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Short title:	DEVISE-HD Statistical Analysis Plan v1.0

Statistical Analysis Plan for

DEVISE-HD : Developing EVIdence for AntidepreSsant ChoicE to Treat Depression in Huntington's Disease (DEVISE-HD)

Eudract/ISRCTN No:	87426672	Version Number:	V1.0

Draft Plan

Based on protocol version: Version 3.0 28/09/2026

SAP Revision History

Protocol version	Updated Sap version no.	Section number changed	Description and reason for change	Date changed

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1. INTRODUCTION

This statistical analysis plan (SAP) provides statistical methods and guidelines for the final analysis and presentation of results for the DEVISE-HD trial (Developing EVIdence for AntidepreSsant ChoicE to Treat Depression in Huntington's Disease), in accordance with the relevant reporting guidelines [1]. This plan, along with all other documents relating to the analysis of this trial, will be stored electronically in the Statistical Analysis Master File within Florence.

This SAP ensures that the statistical sections of the funder reports as well as the manuscripts for publication in peer-reviewed journals are statistically sound and consistent with the planned analyses. When the funder report and manuscripts are submitted, comments and suggestions from the reviewers and journal editors will be considered, and further analysis will be conducted, where necessary, in consensus with the Chief Investigator. Any further analyses or modifications will be conducted in accordance with the principles and guidelines set out in this SAP. Any deviations from the SAP will be documented and justified in amended versions of the SAP and reported in the final study report for transparency.

The statistical analyses for this trial will be conducted either by the author of this SAP or by another statistician assigned to the trial at the time of reporting the study findings. The data manager and statistician will be responsible for ensuring data integrity during data cleaning and final analysis, in accordance with the guidelines of the Centre for Trials Research (CTR) and its relevant Standard Operating Procedures (SOPs).

This SAP and other related documents have been reviewed by the senior trial statistician and approved by the Trial Management Group (TMG) prior to sign-off by the trial statistician (TS), senior trial statistician (ML), and the Chief Investigator (DM & CD). A copy of this SAP will be sent to the Trial Steering Committee (TSC) for review. Any comments or recommendations from the TSC will be considered and incorporated, where appropriate.

For consistency, some of the sections of this SAP have been adapted from the DEVISE-HD protocol and/or project plan included in the funding application [2].

2. BACKGROUND

A detailed background of DEVISE-HD trial is provided in the protocol [2]; here we only present a brief of summary.

Huntington's disease (HD) is a progressive neurodegenerative disorder characterised by motor, cognitive, and psychiatric symptoms [3]. Depression is one of the most common psychiatric manifestations of HD, with a reported lifetime prevalence of 33-69% [4]. Depressive symptoms have a substantial impact on quality of life, functional ability, caregiver burden, and healthcare resource utilisation [5][6]. Despite the high prevalence and clinical importance of depression in HD, there remains considerable uncertainty regarding its optimal management.

To date, there have been no randomised controlled trials specifically designed to evaluate antidepressant treatment for depression in HD. Existing evidence is limited to small studies and observational analyses, which have produced inconsistent findings [7][8][9][10]. Furthermore, evidence suggests that depression in HD may differ from depression in the general population, both in its underlying neurocognitive mechanisms and in its response to antidepressant treatment [11]. There is also uncertainty regarding the most appropriate outcome measures for assessing depression in HD [12][13]. These clinical and methodological uncertainties highlight the need for a feasibility trial to inform the design of a future definitive randomised controlled trial.

2.1 RATIONALE AND RESEARCH QUESTION

Given the burden of depression in Huntington's disease and the limited evidence available to guide antidepressant treatment in this population, there is a need to establish the feasibility of conducting a definitive randomised controlled trial. Key uncertainties remain regarding the willingness of people with HD to participate in such a trial, participant retention, treatment adherence, and the suitability of candidate outcome measures for assessing depressive symptoms and treatment response.

The DEVISE-HD trial is a double-blind, placebo-controlled feasibility trial of sertraline in people with HD and mild-to-moderate depressive symptoms. In addition to assessing feasibility, the study will explore the performance of potential clinical and biological outcome measures, including depression scales and biomarkers associated with neurodegeneration and inflammation, and will generate effect size estimates. The findings will inform the design, conduct, and sample size calculations of a future definitive efficacy trial.

2.2 OBJECTIVES

The main aim of this trial is to assess the feasibility of conducting a randomised controlled trial (RCT) to evaluate the effectiveness of antidepressant treatment for depression in individuals with Huntington's disease. The trial will recruit 40 participants from 3 hospital sites across the UK and will obtain data to inform the design for subsequent RCT.

The primary objective is to determine the feasibility of a blinded, placebo-controlled trial of antidepressants in people with HD.

The secondary objectives include:

- Determine the minimal clinically important difference (MCID), ceiling and floor effects for established measures of depression in HD, to inform outcome selection for a future efficacy trial
- Determine potential effect sizes in outcome of interest to inform power calculations for a future efficacy trial
- Determine if there are differences on clinical and fluid biomarkers of disease progression with antidepressant treatment
- Determine the percentage of participants who are registered in ENROLL
- Determine the percentage of participants who are registered in HDClarity

3. STUDY MATERIALS

3.1 TRIAL DESIGN

This is double-blind randomised control feasibility trial of sertraline vs placebo in participants with confirmed genetic diagnosis of HD with a new depressive episode. The trial will recruit 40 participants from 3 hospital sites across the UK. Participants will receive either 50mg of Sertraline or a placebo daily for 4 weeks and then escalating to 100mg Sertraline/placebo daily for a further 20 weeks. The trial is planned to run for 24 months overall, including a 10-month recruitment period. Each participant will be followed up for 6 months after randomisation.

3.2 RANDOMISATION

Participants will be individually randomised in a 1:1 ratio to Sertraline or placebo using a pre-defined randomisation list generated in STATA and implemented in REDCap through Kitsune. Random permuted blocks, stratified by the Huntington's Disease Integrated Staging System (HD-ISS), will be used to ensure the balance of numbers between arms within each disease

stage stratum. As this is a blinded trial, the trial statistician will remain blinded to participants' allocation to the randomisation arms. All details of the randomisation schedule, testing procedures, and implementation are given in the randomisation strategy document on the CTR required template.

3.3 SAMPLE SIZE

A sample size of 40 has been chosen to assess the feasibility of this study. This will allow for a total proportion to be estimated to within +/-14.8% margin of error at 95% confidence interval (CI), using the Wilson score method [14].

3.4 FRAMEWORK

This is a feasibility study with double-blind randomised controlled design, comparing sertraline versus placebo, in adult participants with confirmed genetic diagnosis of HD and a new depressive episode. As a feasibility trial, the focus is on assessing recruitment, retention, data completeness, adherence, and acceptability of study procedures. Clinical and safety outcomes will be summarised descriptively, with any between-group comparisons considered exploratory.

3.5 INTERIM ANALYSES

Not applicable.

3.5.1 PLANNED SAMPLE SIZE ADJUSTMENT

Not applicable.

3.5.2 STOPPING RULES

Not applicable.

3.6 TIMING OF FINAL ANALYSIS

The final statistical analysis will be conducted after completion of the 6-month (24-week) follow-up period for all participants, completion of the planned data collection, and database lock. The final analysis will be performed following completion of data cleaning and resolution of data queries, in accordance with the finalised Statistical Analysis Plan.

No formal interim analysis of treatment efficacy is planned. The primary feasibility outcomes will be assessed at the end of the recruitment period and following completion of the relevant follow-up assessments, as specified in the outcome definitions.

