

Research Report

Which Patients with Parkinson's Disease Participate in Clinical Trials? One Centre's Experiences with a New Cell Based Therapy Trial (TRANSEURO)

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Abstract.

Background: There is currently little evidence regarding the selection of patients for clinical trials in Parkinson's Disease (PD), especially those involving experimental therapies delivered using invasive techniques.

Objective: Understanding which patients are recruited will increase awareness of issues regarding parity of access to clinical trials and have an impact on the wider applicability of results, as well as provoking discussion regarding future improvements in the enrolment process.

Methods: TRANSEURO is an open label multi-centre surgical transplant trial which seeks to investigate the feasibility and efficacy of grafts of human foetal ventral mesencephalic tissue in patients with PD. The Cambridge based cohort of TRANSEURO participants ($n=26$) was compared with a population representative sample of patients with PD eligible for, but not enrolled in, TRANSEURO ($n=33$). Measurements were available in both populations for demographics, neuropsychological tests, tests of motor and non-motor function and quality of life.

Results: Patients enrolled in TRANSEURO were younger and had significantly more years of education with higher scores on the revised Addenbrooke's Cognitive Examination. This difference was accounted for by memory, fluency and visuospatial subscores. There were significant differences in the Movement Disorder Society Unified PD Rating Scale scores with better motor function but more motor complications in the enrolled group. Those enrolled were also more likely to be under the care of the principal investigator of the study.

Conclusions: In this trial our population was younger and more educated with higher cognitive scores and better motor function than eligible PD patients not enrolled. This raises interesting questions about the parity of access to clinical trials of this nature amongst patients with PD.

Keywords: Parkinson disease, clinical trials as topic, patient participation, neurodegenerative diseases, cell- and tissue-based therapy

INTRODUCTION

It is crucial to be aware of how patients are being recruited into trials, especially those investigating invasive experimental therapies. This not only helps to negate sampling bias, thus improving the widespread applicability of the results, but also raises awareness of

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poor parity of access to clinical research across patient populations.

There has been little research into this important area in patients with neurological and neurodegenerative diseases, and that which has been done has tended to compare patients who enrolled in the study to those who declined. For example a previous study in patients with Parkinson's Disease (PD) investigated differences between patients enrolling in and declining a sham surgery controlled trial and found that those declining were significantly more educated [1]. However it is also important to compare patients enrolled in a trial to those eligible to be enrolled but who were never approached. This has been done in Alzheimer's Disease and it was found that those who participated in the clinical trials were younger and more highly educated [2].

Historically more research in this area has been conducted in oncology with evidence to suggest that those patients who are older with lower income and less years of education are less likely to enrol in clinical trials [3]. In addition it has been shown that a patient's physician could influence their enrolment, with physicians that spend most of their time in clinical, as opposed to academic, practice being less likely to refer patients to oncology clinical trials [4].

In Cambridge, UK we have a unique opportunity to investigate trial participation by comparing those enrolled in a new clinical trial of a cell based therapy (TRANSEURO) to those in matched incident population representative cohorts being followed as part of natural history studies.

TRANSEURO is a multi-centre European collaborative trial of foetal ventral mesencephalic tissue transplantation for PD. The criteria for entry to the trial define a group of patients for whom the evidence to date would suggest that they will most likely benefit from the therapy with the least risk of side effects (see box 1 for criteria and review by Petit et al. [5]). Despite the tight definition of patients eligible for our trial we hypothesised that a geographically matched population of patients with PD, who fit the clinical criteria for inclusion in the TRANSEURO trial but had not been approached, would be significantly older and less educated than those patients enrolled.

MATERIALS AND METHODS

TRANSEURO has two arms, an observational cohort and an open label surgical trial. The observational cohort consists of 150 patients and the surgical

Box 1
TRANSEURO inclusion/exclusion criteria

Inclusion:	Exclusion:
<ul style="list-style-type: none"> • PD defined by Queen's Square Brain Bank Criteria • Disease Duration ≥ 2 years and ≤ 11 years • Age ≥ 30 years and ≤ 68 years at time of grafting • Hoehn & Yahr ≤ 2.5 on medication • Standard PD medication without significant dyskinesias • Right handed 	<ul style="list-style-type: none"> • MMSE score < 26 • Unable to copy interlocking pentagons and/ or semantic fluency < 20 animals in 90 secs • Ongoing major medical/psychiatric disorder • Treatment with cholinesterase inhibitors/ neuroleptics • Previous neurosurgery/cell therapy/organ transplantation • Contraindications to immunosuppression • Anticoagulant Therapy

cohort consists of 40 patients drawn from the observational group of whom 20 patients will be randomised to surgery and PET imaging and 20 to follow up and PET imaging. Patients enrolled into the TRANSEURO study were initially recruited into the observational arm of the study with the knowledge they might be selected for the surgical arm but with no obligation to participate in this. Recruitment took place by patient self-referral; after being informed of the study by their neurologist; or hearing about it from other sources such as publicity surrounding the trial and a trial website (www.transeuro.org.uk). No search was performed of existing databases to ascertain all potentially eligible patients to offer them an opportunity to take part. No records were kept of those patients with whom the study was discussed but not pursued.

