reduction group who reduced their antipsychotic dose by at least 50% during the course of the trial had a severe relapse, compared with seven (33%) of the 21 participants in the maintenance group (appendix p 17). By 24 months, 13 participants from the reduction group and eight from the maintenance group were not taking antipsychotics.

Serious adverse events were more common in the reduction group, largely due to a higher number of hospital admissions for relapse (table 4). There were eight deaths in the reduction group during the study and four in the maintenance group. In the reduction group, five deaths were due to natural causes, one was an accidental drug overdose, one was attributed to the effects of antipsychotic medication, and the cause of another remains unknown at the time of writing, but there were no suspicious circumstances. In the maintenance group, two deaths were due to natural causes, one was an accidental overdose, and one was a suicide (as determined by the coroner's investigation). Non-serious adverse events were more common in the reduction group, but the number of people experiencing one was lower in the reduction than the maintenance group.

Discussion

The RADAR trial found that a gradual reduction over several months in the dose of maintenance antipsychotics in people diagnosed with schizophrenia and related psychotic disorders did not lead to benefits in social functioning and was more likely to lead to relapse than continuing on maintenance treatment. The difference in relapse rates was slightly above the 10% non-inferiority boundary used to indicate a potentially acceptable level of increase.

To our knowledge, this is the first full trial conducted with people with multiple episodes or recurrent psychotic conditions in which antipsychotic medication was reduced gradually over a period of months in a flexible way, with the aim of discontinuing medication when possible. In placebo-controlled trials of antipsychotic maintenance treatment, antipsychotic medication has been reduced over days or at most a few weeks.[2] Our trial also measured social functioning, an outcome that has been neglected in most trials[3] but is valued by service users. The results show that despite the reduction of antipsychotic medication being conducted gradually over a period of months, the risk of relapse over 24 months was still increased, compared with continuing maintenance treatment. However, most of those randomised, and more than two thirds of those who actually discontinued antipsychotic treatment or reduced it by at least 50%, did not relapse, although the numbers of the last two groups were small.

The results are similar to those in the trial by Wunderink and colleagues[8] of gradual antipsychotic dose reduction and discontinuation in people with a first episode of psychosis. In that trial, at the 18-month follow-up, there was an increased rate of relapse in participants allocated to antipsychotic reduction, with no difference in social functioning.[8] However, the 7-year follow-up of this cohort found higher levels of social functioning in people originally allocated to antipsychotic dose reduction and an equivalent risk of relapse between the groups.[9] In contrast, the long-term follow-up of a placebo-controlled trial of quetiapine found poorer composite outcomes for patients initially allocated to discontinuation and placebo substitution, compared with those allocated to continuing treatment, but there was no difference between groups on social functioning.[26] However, the original trial involved stopping medication over 6 weeks and only involved short periods of placebo treatment.

The rates of hospitalisation in our trial are similar to those found in a meta-analysis of placebo-controlled trials,[2] which found that 26% of those transferred to placebo were readmitted, compared with 10% of those receiving maintenance treatment, over a median duration of 26 weeks (IQR 1·75–156). Overall relapse rates at 1 year were higher in the meta-analysis than in our trial: 64% of participants randomised to placebo and 27% of those on maintenance treatment. This discrepancy is likely to be because few participants stopped their antipsychotic medication completely in our trial, but it might also reflect the relatively gradual nature of reduction and the efforts made to identify relapse in a rigorous and reproducible way, compared with the broad definitions of relapse employed in most other trials.[27]

Other studies of dose reduction not involving discontinuation also show higher rates of relapse among people allocated to dose reduction compared with maintenance treatment,[4,7] although not in trials involving more modest and gradual reductions.[7,28] Previous evidence suggests that dose reduction might be associated with benefits in terms of improved neurocognitive function,[7,29] but such an effect was not apparent in our trial.

Although relapse was more common among those allocated to antipsychotic dose reduction in the current trial, across both groups around two-thirds of those who reduced their antipsychotic dose by at least 50%, and of the smaller number who discontinued their medication completely at some point, did not experience a severe relapse requiring admission to hospital. The duration of hospitalisation was also not greater among those allocated to reduction despite the greater frequency of relapse.