3.7 TIMING OF OUTCOME ASSESSMENT

In this trial, outcome measurements will be collected at three timepoints. Baseline measurements will be taken prior to randomisation, and the follow-up measurements will be collected at 8 weeks and 6 months (24 weeks) post-randomisation.

4. STATISTICAL PRINCIPLES

4.1 LEVELS OF CONFIDENCE AND P-VALUES

This trial will primarily use descriptive statistical analyses. Where confidence intervals are presented, these will be two-sided 95% confidence intervals (CIs). Results will generally be reported as point estimates with corresponding 95% CIs, where appropriate.

No p-values will be presented for the primary feasibility outcomes, baseline characteristics, or other descriptive analyses. Secondary and exploratory outcome analyses are intended to be descriptive and hypothesis-generating and will not be used to draw definitive conclusions regarding treatment efficacy.

4.1.1 ADJUSTMENT FOR MULTIPLICITY

Not applicable.

4.2 ADHERENCE AND PROTOCOL DEVIATIONS

Adherence and protocol deviations would have been handled according to the CTR SOP on protocol/GCP non-compliance and serious breaches (SOP/009/5 (v4.0)).

4.2.1 DEFINITION AND ASSESSMENT OF ADHERENCE

Adherence will be assessed based on the proportion of the allocated investigational medicinal product (IMP) taken during the treatment period, as determined from the available trial medication accountability and/or adherence records.

For the primary feasibility assessment, full adherence will be defined as taking at least 80% of the allocated IMP during the treatment period. The proportion of randomised participants meeting this criterion at 6 months (24 weeks) assessment will be calculated.

4.2.2 PRESENTATION OF ADHERENCE

Adherence will be summarised descriptively overall and by treatment arm. The number and percentage of participants meeting the predefined adherence criterion (≥80% of allocated IMP taken) will be reported, together with the corresponding numerator and denominator.

Where available, adherence will also be summarised as a continuous percentage of allocated IMP taken using appropriate descriptive statistics.

4.2.3 DEFINITION OF PROTOCOL DEVIATION

A protocol deviation is any deviation from the protocol, including eligibility violations, treatment deviations or non-adherence to the protocol.

4.2.4 PRESENTATION OF PROTOCOL DEVIATIONS

The Principal Investigator should report any non-compliance with the trial protocol or the conditions and principles of Good Clinical Practice (GCP) to the CTR in writing as soon as it is identified. If applicable, deviations that affect the data integrity should be summarised in the final report. These may include participants who were randomised but not treated, and participants subsequently found to be ineligible for inclusion in the trial.

4.3 ANALYSIS POPULATION

In this trial, all participants randomised will be included in the analysis population and analysed according to the treatment arm to which they were randomised, in accordance with the intention-to-treat (ITT) principle, regardless of initiation of, or adherence to, the allocated trial treatment. Missing follow-up data will not be imputed, and analyses will be based on the available data.

A CONSORT flow diagram will be used to summarise the number of participants who were:

a. Eligible at screening.
b. Ineligible at screening, with reasons provided.
c. Eligible and registered.
d. Eligible but not registered, with reasons provided.
e. Randomised to Sertraline and placebo.
f. Received the treatment as per protocol.
g. Did not start receiving the treatment as per protocol, with reasons provided.
h. Lost to follow-up, with reasons provided.
i. Discontinued the treatment, with reasons provided.
j. Included in the final analysis of participants.

5. STUDY POPULATION

5.1 SCREENING DATA

Screening data from each site will be reviewed to calculate the proportion of participants who were eligible and randomised, and to populate the CONSORT flow diagram.

5.2 ELIGIBILITY

Eligibility data will not be reported separately. However, the CONSORT flow diagram will show the number of participants who were eligible for the trial, including any participants who were subsequently found to be ineligible after receiving treatment.

5.3 RECRUITMENT

The trial will recruit 40 participants from 3 hospital sites across the UK, at an expected rate of 1.5 participants per site per month. Recruitment will be presented in the flow diagram.

5.4 WITHDRAWAL/FOLLOW UP

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

5.4.1 LEVEL OF WITHDRAWAL

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

- Withdrawal of Trial Treatment
- Withdrawal from trial due to clinically indicated alternative dose of treatment
- Withdrawal from questionnaires
- Withdrawal from Samples (Blood)
- Withdrawal from follow-up assessments
- Withdrawal of accessing ENROLL-HD data
- Withdrawal of accessing CSF and/or blood samples from HDClarity
- Withdrawal due to pregnancy
- Withdrawal of Consent to all of the above

5.4.2 TIMING OF WITHDRAWAL

Participants have the right to withdraw consent for participation in any aspect of the trial at any time until the database is locked for the final analysis.

5.4.3 REASONS FOR WITHDRAWAL

Reasons for all levels of withdrawal (including adverse events that lead to treatment discontinuation) will be recorded.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Withdrawal of consent for treatment by the participant
- Any alteration in the participants condition which justifies the discontinuation of the treatment in the Investigator's opinion
- Non-compliance

5.4.4 PRESENTATION OF WITHDRAWAL/LOSS TO FOLLOW-UP

The number and percentage of participants lost to follow-up and withdrawals, will be summarised descriptively overall and by arm. Reasons for withdrawal will also be summarised where available.

5.5 BASELINE PARTICPANT CHARACTERISTICS

5.5.1 LIST OF BASELINE DATA

The baseline characteristics to be collected include:

- Demographics: age, sex, ethnic background, education level, living status and work status
- Medical history: absenteeism, prior episodes of depression/anxiety, duration of symptoms, prior treatment, CAG repeat length, HD-ISS stage, and comorbidities
- Pregnancy status
- Concomitant medications
- Depression and suicidality measures: PBAs, MADRS, BDI-II, PHQ-9, C-CCRS, WHODAS and MOS-SSS-6
- Digital assessment outcomes: Reward Reaction Time Task, Effort Discounting Task, Conceptual Bias Task and Brief State Rumination Inventory
- Other assessments: cUHDRS (Total Motor Score, Total Functional Capacity, Symbol Digit Modality, Stroop Word Reading Task)
- Biological samples: blood sample for plasma biomarkers (NfL, TNF-α, IL-4, IL-6, IL-10) and CSF sample (where applicable)

5.5.2 DESCRIPTIVE STATISTICS

Baseline demographic and clinical characteristics will be summarised using means and standard deviations (SD) for normally distributed continuous variables, or medians and interquartile ranges (IQR) for skewed data. Categorical variables will be summarised using counts and percentages. These summaries will be tabulated by arm and overall. Additionally, baseline data will also be summarised for those who complete follow-up compared to those lost to follow-up in order to assess possible drop-out bias.

6. ANALYSIS

6.1 OUTCOME DEFINITIONS

6.1.1 PRIMARY OUTCOMES

The primary objective of the DEVISE-HD trial is to determine the feasibility of conducting a blinded, placebo-controlled randomised controlled trial of antidepressant treatment in people with Huntington's disease. Feasibility will be assessed across four key domains: recruitment, retention, data completeness and adherence.

The primary feasibility outcomes are:

Recruitment

- the proportion of eligible participants approached who consent to participate;
- the proportion of screened participants who are randomised; and
- the number of participants randomised.

Retention

- Proportion of randomised participants attending the 8-week follow-up assessment.
- Proportion of randomised participants attending the 6-month follow-up assessment.
- Proportion of randomised participants attending 6-month follow-up assessment and who remain on IMP.

Data completeness

- Proportion of randomised participants with all depression and suicidality outcomes completed at 8-week follow-up.
- Proportion of randomised participants with all depression and suicidality outcomes completed at 6-month follow-up.
- Proportion of randomised participants with clinical progress outcomes, excluding digital measures, completed at 6-month follow-up.