We compared those patients enrolled in the observational TRANSEURO cohort resident locally in Cambridgeshire and surrounding counties ($n = 26$) to a group of PD patients who were geographically matched and enrolled into a population based cohort study at our centre. Furthermore, the PD control cohort was matched against the TRANSEURO eligibility criteria (see box 1), had been assessed as having idiopathic PD according to the Queen's Square Brain Bank Criteria and should have been seen within 18 months of the start and end date of recruitment (December 2010 to September 2012) to ensure that the data on which they were judged to be eligible would be accurate. After these criteria had been applied, and after searching all available local research databases, a total of 33 patients were deemed eligible controls. Of those included, 28 were from the Parkinsonism-Incidence and Cognitive Heterogeneity in Cambridgeshire (PICNICS) database (an incident cohort of patients from the county of Cambridgeshire), 2 from the CamPaIGN cohort (a previous incident cohort study, the details of which have been

Table 1
Comparison of subjects enrolled in TRANSEURO vs. PD control subjects eligible but not enrolled

		Control PD (n = 33)	TRANSEURO (n = 26)	p value
Gender (% male)	% male	57.6	73.1	0.278
Age (years)	Mean (SD)	59.8 (6.78)	55.7 (6.11)	0.019*
PD duration (years)	Mean (SD)	3.72 (1.89)	4.05 (1.91)	0.500
Education (years)	Mean (SD)	13.2 (2.31)	16.5 (3.70)	0.003**
ACE-R (score out of 100)	Mean (SD)	91.7 (4.33)	96.2 (3.48)	0.000**
MMSE (score out of 30)	Mean (SD)	29.1 (0.93)	29.3 (0.78)	0.517
Semantic fluency (animals in 90 secs)	Mean (SD)	23.1 (5.00)	28.7 (6.25)	0.001**
Digit span total	Mean (SD)	11.8 (2.00)	14.4 (4.44)	0.000**
Levodopa equivalent dose (mg)	Mean (SD)	517 (455)	531 (355)	0.902
Dopamine agonist therapy	% on DA	68.8	57.7	0.275
Beck Depression Inventory	Mean (SD)	6.93 (6.04)	7.55 (4.08)	0.698
Apathy Evaluation Scale	Mean (SD)	28.6 (8.01)	27.0 (6.32)	0.467
PDQ-39	Mean (SD)	24.6 (18.4)	26.5 (18.8)	0.722
UPDRS total score	Mean (SD)	44.6 (17.7)	41.8 (16.9)	0.169

*denotes $p < 0.05$, **denotes $p < 0.01$.

published, see [6]) and 3 from the local Parkinson's Disease Research Clinic (a clinic which captured those patients not referred at a time when incident cohorts were being recruited or when their disease was further advanced).

Measurements were available in both populations for demographics (age, sex, duration of disease, years of education, consultant physician) as well as neuropsychological tests (Addenbrooke's Cognitive Examination-Revised (ACE-R), digit span, Beck Depression Inventory (BDI) and Apathy evaluation scale (AES)), tests of motor and non-motor function (Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS)) and of quality of life (Parkinson's Disease Questionnaire-39 (PDQ-39)).

Statistical analysis was performed using SPSS v.21 [7]. One way ANOVA was used to compare means for continuous data and chi-squared tests for categorical data with correlation performed using the Pearson rank test. In addition logistic regression analysis was performed to control for age and education when investigating cognitive status through total ACE-R score.

All patient data was collected as part of studies approved by the Cambridge Local Research Ethics Committee with informed consent given prior to participation and performed according to the Declaration of Helsinki. Studies included are TRANSEURO observational (10/H0304/77), PICNICS (07/H0302/138), CamPaIGN (08/H0306/26) and PD Research Clinics (08/H0306/26).

RESULTS

Patients enrolled in TRANSEURO were significantly younger than matched PD controls who were

