TRIAL DESIGNS FOR DELIVERY OF NOVEL THERAPIES IN NEURODEGENERATION: THE TRIDENT TRIAL

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BACKGROUND

Huntington's Disease is a progressive, inherited neurological disorder characterised by a triad of motor, cognitive and psychiatric symptoms for which no disease-modifying therapies that slow or halt the progression of the disease exist. It is the most common monogenetic neurodegenerative condition of the central nervous system (CNS), and is a powerful paradigm for understanding and treating neurodegeneration [1]. The specific loss of striatal neurons makes HD suitable for cell replacement therapy (CRT), where donor cells replace those lost as part of the disease. It is expected that the principles underlying effective CRT in HD will be applicable to other neurodegenerative conditions such as Parkinson's disease (PD).

We know from some small studies of CRT in PD and HD that CRT is safe [2,3]. However, these studies were small and the data does not yet support a larger efficacy trial of CRT. Early studies transplanting small numbers (due to concerns of tissue overgrowth) of dissociated foetal cells showed only small graft deposits with an absence of functional improvement. Cell overgrowth was not found to be a problem and so investigation of transplantation of greater cell numbers is warranted.

Evaluation of complex interventions such as neural transplantation is challenging and requires a different approach to that used for drugs. Direct delivery of cells to the brain is complex, presenting several constraints including :

- the need to proceed with very small cohorts for safety reasons (leading to a series of iterative pilot studies prior to larger scale randomised controlled trials to determine efficacy)
- the issue that functional outcomes are a combined effect of the cell therapy and the effectiveness of the delivery device
- the challenge of reducing study bias (due to the ethical constraints surrounding sham surgery and blinding)
- the limited availability of foetal tissue requiring that transplants take place sequentially at approximately monthly intervals
- the lag period (months) before foetal cells start producing functional benefit

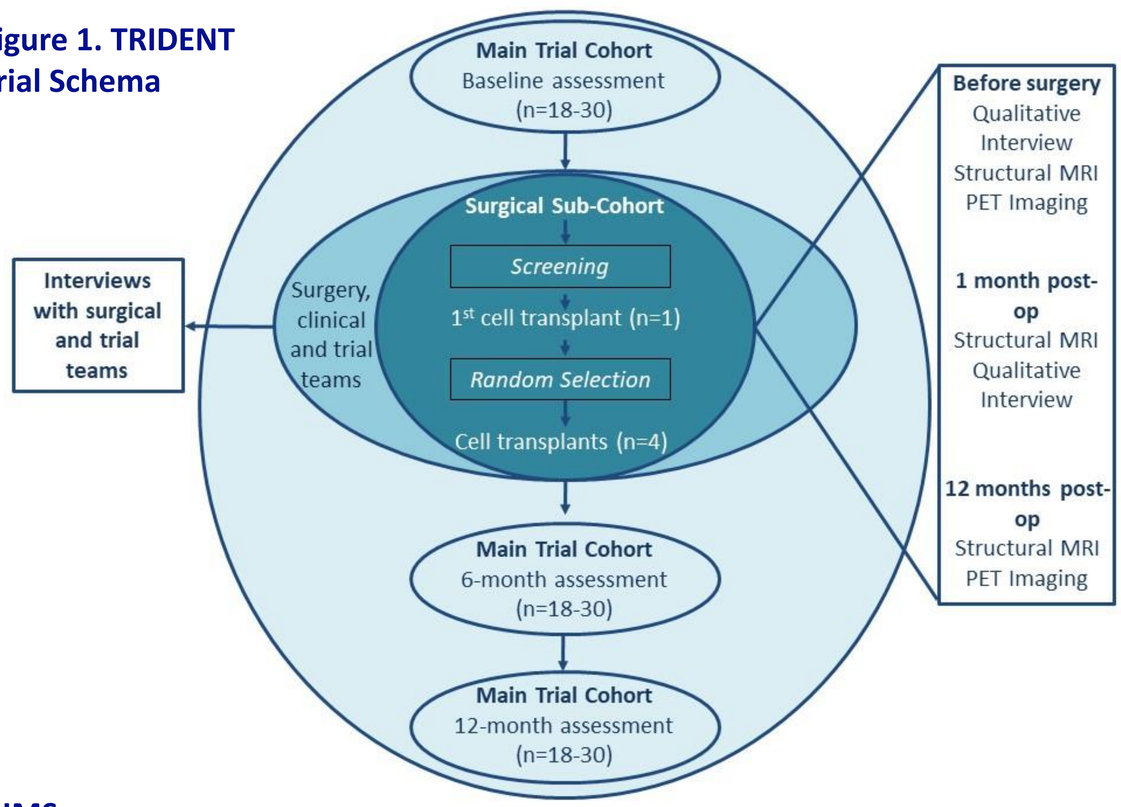
The TRIDENT trial has been designed with these aspects in mind.