- Proportion of randomised participants providing a blood sample at 6-month follow-up.

Adherence

- Proportion of randomised participants with full adherence to allocated treatment at 6-month follow-up, where full adherence is defined as taking at least 80% of the allocated medication during the treatment period.

6.1.2 TIMING, UNITS AND DERIVATION OF PRIMARY

The primary outcomes will be assessed during the recruitment period and at the pre-specified follow-up timepoints of 8 weeks and 6 months following randomisation, according to the outcome-specific definitions described below. Outcomes will be calculated using the population specified for each outcome, with the denominator defined accordingly. All proportion-based outcomes will be presented as percentages, together with the corresponding numerator and denominator.

Table 1: Timing, units and derivation of primary outcomes

Category	Primary outcome	Timing	Unit	Derivation
Recruitment	Proportion of eligible participants approached who consent	Recruitment period	%	Number consenting / number eligible participants approached × 100
	Proportion of screened participants who are randomised	Recruitment period	%	Number randomised / number screened × 100
	Number randomised	Recruitment period	n	Total number randomised
Retention	Proportion attending 8-week follow up assessment	8 weeks post-randomisation	%	Number attending 8-week follow up assessment / number randomised × 100
	Proportion attending 6-month follow-up assessment	6 months post-randomisation	%	Number attending 6-month follow-up assessment / number randomised × 100

	Proportion attending 6-month follow-up assessment and still on IMP	6 months post-randomisation	%	Number attending 6-month follow-up assessment and still on IMP / number randomised × 100
Data completeness	Proportion with all depression and suicidality outcomes completed at 8-week follow-up	8 weeks post-randomisation	%	Number with all specified outcomes completed at 8-week follow-up / number randomised × 100
	Proportion of randomised participants with all depression and suicidality outcomes completed at 6-month follow-up	6 months post-randomisation	%	Number with all specified outcomes completed at 6-month follow-up / number randomised × 100
	Proportion of randomised participants with clinical progress outcomes, excluding digital measures, completed at 6-month follow-up	6 months post-randomisation	%	Number with all specified outcomes completed at 6-month follow-up / number randomised × 100
	Proportion of randomised participants providing a blood sample at 6-month follow-up	6 months post-randomisation	%	Number providing blood sample at 6-month follow-up / number randomised × 100
Adherence	Proportion with full adherence to allocated treatment at 6-month follow-up of those randomised	6 months post-randomisation	%	Number meeting ≥80% adherence / number randomised × 100

6.1.3 LIST OF SECONDARY OUTCOMES

The following secondary outcomes will be assessed during the DEVISE-HD trial.

Depression and suicidality outcome measures

- Beck Depression Inventory-II (BDI-II)
- Problem Behaviours Assessment (short form) (PBAs)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Patient Health Questionnaire-9 (PHQ-9)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- WHO Disability Assessment Schedule 2.0, 12-item version (WHODAS 2.0)
- Medical Outcomes Study Social Support Survey, 6-item version (MOS-SSS)

Assessment of improvement in depressive symptoms

- Patient-completed Success of Treatment form
- Clinician-rated Clinical Global Impression - Improvement scale (CGI-I)

Clinical progression outcomes measures

Clinical progression outcomes will be assessed using measures collected as part of ENROLL-HD. The outcomes comprise:

- Composite Unified Huntington's Disease Rating Scale (cUHDRS)
- Total Motor Score (TMS)
- Total Functional Capacity (TFC)
- Symbol Digit Modalities Test (SDMT)
- Stroop Word Reading Task (SWRT)

These outcomes will be assessed at baseline and 6 months (24 weeks) following randomisation, where available according to the DEVISE-HD assessment schedule.

Biomarkers outcomes measures

Biomarker outcomes will be assessed using blood samples collected as part of DEVISE-HD and, where applicable, samples collected through co-recruitment to HDClarity. The biomarker outcomes comprise:

- Neurofilament light chain (NfL)
- Tumour necrosis factor-alpha (TNF-α)
- Interleukin-4 (IL-4)
- Interleukin-6 (IL-6)
- Interleukin-10 (IL-10)

The specific timing, units, scoring and derivation of these outcomes will be defined in Section 6.1.6.

6.1.4 LIST OF EXPLORATORY OUTCOME

The following measures are exploratory outcomes and are optional for participants. The exploratory assessments are intended to provide information on behavioural and cognitive processes associated with depression and potential treatment response.

Digital assessment outcomes:

- Reward Reaction Time Task

- Effort Discounting Task
- Self-Referent Encoding Task
- Brief State Rumination Inventory (BSRI)

6.1.5 ORDER OF TESTING

Not applicable. No testing will be performed.

6.1.6 TIMING, UNITS AND DERIVATION OF SECONDARYS

The secondary outcome measures will be assessed at baseline and at the pre-specified follow-up timepoints of 8 weeks and 24 weeks (6 months) following randomisation, according to the assessment schedule for each outcome. Clinical progression outcomes will be assessed at baseline and 24 weeks, and the assessment of improvement in depressive symptoms will be performed at 24 weeks.

Outcome measures will be scored in accordance with their respective published scoring guidelines. Where applicable, total or summary scores will be calculated in accordance with the relevant scoring algorithm. The timing, units and derivation of each secondary outcome are described below.

Depression and suicidality outcome measures

BDI-II: The BDI-II is a self-report measure of depressive symptom severity comprising 21 items [15]. Participants rate each item from 0 to 3, giving a total score ranging from 0 to 63. Items assess symptoms including sadness, pessimism, past failure, loss of pleasure, guilt, feelings of punishment, self-dislike, self-criticism, suicidal thoughts, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleep and appetite, irritability, concentration difficulties, fatigue and loss of interest in sex. The total score will be calculated by summing the individual item scores, with higher scores indicating greater depressive symptom severity.

PBAs: The PBAs is a semi-structured clinician-administered interview assessing behavioural and neuropsychiatric symptoms commonly associated with Huntington's disease [16]. The measure assesses symptoms including depressed mood, suicidal ideation, anxiety, irritability, aggression, apathy, perseveration, obsessive-compulsive behaviour, paranoid thinking, hallucinations and disorientation. Each symptom is rated according to its frequency and severity over the preceding four weeks, with each rated from 0 to 4. The frequency and severity scores are multiplied to produce an overall symptom score ranging from 0 to 16 for each item. The depressed mood symptom score will be used as the outcome measure, with higher scores indicating greater symptom severity.

MADRS: The MADRS is a clinician-rated measure of depressive symptom severity comprising 10 items. Each item is scored from 0 to 6, giving a total score ranging from 0 to 60. The scale assesses symptoms including apparent and reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. The total score will be calculated by summing the 10 item scores according to the published scoring guidelines, with higher scores indicating greater depressive symptom severity [17][18].

PHQ-9: The PHQ-9 is a 9-item self-report measure of depressive symptoms [19]. Each item is scored from 0 to 3, giving a total score ranging from 0 to 27. Higher scores indicate greater depressive symptom severity. The total score will be calculated by summing the item scores.

C-SSRS: The C-SSRS is a standardised screening and assessment instrument for suicidal ideation and suicidal behaviour [20]. Participants are asked screening questions regarding suicidal ideation, including thoughts of being better off dead and thoughts of suicide, followed by further assessment where indicated. The intensity of suicidal ideation is rated on a 0-5 scale, with higher scores indicating greater severity. Suicidal behaviour is recorded according to predefined C-SSRS categories. The C-SSRS outcomes will be derived and scored in accordance with the published scoring guidelines.

