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

PROTOCOL V1,28/01/2026

Sponsor: If opening under the Clinical Trials Regulation then include the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol.	Cardiff University **2nd Floor Lakeside Building, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW.**
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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Rachel McNamara			
Name	**Signature**	**Date**	
Chief Investigator:			
Dr Duncan McLauchlan			
Name	**Signature**	**Date**	

General Information This protocol describes the DEVISE-HD clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR

Contact details – Chief Investigator & Co-Investigators

If this trial is opening under EU Clinical Trial Regulation 536/2014 then no names are to be included and functional contact points such as trial mailboxes should be used.

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Trial Co-ordination:

The DEVISE-HD trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University , a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the DEVISE-HD Trial Management Group (TMG).

For **all queries** please contact the DEVISE-HD team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email:	devisehd@Cardiff.ac.uk
Trial Administrator:	Bryony Willcock
Trial Manager:	Paula Foscarini-Craggs
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Trial Statistician:	TongTong Shi
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Randomisation

To randomise a participant access the REDCap Database:

Clinical queries

DEVISEHD@Cardiff.ac.uk

All clinical queries will be directed to the most appropriate clinical person.

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to CTR-Safety@cardiff.ac.uk within 24 hours of becoming aware of the event (See section 16 for more details).

Contact details: CTR-Safety@cardiff.ac.uk

Table of Contents

Glossary of abbreviations

AD	Alzheimer's Disease
AE	Adverse Event
AR	Adverse Reaction
BDI-II	Beck Depression Inventory II
C&C	Capacity & Capability
CA	Competent Authority
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTIS	Clinical Trials Information System
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
cuHDRS	Composite Unified Huntington's Disease Rating Score
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Score
HB	Health Board
HD	Huntington's Disease
HD-ISS	Huntington's Disease Integrated Staging System
HTA	Health Technology Assessment
IB	Investigator Brochure
IC	Informed consent
ICH	International Conference on Harmonization
IDMEC	Independent Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IQ	Interquartile Range
ISF	Investigator Site File
ISR	Investigator Safety Report
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Unit
MA	Marketing Authorisation
MADRS	Montgomery-Asberg Depression Rating Scale
MAOIs	Monoamine Oxidase Inhibitors
MCC	Microcrystalline Cellulose
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicine and Healthcare products Regulatory Agency
MOS-SSS	Medical Outcome Survey Social Support
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging

NCA	National Competent Authority
NFL	Neurofilament Light Chain
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIMP	Non-Investigational Medicinal Product
PBA	Problem Behaviours Assessment
PD	Parkinson's Disease
PHQ-9	Patient Health Questionnaire - 9
PI	Principal Investigator
PIS	Participant Information Sheet
pwHD	People with Huntington's Disease
QA	Quality Assurance
QC	Quality control
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDMT	Symbol Digit Modality Task
SPIS	Study Partner Information Sheet
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWRT	Stroop Word Reading Task
TFC	Total Functional Capacity Score
TMF	Trial Master File
TMG	Trial Management Group
TMS	Total Motor Score
TSC	Trial Steering Committee
UHDRS	Unified Huntington's Disease Rating Scale
USMs	Urgent Safety Measures
WHO-DAS	WHO Disability Assessment Schedule
WNRTB	Welsh Neuroscience Research Tissue Bank (WNRTB)

Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version

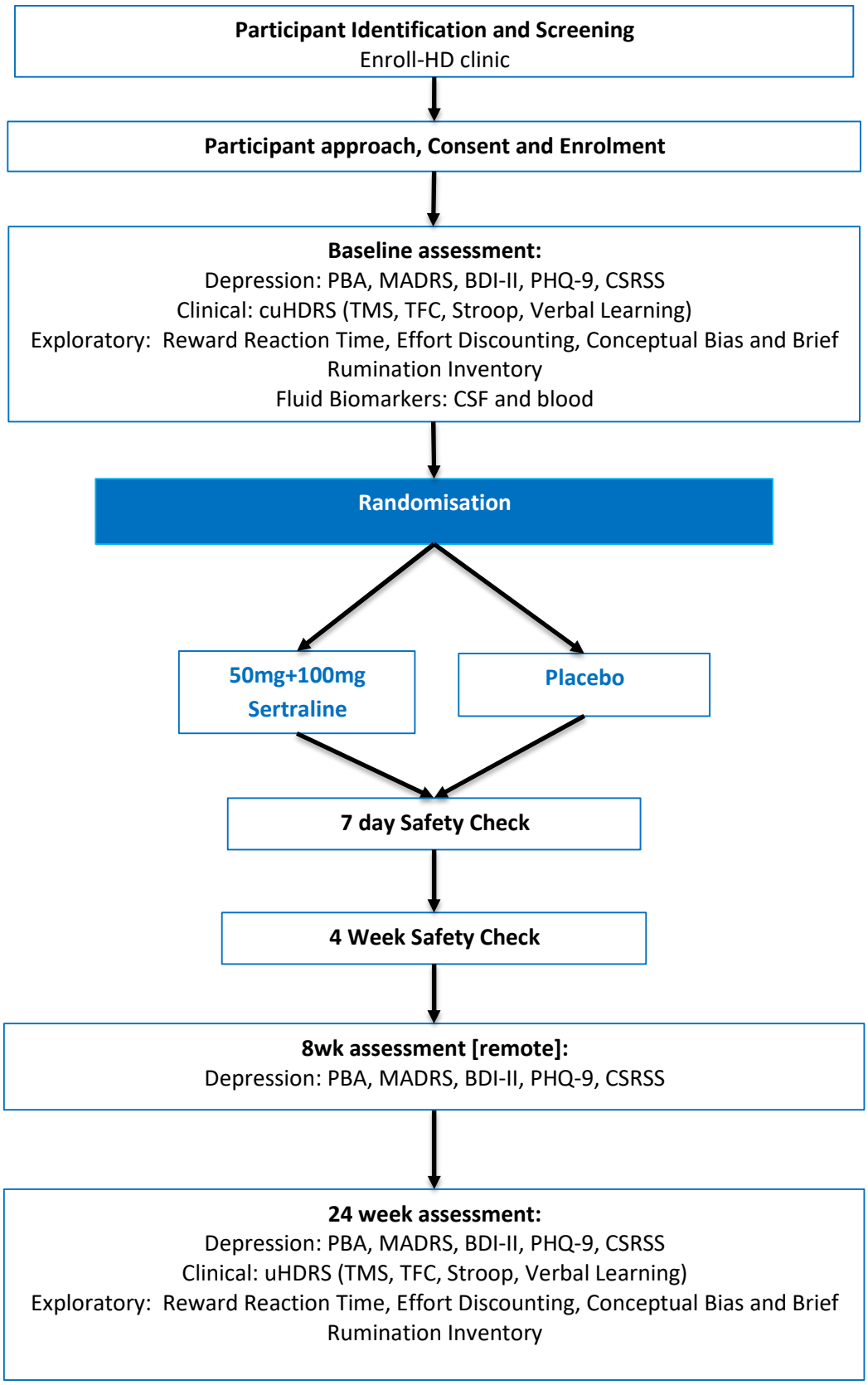
Synopsis

Short title	Antidepressants to treat Depression in HD
Acronym	DEVISE-HD
Internal ref. no.	1735
Clinical phase	Phase IV
Funder and ref.	HCRW 02-24-024
Trial design	double-blind randomised control feasibility trial
Trial participants	Adults (≥18 years) with confirmed genetic diagnosis of HD and a new depressive episode
Planned sample size	40
Planned number of sites	3
Inclusion criteria	Adult participants (age ≥ 18), with a confirmed positive genetic test of HD • Presenting with untreated depressive symptomatology defined by patient report of low mood and/or anhedonia •
Exclusion criteria	• Currently taking an antidepressant medication or have taken antidepressants in the last six months (for any indication) • A previous reaction and/or contraindication to sertraline, and/or Sertraline found to be ineffective • Any medication or brain illness/injury, other than HD that, in the opinion of the principal investigator, is likely to contribute to depressive symptoms • Any participant with severe depression or suicidal ideation in which a clinician deems it necessary to receive treatment (due to higher risk of deterioration and suicide in this group). • Not able to give informed consent
Treatment duration	24 weeks (6 months)
Follow-up duration	24 weeks (6 months)
Planned trial period	18 months
Primary objective	The primary objective is to determine the feasibility of a blinded, placebo-controlled trial of antidepressants in people with HD
Secondary objectives	• 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 effectiveness trial • Determine potential effect sizes in outcome of interest to inform power calculations for a future effectiveness trial • Determine if there are differences on clinical and fluid biomarkers of disease progression with antidepressant treatment • Determine the percentage of participants currently registered in ENROLL • Determine the percentage of participants currently registered in HDClarity
Exploratory Objective	• To determine if computer-based tasks can be used to evaluate the cognitive processes underlying neuropsychiatric disorders

Primary outcomes	Feasibility as defined by; Recruitment, Retention, Data completeness and Medication Adherence
Secondary outcomes	Depression Outcomes: Problem Bheaviours Assessment (short form) Montgomery Asberg Depression Rating Scale Beck Depression Inventory II PHQ-9 The Columbia Suicide Severity Rating Scale WHODAS-12 Medical Outcome Survey Social Support Survey cUHDRS Total Motor Score, Total Functional Capacity, Symbol Digit Modality, Stropp Word Reading Task Biomarkers Markers of neuronal injury Markers of neuronal Inflammation The percentage of participants currently registered in ENROLL The percentage of participants currently registered in HDClarity
	Digital Assessment Outcomes Reward Reaction Time Task Effort Discounting Task Conceptual Bias Task Brief State Rumination Inventory
Investigational medicinal products	Sertraline or Placebo
Form	Capsule
Dose	50mg once daily for 4 weeks and then 100mg once daily for 20 weeks
Route	Oral

1. Trial summary & schema

1.1. Trial schema and participant flow



1.2. Trial lay summary

Background

Huntington's Disease (HD) causes problems with movement, thinking that get worse over time. People with HD also get depression and other mental health problems. Depression is extremely common in HD and has effects on quality of life and people's ability to do things. We know that the inability to do everyday things is main reason that HD has very high healthcare costs. We think that by properly treating depression we can improve quality of life for people with HD and their families, and that this will reduce their need to use expensive healthcare services.

Our data shows that depression in HD is different from depression in people without HD so anti-depressant medicines might work differently in people with HD. We do not know how well anti-depressants work in HD or what is the best way of measuring depression in HD.

Aims and Objectives

We want to know how well anti-depressants work, or don't, to improve depression in HD. The first step in answering this question is to test how well a randomised controlled trial (RCT) of anti-depressants may work.