STUDY DESIGN

TRIDENT is a Phase I, Single centre, Trial within Cohort (TWiC) [4] transplantation study designed to assess safety and feasibility of transplanting foetal cells into the striatum of people with HD.

We aim to recruit 18-30 people into the TRIDENT observational cohort, from which a sub-set of participants will be assessed for suitability for surgery. Those deemed suitable for surgery will be randomly selected to receive the cell transplant (5 in total). The first participant will be hand-picked by a multi-disciplinary team as the most suitable candidate for surgery.

Figure 1. TRIDENT Trial Schema



AIMS

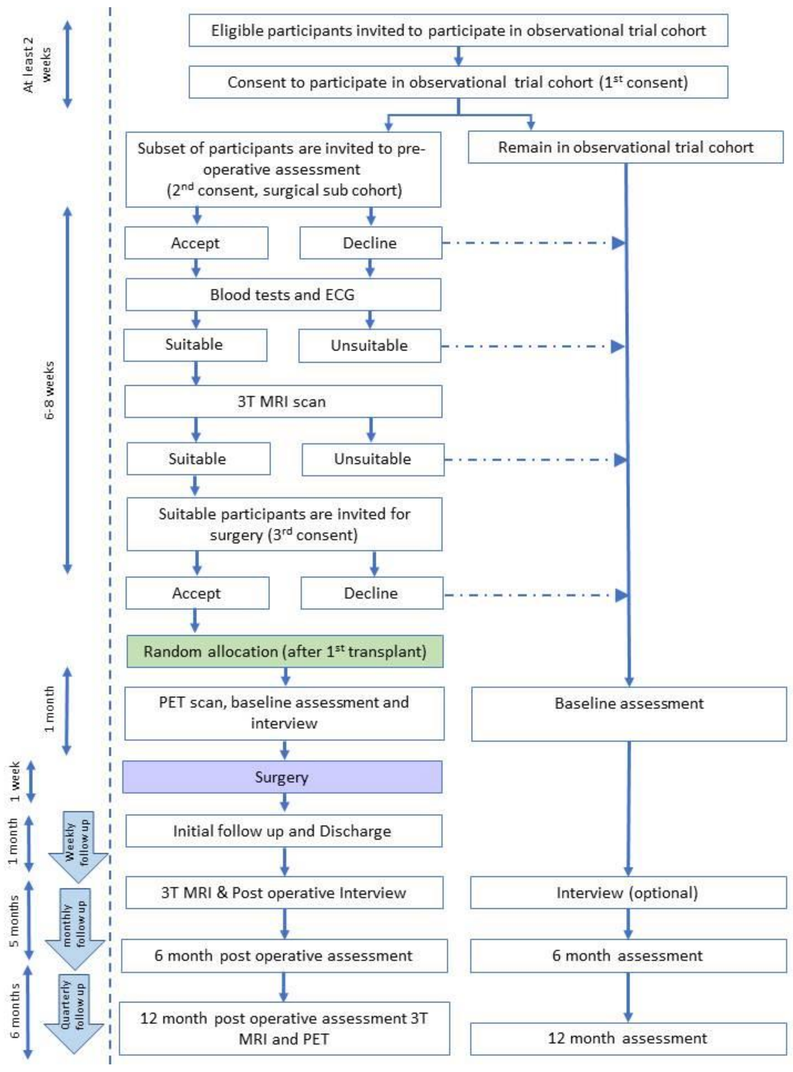
Primary objective

- The primary objective of this study is to evaluate the safety of transplantation surgery using increased numbers of human foetal ganglionic eminence cells for the treatment of patients with HD.