WHODAS 2.0: The WHODAS 2.0 is a measure of functioning and disability across six domains: cognition, mobility, self-care, getting along, life activities and participation. The 12-item version provides an overall measure of functioning. The score will be calculated according to the published WHODAS 2.0 scoring guidelines, with higher scores indicating greater disability [21].

MOS-SSS: The MOS-SSS is a self-report measure of perceived availability of social support [22]. Items are rated using the response options specified in the instrument, with the resulting score calculated according to the published scoring guidelines. Higher scores indicate greater perceived social support.

Assessment of improvement in depressive symptoms

Success of Treatment form: The Success of Treatment form is a participant-reported assessment of perceived improvement in depressive symptoms and treatment success. The outcome will be analysed according to the response categories specified on the study form.

CGI-I: The CGI-I is a clinician-rated measure of global improvement in the participant's condition relative to baseline. The scale comprises seven ordinal response categories ranging from 1 (very much improved) to 7 (very much worse), with 4 representing no change [23][24]. The CGI-I will be analysed according to these predefined ordinal categories.

Clinical progression outcomes measures

Clinical progression outcomes will be assessed at baseline and 24 weeks following randomisation using measures collected as part of ENROLL-HD.

cUHDRS: The cUHDRS is a composite measure of clinical progression in Huntington's disease incorporating the Total Motor Score (TMS), Total Functional Capacity (TFC), Symbol Digit Modalities Test (SDMT) and Stroop Word Reading Task (SWRT). The cUHDRS will be calculated using the pre-specified formula [25]:

$$cUHDRS = \left(\frac{TFC - 10.4}{1.9}\right) - \left(\frac{TMS - 29.7}{14.9}\right) + \left(\frac{SDMT - 28.4}{11.3}\right) + \left(\frac{SWRT - 66.1}{20.1}\right) + 10$$

Higher cUHDRS scores indicate better clinical status, with a decline in score indicating worsening disease progression.

TMS: The TMS is a clinician-rated assessment of motor impairment in Huntington's disease. It assesses motor features including gait, eye movements, dystonia, bradykinesia, motor impersistence, chorea and postural instability. Scores range from 0 to 124, with higher scores indicating greater motor impairment.

TFC: The TFC assesses functional capacity across five domains: occupation, finances, domestic activities, activities of daily living and care requirements. Scores range from 0 to 13, with higher scores indicating better functional capacity.

SDMT: The SDMT is a measure of cognitive processing speed. Participants match symbols to numbers using a reference key, and the number of correct responses within the specified time period is recorded. Higher scores indicate better cognitive performance.

SWRT: The SWRT is a measure of cognitive processing speed. The number of correctly read words within the specified assessment period is recorded. Higher scores indicate better cognitive performance.

Biomarkers outcomes measures

Biomarker outcomes will be assessed at baseline and 24 weeks where a biological sample is available.

NfL: NfL is a biomarker of neuronal injury. NfL concentration will be analysed as a continuous outcome using the measured concentration in the available biological sample.

TNF-α, IL-4, IL-6 and IL-10: These biomarkers will be used as measures of inflammatory activity. Concentrations will be analysed as continuous outcomes using the measured concentration in the available biological sample.

6.1.7 TIMING, UNITS AND DERIVATION OF EXPLORATORY OUTCOMES

The exploratory outcome measures are optional for participants and will be assessed at the pre-specified follow-up timepoints according to the assessment schedule for each outcome. The timing, units and derivation of each exploratory outcome are described below.

Outcome measures will be scored and derived in accordance with the relevant task or instrument scoring procedures. Analyses of exploratory outcomes will be based on available data from participants who complete the relevant optional assessment. Missing exploratory outcome data will not be imputed.

Reward Reaction Time Task: The Reward Reaction Time Task is a computerised measure of effort for reward [26]. The outcome measure will be the change in reaction time from baseline, corrected for reward value. Reaction time will be recorded in milliseconds (ms). Baseline reaction time will be calculated as the participant's mean reaction time during the baseline condition. Reaction times during the reward condition will be assessed in relation to the reward value of the stimulus (10, 20 or 40 points). The outcome will be derived according to the pre-specified task scoring procedure, with higher values indicating a greater change in reaction time from baseline after accounting for reward.

Effort Discounting Task: The Effort Discounting Task is a computerised measure of effort-based decision-making. The outcome measure will be choice behaviour, defined as the proportion of valid trials on which the participant selects the high-effort/high-reward option. This will be calculated as the number of high-effort/high-reward choices divided by the total number of valid trials and expressed as a percentage [27]. The outcome will therefore range from 0% to 100%, with higher values indicating a greater propensity to choose the high-effort/high-reward option.

Self-Referent Encoding Task: The Self-Referent Encoding Task assesses the processing of positive- and negative-valence self-referent information [28]. Two exploratory outcomes will be derived.

The first outcome will be the ratio of the total number of positive-valence words endorsed as self-relevant to the total number of negative-valence words endorsed as self-relevant. Higher values will indicate relatively greater endorsement of positive compared with negative self-referent information.

The second outcome will be reaction time according to word valence. Reaction time will be recorded in milliseconds (ms) and summarised separately for positive- and negative-valence words using valid trials only, in accordance with the task scoring procedures.

Brief State Rumination Inventory [29]: The Brief State Rumination Inventory is a 13-item self-report measure of state rumination. Each item is scored from 0 to 100. The total score will be calculated by summing the 13 item scores, giving a possible range from 0 to 1300. Higher scores indicate greater levels of rumination.

6.2 ANALYSIS METHODS

6.2.1 LIST OF METHODS AND PRESENTATION

Baseline analysis

Baseline demographic and clinical characteristics will be summarised overall and by treatment arm. Continuous variables will be summarised using means and standard deviations where approximately normally distributed, or medians and interquartile ranges where distributions are skewed. Categorical variables will be summarised using frequencies and percentages.

Baseline characteristics will also be summarised according to follow-up status, including participants who complete the relevant follow-up assessment and those who are lost to follow-up, to assess potential differences associated with loss to follow-up.

No formal statistical comparisons of baseline characteristics between treatment arms will be undertaken, as baseline comparisons are not intended to test the success of randomisation.

Primary outcome analysis

The primary feasibility outcomes will be analysed descriptively to assess the feasibility of conducting a future blinded, placebo-controlled randomised controlled trial of antidepressant treatment in people with HD. Feasibility will be assessed across the four pre-specified domains of recruitment, retention, data completeness and adherence, as defined in Section 6.1.1.

For each primary feasibility outcome, the relevant numerator, denominator and proportion will be reported. Proportions will be presented as percentages, together with 95% confidence intervals where appropriate. The denominator for each outcome will be defined according to the outcome-specific definition in Table 1.

No formal hypothesis testing or adjustment for multiple comparisons will be undertaken for the primary feasibility outcomes. The results will be assessed against the pre-specified modified traffic-light progression criteria presented in Table 2.

Table 2: Primary outcomes and progression criteria

Category	Outcome	Progression criteria		
		Red	Amber	Green
Recruitment	Proportion of participants consented of eligible participants approached	p < 5%	5% ≤ p < 20%	p ≥ 20%
	Proportion randomised of those screened	p < 50%	50% ≤ p < 75%	p ≥ 75%
	Number randomised	n < 10	10 ≤ n ≤ 30	p ≥ 31
Retention	Proportion reaching 6-month follow-up and still on IMP of those randomised	p < 30%	30% ≤ p < 60%	p ≥ 60%
	Proportion reaching 8-week follow-up of those randomised	p < 50%	50% ≤ p < 80%	p ≥ 80%
	Proportion reaching 6-month follow-up of those randomised	p < 50%	50% ≤ p < 70%	p ≥ 70%
Data completeness	Proportion with all depression and suicidality outcomes completed at 8-week follow-up of those randomised	p < 50%	50% ≤ p < 75%	p ≥ 75%
	Proportion with all depression and suicidality outcomes completed at 6-month follow-up of those randomised	p <40%	40% ≤ p < 65%	p ≥ 65%
	Proportion of Clinical progress (excluding digital measures) outcomes completed at 6-month follow-up of those randomised	p < 50%	50% ≤ p < 75%	p ≥ 75%
	Proportion of those randomised donating Blood sample at 6-month follow-up	p< 40%	40%< p < 60%	p ≥ 60%
Adherence (80% of medication taken)	Proportion with full adherence to allocated treatment at 6-month follow-up of those randomised	p < 50%	50% ≤ p < 80%	p ≥ 80%

Note: IMP = investigational medicinal product; p = proportion; n = number of participants.