Although this trial was not set up as a non-inferiority trial (except for the severe relapse outcome), it is notable that there were no differences between the groups at 24 months on any measures except for relapse. In particular, we defined 4 points as the minimal clinically significant difference on the SFS, and the 95% CI excluded this difference in either direction. Symptom scores at follow-up were also not higher in the reduction group, and the 95% CI excluded a difference of 10–15 points corresponding to a minimal level of change on the Clinical Global Impressions scale.[30] Given the higher rate of relapse in the reduction group, this suggests that symptoms returned to baseline following relapse.

Our findings provide information for people with schizophrenia and related conditions about the probable medium-term impact of reducing the dose of their antipsychotic medication, and they highlight the need for collaborative decision making based on the sharing and careful consideration of all the evidence. The qualitative analysis associated with this trial provides evidence of the personal experiences of people undergoing guided antipsychotic reduction.[31]

Consistent with previous research studies, our findings suggest that antipsychotic reduction carries an increased risk of relapse compared with continuing treatment, even when this is done gradually over months, although this does not mean that relapse is the inevitable result of such a process. Our findings do not provide evidence about the benefits and harms of starting maintenance treatment, since discontinuing antipsychotics is not equivalent to not starting long-term treatment in the first place. It has been suggested that antipsychotic discontinuation might itself be a risk factor for relapse.[5] Although some evidence suggests that gradual reduction might reduce this risk,[32] our findings do not support this. Whether an even more gradual dose reduction, taking years rather than months, would mitigate the increased risk of relapse requires further research. It has been suggested that it might take years for the brain to adapt slowly to lower levels of a drug that has been taken for a long period.[33] Future studies could also explore whether additional psychological and social support could reduce the excess risk of relapse associated with antipsychotic dose reduction and discontinuation.

Our trial does not show any benefits to people from reducing antipsychotic medication in terms of improving social functioning or reducing adverse effects, including bodyweight, in the short to medium term. The lack of alleviation of adverse effects is surprising in view of the lower dose reached in the reduction group and the findings of the qualitative analysis.[31] It is possible such benefits take time to appear or it might be that the dose reduction was not substantial enough to make an overall difference. We did not find an association between antipsychotic dose reduction and other negative clinical outcomes.

Our trial has various limitations. The generalisability of results is a concern with randomised trials in mental health populations. A comparison at one site showed that trial participants were similar to patients who had

the same diagnoses but were not included in the trial with regard to clinical characteristics, such as the number of previous admissions and having been subject to compulsory admission under mental health legislation.[34] This suggests that the results might be applicable to people with psychotic disorders in secondary care more generally. However, our results might not apply to people with a longer duration of stability preceding dose reduction who might be less likely to be engaged in secondary psychiatric care. The median baseline antipsychotic dose was relatively low in both groups, and the difference in median dose reduction was small in absolute terms (200 mg chlorpromazine equivalent), although the changes relative to baseline dose at some point during the trial were substantially different between the groups. The median dose reduction was lower at the end of follow-up than the maximum change at some point during the trial due to some people increasing their dose following relapse or deterioration. The trial could not be conducted double blind due to patients being on multiple treatment regimes. The initially planned sample size was not achieved, but the current sample size was adequate to provide reasonably precise estimates of the main outcomes. Inevitably with a group of people with severe disorders, there was a loss to follow-up. Due to the COVID-19 pandemic, which started just after recruitment finished, many follow-up assessments were conducted via telephone and online platforms, which might have resulted in more missing data than expected. Missing data were high for some secondary outcomes, particularly the ASEX, which people mostly preferred not to answer. Moreover, lockdowns might have impacted social functioning scores and curtailed potential improvements, since the SFS includes ratings of participation in many social activities that were unavailable or restricted. We did not conduct sex or gender specific analyses.

Although the follow-up period was 24 months, it is possible that it did not capture the ultimate effects of antipsychotic dose reduction and discontinuation, since other research points to an equalising of relapse rates and possible improvements in functioning 7 years after reduction is implemented.[9] A follow-up is currently underway involving masked assessments and data collection from clinical notes, which will take place between 4 and 7 years from randomisation.