Design and Methods

Forty people with HD who report mild or moderate symptoms of depression to their doctor will be included. Half the people will be treated with a common antidepressant (Sertraline) and the other half will be given a dummy pill (placebo) for 24 weeks. We will measure depression and other HD symptoms at the beginning of the study and after 24 weeks. We will also collect blood and the fluid that surrounds the brain to see if anti-depressant treatment changes substances the body normally produces in response to damaged cells (inflammation). We will use the data to see if people with HD are willing to join the study, if they stay in the study and what is the best way of measuring depression.

Public and Patient Involvement (PPI)

We have worked with people with HD and family members to develop this research question. They have provided input to this application. In addition to our PPI co-applicant we will involve people with lived experience in the delivery of the study. The PPI research partners will lead on how to communicate with study participants in how we share study results with the wider public.

Potential Impact

The results of this study will be used to design a full RCT to answer our question about what, if any, anti-depressants are best for treating depression in HD. We will share our results with the people taking part in the study and the wider HD community via HD Buzz and patient focussed organisations. The results will be presented to other doctors and researchers at scientific conferences and journals.

2. Background

Why Does Depression in Huntington's Disease Matter?

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder focussed on networks originating in the basal ganglia of the brain[1]. HD causes cognitive decline leading to dementia; a movement disorder with chorea and falls; and debilitating psychiatric symptoms. It has a prevalence of 10-15/100 000[2]; similar to that of motor neuron disease[3]. In contrast to commoner neurodegenerative diseases affecting the basal ganglia, such as Parkinson's disease (PD), it is caused by a genetic mutation; a CAG repeat expansion of ≥40 in exon 1 of the huntingtin gene will inevitably lead to the disease[4]. Thus, it can be diagnosed with complete certainty in life. Hence HD has great value as a model: finding the best treatment for depression in HD will inform depression treatment in other basal ganglia disorders.

Depression in HD is Common

In common with PD[5] and Lewy Body disease[6], depression, amongst other psychiatric symptoms, is extremely common in patients affected by HD. The lifetime prevalence of depression was reported to be between 33 and 69% of patients in a systematic review[7]. Depression and self-harm (including suicide and suicidal ideation) both occur at substantially higher rates in HD gene carriers compared with both gene-negative individuals and family controls[8].

Depression in HD has a Major Impact on Quality of Life and Function

Psychiatric symptoms and behavioural changes caused by HD have substantially greater impact on quality of life, for both people with HD (pwHD) and caregivers, than movement problems. Early small studies showed depression, irritability and cognitive decline significantly influenced quality of life in HD, but motor problems much less[9]. A recent systematic review has confirmed the centrality of depressive symptoms to impaired quality of life, highlighting the impact that effective anti-depressant treatment might have on quality adjusted life yearss[10]. Depression and psychiatric symptoms also have a significant impact on patients' function; a systematic review from 202011 showed strong associations between function and both depressive symptoms and self-harm.

Societal cost of HD

Although HD is rare, the healthcare resource consumption is very high. Data from the UK estimates the cost per patient per year as £18000 in the early stages of HD, rising to £89000 in later stages[12]. Much of these costs are care costs, driven by deteriorating function. Depression is a major contributor to deteriorating function, therefore effective treatment will reduce a substantial healthcare cost.

3) What evidence exists to guide treatment of depression in Huntington's disease?

A PubMed search using Mesh terms and free text included 1] Huntington's disease AND 2] psychiatric symptoms, neuropsychiatric symptoms, apathy, depression, mood disorder, psychosis, anxiety, irritability, suicide, behavioural disorder, nonmotor symptoms AND 3] antidepressant, neuroleptic, anti-psychotic, psychoactive drug, psychopharmacology, benzodiazepine, anti-convulsant, tetrabenazine, cholinesterase inhibitor, bupropion; yielded 419 results. Studies were limited to genetically confirmed HD, in humans, including more than 10 participants and reporting depression as a primary or secondary outcome using a recognised diagnostic instrument, leaving seven studies as follows.

There are no randomised controlled trials of antidepressants for depression in HD. Four randomised controlled trials (RCTs) reported depression as a secondary outcome measure13–16. All four RCTs excluded patients with depression at study entry, and contained 20 pwHD or fewer in each arm. Trend level effects of bupropion on depression using the Neuropsychiatric inventory subscore, fluoxetine on depression measured by the Hamilton depression score, and citalopram on depression measured using the Hamilton depression score were reported. A novel monoamine stabilising agent (PNU-96391A) showed an improvement in depression scores using the Beck depression inventory, but this drug does not have a licence. Three case series or open label studies (all containing fewer than 20 pwHD in each group) reported the effects of venlafaxine17, cariprazine18 and olanzapine19. Improvements in the UHDRS total behavioural score, Beck depression inventory, and 2 instruments (Beck depression inventory and Hamilton depression score) were reported respectively.

Structured Search of the International Clinical Trials Registry Platform

A structured search for 1] Huntington's disease AND 2] psychiatric symptoms, neuropsychiatric symptoms, apathy, depression, mood disorder, psychosis, anxiety, irritability, suicide, behavioural disorder, non-motor symptoms limited to randomised clinical trials in pwHD, returned **no randomised controlled trials of antidepressants for depression in HD registered on ISRCTN.**

Seven trials of other interventions were identified: 1) a trial of music therapy as an intervention to improve a range of clinical symptoms, including depression (NCT00178360) 2) a randomised crossover study of nabilone (a cannabinoid) including 44 pwHD (ISRCTN16782845). The total score on the neuropsychiatric inventory (a semi-structured multi-domain psychiatric assessment) was lower on nabilone(p=0.04). 3) a pilot study (NCT02216474) recruiting 20 participants with Tourette's syndrome, HD and healthy controls randomised to sham or active treatment with transcranial magnetic stimulation completed over 4 years ago. One of the secondary outcomes was depression, but this study has not been reported. 4) a pilot trial of transcranial magnetic stimulation, reporting depression as a secondary outcome is recruiting (NCT05326451). 5) a phase 1 randomised trial of a novel agent (SRX246) for irritability (NCT02507284) reported safety and tolerability outcomes, found a higher rate of depressive symptoms in the active intervention arm. 6) a randomised feasibility trial of self help techniques for managing symptoms of anxiety in HD is currently recruiting (ISRCTN47330596), and includes depression as a secondary outcome. 7) a randomised controlled feasibility trial (NCT03854019, target recruitment – 20) of Dextromethorphan/Quinidine for

treatment of irritability has recently closed to recruitment, and will report depression as a secondary outcome.

Observational Evidence of Antidepressant Efficacy in HD

Analysis of data from a number of large longitudinal cohort studies (REGISTRY20, ENROLL-HD21 and TRACK-HD22) has shown a lack of effect of antidepressants on depression outcomes in pwHD. Collectively these studies have recruited >25000 pwHD and healthy controls, with yearly clinical assessments and up to 12 years follow-up data. Ogilvie et al23 selected HD gene positive participants from the ENROLL-HD observational study with an episode of depression (from the Hospital Anxiety and Depression score (HADS) > 8) who started antidepressant medication before the next study visit. They matched this cohort with non-users, also scoring >8 on the HADS on baseline characteristics of CAG repeat length, clinical measures of disease progression, age and psychiatric co-morbidities. The main outcome measure was depression at first follow-up. This analysis found 86 users of antidepressants and matched them with 86 non-users. Depression outcome at first follow-up (HADS depression score) did not differ between the 2 groups. A similar analysis in the TRACK-HD study24 (a 36 month study of patients carrying the HD gene and controls who were intensively studied with multiple clinical measures, MRI and plasma biomarkers of disease progression), followed HD gene positive antidepressant users over time and compared them with non-users, including baseline scores for cognitive, motor and neuropsychiatric measures of disease progression. They did not find any differences between antidepressant users (57/123) and non-users (66/123) on any of the PBAs or HADS scores at final follow-up.

Animal Data on Antidepressant Efficacy in HD

In contrast to the observational evidence from cohort studies of HD outlined above, **but in keeping with our own findings (described below)**, data from animal models is generally supportive of an effect of antidepressive medication on depression-like behaviours. Sertraline has been shown to rescue depressive-like behaviours (anhedonia, effort for reward) in the R6/1 mouse model of HD, but sertraline did not affect hippocampal neurogenesis(which has been hypothesised as a substrate for depression)25. Fluoxetine treatment in the R6/1 model showed improvement on a task of effort for reward, and also improved hippocampal neurogenesis26. Bupropion has also shown effects on depressive-like behaviours in the R6/1 model37.

4) Why might responses to standard antidepressants in HD differ from those in the general population?

Efficacy of Antidepressants in Other Neurodegenerative Disease

A previous Cochrane review28 showed a lack of efficacy of antidepressants for depression in Alzheimer's disease(AD), whilst observational studies have shown increased mortality in AD with psychoactive medication29. This suggests that depression in neurodegenerative disease is likely to differ from that in the general population and that psychoactive medication can have negative outcomes.

Cognitive Mechanisms of Depression in HD Differ from the General Population

Previous work from our group explored this further: we recruited 51 participants with HD, and 26 familial controls, and measured cognitive processes underlying depression, apathy and other psychiatric disorders. **We found marked differences in the neurocognitive profile of depression in HD compared with depression in control populations.** Depression in HD was associated with marked motivational anhedonia (reduced effort for reward on the Reward Reaction Time Task), but in contrast to depression in the general population, there was no evidence of hypersensitivity to negative stimuli or rumination30.

Antidepressant Drug Class Efficacy in HD Differs from the General Population

We subsequently performed a propensity score analysis of the effect of different antidepressant classes on long term depression outcomes in HD from the ENROLL-HD worldwide cohort study. We found that, **in contrast to depression in the general population, SSRIs and bupropion outperformed SNRIs in alleviating depression in HD,** both at first follow-up after antidepressant initiation and throughout subsequent study visits30.

5) Do antidepressants affect disease progression in HD?

Animal Evidence of Antidepressant Effect on Disease Progression in HD

A number of studies in animal models (summarised in a review by Jamwal et al) have demonstrated an effect of antidepressants on purported mechanisms of cell damage in HD, but none to date have shown an effect on survival or accumulation of mutant Huntingtin in cells.

Observational Evidence of Antidepressant Effect on Disease Progression in HD

Antidepressants are the most frequently prescribed medication class in HD patients32. However ,a recent study raised concern that they might have a negative effect on disease progression. Griffin et al33 performed a propensity score analysis in the ENROLL-HD study data, comparing patients who received an antidepressant with those who did not, and reported that patients on antidepressants had faster disease progression. This contrasts to studies using the ENROLL-HD data by Ogilvie et al23 and Achenbach et al34, who did not find any effect of antidepressants on disease progression.

