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: Basic Results Summary

Project Summary

The overarching aim of TRIDENT was to evaluate CRT in HD, with a view to developing innovative approaches for minimising the impact of design constraints and maximising efficiency for future trials of CRT and similar therapies in HD and related disorders. Specifically, TRIDENT aimed to evaluate the safety of foetal cell transplantation of people with HD in greater numbers than had previously been trialled using a Trial Within a Cohort (TWiC) design. Participants were recruited to an observational cohort, completing longitudinal clinical and functional assessments. Participants potentially suitable for surgery were then approached about undergoing further assessments to assess suitability to receive CRT. As this involves the use of allogenic cells, we planned to immunosuppress transplanted participants for at least a year to give the cell graft the best chance of survival, therefore suitability to receive long-term immunosuppression and a long general anaesthetic was vital to establish. We planned to recruit 18-30 people to the observational cohort and transplant up to 5 suitable participants. We also planned a comprehensive process evaluation to gain a better understanding of how both participants and researchers experienced the trial.

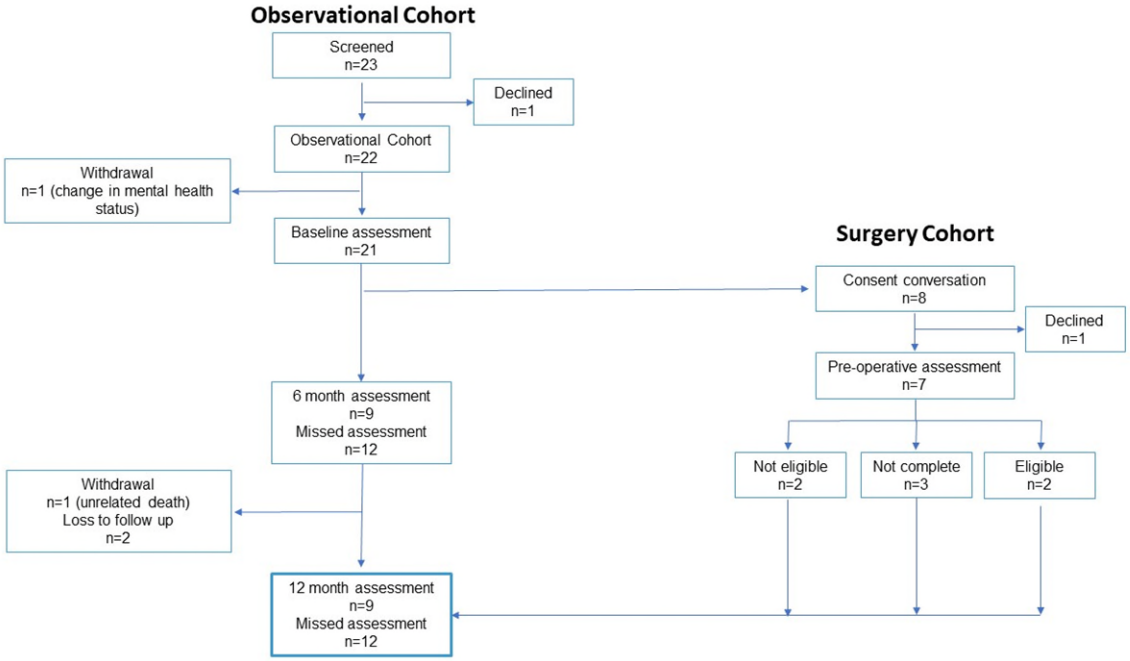
We recruited a total of 22 participants into the observational cohort. Of these participants, 8 had conversations about undergoing pre-surgical assessment, one participant declined, remaining in the observational cohort. Five participants started the screening process, in the time period of the trial, four participants completed assessment, with two participants deemed eligible to undergo CRT. The reasons for ineligibility included insufficient striatal volume and low-grade viral infection that is not compatible with the use of long-term immunosuppression.

In total, we scheduled 10 surgeries across three different surgical candidates, but were unsuccessful in completing any transplants. Cancellations occurred due to; Covid-19, concerns over participant safety (medical), critical clinical need for surgical theatres for emergency healthcare provision and most frequently the lack of viable foetal tissue.

We were able to conduct a part of the process evaluation, with 17 interviews completed, including 8 people across the trial team and healthcare professionals

involved in the trial, 3 participants in the surgical cohort and 2 participant supporters. Data gathered from these interviews showed that the TWiC design is acceptable to both participants and researchers and suitable for investigating CRT in HD.

PARTICIPANT FLOW



BASELINE CHARACTERISTICS

Baseline demographics of the whole TRIDENT cohort are summarised in Table 1. Ethnicity was mostly White; a detailed breakdown is not provided due to risk of identification of non-White participants.

Table 1. Demographic characteristic of TRIDENT participants at baseline

	Total (N=22)
Age, **median [IQR]**	51.90 [47.83, 59.32]
CAG‡, **median [IQR]**	43 [42, 44]
Gender, **n (%)**	
Female	5 (22.73%)
Male	17 (77.27%)

‡ CAG = the trinucleotide repeat length that denotes if the gene copy is pathogenic

OUTCOME MEASURES

Primary Outcome

Within this study we were unable to transplant a participant. Therefore, it was not possible to establish the primary outcome of safety.

Secondary Outcomes

Secondary outcomes were assessed as follows:

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

Of the 23 participants approached to take part in the observational cohort, only 1 participant declined. Further, for inclusion into the surgical cohort, 1 out of 8 participants approached declined further screening. We conclude that recruitment of participants to a trial of CRT in HD is feasible and acceptable to participants.

1.2. Retention of participants assessed from any participant withdrawal forms at the end of the trial

From the 22 participants that completed baseline assessment in the observational cohort, there was one withdrawal and 2 loss to follow-up. The withdrawal was the unrelated death of a participant and the loss to follow up were largely due to scheduling issues precipitated by Covid-19 restrictions. Therefore, we conclude that retention of participants in the trial was feasible and acceptable to participants.

1.3. Participant and carer experiences elicited from the pre- and post-operative interviews

Qualitative interviews with 3 participants in the surgical sub cohort and 2 participant support partners, the trial design and procedures were regarded as acceptable. We recognise our inability to capture the full experience of participants subject to CRT surgery and follow-up procedures is a limitation of the study.

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)

It was not possible to assess this outcome given that CRT surgery did not take place.

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.

It was not possible to assess this outcome given that CRT surgery did not take place.

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

It was not possible to assess this outcome given that CRT surgery did not take place.

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

It was not possible to assess this outcome given that CRT surgery did not take place.

ADVERSE EVENTS

There were no reported adverse events in this study. One participant in the observational cohort was withdrawn due to death. This was not related to inclusion in the study.