The current trial provides data that can help people to make more informed decisions about long-term antipsychotic treatment. The findings show that a strategy of reducing and stopping antipsychotic medication over several months increases the risk of relapse compared with maintenance treatment, although most people did not have a severe relapse requiring hospital admission. The reduction strategy did not measurably improve social functioning or affect other clinical and social outcomes after 2 years. Further follow-up data will provide information about longer-term outcomes.

Contributors

JM is the Chief Investigator on this study and JM and SP conceived the study design. NC, JM, NF, and RHu wrote the protocol with advice from other authors. JM, NC, JS, RC, and ML were responsible for implementation and general project management. NC, JS, RC, and ML were responsible for study recruitment and follow-up. NF, LM, VV, and JM drafted the statistical analysis plan. LM conducted the analysis. GL and TB advised on trial design and implementation. RHu advised on health economics and quality of life. SJ and TB contributed clinical and psychopharmacology expertise to the design and implementation. VP contributed to the design and recruited and coordinated Patient and Public Involvement volunteers. LK contributed a patient perspective and RS a carer perspective to the design and implementation. KD contributed a statutory sector perspective and helped develop participant and public information. RHo advised on adherence measures and contributed a behavioural medicine perspective. VV and LM had access to all the data in the study and verified the underlying data. MJ recruited patients and oversaw a trial site. JM wrote the original manuscript and all authors contributed to the interpretation of the data and re-drafting. All authors approved the final draft and had responsibility for the decision to submit for publication. JM is guarantor of the study.

Declaration of interests

JM has grants from National Institute for Health Research (NIHR) and is a co-applicant on grants from the Medical Research Future Fund (MRFF) in Australia. She receives royalties from six books about psychiatric drugs, she has received lecture fees from Alberta Psychiatric Association, British Psychological Association, Universite de Sherbrooke, Case Western Reserve University, and University of Basal. She is co-chair person of the Critical Psychiatry Network and a board member of the Council for Evidence-based Psychiatry (both unpaid roles). RC is an unpaid Board Member of the International Institute for Psychiatric Drug Withdrawal (IIPDW), has undertaken paid work for the All Party Parliamentary Group for Prescribed Drug Dependence, and is a member of the Advisory Board for the PARTANE Study (a paid role). NF has grants from NIHR, Medical Research Council, Cure Parkinson's Trust, and the EU. He has received consulting fees from ALK, Sanofi Avantis, Gedeo Richter, Abbott, Galderma, Astra Zeneca, Ipsen, Vertex, Thea, Novo Nordisk, and Aimmune, speaker fees from Abbott Singapore, and been paid to sit on a data safety monitoring or advisory board by Orion. GL is chair of an NIHR-funded trial steering committee. SJ has grants from NIHR and UK Research and Innovation. She is chair of programme advisory committees for two studies funded through NIHR Programme Grants and has acted as a paid reviewer of grant applications for programmes on social interventions for Austrian foundation–Wiener Wissenschafts-, Forschungs- und Technologiefonds (Vienna Science and Technology Fund). TB is joint head of the Prescribing Observatory for Mental Health, Royal College of Psychiatrists. MH is co-applicant on grants from the MRFF in Australia, he has received consulting fees from Outro Health, a digital clinic aimed to support people to stop unnecessary antidepressants, lecture fees from National Health Service Trusts for grand rounds presentations, Salomon's University and University of Washington. He sits on the data safety monitoring board of the RELEASE trial in Australia, and is a co-founder of Outro Health. He is a member of the Critical Psychiatry Network and IIPDW (both unpaid roles). SP has grants from NIHR. All other authors declare no competing interests.

Data sharing

The study investigators own and have complete control of the research data, which can be accessed at any time. For statistical analysis, the data will be downloaded and safely stored on a computing system maintained by University College London (UCL), London, UK. Deidentified participant data and a data dictionary will be made publicly available after publication through UCL's data repository (https://www.ucl.ac.uk/library/open-science-research-support/research-data-management/ucl-research-data-repository) according to NIHR policy. The study protocol has been published and the statistical analysis plan is provided in the appendix (pp 18–30).

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