Importantly, none of these studies addressed causality; i.e. antidepressant use may be a marker of underlying disease severity rather than a cause of decline. Preliminary data from our group suggests the former hypothesis. Using data from the ENROLL-HD study, we showed that the **early occurrence of depressive symptoms in pwHD was associated with a more rapid decline in both the composite measure of disease progression and also the motor score (p<2x106)**, compared to participants free of these symptoms. We then selected antidepressant-naive HD participants with incident depression in the ENROLL-HD study and compared disease outcomes (composite score of disease progression (cUHDRS35) and motor scores) between those started on antidepressants (194/1877 participants with incident mood symptoms) at the time to those not on antidepressants, matching on baseline age, measures of disease progression, age, mental health events, comorbidities, psychoactive drug use and antidepressant dose. **We found slower disease progression in patients treated with antidepressants on both the composite and motor score(p=0.011&0.026).**

We extended this analysis to the imaging and plasma biomarker data in TRACK-HD. Participants in TRACK-HD with incident depression or anxiety treated with antidepressants (6/55) had smaller increases in Neurofilament light chain (a marker of neuronal injury, p=0.039) and also reduced rates of caudate atrophy (p=0.0003), grey matter atrophy(p=0.036)and putamen atrophy(p=0.032). **This is in keeping with a beneficial effect of antidepressants on clinical, imaging and plasma biomarkers of disease progression in HD: the first evidence of efficacy *of any agent* on disease progression.**

6) Uncertainty in Measuring Disease Progression in HD

What evidence exists to guide choice of outcome measure to measure depression in HD?

Two systematic reviews by Carlozzi et al36 and Mestre et al have addressed the evidence base on outcome measures to assess depression in HD. Mestre classified each scale as: recommended, suggested or listed for use in HD, for the purposes of screening, diagnosis or severity. Recommended scales met all 3 criteria, whilst suggested scales only met two. They report that the Montgomery-Asberg Depression Rating Scale (MADRS), Beck depression inventory (BDI) and Hamilton depression score are all suggested for measuring depression severity, but no scales met the recommended criteria. Carlozzi and co-workers specifically looked at instruments used in clinical trials: They rated each scale as 'recommended' or not, based on previous studies showing use in HD populations, sensitivity to change, reliability and validity. Based on these criteria, they recommended the updated version of the UHDRS behavioural scale: the Problem Behaviours Assessment (short form – PBAs). The minimal clinically important difference (MCID) is an important concept in clinical trials38; the change in an outcome measure that is meaningful to patients. To date, no depression outcome in HD has been assessed on this criterion. Neurofilament light chain (NFL) has robust evidence as a measure of progression in HD; showing differences between cases and controls, even in gene carriers far from motor onset, with significant change over 1 year in plasma and cerebrospinal fluid (CSF)39 Inflammatory biomarkers (TNF-alpha, YKL40,IL4,IL6,IL8,IL10,C3,clusterin) have also shown elevations in CSF and plasma in HD that correlate with imaging and clinical measures of disease progression40.

2.1. Rationale for current trial/Justification of Treatment Options

The experience of depression in HD has significant impact on individuals' quality of life but currently has a high level of uncertainty around the impact of anti-depressants on the disease progression of HD. This makes it clinically unclear whether antidepressants should be prescribed. There are also several methodological uncertainties that need to be resolved prior to conducting a full-scale randomised control trial (RCT). A double-blind feasibility RCT will be conducted to address some of the clinical and methodological uncertainties.

3. Trial objectives/endpoints and outcome measures

3.1. Primary objectives

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

3.2. Secondary objectives

This feasibility trial has five secondary objectives:

- 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 effectiveness trial
- Determine potential effect sizes in outcome of interest to inform power calculations for a future effectiveness trial
- Determine if there are differences on clinical and fluid biomarkers of disease progression with antidepressant treatment
- Determine the percentage of participants currently registered in ENROLL
- Determine the percentage of participants who are currently in HDClarity

3.3. Exploratory *Objectives*

- To determine if computer-based tasks can be used to evaluate the cognitive processes underlying neuropsychiatric disorders

3.4. Primary outcomes measure(s)

The feasibility of key trial processes will be assessed according to pre-specified criteria outlined in the table below:

Table 1: Primary outcome 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 6mfu and still on IMP of those randomised	p < 30%	30% ≤ p < 60%	p ≥ 60%
	Proportion reaching 8wfu of those randomised	p < 50%	50% ≤ p < 80%	p ≥ 80%
	Proportion reaching 6mfu of those randomised	p < 50%	50% ≤ p < 70%	p ≥ 70%
Data completeness	Proportion with all depression and suicidality outcomes completed at 8wfu of those randomised	p < 50%	50% ≤ p < 75%	p ≥ 75%
	Proportion with all depression and suicidality outcomes completed at 6mfu of those randomised	p <40%	40% ≤ p < 65%	p ≥ 65%
	Proportion of Clinical progress (excluding digital measures) outcomes	p < 50%	50% ≤ p < 75%	p ≥ 75%

	completed at 6Mfu of those randomised			
	Proportion of those randomised donating Blood sample at 6mfu	p< 40%	40%< p < 60%	p ≥ 60%
Adherence (80% of medication taken)	Proportion with full adherence to allocated treatment at 6mfu of those randomised	p < 50%	50% ≤ p < 80%	p ≥ 80%

3.5. Secondary outcomes measure(s)

To determine the MCID participants will complete a set of seven depression outcomes. The measures will be completed at baseline, 8 weeks, and 24 weeks (i.e. 6 months).

Self-Complete Depression Outcomes:

Beck Depression Inventory II (BDI-II): This self-report scale comprises 21 statements that participants rate from 0-3 (range 0-63). Domains include sadness, pessimism, past failure, loss of pleasure, guilt, punishment, self-dislike, self-criticism, crying, suicidal thoughts, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleep, change in appetite, irritability, concentration, fatigue, loss of interest in sex. Administration time 5 minutes.

The following outcomes measures will be completed by a clinician after psychiatric interview with the participant and if appropriate input from the study partner:

Problem Behaviours Assessment (short form) (PBA): This is a well-established measure of psychopathology in HD, and is used in the worldwide observational study of HD; ENROLLHD. It takes the form of a semi-structured interview with participants and ideally a carer or individual who knows the participant well. This instrument covers 11 common behavioural and neuropsychiatric symptoms seen in HD: depressed mood, anxiety, suicidal ideation/behaviour, irritability & aggression, apathy (reduced motivation), perseveration, obsessive-compulsive behaviours, delusions & hallucinations; and disorientated behaviour. Each symptom is scored from 0-4 on both severity and frequency, the product of severity and frequency is the main outcome measure. We will use the depressed mood symptom score (range 0-16). The administration time for the whole instrument is 15 minutes

Montgomery Asberg Depression Rating Scale: (MADRS): This 10 item scale is one of the most widely used measures in clinical trials of treatments for depression. It comprises domains, each scored from 0-6: total score range 0-60. It is administered by a clinician and includes both patients report of symptoms and clinicians' observation of behaviours. The domains include sadness, inability to feel, lassitude, inner tension, suicidal thoughts, difficulty with concentration, difficulty with sleep, changed appetite and pessimistic thoughts. Administration time is 20 minutes.

PHQ-9: This 9 item scale asking participants to report the frequency of symptoms including depressed mood, lack of interest, change in sleep, change in appetite, feelings of failure, difficulty concentrating, suicidality, psychomotor changes. Each item is scored from 0-3, and the total score ranges from 0-27. The administration time is 5 minutes

The Columbia Suicide Severity Rating Scale (CSSRS): This screening and assessment instrument is the established measure of suicidal ideation and behaviour in ENROLL-HD and many clinical trials. Participants are asked screening questions regarding suicidal ideation ("wish to be dead" and "thoughts of suicide") and behaviour, and then further enquiry depending on the responses. The intensity of ideation is scored from 0-5. Specific suicidal behaviour is recorded as free text. The administration time is 5-10 minutes.

The following questionnaires which are part of the Depression Core Outcome set, will be completed by participants with support from their study partner:

WHO Disability Assessment Schedule 2.0 (WHODAS)-12 item version: A general assessment for health and disability that is applicable across numerous diseases areas including neurological disorders. It assesses functioning 6 domains: Cognition, Mobility, Self-care, Getting along, Life activities, Participation. The 12-item version provides an overall functioning score and takes approximately 5 min to complete.

Medical Outcome Survey Social Support Survey 6 item (MOS-SSS): This is a general assessment of the availability of support for an individual. This scale is part of the core outcome set for depression.

Clinical progression outcomes

To measure clinical outcomes between groups, participants will be asked to complete a batter of clinical progression outcomes (completed as part of ENROLL-HD), and to donate a CSF (Co-recruited into HDClarity) and blood samples (Co-recruited into HDClarity or donated as part of DEVISE-HD). The clinical progression outcomes will be measured at baseline and 24-weeks post randomisation. The digital assessment outcomes (exploratory outcomes) will be measured at baseline, and 24 weeks post randomisation. Blood samples will be collected at baseline (HDCLarity or DEVISE-HD) and 24 weeks (DEVISE-HD).

These will be used to measure if there are any differences between participants receiving the sertraline and placebo. They will be collected from ENROLL-HD at baseline, and 24 weeks post randomisation.

cUHDRS: Disease progression in HD has historically relied heavily on the Unified Huntington's disease rating scale (UHDRS), with an emphasis on the motor assessment section, however, accumulating evidence has shown that cognitive changes start many years before motor changes and are a sensitive marker of disease progression, whilst functional changes are also a reliable dimension of disease progression. Schobel et al used the ENROLL-HD cohort to construct a composite UHDRS score which combines four separate UHDRS elements and performs better than the complete UHDRS or individual UHDRS components. The composite UHDRS (cUHDRS) sub-elements included are the total motor score (TMS), the total functional capacity score (TFC), take from the UHDRS, the symbol digit modality task (SDMT) and the Stroop word reading task (SWRT). The scores are combined in the following equation (((TFC-10.4)/1.9) - ((TMS-29.7)/14.9) +((SDMT-28.4)/11.3) +((SWRT – 66.1)/20.1))+10. This score declines with advancing disease.

Sub-elements description:

TMS: This motor assessment scores the severity of motor signs in seven different domains: gait, eye movements, dystonia, bradykinesia, motor impersistence, chorea, postural instability. Higher scores indicate more severe motor features. The range is 0-124. Administration time is 5-10 minutes.

TFC: This functional assessment comprises 5 different areas (work, finances, activities of daily living, personal care and ability to be cared for at home). Lower functional ability results in lower scores on the assessment. The range is 0-13. The administration time is 5 minutes.

SDMT: This cognitive assessment measures bradyphrenia and visual association. Participants have 90 seconds to match a series of 10 different symbols to numbers using a reference key at the head of the test paper. The maximum score is 110, with lower scores indicating worse performance on the task. Administration time is 2 minutes. Clinical progression measures will be collected at baseline and 12 months through the use of routinely collected data: these assessments are part of routine clinical assessment.