The traffic-light system will be interpreted as follows:

- Green: Proceed to a future definitive RCT as planned.
- Amber: Proceed to a future definitive RCT subject to modifications to the relevant trial process.
- Red: Do not proceed to a future definitive RCT without substantial reconsideration of the trial design and/or processes.

The traffic-light classification will be reported for each primary feasibility outcome. The findings across the four feasibility domains will be considered collectively when assessing the overall feasibility of progression to a future definitive trial.

Secondary outcome analysis

Secondary outcomes will be summarised descriptively at baseline and at all follow-up time points, overall and by treatment arm. Outcome measures will be scored in accordance with their respective published scoring guidelines or validated scoring algorithms.

Where possible (in relation to the rules set below), MCIDs will be estimated for PBA, MADRS, BDI-II, PHQ-9, and C-SSRS at 6 months post-randomisation. The MCID analyses are intended to inform the selection of the most appropriate primary outcome and the sample size calculation for a future effectiveness trial.

MCIDs will be derived using an anchor-based approach, with estimates triangulated across participant-, and clinician-reported anchors, where available [30]. The correlation between each anchor and change from baseline to 6 months post-randomisation will be checked to ensure it meets the minimal threshold of ≥ |0.3| [30][31].

The seven-point clinician-reported anchor will be categorised into five groups as follows:

- Very much worse = Large and important negative change;
- Much worse and Minimally worse = Small but important negative change;
- No change = No change;
- Minimally improved and Much improved = Small but important positive change;
- Very much improved = Large and important positive change.

The categories of the five-point patient-reported anchor will translate directly to the five groups.

The sign of the change from baseline to follow-up for those reporting a ‘Large and important negative change’ or ‘Small but important negative change’ will be reversed, and then the two ‘Large and important’ categories and the two ‘Small but important’ categories will be combined to create three categories of ‘No change’, ‘Small but important change’ and ‘Large and important change’ [31].

The value of the MCID will be determined as [31]:

- within the ‘Small but important change’ group interquartile range;
- close to the median of the ‘Small but important change’ group;

- the value that jointly maximises the percentage of those in the 'No change' group with a lesser value and the percentage of those in the 'Large and important change' group with the same or a greater value.

These MCIDs will be used in the decision-making process for future primary outcome choice and the sample size calculations that would follow that choice

As part of the secondary analyses, percentage change in NfL concentrations from baseline to 24 weeks will be compared between treatment arms using the Mann-Whitney U test, as the distribution of NfL is expected to be non-normal. The inflammatory biomarkers TNF-α, IL-4, IL-6 and IL-10 will be summarised descriptively. The cUHDRS composite score at 24 weeks will be compared between treatment arms using analysis of covariance (ANCOVA), with treatment arm as a fixed effect and baseline cUHDRS score as a covariate. These analyses will be considered exploratory and interpreted cautiously given the feasibility nature of the trial.

Exploratory outcome analysis

The exploratory digital assessment outcomes (Reward Reaction Time Task, Effort Discounting Task, Self-Referent Encoding Task, and Brief State Rumination Inventory) will be summarised descriptively at baseline and follow-up, overall and by arm, among participants who consented to these optional assessments. Continuous measures will use means (SD) or medians (IQR) as appropriate, following the same approach as the secondary outcomes. The Effort Discounting Task will be summarised as the percentage of high-effort/high-reward choices (Section 6.1.7); the Brief State Rumination Inventory as its total score. Completion rates for each task will be reported given their optional nature.

6.2.2 COVARIATE ADJUSTMENT

Not applicable.

6.2.3 ASSUMPTION CHECKING

The distribution of continuous secondary outcomes will be assessed using descriptive statistics and graphical methods, including histograms and/or Q-Q plots, where appropriate. Particular consideration will be given to the distribution of biomarker outcomes, including NfL, which is expected to be non-normally distributed.

No formal assessment of distributional assumptions will be required for the primary feasibility outcomes, as these will be analysed descriptively.

6.2.4 ALTERNATIVE METHODS IF DISTRIBTIONAL ASSUMPTIONS NOT MET

Not applicable.

6.2.5 SENSITIVITY ANALYSES

No formal sensitivity analyses are planned.

6.2.6 SUBGROUP ANALYSES

Not applicable.

6.3 MISSING DATA

Data completeness will be reported as part of the statistical report. The frequency and percentage of missing values will be reported overall and by arm. Missing data may occur in the primary and secondary outcomes.

Where item-level scoring or missing-item guidance is available for a given measure, missing items will be handled in accordance with the prespecified scoring guidance prior to derivation of the total or scale score. For the PHQ-9, where one or two items are missing, the missing item(s) will be replaced by the mean of the non-missing items; the score will be treated as missing if more than two items are missing. For the WHODAS 2.0 12-item version, where one item is missing, the missing item will be replaced by the mean of the remaining 11 items; this approach will not be used if more than one item is missing. For the MOS-SSS, the published scoring instructions will be followed, including the specified approach to missing items.

For measures for which no specific item-level missing-data rule has been prespecified, no ad hoc item-level imputation will be undertaken. For the BDI-II and MADRS, scoring and handling of missing items will follow the specific scoring guidance adopted for the trial. For the PBAs, C-SSRS, CGI-I, cUHDRS and its component measures, and biomarker outcomes, where a valid outcome cannot be derived according to the relevant scoring procedures, the outcome will be treated as missing.

Following derivation of outcome scores in accordance with the relevant scoring guidance, analyses will use a complete-case approach for each outcome and assessment time point. No imputation of missing outcome values will be undertaken. The frequency and percentage of missing outcome data will be reported, and the extent of missingness will be considered when interpreting the results. If a substantial amount of missing data occurs for outcomes of main interest, this will be highlighted and the results will be interpreted with appropriate caution.

6.4 ADDITIONAL ANALYSES

Not applicable.

6.5 HARMS

Adverse events (AEs) and serious adverse events (SAEs) will be summarised descriptively by treatment arm.

The number and proportion of participants experiencing at least one AE and at least one SAE will be presented for each treatment arm. The number of events will also be reported where appropriate. AEs will be summarised according to severity, seriousness, relationship to the IMP, and whether the event resulted in discontinuation of the IMP, in accordance with the trial safety reporting procedures.

No formal hypothesis testing of treatment differences in adverse events is planned. Safety analyses will be descriptive and will be used to characterise the safety and tolerability of the trial interventions.

6.6 STATISTICAL SOFTWARE

Stata (StataCorp LLC, TX USA) version 19 (or higher) will be used for the statistical analysis.