Secondary objectives

- Define framework for assessing the fidelity of cell transplantation devices and procedures
- Explore effect estimates to inform sample size calculations for future trials
- Evaluate feasibility of health economic evaluation for future trials
- Explore attitudes and understanding, feasibility and acceptability of this process in HD patients and their supporters/carers, trial deliverers, and health professionals
- Capture the social experience of patients and family members/carers over the entire lifecycle of the cell transplantation process, including the time period before, during and after the event
- Identify the support needs of patients undergoing neural transplantation and their family members/carers

FIGURE 2. TRIDENT PARTICIPANT FLOW



Pre-Operative Assessments

To assess suitability for surgery participants will undergo

- Blood tests (biochemistry, haematology and virology)
- ECG
- 3T MRI (to ensure suitable striatal volume for transplant)

Functional Assessments

Conducted at baseline, 6 months and 12 months in all participants

Safety Assessments

Participant will be monitored regularly following surgery with a total of 12 follow-up visits over 12 months following discharge

Imaging Assessments

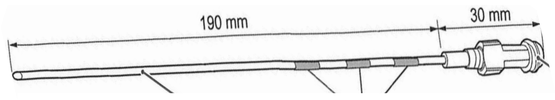
These will be performed to look at;

1) Physical placement of graft (3T MRI)
2) Functional integration of graft (18-Fallypride PET)

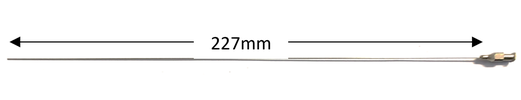
SURGICAL INTERVENTION

The current method for delivering cells to the transplant region of the brain is via an injection based delivery system using a catheter/needle whereby the cells are deposited in beads along a preformed track as the catheter/needle is withdrawn [5]. In TRIDENT we will be using a CE marked injection device, with an in house manufactured needle coupled with a luer locked syringe for loading and injecting cells. The introduction on the inner cannula is designed to reduce the total volume of cell suspension required and reflux at the injection site.

Outer Cannula



Inner Cannula



Up to six injection tracts will be created in the striatum with a total of 5 deposits per tract. The density of cell suspension will be increased with subsequent surgeries from a total of 12 million cells in the first surgery to 22 million cells in the last surgery. All surgeries will be video recorded.

Following the transplant surgery, participants will commence a 12 month regime of immunosuppression.

PRIMARY OUTCOME

The primary outcome of TRIDENT is safety. The independent trial steering committee (TSC) will review safety data (adverse event reports, laboratory reports and 3T MR images) following the 4 week primary endpoint. Subsequent surgeries will only be performed on the authority of the TSC.

ANALYSIS APPROACH

Quantitative Data

TRIDENT is a feasibility study and as such no formal statistical hypothesis testing will be carried out. Exploratory evaluation of outcomes will be carried out to explore plausible trial designs for subsequent randomised controlled trials aimed at evaluating efficacy of CRT.

Qualitative Data

Participant interviews will be analysed using a framework approach to incorporate thematic and case analysis.

Video data of the surgery will be analysed to identify fidelity markers which will involve documenting and describing movements, instruments and actions to provide a stepwise account of the procedure.

CONCLUSIONS

This study will be pivotal for establishing the principles for conducting the first wave of therapies that have a realistic chance of being disease-modifying in neurodegeneration. This trial will test a potentially efficacious dose of primary foetal cells, but will also pave the way for the next generation of donor cells for HD, which will be striatal neurons differentiated from human pluripotent precursors (such as embryonic stem cells) [6].

References:

1) Leegwater-Kim J, Cha J-HJ: The paradigm of Huntington's disease: Therapeutic opportunities in neurodegeneration. *NeuroRX* 2004, 1:128–138. **2)** Petit GH, Olsson TT, Brundin P: Review: The future of cell therapies and brain repair: Parkinson's disease leads the way. *Neuropathol Appl Neurobiol* 2014, 40:60–7 **3)** Rosser AE, Barker RA, Harrower T, Watts C, Farrington M, Ho AK, Burnstein RM, Menon DK, Gillard JH, Pickard J, Dunnett SB, NEST-UK: Unilateral transplantation of human primary fetal tissue in four patients with Huntington's disease: NEST-UK safety report ISRCTN no 36485475. *J Neurol Neurosurg Psychiatry* 2002, 73:678–85. **4)** Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ*. 2010 Mar 19;340:c1066. **5)** Torres EM, Trigano M, Dunnett TB: Translation of Cell Therapies to the Clinic: Characteristics of Cell Suspensions in Large-Diameter Injection Cannulae. *Cell Transplant* 2015, 24:737–749. **6)** Rosser A, Svendsen CN: Stem cells for cell replacement therapy: A therapeutic strategy for HD? *Mov Disord* 2014, 29:1446–1454.