SWRT: This cognitive assessment was originally developed to measure the cognitive process of inhibition. Participants are asked to read words aloud, all of which are a colour: green, red or blue. In the simplest condition of the task, the text the words are written in matches the meaning of the word i.e. 'green' is coloured green. In the interference condition, the text colour and the word meaning do not match. Previous work has shown that the simpler condition is more sensitive to disease progression. Lower scores indicate worse performance on the task. The administration time is 5-10 minutes and the range is 0-220.

Biomarkers

The biomarkers will be analysed to measure any difference between trial arms. Participants will be given the option to be co-recruited into HDClarity and to blood and CSF at baseline. If they decline participation in HDClarity, they will be asked to consent to donate a blood sample only at baseline. all participants will be asked to consent to donate a blood sample at 24 weeks. The blood samples are optional. They will be used to analyse markers of neuronal injury (Neurofilament light chain: NfL) and inflammation (TNF-alpha, IL4, IL6, IL10,).

3.6. Exploratory Outcome Measures

The following measures are exploratory and therefore optional for participants:

Reward Reaction Time Task: This task of effort for reward has been adapted from a previous version, and shown sensitivity to effort for reward in both healthy controls and people with HD. In this computerised task, participants are shown a fixation cross on screen and told to "react as quickly as possible when you see a circle" in the baseline condition. Participants are shown a series of circles and their mean reaction time is calculated. Following this, they are told that they are entering the active part of the task where they can win points, and told that darker coloured circles are worth more points than lighter ones, but also on each circle, faster reaction times win higher points. Three types of circle are shown. Reaction times slower than mean reaction time win zero points, whilst for

maximum points, participants have to react 20% more quickly than their baseline reaction time. Three values of circle (demarcated by circle darkness), worth 10, 20 and 40 points respectively. Participants face three trials, each containing 20 stimuli that are pseudo-randomised between different circle values. The outcome measure is the change in reaction time from baseline, corrected for reward47. Duration 15 minutes.

Effort Discounting Task: This task is based on a protocol, that has shown sensitivity to effort-based discounting in both healthy controls and patients with PD. Participants are shown 100, 10 second long trials and asked to monitor the screen, and respond with a keyboard press whenever they see the letter 'T'. In the simplest condition, there is a single locus, with a letter that changes every second. The maximum number of loci shown on screen is six. Each trial participants are offered the choice between a low effort/low reward condition (maximum 10 points) or a high effort/high reward condition (maximum points on offer for each successive increase in loci 20, 40, 60, 80, 100). The outcome measure will be the choice behaviour (frequency of high effort/high reward trials as a percentage of total trials). The duration is 15 minutes.

Conceptual Bias Task: This task has been shown to be sensitive to depression in the general population. Participants are shown 24 priming words which are evenly split between positive ("awarded"), neutral("giraffe"), or negative ("failure") valenced exemplars. Each word is shown for 10 seconds and participants are asked to imagine themselves in a scene evoked by the word. Following the priming phase, participants are shown 24 cue words that are associated with one of the priming words (e.g. disaster-failure) and asked to think of as many words as they can relating to that word in 30 seconds. The outcome measures will be the ratio of total positive: neutral valenced words, ratio of total negative to neutral valenced words and the proportion of pre-primed words in each condition that are produced. Task duration is 20 minutes.

Brief State Rumination Inventory: This 13 item self-report scale measures participants propensity to dwell on negative thoughts, and has been strongly linked with depression in the general population. Each statement is rated from 0-100, maximum score 1300. Higher scores are linked with increased levels of rumination.

4. Trial design and setting

This a 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 placebo daily for 4 weeks and then escalating to 100mg Sertraline/placebo daily for 20 weeks. A total trial duration is 24 months with a 10-month recruitment and 6 month follow up period. The trial end point is defined as last patient last visit. Data comprising questionnaires and clinical assessments will be collected at baseline, 7 day (safety check), 8 weeks ,and 24 weeks. Samples will be collected at baseline and 24 weeks only. Data from the studies, ENROLL-HD and HDClarity with be linked with data from DEVISE-HD at baseline, and 24 weeks (Enroll data only). A 12 month post randomisation data collection time point will occur outside of trial through the linking of routine data from ENROLL-HD and sample biomarkers collected as part of HDClarity.

4.1. Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a TYPE A, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

5. Site and Investigator selection

This trial will be carried out at three sites within the UK. Where electronic health records are being used, Site teams must be willing and able to take steps to avoid unintentional unblinding through EHR system.

Before any Site can begin recruitment a Principal Investigator, who has experience with the neuro-psychiatric phenotype of HD, at each site must be identified. The following documents must be in place and copies sent to the DEVISE-HD Trial email account (see contact details on page 4):

- Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- A signed Trial Agreement that includes MTA for translational component.
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper

- laboratory certification/accreditation or Standard operating procedures
- Pharmacy confirmation that they have received the first shipment of IMP prior to opening the site. N.B. This is not a regulatory requirement more good practice.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial drug supplies and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to obtain an acknowledgement that the documents have been received by the site and R&D approval where appropriate.

Site initiation will be by teleconference. The site initiation will be attended by the PI, at least one research nurse/clinical support officer, and one pharmacist.

6. Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

6.1. Inclusion criteria

Participants are eligible if they meet the following criteria:

Adult participants (age ≥ 18), with a confirmed positive genetic test of HD

- Presenting with untreated depressive symptomatology defined by patient report of low mood and/or anhedonia

6.2. Exclusion criteria

Participants are not eligible if they meet any of the following criteria:

- Currently taking an antidepressant medication or have taken antidepressants in the last six months (for any indication)
- A previous reaction and/or contraindication to sertraline, and/or Sertraline found to be ineffective
- Any medication or brain illness/injury, other than HD that, in the opinion of the principal investigator, is likely to contribute to depressive symptoms
- Any participant with severe depression or suicidal ideation in which a clinician deems it necessary to receive treatment (due to higher risk of deterioration and suicide in this group).
- Not able to give informed consent

In the event the clinician believes the depressive episode can be attributed to any current the medication being taken by the participant, this should be managed as a medication side effect, in

accordance with local policy. In such instances re-screening of the participant is permitted once medications are stable.

Where there are concerns about patient's capacity, they should be fully evaluated, and consideration should be given to determine if they can be supported to provide a fully informed decision on their participation. If a participant loses capacity, this is not a reason to withdraw them, but a legal representative should be approached to consult on any future withdrawal situations. It is recommended that the study partner acts as the legal representative but another individual could be approached.

7. Recruitment, Screening and registration

7.1. Participant identification

Participants will be identified from a variety of different sources including Enroll-HD participants, HD clinics, HD public engagement activities, and HDClarity participants. Enroll-HD monitors the onset of the disease and its progression in different people and is open to the following categories: gene carriers, gene negative and family controls. Information on potentially eligible participants (along with race, age, gender and BMI) will be provided to sites from the central Enroll-HD study teams following Enroll-HD standard operating procedures.

One of the optional components within the Enroll-HD study (REC Ref 13/WA/0192; NCTNCT01574053) is the request to give permission to be contacted to receive information about other additional and affiliated HD research projects. In consenting to participate in the Enroll-HD study, participants also give their permission for their coded data to be made available to any researchers with a legitimate research project who wants to better understand HD. Only coded clinical and genetic data are shared with the researchers therefore, the risk that identifying information will be accidentally disclosed is low.

Records of participants registered on Enroll-HD will be reviewed centrally by Enroll-HD staff for potential eligibility for inclusion in the study. Local Enroll-HD staff will then use the lists generated to target recruitment after more detailed review for eligibility. Those that fit the inclusion criteria and none of the exclusion criteria will be invited to participate in DEVISE-HD by the local research team prior to or at their next Enroll-HD visit, provided that in Enroll-HD the participants have consented to be contacted between trial visits to receive information about HD research studies.

All interested potential participants will be given as long as they need to read the material and discuss with their families and carers before being asked to make any decisions. Participants will have the opportunity to ask any questions they have about the study and discuss their potential involvement before providing informed consent.

For patients not in ENROLL-HD, established clinical practice is routine assessment annually for clinical review. Annual assessment includes history and examination to determine motor, cognitive and neuropsychiatric changes since the last visit. As standard clinical practice, any patients attending

clinic and reporting low mood are then assessed by a trained clinician for a diagnosis of depression. Once patients have been identified as potentially suitable, eligibility will be confirmed by a clinician listed on the delegation log and recorded in the patient notes.

The trial team will also engage with potential participants through leaflets and other published material, and through virtual dropping in sessions. This will allow the trial team to discuss the trial and what it would mean for the individual to participate. The final decision on whether the individual is eligible will remain with the site PI or appropriately delegated individual.

7.2. Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept at each site so that any biases from differential recruitment will be detected. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the DEVISEHD@cardiff.ac.uk every month (see section 19 for further detail on data monitoring/quality assurance).

7.3. Recruitment rates

A total of 40 participants will be recruited at an expected rate of 1.5 participants per site per month.

7.4. Informed consent

Informed consent must be obtained from the patient prior to any trial procedures being undertaken. It will also be necessary to collect contact details for friend or relative who will act as a study partner for the participant. This will facilitate data collection and participants safety checks during the trial.

The following information sheets apply:

Participant

- Participant Information Sheet
- Participant Consent Form
- Pictorial Participant Information Sheet

Study Partner

- Study Partner Information Sheet
- Study Partner Consent Form

Participant informed consent: Consent may be taken by the local Principal Investigator or a trained member of the study team delegated to do so. The potential participant will be provided with information about the trial via the Participant Information Sheet (PIS).

The participant will be given sufficient time after the initial invitation to participate, and the opportunity to ask questions, before being asked to sign the Consent Form. Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. One copy of the signed Consent Form to be given to the participant, and the original copy to be

kept in the investigator site file and a further copy to be kept with participant's hospital notes. All trial procedures that are mandatory vs optional will be clearly outlined in the trial consent form, including which samples are collected, required participation and data sharing between DEVISE-HD and ENROLL-HD/HDCLarity, as well as the possibility of samples and data being shared for future research. It will be made clear that participants will not receive the results of their blood tests.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. Similarly, the participant remains free to withdraw at any time from the protocol treatment or any trial activity, including use of samples, without giving reasons and without prejudicing his/her further treatment.

Study Partner: Due to the nature of HD it may be necessary to ask the patient's friend or a family member to help support the individual during the trial. The friend or family member will be approached at the same time that the participant will be approached. The friend or family member will be provided with information about the trial and their role in the trial (i.e. Study Partner Information Sheet (SPIS). The detailed SPIS will include: the exact nature of the trial; what it will involve for the participant and the patient's friend or relative, the implications and constraints of the protocol; and any risks involved in taking part. They will be given sufficient time to review the information sheet and ask any necessary questions. Participants will also be asked to confirm they are happy for the friend or a family member to act as the study partner. The Study Partners are not considered participants in the trial nor will they be asked to provide consent on behalf of the participant (who will be deemed to have capacity to provide consent). Study Partners will be asked to consent to their personal data being stored and processed for the purposes of DEVISE-HD at Cardiff University and to take part in some of the DEVISE-HD assessments (such as the Problem Behaviours Assessment) where required.