7. REFERENCES

1. Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. BMJ. 2025;389:e081123.
2. Foscarini-Craggs P, et al. DEVISE-HD: Developing EVIdence for AntidepreSsant ChoicE to Treat Depression in Huntington's Disease - Study Protocol, Version 3.0, 28 September 2026.
3. Walker FO. Huntington's disease. Lancet. 2007;369(9557):218-228. doi:10.1016/S0140-6736(07)60111-1.
4. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007;19(4):441-448. doi:10.1176/jnp.2007.19.4.441.
5. Ready RE, Mathews M, Leserman A, Paulsen JS. Patient and caregiver quality of life in Huntington's disease. Mov Disord. 2008;23(5):721-726. doi:10.1002/mds.21920.
6. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Different depression: motivational anhedonia governs antidepressant efficacy in Huntington's disease. Brain Commun. 2022;4(6):fcac278. doi:10.1093/braincomms/fcac278.
7. Como PG, Rubin AJ, O'Brien CF, et al. A controlled trial of fluoxetine in nondepressed patients with Huntington's disease. Mov Disord. 1997;12(3):397-401.
8. Beglinger LJ, Adams WH, Paulson H, et al. Randomized controlled trial of citalopram in Huntington's disease. *Mov Disord*. 2014;29(3):401-405. doi:10.1002/mds.25752.

9. Ogilvie AC, Carnahan RM, Chrischilles EA, Schultz JL. The effects of antidepressants on depressive symptoms in manifest Huntington's disease. J Psychosom Res. 2022;162:111023. doi:10.1016/j.jpsychores.2022.111023.
10. Keogh R, et al. Medication use in early-HD participants in Track-HD: an investigation of its effects on clinical performance. PLoS Curr. 2016;8:ecurrents.hd.8060298fac1801b01ccea6acc00f97cb.
11. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Different depression: motivational anhedonia governs antidepressant efficacy in Huntington's disease. Brain Commun. 2022;4(6):fcac278. doi:10.1093/braincomms/fcac278.
12. Carlozzi NE, Miciura A, Migliore N, Dayalu P. Understanding the outcome measures used in Huntington disease pharmacological trials: a systematic review. J Huntingtons Dis. 2014;3(3):233-252. doi:10.3233/JHD-140105.
13. Mestre TA, Forjaz MJ, Mahlknecht P, Cardoso F, Ferreira JJ, Martinez-Martin P, et al. Rating scales and performance-based measures for assessment of functional ability in Huntington's disease: critique and recommendations. Mov Disord Clin Pract. 2018;5(4):361-372. doi:10.1002/mdc3.12642.
14. Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc. 1927;22(158):209-212. doi:10.1080/01621459.1927.10502953.
15. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
16. McNally G, Rickards H, Horton M, Craufurd D. Exploring the Validity of the Short Version of the Problem Behaviours Assessment (PBA-s) for Huntington's disease: A Rasch Analysis. (1879-6400 (Electronic)).
17. Montgomery & Åsberg (1979), A new depression scale designed to be sensitive to change.
18. Williams JBW, Kobak KA. Development and reliability of a structured interview guide forthe Montgomery-Åsberg Depression Rating Scale (SIGMA). British Journal of Psychiatry. 2008;192(1):52-8.
19. Kroenke, Spitzer & Williams (2001), The PHQ-9: Validity of a brief depression severity measure.
20. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266–1277. doi:10.1176/appi.ajp.2011.10111704.
21. World Health Organization. Measuring health and disability: manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva: World Health Organization; 2010. ISBN 9789241547598.

22. Sherbourne CD, Stewart AL. The MOS Social Support Survey. Social Science & Medicine. 1991;32(6):705-714. doi:10.1016/0277-9536(91)90150-B.
23. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. Revised ed. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health; 1976.
24. Busner J, Targum SD. The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry (Edgmont). 2007;4(7):28-37.
25. Schobel SA, Palermo G, Auinger P, Long JD, Ma S, Khwaja OS, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early Huntington disease. Neurology. 2017;89(24):2495-2502. doi:10.1212/WNL.0000000000004743.
26. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Different depression: motivational anhedonia governs antidepressant efficacy in Huntington's disease. Brain Communications. 2022;4(6). doi:10.1093/braincomms/fcac278.
27. Atkins KJ, Andrews SC, Stout JC, Chong TT-J (2020). Dissociable motivational deficits in pre-manifest Huntington's disease. Cell Reports Medicine, 1(9): 100152. doi:10.1016/j.xcrm.2020.100152.
28. Dainer-Best J, Lee HY, Shumake JD, Yeager DS, Beevers CG. Determining optimal parameters of the Self-Referent Encoding Task: A large-scale examination of self-referent cognition and depression. Psychological Assessment. 2018;30(11):1527-1540. doi:10.1037/pas0000602.
29. Marchetti I, Mor N, Chiorri C, Koster EHW. The Brief State Rumination Inventory (BSRI): Validation and Psychometric Evaluation. Cognitive Therapy and Research. 2018;42(4):447-460. doi:10.1007/s10608-018-9901-1.
30. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008;61(2):102-109. doi:10.1016/j.jclinepi.2007.03.012.
31. Pickles T, Ingram JR. Minimal important difference of pain numeric rating scale in patients with hidradenitis suppurativa: results from THESEUS. Br J Dermatol. 2025;192(4):761-763. doi:10.1093/bjd/ljae486.

