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A single site, open label, phase I study to assess the safety and feasibility of foetal cell transplants in the striatum of people with Huntington's disease

Submission date
04/01/2018

Recruitment status
No longer recruiting

Registration date
04/04/2018

Overall study status
Completed

Last Edited
20/06/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Huntington's disease (HD) is a brain disorder that is passed down from parent to child. In HD, cells in a part of the brain called the striatum are slowly lost. This leads to problems with movement, thinking and learning, which get worse over time. At the moment, there are no proven treatments to slow or stop the progression of HD. One possible way of treating HD (and other brain diseases where brain cells are lost) is to replace the cells that die with cells that do not carry the gene mutation, in a procedure called cell replacement therapy (CRT). Some studies of CRT have been done in people with HD and another brain disorder called Parkinson's disease (PD). The treatment was found to be safe, but because the studies were small, it is not certain whether this is a reliable long-term treatment for HD. A study of CRT in five patients with HD found it to be safe, but the data suggested that not enough cells were put into the brain for it to be effective. Therefore, the current study tests the safety and how straightforward it is to put more cells into the brain.

Who can participate?
Patients aged 18 and over in the early stages of HD

What does the study involve?
Participants are asked to do some tests to measure their movement and thinking. From these participants, five are randomly chosen to have CRT. Participants have a brain scan before the transplant, in which 11-22 million foetal cells are put into one side of the brain during a procedure under general anaesthetic. This is a larger number of cells than has been used in earlier studies. Because this is a transplant, participants have to take special drugs to stop their immune system from attacking the new cells. Interviews with the participants are done before and after the surgery. More pictures of the brain are taken at 3 and 12 months after the surgery. Participants are followed up using a range of tests including regular blood tests and tests of function at 6 and 12 months after surgery, although the aim is to continue following up patients life-long. Participants are asked about their views and understanding of the study processes and

taking part in the study. The same questions are asked of participants who were not selected for transplant. Members of the team working on the study are also interviewed to understand which the most important parts of the process are.

What are the possible benefits and risks of participating?
The study will provide information needed to design studies to test how cells, medicines or other treatments can be delivered directly into the brain in patients with neurodegenerative disease. This is extremely important, as many treatments that could possibly change the course of neurodegenerative disease (such as cells or gene therapies) will need to be put directly into the brain. It is not known whether participants will receive any direct benefit from taking part in this study. This is because cell replacement therapy is still very experimental and it is not yet know if this will be an effective treatment for people with HD, and is why this study is being done. It is hoped that the information collected will help with the development of better treatments for people with HD in the future. There is significant risk associated with taking part in this study. Having the transplant will mean that participants need to take drugs that weaken their immune system known as immunosuppression. Immunosuppression can increase the overall risk of infection, cancer, heart disease and bone marrow suppression. The risk of complications from surgery is low but could include bleeding, infection and permanent brain damage.

Where is the study run from?
1. University Hospital Wales (UK)
2. Cardiff Huntington's Disease Centre (UK)

When is the study starting and how long is it expected to run for?
October 2017 to February 2023

Who is funding the study?
Health and Care Research Wales (UK)

Who is the main contact?
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Contact information

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Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
TBC

Study information

Scientific Title
TRIal designs for DElivery of Novel Therapies for Neurodegeneration

Acronym

TRIDENT

Study objectives
Neurodegenerative conditions are a common cause of dementia and disability and represent a huge societal burden. Currently most are untreatable, but we are on the cusp of a new era of potential disease-modifying therapies for neurodegeneration, with many of the most promising requiring direct delivery into the central nervous system.
Cell replacement therapy (CRT) may provide a way of treating the many neurodegenerative conditions for which the underlying cellular pathology is currently uncertain. It can be considered in any condition in which there is a relatively focal loss of cells in the central nervous system (CNS). Neurodegenerative diseases comprise a large number of relatively rare genetic conditions that together constitute a substantial disease burden, and indeed even “common” conditions, such as Parkinson’s (PD), are now known to be heterogeneous in terms of genetic origin and cellular pathogenesis. This presents a problem therapy depend on targeting specific cellular pathways, but CRT has the potential to circumvent this situation by directly treating the cell loss.

Huntington’s Disease (HD) is a powerful paradigm for understanding and treating neurodegeneration. It is the most common monogenetic neurodegenerative condition of the CNS. It is an autosomal dominant disease with full penetrance; thus it is possible to make a firm diagnosis in life, even prior to symptom onset, which provides substantial power for clinical studies. There is relatively focal loss of a specific neuronal cell type, striatal medium spiny neurons (MSNs), which makes it suitable for CRT. The vision is that the principles underlying effective cell therapy in HD will be applicable to other neurodegenerative conditions. Previous work has shown that CRT in HD is safe and potentially efficacious, but to date only a relatively small number of cells have been transplanted due to prior concerns regarding overgrowth of the graft. This trial intends to transplant a much higher number of cells as it is hoped increased cell number would provide greater efficacy.