Please note, only when informed consent has been obtained from the participant and they have been randomised/enrolled into the trial can they be considered a trial participant. In the event that participants have difficulty signing their name, sites will use the same procedure as ENROLL-HD, . Participants will sign their name and then a witness (i.e. study partner) will countersign to provide confirmation that consent was obtained appropriately.,

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

7.5. Registration and Randomisation

7.5.1. Registration

Once patients are identified and screened for eligibility, informed consent is taken from the participant (see section 9.4 for details), and participant's study partner will provide consent for their contact details to be stored. Consent and eligibility will then be confirmed on the trial database for participant registration. On registration, all participants will be assigned a unique identification number. All screening procedures are part of standard of care, and no protocol-required evaluations will be conducted until after informed consent is obtained.

7.5.2. Randomisation

Following confirmation of consent, sites will complete of the baseline assessments. Patients will be randomised 1:1 to Sertraline or placebo using a randomly permuted block list, stratified by disease stage. Full details of the randomisation plan can be found in section 15.1.

8. Withdrawal & lost to follow-up

8.1. Withdrawal

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.

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:

1. Withdrawal of Trial Treatment
2. Withdrawal from trial due to clinically indicated alternative dose of treatment
3. Withdrawal from questionnaires
4. Withdrawal from Samples (Blood)
5. Withdrawal from follow-up assessments
6. Withdrawal of accessing ENROLL-HD data
7. Withdrawal of accessing CSF and/or blood samples from HDClarity
8. Withdrawal due to pregnancy
9. Withdrawal of Consent to all of the above

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal and the legal basis of the trial.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts. It is important to discuss an appropriate treatment tapering regime (see section 11.4) during the withdrawal process.

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

In all instances a withdrawal form should be completed for all participants who consent and subsequently withdraw. This form should be completed in conjunction with the participant to ensure that their wishes are clearly documented in the form. Information from the withdrawal form should be entered onto the online database. In the event a withdrawal form is not completed, it must be assumed that the participant withdraws from all aspects of the trial, and the samples must be disposed unless the participant has signed the optional statement in the consent form that allows the samples to be retained, used and stored as per original consent. Any queries relating to potential withdrawal of a participant should be forwarded to DEVISEHD@Cardiff.ac.uk.

8.2. *Lost to follow up*

Participants will be classed as lost to follow up if we are not able to contact them at 8 weeks and then again at 24 weeks- post randomisation. Participants will be contacted to complete an individual follow up visits a maximum of three times. To reduce participant burden, follow up visits at 8 weeks post randomisation will be completed remotely. Funding is available to help support travel costs for clinical visits if preferred. In addition, contact details for participant's study partner will be collected. The Study partner should be contacted a maximum of twice. If there are concerns regarding the participants' wellbeing, their GP should be contacted. All data from participants will be collected regardless of their adherence to the protocol.

However, for avoidance of doubt, in respect to sample collection, if the participant is lost to follow up, then they are not subject to the withdrawal processes, and the original consent stands.

9. Trial Intervention

Participants will receive either 50mg sertraline or placebo daily for 4 weeks and then escalating to 100mg daily for 20 weeks. Participants will be advised to take either in the morning or evening and can be taken with or without food. Sertraline is a film-coated tablet that will then be over encapsulated to maintain the blind. Sertraline is indicated for the treatment of depression, but it is not known how effective it is for the treatment of depression in HD and the impact on disease progression of HD. The chosen dose of 50mg with escalating was selected as it meets NICE guidance and standard for care for treating for mild to moderate depression.

9.1. Treatment(s)

The trial is being carried out under a CTA. The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial. Sertraline will be used under its current marketing authorisation. The Sertraline and placebo will be supplied to sites directly from Simbec Orion. The Sertraline 50 mg tablet will be over encapsulated with a HPMC capsule (Swedish orange size A). The active ingredient of a sertraline tablet is sertraline hydrochloride. The placebos capsule will contain an inert filler, microcrystalline cellulose Ph. Eur. Participants will take 50mg daily orally for 4 weeks and then the dose will be escalated to 100mg for 20 weeks, unless clinically indicate otherwise. The current trial will use a Summary of Product Characteristics as the reference safety information.

9.2. Treatment supply and storage

Sites will only use the supplied IMP. The IMP will arrive in appropriate packaging for dispensing and prelabelled in identical and numbered packages. The IMP will be supplied in HDPE bottles with 28-day (i.e. 4 week) supply of capsule in each bottle. The labelling will be in accordance with Annex 13 of the Rules Governing Medicinal Products in the EU: Manufacturing Practices. The sequential numbering will remain on the packaging to allow for emergency unblinding. The manufacturing facility will meet Good Manufacturing Practice (GMP). The manufacturing unit, Simbec Orion, will be responsible for the final IMP QP certification. The manufacturing unit will supply the individual sites with the IMP. IMP will be stored at room temperature. Sites should follow the supplied guidance and local practices for monitoring temperature.

Sites can order additional treatment by completing the order form and returning it to the central trial team by email. Full details can be found in the pharmacy manual.

9.3. Treatment prescribing and dispensing

Sites will use the supplied stock of IMP. The IMP will be distributed to each site pharmacy by the manufacturing pharmacy unit. A drug accountability log that records drug receipts, dispensing, and disposal activity must be maintained. Once a patient is randomised, a randomisation email will be sent to the pharmacy team who will prepare the correct treatment for dispensing. Four weeks of IMP will be initially dispensed and if the participant does not experience any significant adverse effects (monitored through a telephone safety checks at 7 days and 4 weeks), they will then receive a further five months (1 month =28 days). A second prescription will need to be submitted to allow dispensing of the 20 weeks' worth of medication. Medication compliance will be done via pill counts. Participants will be asked to return all unused medication and pill bottles. In the event that the participant loses their medication, they should be issued a new prescription for the remaining treatment period.

The blinded trial label will be Annex 13 compliant and will list the PackID for emergency unblinding. The trial prescription should contain at minimum the following information:

- Participant study ID

- Participant Initials
- Date
- Dose Number
- Participant DOB

9.4. Dosing schedule

The IMP dosing schedule is 50mg once daily orally for 4 weeks and then escalated to 100mg once daily orally for 20 weeks unless the participant has a strong preference and it is clinically indicated to remain at 50mg. Participants should be advised to take the treatment either in the morning or evening and that it can be taken with or without food. If participants decided to withdraw from the trial, the clinicians should follow a tapering regime based on the Maudsley deprescribing guidelines.

At the end of 24 weeks, participants will be unblinded. They will be given the option to continue take sertraline or to start taking it if they were on the placebo if clinically indicated. If the participant declines to continue taking Sertraline, they will begin a tapering regime. The tapering regime will follow the Maudsley deprescribing guidelines as described below and taking into consideration participant's tolerance of the tapering regime. The first 24 weeks of the tapering regime will be monitored as part of the trial.

Withdrawal from sertraline is based on the Maudsley guidelines for hyperbolic discontinuation from known data on receptor occupancy. Smaller dose reductions occur towards the end of this process as receptor occupancy is known to change in a hyperbolic fashion. All stages last between 2-4 weeks depending on clinical judgment and participant preference. Liquid preparations of sertraline are available for smaller dose preparation.

Stage	Daily Sertraline Dose (mg)
1	100
2	50
3	25
4	15
5	10
6	5
7	2.5
8	1.5
9	1
10	0

Management of the new or ongoing Sertraline course will be in accordance with clinician judgement and local practice (i.e. via HD clinic or local GP depending on local procedures), and is considered outside the scope of the trial.

9.5. Dose modification for toxicity

Treatment will be supplied in 50mg capsules only; dose modification is permitted if adjusting between 50mg or 100mg. In the event, the participant experiences any significant adverse events or toxicities due to the dose strength, and it is in the best interest of the participant, clinicians should consider stopping the IMP (or reducing to the previous 50mg dose if escalated to 100mg dose). Any decisions to stop treatment should be recorded on the appropriate CRF (trial withdrawal CRF) Even if the IMP is stopped participants should remain on the trial, unless they decide to withdraw completely. If a clinician decides to treat the depression with an alternative dose to the protocol prescribed dose of Sertraline, the participant should be withdrawn from the trial.

9.6. Management of toxicity and hypersensitivity reactions

Sites should follow local practice procedures for managing toxicity and any hypersensitivity reactions. It is important to evaluate if any of the reactions meet the definition of an SAE and report it according to procedures outlined in section 14.

9.7. Management of overdose

In the event of an overdose, medical care should be provided immediately. Symptoms of an overdose include gastrointestinal disturbances (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness.

It is important to establish and maintain an airway, ensure adequate oxygenation and ventilation, monitor vital signs and administer general symptomatic and supportive measures. Activated Charcoal along with a cathartic should be considered. Induction of emesis is not recommended.

9.8. Prohibited medications and interaction with other drugs

Treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome. Sertraline must not be prescribed for at least 14 days after discontinuation of irreversible MAOI (refer to section 8 for inclusion/exclusion criteria relating to medication). The administration of Pimozide is also contraindicated.

The following medication listed below may required additional monitoring if co-administered:

CNS depressants and alcohol
Other serotonergic drugs, including opioids
Drugs that Prolong the QT Interval
Lithium
Phenytoin
Triptans
Warfarin
Cimetidine
Drugs that affect platelet function

Neuro muscular blockers
Drugs Metabolized by Cytochrome P450
Metamizole

9.9. Permitted concomitant medications

Sites should follow local standard of care.

9.9.1. Trial restrictions

Participants should be asked to refrain from consuming grapefruit, and St John's Wort. Participants should be informed that Sertraline can impact their alcohol tolerance and be encouraged to reduce their intake.

9.10. Accountability procedures

All accountability procedures will be outlined in the trial specific pharmacy manual and IMP management plan. Local pharmacies will be asked to log packID, batch number, expiry date, date drug was dispensed, initials of trial member who requested the treatment, using the online REDCap accountability database.

At the end of the trial participants will be given the option to continue taking Sertraline or to start as per the guidance in section 11.4 of this protocol.

9.11. Compliance

Any deviations from dosing schedule outlined in the trial protocol will be recorded on the appropriate CRF. Participants will be asked to return bottles to allow site staff to complete pill count to monitor compliance. Site research staff should remind participant that they need to return the bottles at each contact point. Where possible two compliance checks will be undertaken. One will be completed 4 weeks after randomisation, and the second will be completed 24 weeks after randomisation.

10. Sample Management

We will recruit study participants already enrolled into HDClarity (IRAS 185506), or explore co-recruitment where the participant is not already enrolled in HDClarity. HDClarity is a biomarker study collecting cerebrospinal fluid (CSF) and plasma at baseline and 1 year intervals, in order to collect information on markers of neuronal injury (Neurofilament light chain: NfL) and inflammation (TNF-alpha, IL4, IL6, IL10,). Involvement in HDClarity if optional for participants.