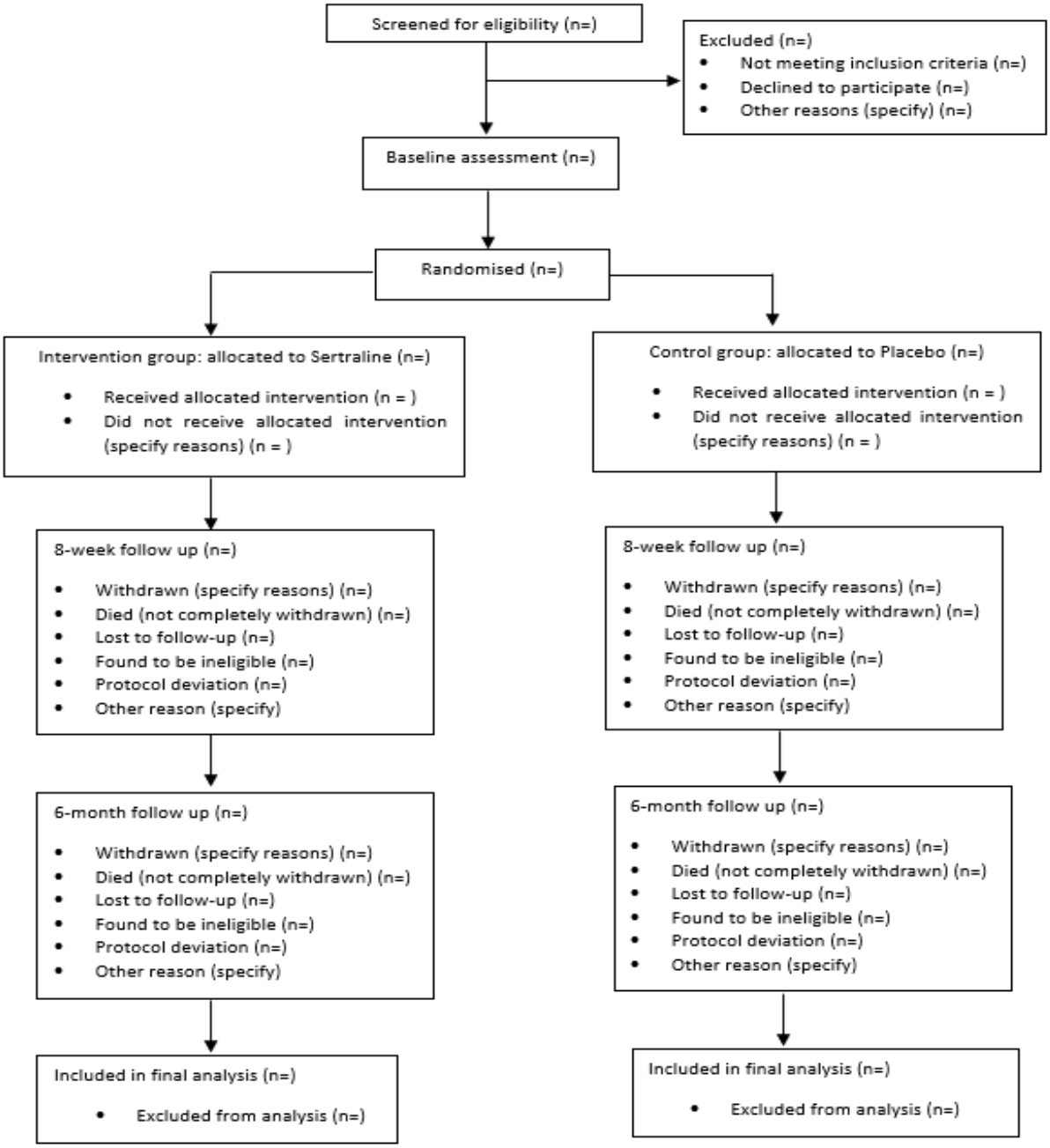
SAP/ISAP DEVIATION LOG

Document number:		**Document version:**	
Reason for deviation:			

8. APPENDICES

Appendix I: Figures

Figure 1: CONSORT flow diagram



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Appendix II: Tables

Table 1: Completion rates for each form

Form name	Completion (n/N)	%
Registration		
Eligibility		
Consent		
Medical History & Demographics		
Pregnancy		
Concomitant Medications		
Randomisation		
Baseline BDI-II		
Baseline PBAs		
Baseline MADRS		
Baseline PHQ-9		
Baseline C-SSRS		
Baseline WHODAS 2.0		
Baseline MOS-SSS		
Baseline Participant Assessment of Treatment		
Baseline cUHDRS		
Baseline Reward Reaction Time Task		
Baseline Effort Discounting Task		
Baseline Conceptual Bias Task		
Baseline Brief State Rumination Inventory		
Week 8 BDI-II		
Week 8 PBAs		
Week 8 MADRS		

Week 8 PHQ-9		
Week 8 C-SSRS		
Month 6 BDI-II		
Month 6 PBAs		
Month 6 MADRS		
Month 6 PHQ-9		
Month 6 C-SSRS		
Month 6 WHODAS 2.0		
Month 6 MOS-SSS		
Month 6 Participant Assessment of Treatment		
Month 6 CGI-I		
Month 6 cUHDRS		
Month 6 Reward Reaction Time Task		
Month 6 Effort Discounting Task		
Month 6 Conceptual Bias Task		
Month 6 Brief State Rumination Inventory		

Table 2: Descriptive summary of demographics and medical history at baseline (by arm and overall)

Characteristic	Arm 1: Sertraline (n=)	Arm 2: Placebo (n=)	Overall (n=)
Demographics			
Age (median (IQR, range, n))			
Sex at birth (n (%))			
Male			
Female			
Prefer not to answer			
Missing			
Ethnicity (n (%))			
Asian or Asian British: Indian			
Asian or Asian British: Pakistani			
Asian or Asian British: Bangladeshi			
Asian or Asian British: Chinese			
Any other Asian background (please describe below)			
Black, Black British, Caribbean or African: Caribbean			
Black, Black British, Caribbean or African: African			
Any other Black, Black British, or Caribbean background (please describe below)			
Mixed or multiple ethnic groups: White and Black Caribbean			
Mixed or multiple ethnic groups: White and Black African			
Mixed or multiple ethnic groups: White and Asian			

Characteristic	**Arm 1: Sertraline (n=)**	**Arm 2: Placebo (n=)**	**Overall (n=)**
Any other Mixed or multiple ethnic background (please describe below)			
White: Welsh/English/Scottish/Northern Irish/British			
White: Irish			
White: Gypsy or Irish Traveller			
White: Roma			
Any other White background (Please describe below)			
Arab			
Any other ethnic group (Please describe below)			
Missing			
Education (n (%))			
Pre-primary education			
Primary education			
Lower secondary education			
Upper secondary education			
Post-secondary non-tertiary education			
First stage of tertiary education			
Missing			
Living status (n (%))			
With partner/spouse/family/friends			
Alone			
Nursing home/hospital/long-term care home			
Other			

Characteristic	**Arm 1: Sertraline (n=)**	**Arm 2: Placebo (n=)**	**Overall (n=)**
Missing			
Employment status (n (%))			
Unable to work (due to HD)			
Unable to work (due to depression or anxiety)			
Unable to work (due to another condition)			
Not working by choice (e.g. student, retired, homemaker)			
Working part-time			
Seeking employment (I consider myself able to work but cannot find a job)			
Working full-time			
Missing			
How many working days has the participant missed within the last month due to illness? (median (IQR, range, n))			
Medical History			
Date of positive genetic test for HD (median (IQR, range, n))			
CAG repeat length (median (IQR, range, n))			
Previous episodes of depression (n (%))			
This is the first episode			
One similar episode before the current one			
Several similar episodes before the current one			
Symptoms of depression do not occur in episodes			
Missing			

Characteristic	Arm 1: Sertraline (n=)	Arm 2: Placebo (n=)	Overall (n=)
Duration of current depressive symptoms (n (%))			
1 month or less			
>1 month to 3 months			
> 3 months to 6 months			
> 6 months to 1 year			
1 year or more			
Missing			
Antidepressant medication in previous 12 months (n (%))			
No			
Yes - 1 month or less			
Yes - > 1 month to 3 months			
Yes- > 3 months to 6 months			
Yes - for > 6 months			
Missing			
Antidepressant medication in previous 6 months (n (%))			
Yes			
No			
Missing			
Psychological treatment in previous 12 months (n (%))			
No			
Yes - 1 month or less			
Yes - > 1 month to 3 months			

Characteristic	Arm 1: Sertraline (n=)	Arm 2: Placebo (n=)	Overall (n=)
Yes- > 3 months to 6 months			
Yes - for > 6 months			
Missing			
Other treatment for depression in previous 12 months (n (%))			
No			
Yes - 1 month or less			
Yes - > 1 month to 3 months			
Yes- > 3 months to 6 months			
Yes - for > 6 months			
Missing			
Comorbidities (n (%))			
Yes			
No			
Missing			
Brain illness/injury other than HD (n (%))			
Yes			
No			
Missing			
PI considers factor likely to contribute to depressive symptoms (n (%))			
Yes			
No			
Missing			
Cardiovascular comorbidity (n (%))			

Characteristic	Arm 1: Sertraline (n=)	Arm 2: Placebo (n=)	Overall (n=)
Pulmonary comorbidity (n (%))			
Neurologic comorbidity (n (%))			
Ent comorbidity (n (%))			
Gynecologic/Urologic comorbidity (n (%))			
Reproductive comorbidity (n (%))			
Gastrointestinal comorbidity (n (%))			
Metabolic/Endocrine comorbidity (n (%))			
Hemato/Lymphatic comorbidity (n (%))			
Dermatological comorbidity (n (%))			
Psychiatric comorbidity (n (%))			
Musculoskeletal comorbidity (n (%))			
Allergy/Immunologic comorbidity (n (%))			
Ophthalmological comorbidity (n (%))			
Hepatobiliary comorbidity (n (%))			
Renal comorbidity (n (%))			
Other comorbidity (n (%))			