The aim of the study is to conduct a pilot feasibility study of neural transplantation in Huntington’s disease (HD), with embedded process evaluation. This will involve trial within a cohort where eligible cohort participants will be randomly selected to receive the intervention.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/06/2018, Wales REC 3 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; Tel: +44 (0)2920785741 / +44 (0)7676982591, +44 (0)2920785739 / +44 (0)2920785736; Email: Wales.REC3@wales.nhs.uk)

Study design
Phase I single-centre open-label study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)

Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Huntington's disease

Interventions
A subset of participants within a comparator cohort will be assessed for suitablilty and safety of undergoing transplant surgery. Those deemed to be eligible for surgery will be randomly ordered and 5 participants selected for surgery. The first participant to be transplanted will not be randomly ordered but will be selected as the most suitable participant to be transplanted first.

The intervention is surgical implantation of 11-22 million foetal striatal cells in the striatum of participants with manifest Huntington’s Disease. The transplant surgery is followed by at least 12 months immunosuppression therapy.

Intervention Type
Procedure/Surgery

Primary outcome measure
Safety will be assessed at 4 weeks by the trial steering committee, who will review pre and post-operative 3T MRI scans, surgical records from the transplant procedure, medical records from the participants inpatient stay and any case report forms completed during the postoperative inpatient stay, including blood results, vital signs and any serious adverse events reported. Defined by:
1. The incidence of significant additional, permanent neurological deficits
2. The incidence of a clinically significant intracranial haemorrhage
3. The incidence of clinically significant intracranial infection

Secondary outcome measures
1. Feasibility and acceptability of clinical trial processes as determined by:
1.1. Recruitment rates assessed using screening and recruitment logs at the end of the trial
1.2. Retention of participants assessed from any participant withdrawal forms at the end of the trial
1.3. Participant and carer experiences elicited from the pre- and post-operative interviews
2. Fidelity of neurosurgery is measured using the evaluation of MRI and PET scanning to measure the successful delivery of cells and accurate neurosurgical graft placement at 1 month post-operatively (3T MRI) and 12 months postoperatively (PET)
3. Long-term (12 months) safety of transplantation is measured using MRI and PET scans to assess the growth profile of the graft and the development of clinically significant inflammatory or immune reactions as assessed by clinician and advisory groups at 12 months
4. Research, treatment and immunosuppression costs will be documented across the duration of

the trial using a mix of standard unit costs and detailed research costs for all research procedures
5. Development of fidelity markers through analysis of video-data capture of the surgery and graft survival over 1 year as determined by structural MRI/PET

Overall study start date
01/10/2017

Completion date
28/02/2023

Eligibility

Key inclusion criteria
1. Confirmed diagnosis of HD through genetic testing (CAG≥39)
2. ≥18 years of age
3. Stage I or II disease (assessed using the Total Functional Capacity Scale with a score equal to 12 or below) and diagnosed as having motor onset
4. Participant is ambulatory

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
18-30 participants for the comparator cohort, from which 5 will be selected for transplant surgery

Total final enrolment
22

Key exclusion criteria
1. People without capacity to consent to the trial
2. Any ongoing major psychiatric disorder that would preclude the ability to take part in functional assessments and the ability to give informed consent
3. Lack of carer, significant other or family member to support attendance at regular assessments.

Exclusion criteria for the surgical intervention are:
4. Participants on any long-term anticoagulant medication (to include aspirin, warfarin, clexane)
5. Any significant medical condition that would compromise the safety of anaesthesia and/ or surgery including; Q-T interval prolongation, torsades des pointes or ventricular arrhythmia
6. Participants not deemed to be suitable for transplant surgery (e.g. inadequate striatal volume

on MRI)
7. Pregnancy and breastfeeding
Added 31/07/2019: 8. Previous immunizing event such as blood transfusion or previous transplant
9. Contraindications to 3T MRI (such as a fitted pacemaker)
10. Contraindications to PET
11. Any contraindication to immunosuppressive therapy
12. Positive blood tests for; Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), active Cytomegalovirus (CMV)infection, active Toxoplasma Gondii (Toxo G), Human T-cell lymphotropic virus type 1 (HTLV 1), serology for active treponema pallidum
13. Women of childbearing potential and male participants with partners of childbearing potential who will not commit to the prevention of and active monitoring for pregnancy by using a highly effective form of contraception and undertaking regular pregnancy tests whilst enrolled in the study/or on immunosuppressant

Date of first enrolment
10/08/2018

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
University Hospital Wales
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Heath Park
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Study participating centre
Cardiff Huntington's Disease Centre
Hadyn Ellis Building
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Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Research council

Funder Name
Health and Care Research Wales

Alternative Name(s)
Health & Care Research Wales, Ymchwil Iechyd a Gofal Cymru, Health Care Research Wales, HCRW

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The protocol will be published. The trialists plan to publish the results of this study in the medical and scientific literature. A summary of the results will also be made available on the Cardiff University and BRAIN (Brain Research and intracranial Neurotherapeutics) Unit websites.

Intention to publish date
01/09/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Centre For Trials Research (ctrdatasamplerequests@cardiff.ac.uk)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	19/01/2021	08/02/2021	Yes	No
Other unpublished results		20/06/2024	20/06/2024	No	No
Statistical Analysis Plan	version 1.0	10/03/2023	20/06/2024	No	No