Brief details relating samples collected as part of HDClarity are included below but sites should refer to the HDClarity protocol and lab manual for full details. Samples collected as part of HDClarity will be held and managed according to the HDClarity regulatory approvals. At the end of the DEVSIE-HD

trial, HDClarity samples will be requested through the established sample and data request process (https://enroll-hd.org/for-researchers/access-data-biosamples/), and then transferred and analysed at the Welsh Neuroscience Research Tissue Bank (WNRTB).

Table 2. Sample collection for HDClarity schedule and quantities

Timepoint	Baseline pretreatment	6 month	12 month*
Lumbar Puncture	20ml		20ml
Translational blood sample	50ml		50ml

*outside of DEVISE-HD trial period.

If participants decline involvement in HDClarity, or their last HDClarity visit was more than 3 months prior to recruitment into DEVISE-HD, blood sample for plasma analysis will be collected at baseline but no Lumbar puncture will be performed. Optional blood samples will be collected at 24 weeks for all participants as part of the DEVISE-HD trial. Details of schedule and quantities can be found in the table below. Sites should refer to the sample and lab manual for full sample collection details.

Table 3. Sample collection for DEVISE-HD schedule and quantities

Timepoint	Baseline pretreatment	24 weeks
EDTA blood sample	6ml	6ml
SST Blood Sample	6ml	6ml

Samples will be collected, and initially be centrifuged, processed, frozen and stored at hospital site in accordance with local policy and the DEVISE-HD sample management and lab manual. Samples will then be transferred at the end of the follow up period to the WNRTB. The samples will be used to analysis differences in plasma biomarkers of disease progression between arms. After the analysis is complete, any remaining samples from participants who have consented, will be adopted into the biobank at WNRTB.

10.1. Biomarker Sampling

Sites should use their local supply of EDTA and SST tubes for blood sample collection. Sites should refer to the sample and lab manual for full details of collection and storage procedures.

10.2. Biobanking and future use of samples

Participants in DEVISE-HD will be given the option to donate their blood samples to the WNRTB for long-term biobanking and use in future research. This will only apply to samples collected as part of DEVISE-HD. HDClarity samples will not be adopted as part of the DEVISE-HD trial. The biobank is a repository specialising in samples collected for the purpose of advancing the understanding of, and care of neurological disease. WNRTB received ethical approval in March 2024 (REC reference: 24/WA/0049). Samples may be distributed to researchers in the UK and abroad for further research according to ethically approved procedures. At this stage we do not know what the research will involve but some of it could include DNA analysis, animal research or use in the commercial sector. Sample can be requested by following the sample request procedure at WNRTB. All sample requests will be reviewed by the WNRTB governance committee and if necessary external reviewers.

11. Trial procedures

Trial assessments will take place at baseline, 7 days (7D), 4 week (4 weeks), 8 weeks (8W), 24 weeks (24W) (see table 4). An additional follow up that is outside of the scope of this trial protocol will occur at 12-month (12M) post randomisation. The primary outcome, trial feasibility, will be measured at 6-month post randomisation. The trial feasibility outcomes will consist of assessments of recruitment, retention, data completeness, and adherence (see section 5.3 for definitions).

The DEVISE-HD mechanistic sub-study will comprise of blood and CSF sample collected at baseline prior to the start of treatment, through HD Clarity (or as part of the DEVISE-HD-blood only sample collection), and blood sample collected at 6 month as part of DEVISE-HD.

11.1. Assessments

Trial feasibility outcomes will be assessed through the development of reports in REDCap that will monitor recruitment and retention rates, as well as the completeness of data collection. Progress of these will be reviewed monthly.

The full schedule of assessments and trial procedures can be found in the table below. Data can be collected from ENROLL-HD if the core assessment has been completed in the previous 3 months of the DEVISE-HD assessment visit, in line with ENROLL-HD follow up windows. If the ENROLL-HD or HDClarity visit falls outside of that window, the site will need to assess clinical progression by completing the measures that make up the cUHDRS (see section 5.4) and collect the relevant samples. Where possible, sites should align ENROLL-HD/HDClarity and DEVISE-HD visits. Sites can complete an unscheduled ENROLL-HD visit at 24 weeks post randomisation. A series of decision trees can be found in Appendix 2 to aid in determining which trial procedures need to be completed as part of DEVISE-HD at baseline and 24 weeks.

Table 4. Schedule of enrolment, interventions and assessments[1]

Procedures	**Screening**	**Baseline**	**7 day**	**4W**	**8W Follow up**	**24W Follow Up**	**Tapering regime**	**Ad hoc**
Eligibility assessment	X							
Informed consent	X							
Randomisation		X						
Medical History & Demographics		X						
Pregnancy questions		X			X	X		X
HD-Clarity sample collection		X						
DEVISE Sample collection[Ŧ]		X				X		
Dispensing of trial drugs		X		X				X
Medication Adherence				X		X		
Problem Behaviours Assessment (short form)		X*			X	X*		
Montgomery Asberg Depression Rating Scale		X			X	X		
Beck Depression Inventory		X			X	X		
PHQ-9		X			X	X		
The Columbia Suicide Severity Rating Scale		X*			X	X*		
WHODAS 2.0		X				X		
MOS-SSS-6		X				X		
Outcome expectancy		X						
Success of treatment						X		
UHDRS (ENROLL-HD*)		X				X		
SWRT (ENROLL-HD*)		X				X		
SDMT (ENROLL-HD*)		X				X		

[1] Taken from the HRA CTIMP protocol template (2016).

Table 4. Schedule of enrolment, interventions and assessments[1]

Procedures	**Screening**	**Baseline**	**7 day**	**4W**	**8W Follow up**	**24W Follow Up**	**Tapering regime**	**Ad hoc**
Reward Reaction Time Task		X				X		
Effort Discounting Task		X				X		
Conceptual Bias Task		X				X		
Brief State Rumination Inventory		X				X		
Safety Check/ Adverse events			X	X	X	X	X	X
Participant unblinding						X		X
Concomitant medications		X					X	X
Physician's Withdrawal Checklist								X
Drug Tapering							X	

~~Ŧ~~ – only if participant not recruited to HDClarity

* Can be collected from ENROLL-HD if visit occurred in the previous 3 months of follow up visit

11.2. Follow-up

Participant follow up will occur at 7 day, 4 weeks, 8 weeks, and 24 weeks (i.e. 6 month). The 7 day, 4 weeks, and 8 week follow up visit will be completed remotely unless the participant choses to attend in person. The 24 week visit will be completed in-person. To mitigate potential loss to follow up, acceptable windows for follow up assessments will be; ± 1 week for the 8 week follow up visit and ±2 weeks for the 24 week- follow-up visit.

The site research staff will contact the participant to check how they are tolerating the treatment and whether there have been any adverse events, including self-harm between 7-10 days and 4 weeks post-randomisation. If research staff cannot get a hold of the participants, they should contact the study partner, and/or escalate to the participant's GP.

12. Pharmacovigilance

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI, or appropriately delegated individual, at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 16.2). This includes SAEs related to IMPs and non-Investigational Medicinal Products (nIMPs).

Rates of depression and self-harm occur at higher rates in participants with HD. Suicidality will be monitored by the investigating site. Clinically significant worsening depression or suicidal ideation will prompt urgent clinical review, and are to be recorded on the Safety Check form and Adverse Events Assessment form. Participants (and the study partner) will have access to a study telephone number to contact if they are experiencing rapidly deteriorating mood or suicidal ideation. Participants will be withdrawn if deemed medically appropriate by the treating team. Safety Checks are scheduled at 7 days, 4 weeks, 8 weeks and 24 weeks.

12.1. Definitions

Table 5. Pharmacovigilance definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.2. AE of Special Interest

Clinically significant worsening of depression symptoms or increased suicidal ideation should be reported on the adverse events and safety check form. This should be monitored for at least the first month, with the frequency determined by the patient's individual circumstances and risk level. Reviews should be scheduled no later than four weeks after the initial prescription. Based on clinical judgment some participants may require more frequent reviews. If the events meet the definition of an SAE they should be reported in line with the procedure outlined in 14.6.1.

12.3. Trial Specific SAE Reporting requirements

There are no trial specific SAEs

12.4. Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

IMPs: Sertraline, Placebo
nIMPs: N/A
Procedures: venepuncture

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 6. definitions of causal relationships

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the IMP?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after	No

	administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

12.5. Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness. The expectedness assessment will be completed based on the assumption that participant received the Sertraline.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The table below lists the RSI's that should be referenced

Table 7. Relevant trial RSI		
IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Sertraline	SmPC – Aurobindo Pharma	Table 1 in section 4.8.

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

Blood draw procedures risks: Pain, bruising, fainting, infection, and nerve damage. Sites should monitor for these adverse events in accordance with their local policy.

12.6. Reporting procedures

12.6.1. Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, month and day of birth, and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

Serious adverse events should be reported from time of signature of informed consent, to the end of the treatment period up (24 weeks). Serious adverse reactions (such as long term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol. Severity will be classified as mild, moderate or severe.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 17.

12.6.2. The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until the end of the trial Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA. SUSARs do not need to be reported the manufacturing pharmacy unless there are concerns regarding quality of the IMP, over encapsulation, or the placebo.

12.7. SUSAR reporting

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs):

SUSARs which are fatal or life-threatening must be reported to the MHRA within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life-threatening

Any additional, relevant information must be reported within a further 15 days.

12.8. Unblinding for the purposes of SUSAR reporting

To enable processing of a SAR in this blinded trial, expectedness should be assessed initially using the assumption that the IMP has been given to the trial participant.

If it is assessed as unexpected as per the RSI of the IMP, the SUSAR will be unblinded by the CTR safety group prior to reporting to any onward reporting.

If after unblinding it is evident that the trial participant received the placebo, this event will not require expedited reporting to the NCAs, unless in the opinion of the Principal Investigator or Chief Investigator the event was related to the placebo (for example an allergic reaction to an excipient).

12.9. Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

The manufacturing pharmacy does not require any safety reporting unless there are concerns regarding the quality of the IMP, over encapsulation or placebo. In the event there are concerns, they should be reported to the central trial team via email. They will then be onward reported to the manufacturing pharmacy and managed in accordance with their GMP complaints process.

12.10. Contraception and pregnancy

In line with standard practice and NICE guidelines, the trial will not exclude pregnant people or those who are breast feeding. Sertraline is regularly prescribed to pregnant people and there has been no causal link between anti-depressant use and birth defects. While there have been association between anti-depressant use and adverse pregnancy outcomes, the overall risk is considered low. If a participant is pregnant or becomes pregnant during the trial, the PI (or an appropriately qualified individual on the delegation log) will discuss the risks and benefits of staying on the Sertraline. The participant will be supported to make a decision on whether it is in their best interest to stay in the trial or to withdraw. Any adverse events that may be related to the pregnancy will be monitored according to the process in section 14.9.1.