Table 3: Primary feasibility outcomes and progression criteria

Feasibility outcome	Arm 1: Sertraline (n=)	Arm 2: Placebo (n=)	Overall (n=)	Progression criteria met	Rating
Recruitment (n/N(%))					
Proportion of eligible participants approached who consent					
Proportion of screened participants who are randomised					
Number randomised					
Retention (n/N(%))					
Proportion of randomised participants attending the 8-week follow-up assessment					
Proportion of randomised participants attending the 6-month follow-up assessment.					
Proportion of randomised participants attending 6-month follow-up assessment and who remain on IMP					
Data completeness					
Proportion with all depression and suicidality outcomes completed at 8-week follow-up					
Proportion of randomised participants with all depression and suicidality outcomes completed at 6-month follow-up					
Proportion of randomised participants with clinical progress outcomes, excluding digital measures, completed at 6-month follow-up					

Feasibility outcome	**Arm 1: Sertraline (n=)**	**Arm 2: Placebo (n=)**	**Overall (n=)**	**Progression criteria met**	**Rating**
Proportion of randomised participants providing a blood sample at 6-month follow-up					
Adherence					
Proportion with full adherence to allocated treatment at 6-month follow-up of those randomised					

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Table 4: Secondary depression and suicidality outcome measure scores at baseline, 8-week, 6-month follow-up

Timepoints	**Baseline**						**8-week follow-up**						**6-month follow-up**					
Outcome	**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
BDI-II																		
PBAs																		
MADRS																		
PHQ-9																		
WHODAS 2.0																		
MOS-SSS																		

Note: BDI-II = Beck Depression Inventory-II; MADRS = Montgomery Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire-9; PBAs = Problem Behaviours Assessment (short form); WHODAS 2.0 = WHO Disability Assessment Schedule 2.0; MOS-SSS = Medical Outcomes Study Social Support Survey. C-SSRS summarised separately by category (not shown - placeholder).

Table 5: Clinician- and participant-rated improvement outcome measure scores at 6-month follow-up

Outcome	Arm 1: Sertraline (n=)		Arm 2: Placebo (n=)		Overall (n=)	
	n	%	n	%	n	%
Participant Assessment of Treatment						
Has the treatment of your depression over the last 6 months been successful						
Very successful						
Moderately successful						
Somewhat successful						
Not at all successful						
Perceived change in depression vs pre-treatment						
Large positive change						
Small positive change						
No change						
Small negative change						
Large negative change						
Additional episodes of depression in the last 6 months						
I experienced no additional episodes						
I had one additional episode						
I had several additional episodes						
My symptoms of depression do not occur in episodes						
CGI-I						
Rate the overall change in the participant's depression vs baseline						

Outcome	**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**	
	n	%	n	%	n	%
Very much improved						
Much improved						
Minimally improved						
No change						
Minimally worse						
Much worse						
Very much worse						

Note: CGI-I = Clinical Global Impression - Improvement scale.

Table 6: Clinical progression outcome measure scores at baseline and 6-month follow-up (ENROLL-HD)

Timepoints	**Baseline**						**6-month follow-up**						**Adjusted mean difference (95% CI)**	**p-value**
Outcome	**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
cUHDRS														
TMS														
TFC														
SDMT														
SWRT														

Note: cUHDRS = composite Unified Huntington's Disease Rating Scale, calculated per the pre-specified formula in the SAP; higher scores indicate better clinical status. TMS = Total Motor Score; TFC = Total Functional Capacity; SDMT = Symbol Digit Modalities Test; SWRT = Stroop Word Reading Task; ; SD = standard deviation; CI = confidence interval. Measures assessed at baseline and 24 weeks, where available. The adjusted mean difference for cUHDRS will be estimated using ANCOVA, with 24-week cUHDRS score as the dependent variable, treatment arm as a fixed effect, and baseline cUHDRS score as a covariate. The p-value is two-sided.

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Table 7: Biomarker outcomes at baseline and 6-month follow-up

Timepoints	**Baseline**						**6-month follow-up**						**% change from baseline to 6-month**						**Mann–Whitney U p-value***
Biomarker	**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
NfL, pg/mL																			
TNF-α, pg/mL																			
IL-4, pg/mL																			
IL-6, pg/mL																			
IL-10, pg/mL																			

*Note: *Exploratory comparison for NfL only, as pre-specified; inflammatory markers (TNF-α, IL-4, IL-6, IL-10) summarised descriptively only.*

Table 8: Minimal Clinically Importance Difference (MCID) summary

Outcome measure	Estimated MCID (change score)	Anchor(s) used	Correlation with between anchor and change from baseline to 6 months post-randomisation
BDI-II			
PBAs			
MADRS			
PHQ-9			
C-SSRS			

Table 9: Exploratory digital assessment outcomes at baseline, 6-month follow-up

Timepoints	Baseline						6-month follow-up					
Outcome	Arm 1: Sertraline (n=)		Arm 2: Placebo (n=)		Overall (n=)		Arm 1: Sertraline (n=)		Arm 2: Placebo (n=)		Overall (n=)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Reward Reaction Time Task, ms												
Effort Discounting Task, % high-effort choices												
Self-Referent Encoding Task, % positive descriptors endorsed												

Timepoints	**Baseline**						**6-month follow-up**					
Outcome	**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**		**Arm 1: Sertraline (n=)**		**Arm 2: Placebo (n=)**		**Overall (n=)**	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Brief State Rumination Inventor, total score												

Table 10: Summary of withdrawal/lost to follow-up (by arm and overall)

	Arm 1: Sertraline (n=)	**Arm 2: Placebo (n=)**	**Overall (n=)**
Withdrawals(n(%))			
Aspect of withdrawal (n(%))			
Withdrawal from trial treatment/intervention			
Withdrawal from further data collection			
Withdrawal from accessing further data from ENROLL-HD			
Withdrawal from accessing further sample data from HD-Clarity			
Withdrawal from further trial blood sample collection			
Consent to retain trial blood samples already provided			
Reason for Withdrawal (n(%))			
Patient choice			
Serious Adverse Event			
Inability to follow trial protocol (including clinically-indicated alternative dose of treatment)			
Investigator's decision			
Other			
Lost to follow-up (n(%))			
Participant moving outside of clinical team care			
Participant missing multiple visits			
Participant not contactable			
Other			

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Table 11: Summary of Adverse Events and Serious Adverse Event (by arm and overall)

	Arm 1: Sertraline (n=)	**Arm 2: Placebo (n=)**	**Overall (n=)**
Participants with ≥1 AE (n (%))			
Participants with ≥1 SAE (n (%))			
Side effects (n (%))			
Weight gain			
Sexual dysfunction			
Sleep disturbances			
Dry mouth			
Drowsiness/sedation			
Cardiovascular side effects (e.g. palpitations)			
Gastrointestinal side effects (e.g. diarrhea, nausea, vomiting)			
Other			
Severity (n (%))			
Mild			
Moderate			
Severe			

Table 12: SAE line listing from CTR safety team

Event Number	Event Name	Grade	Seriousness	Event onset date	Event resolved date	IMP	Last admin date	Reviewer category	Overall Category	Comments

Current Electronic Signatures (v.4):

Signed electronically by: Duncan McLauchlan (mclauchland@cardiff.ac.uk)
Date: *11-Nov-2026 @ 01:40 PM GMT*
Reason: *Approval*

Previous Electronic Signatures:

Version 3

Signed electronically by: Cheney Drew (drewc5@cardiff.ac.uk)
Date: *11-Nov-2026 @ 11:47 AM GMT*
Reason: *Approval*

Version 2

Signed electronically by: Tongtong Shi (shi5@cardiff.ac.uk)
Date: *11-Nov-2026 @ 11:17 AM GMT*
Reason: *Approval*