12.10.1. Pregnancy reporting whilst participating in the trial

Pregnancy, occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol(see section 14.6.1). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, and the drug manufacturer of the IMP (to comply with any contractual agreement).

12.11. Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health

or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

13. Statistical considerations

13.1. Randomisation

Participants will be 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. As this is a blinded trial, the trial statistician will remain blinded to participants' allocation to the randomisation arms. The trial statistician will write a STATA program with a 'set seeds' option while an independent statistician will specify the final seed number and generate the final randomisation list. The randomisation will be stratified by Huntington's Disease Integrated Staging System (HD-ISS), with random permuted blocks used to maintain the balance of numbers between arms within each disease stage stratum. The HD-ISS strata will be stage 0/1 (combined), stage 2, and stage 3.

The final randomisation lists, which will contain investigational medicinal product identifications and corresponding allocations (Sertraline/ placebo), will be generated by a statistician otherwise not involved in the trial and will be supplied to Simbec Orion for appropriate labelling, as well as the CTR safety team. Randomisation will take place online using REDCap. It will be available 24 hours a day. On randomisation, a participant will be allocated to the next available treatment via the online form. Sites staff will receive an email confirming the participant was successfully randomised. Pharmacy will receive an email confirming randomisation that includes the treatment allocation to allow them to prepare and dispense the correct treatment. The research team, treating healthcare professionals, participants and their families will remain blind to allocated treatment for the duration of the study. Unblinding will be available 24 hours a day by contacting their local research pharmacy.. Pharmacy will maintain a log of participant identification numbers, treatment allocation, and package number. Participants will be provided with a trial card that contains trial details and contact numbers in the event that they require care from outside of the trial team and this care requires the treating clinician to be unblinded.

All details of the randomisation schedule, testing procedures, implementation are given in the randomisation strategy document on the CTR required template.

13.2. Blinding

The is a double blind two arm placebo controlled randomised feasibility trial of Sertraline in adults with a confirmed genetic marker for HD. Participants will be unblinded at the final follow up time point (6 month) and given the choice to continue on the Sertraline or to start taking Sertraline.

Blinding information (i.e. codes corresponding to Sertraline/placebo allocations) will be held by:

- Manufacturing Pharmacy Unit

- The Pharmacovigilance team at the Centre for Trials Research, Cardiff University;
- A study-independent statistician at the Centre for Trials Research, Cardiff University.
- Site Research Pharmacy
- The unblinded trial manager

Planned unblinding at 24 weeks

At the 6 month follow up participants will be told whether they were allocated to the Sertraline or the placebo arm and given the option of continuing Sertraline or if clinically indicated to start Sertraline. To unblind at the 6 month follow up:

1. After the clinician has completed their initial review with the participant and if a research nurse is supporting the participant to complete the measures, the clinicians can contact the pharmacy and request to be unblinded. The clinician should provide PID and Month and Year of birth.
    a. If the clinician is supporting the participant to complete the outcome measures, they should wait until all follow up activity is completed prior to contacting the pharmacy.
2. Pharmacy should complete the notification of allocation form and send it to the requesting clinician via secure trust approved method.

Final unblinding prior to statistical analysis

The statistician responsible for conducting the final statistical analysis will be unblinded following database lock, data cleaning, and derivation of variables required to perform analysis has taken place.

Emergency unblinding

Unblinding may occur in situations in which it is critical for the clinical management of the patient. In the cases of an SAE, the reporting clinician should treat the participant as if they had received the IMP. In the event of a SUSAR, the CTR safety team will be able to break the blind.

Site PI or appropriately delegated individual (listed in delegation log) is responsible for making decisions regarding emergency unblinding.

The following procedure should be followed in all instances of emergency unblinding:

1. The site PI (or appropriately delegated individual) will contact the clinical trials pharmacy and provide the pharmacy with PID, Year and Month of Birth.
2. Pharmacy should complete the notification of allocation form and sending it to the requesting clinician via a secure trust approved method.
3. The clinician should complete the Clinician emergency unblinding form on REDCap at the soonest available opportunity after receiving the notification of allocation form

4. The pharmacy should complete the pharmacy unblinding form on REDCAP at the soonest available opportunity after sending the notification of allocation form.

13.3. 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 (Wilson, 1927).

13.4. Missing, unused & spurious data

Data completeness will be reported as part of the statistical report. Detail provided in the Statistical Analysis Plan (SAP).

13.5. Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

13.6. Termination of the trial

As this is a feasibility trial there are no prespecified stopping criteria.

13.7. Inclusion in analysis

All randomised participants will be included.

14. Analysis

14.1. Main analysis

The primary analyses will assess the feasibility of the trial. Data for all feasibility primary outcomes including recruitment, retention at each time point, adherence, and data completeness will be explored descriptively

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.

For secondary outcomes, we will also estimate minimal clinically important difference (MCID) for a proposed set of six depression outcome measures: Problem Behaviours Assessment, Montgomery

Asberg Depression Rating Scale , Beck Depression Inventory, PHQ-9 and the Columbia Suicide Severity Rating Scale, which will be helpful to inform outcome selection for a future effectiveness trial. MCIDs will be calculated using the anchor method and results triangulated across MCIDs calculated using participant-, carer- and clinician-reported anchors. 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. Outcome measures will be scored according to individual measure rubrics or algorithms. Summary statistics (means, SDs, medians, IQRs as appropriate) will be presented for each outcome at baseline and follow-up time points, by treatment arm and overall. As part of the secondary analyses, Neurofilament light chain (NfL) will also be compared between treatment arms using the Mann-Whitney U test, as the distribution of NfL is expected to be non-normal.

A more detailed statistical analysis plan (SAP) will be produced by the trial statistician during the trial set-up and recruitment. The analysis plan will be completed and signed off before the trial database in completed and locked. All analyses will be carried out blind to allocation.

15. Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement. The source data is outline in the table below:

Table 8. source data definitions

Trial Data	*Source Data*					
	CRF	*Participant medical notes*	*Electronic System*	*Pharmacy File*	*Questionnaire (electronic or paper as indicated upon data entry to database)*	*SAE form*
Eligibility assessment			*X*			
Informed consent	*X*					
Randomisation			*X*			
Demographics		*X*				
Medical History		*X*				
Pregnancy			*X*			

Problem Behaviours Assessment (short form)					*X**	
Montgomery Asberg Depression Rating Scale					*X*	
Beck Depression Inventory					*X*	
PHQ-9					*X*	
CSSRS					*X**	
WHODAS 2.0					X	
MOS-SSS-6					X	
Outcome expectancy			X			
Success of treatment			X			
Clinical progression Outcomes(cUHDRS)*					X	
Reward Reaction Time Task			*X*			
Effort Discounting Task			*X*			
Conceptual Bias Task			*X*			
Brief State Rumination Inventory			*X*			
Safety Check			*X*			
Sample collection			*X*			
Drug adherence			*X*			
Concomitant medications		*X*				
Adverse event assessments			*X*			
Drug accountability				*X*		
Physician's Withdrawal Checklist			*X*			

*Where participants have consented to take part in ENROLL-HD, source data will be from ENROLL-HD at baseline (PBA-s, CSRSS, cUHDRS) and 6-month (cUHDRS)

15.1. Data collection

15.1.1. Completion of CRFs

In accordance with the principles of Good Clinical Practice (GCP), the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

Paper CRFs and consent forms

Paper CRFs and consent data should be entered into the database in a timely manner, and it is the site's responsibility to ensure that it accurately reflects the source data. In some instances, the source data (i.e paper CRFs/questionnaires) may be requested from sites for quality assurance checks. Sites should send scanned copies to the CTR via Fastfile or another secure trust/health board approved method.

Electronic CRFs

Trial data will be collected and managed using REDCap, a secure, encrypted web-based data capture system which complies with UK General Data Protection Regulation (GDPR) 2018. The two DEVISE-HD REDCap systems (main trial database and pharmacy accountability database) will be hosted by Cardiff University. Password-protected user accounts and access to the trial REDCap system will be provided to investigators upon completion of all processes required prior to opening. Data will be entered directly to the relevant eCRFs in the REDCap system or retrospectively entered from completed paper CRFs (where applicable), following the data collection schedule outlined in protocol section 13.1. REDCap maintains a secure, automatic audit trail of all data entries and changes, ensuring transparency and compliance with regulatory standards.

Data Queries

The CTR Data Manager will regularly review data entered by sites and send reminders for any overdue data. If missing or questionable data are identified, a data query will be raised with the investigating site using the data query system within REDCap. Sites may also be notified via email for response. It is the site's responsibility to submit complete and accurate data and respond to data queries in timely manner.

Full details for the study data management procedures are documented in the internal DEVISE-HD Data Management Plan, maintained by the study team.

15.1.2. Import of linked ENROLL-HD data

The DEVISE-HD study will make a request for data linkage to be approved by the ENROLL-HD scientific planning committee (see Appendix 1 for details of data request). Each site will have a signed data sharing agreement in place prior to ENROLL-HD data being shared with DEVISE-HD. Sites will access and download ENROLL data for each DEVISE-HD participant by linking their HD-ID to their DEVISE-PID. This will occur on a minimum of two occasions; 1) at the close of recruitment and 2) at the completion of the 6-month follow up assessment. Data exports will contain pseudoanonymised datasets. Data exports will be sent and stored in compliance with the ENROLL-HD data sharing agreement, and data integrity and reliability guidelines.

16. Translational research or sub trial

We will co-recruit study participants into HDClarity (IRAS 185506); a biomarker study collecting cerebrospinal fluid (CSF) and plasma at baseline and 1 year intervals, in order to collect information on markers of neuronal injury (Neurofilament light chain: NfL) and inflammation (TNF-alpha, IL4, IL6, IL10,). These biomarkers will be collected as part of the HDClarity study, but funding is costed into this application for the analysis. We will collect plasma at 24 weeks (primary endpoint), as repeating the lumbar puncture at this visit imposes a significant burden on participants. Samples will be analysed in the WNRTB using the SiMoA Hdx analyser. Samples stored in HDClarity (CSF and plasma) will be requested from the HDClarity repository (see https://hdclarity.net/ for request process) and analysed on the same system.

17. Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

18. End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as last patient last visit.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

19. Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor.

Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

20. Regulatory Considerations

20.1. CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority: MHRA.

Classification of whether any changes to the protocol is defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and sponsor rep, for approval prior to being submitted, via IRAS to REC, HRA, and if necessary. the MHRA. The central trial team will alert all site trial teams and R&D departments once approval has been received for the amendment via email. The amendment history will be listed in the protocol and in the amendment log which is filed in the TMF.

20.2. Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review via HCRW.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

20.3. Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the Cardiff University.

Participant Identification number will be linked to their ENROLL-HD-ID and HDClarity-ID to allow the collection of clinical disease progression from ENROLL-HD and biomarker data from HDClarity. DEVISE-HD will collect the ENROLL-HD ID to facilitate data linkage at DEVISE-HD sites. the linking for HDClarity will be done by the research staff that are part HDClarity.

20.4. Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and

they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

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

20.5. Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial.

The trial is being sponsored by Cardiff University with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2016.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol, and Good Clinical Practice as required by the regulations.

20.6. Funding

This project was funded by Health and Care Research Wales Integrated Funding SCHEMA (reference: 02-24-024). The trial will be adopted onto the NIHR portfolio.

21. Trial management

21.1. TMG (Trial Management Group)

The TMG will typically meet monthly by teleconference. As the trial progresses this may be adjusted based on recruitment success. It will include the Chief Investigators (CIs), all other co-applicants, and the central project team. The TMG will provide specialist advice, develop study procedures/documents and advise on the conduct of the study. The Trial Manager will be responsible for trial conduct and will be accountable to the CI. Regional research staff supervised by the site Principal Investigator (PI) will be responsible for recruitment, assessments and data collection. Data will be securely stored locally and entered on a secure electronic recording system compliant with data management procedures. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

21.2. TSC (Trial Steering Committee)

A TSC will be established with an independent chair and at least two other independent members including PPI representatives and an independent statistician. The TSC will meet prior to trial commencement to review the protocol, roles, responsibilities, and timelines for meetings and agree the remit and conditions set out in the TSC Charter.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

21.3. Independent Data Monitoring and Ethics Committee (IDMEC)

An IDMEC will be convened, with at least three independent members including one clinician and one statistician. The IDMEC will meet within 24 weeks of the trial opening to recruitment. The IDMEC will review trial progress, trial safety, and make recommendations to the TSC.

IDMEC members will be required to sign up to the remit and conditions as set out in the IDMEC Charter which will be filed in the eTMF

22. Quality Control and Assurance

22.1. Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the DEVISE-HD trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

22.2. Audits & inspections

The trial is participant to inspection by the MHRA as the regulatory body for CTIMP trials and the HTA as the regulatory body for the use of human tissue. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

23. Public Involvement and Engagement

The trial will have at least one public involvement and engagement (PI&E) representative on the TMG, TSC, and IDMEC. They will contribute to the overall development and progress monitoring of the trial. Full details of their roles and responsibilities can be found in the trial relevant PI&E plan.

24. Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. The trial will follow acknowledgement requirements of ENROLL-HD and HDClarity.

25. Milestones

The following provisional milestones were outline in the funding application: Trial Month 6- Secure Sponsor Green Light for study opening

Trial Month 16 – Complete participant recruitment

Trial Month 22- Complete participant Follow Up

Trial Month 24 – Final report to funder

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27. Appendices

27.1. Appendix 1 ENROLL-HD Data request details

Specified Dataset Request

The following variables from the core and extended battery data will be requested for participants via a specific data request to the Enroll-HD Scientific Review Committee. We will request this data for the Enroll-HD clinic visit closet to baseline DEVISE-HD data collection point and 12 months post-randomisation.

Label and variable names per data file/form are given below in the form: label name(s) – **variable names(s)**

cUHDRS

TMS:

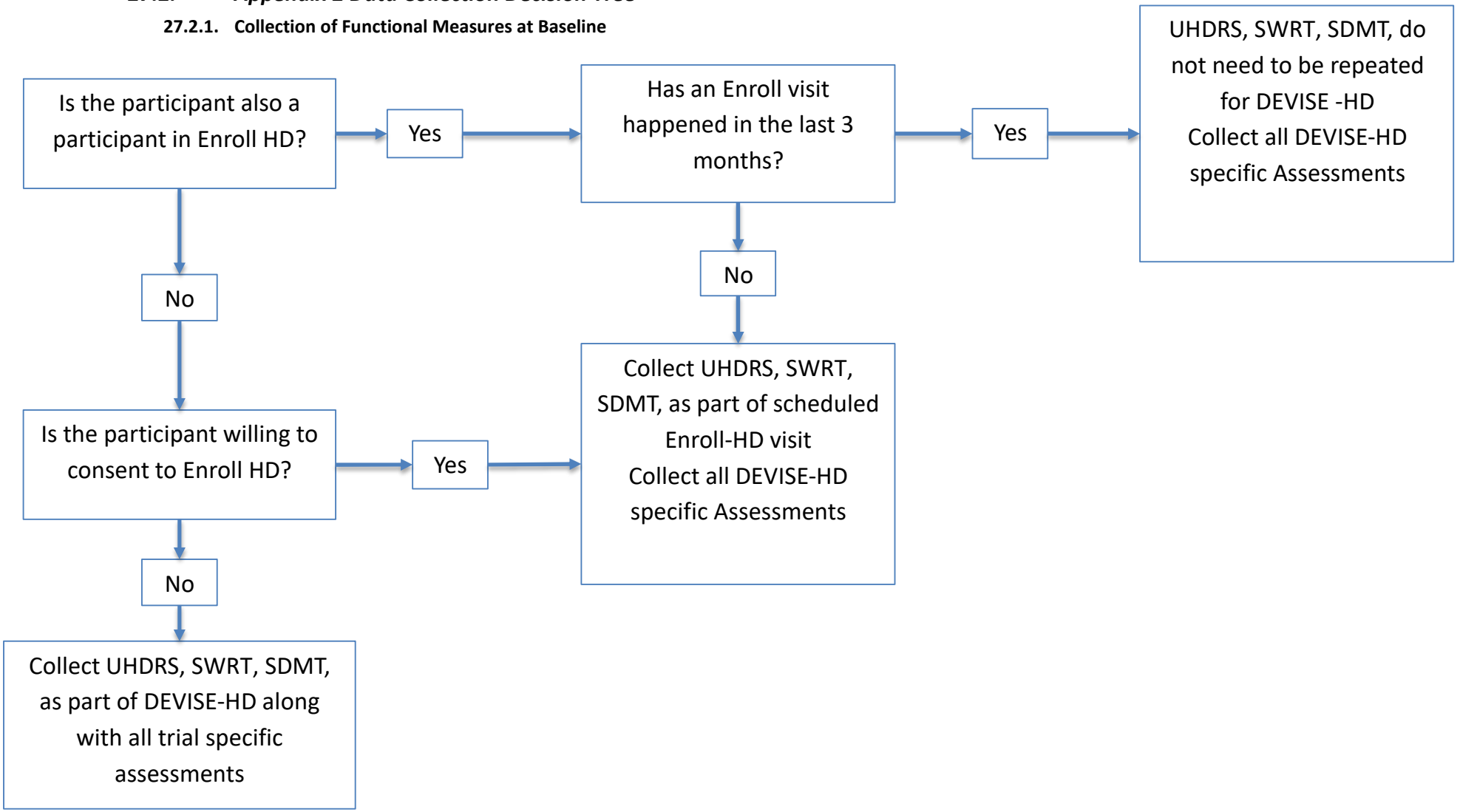
TFC

SWRT:

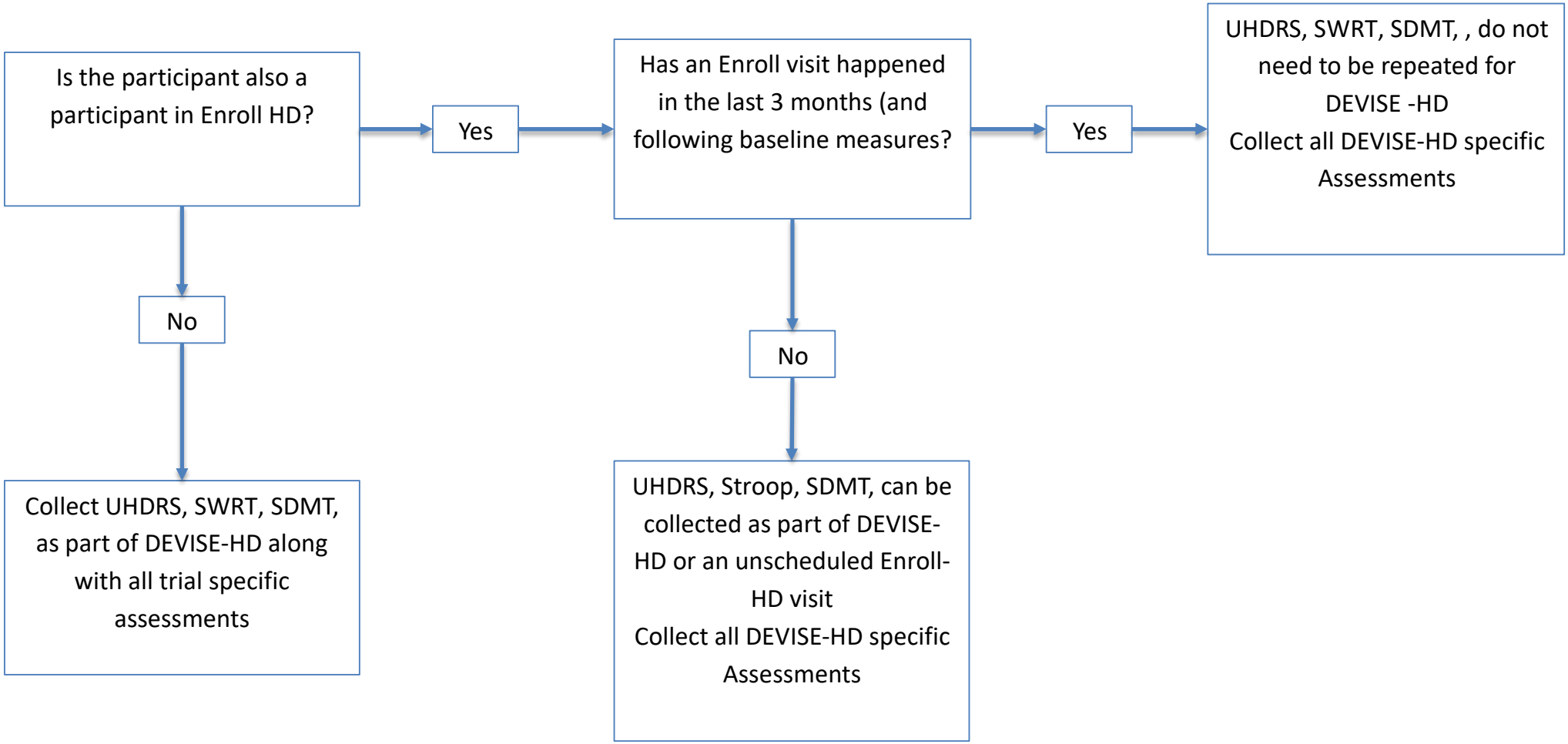
SDMT:

27.2. Appendix 2 Data Collection Decision Tree

27.2.1. Collection of Functional Measures at Baseline



27.2.2. Collection of Functional Measures at 6 Month



27.2.3. Collection of Samples