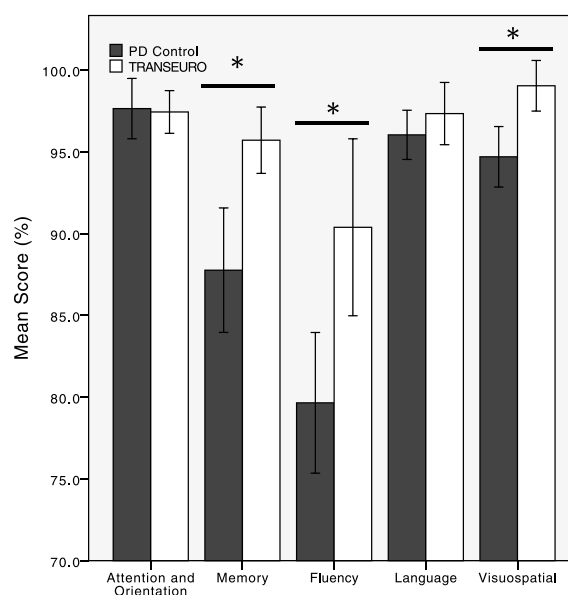


Fig. 1. Difference in percentage score on ACE-R subdomains between PD control and TRANSEURO participants. Error bars represent 95% confidence intervals, *indicates $p < 0.01$.

eligible but not enrolled with a higher percentage of male participants, though this was not significant (see Table 1).

Participants had significantly more years of education, which correlated significantly with younger age ($p = 0.023$). Participants also had higher scores on the ACE-R; this difference was accounted for by memory, fluency and visuospatial subscores (see Fig. 1). ACE-R scores were not significantly correlated with age and years of education except in the fluency subdomain. To confirm that the difference in total ACE-R score was not due to the difference in age and education,

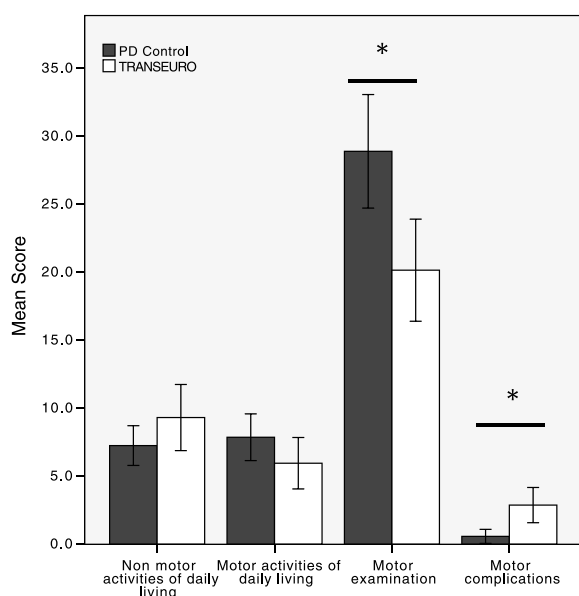


Fig. 2. Difference in UPDRS subdomain scores between TRANSEURO participants and PD controls. Error bars represent 95% confidence intervals, *indicates $p < 0.01$.

a logistic regression analysis was performed against the total sample of participants and non-participants. It showed that total ACE-R score remained significant ($p = 0.002$) even when controlling for age and education. Digit span and semantic fluency were also significantly different between groups but these were both significantly correlated with years of education and total ACE-R score.

Whilst there was no significant difference in total UPDRS score, there were significant differences in the motor examination and motor complication subscores of the UPDRS *on* medication. Enrolled subjects had objectively better measures of motor function but reported more motor complications (see Fig. 2).

Patients enrolled in the TRANSEURO trial were also much more likely to have a consultant physician who was involved in the trial than those not enrolled. Of TRANSEURO participants, 50% had the principal investigator of the study as their consultant neurologist as opposed to only 3% of PD control patients. In other words, of the eligible patients captured in this study and seen by the principal investigator, 93% were enrolled into TRANSEURO whereas only 31% of eligible patients seen by other clinicians were enrolled.

There were no significant differences in the analysis of non-motor subscores of the UPDRS or PDQ-39 subdomains, nor in medication as assessed using levodopa equivalent dose or use of a dopamine agonist.

Mean BDI and AES scores did not differ significantly between TRANSEURO cohort and PD controls, although as expected they were significantly correlated with each other. For those patients with available AES scores, only 2 of the 22 (9.09%) TRANSEURO patients had scores in the pathological range with an AES of ≥ 38 whereas 5 of 25 (20%) patients from the control PD group did, although this difference was not statistically significant ($p = 0.265$).

DISCUSSION

This study has shown that the patients enrolled into a new cell based therapy trial for PD (TRANSEURO) in Cambridge are not representative of the relevant PD population. They are younger with more years of education and better cognitive status. They are also more likely to have been a patient of the study investigator and have good motor control of their symptoms but with more reported motor complications.

There appears therefore to be sampling bias in our population introduced as a result of patient self-selection and clinician referral, which is not unexpected. However this is an important new finding because at the end of the trial we will need to highlight the biased nature of our cohort and thus its relevance to the wider population of patients with PD, even those who are in the demographic defined by the trial.

Indeed this study raises much wider and more interesting questions regarding clinical trial participation in patients with PD and other neurodegenerative disorders. One might argue that in the early stages of a new therapeutic trial it is of little importance how patients are recruited. Indeed some may even contend that it benefits the trial to have the involvement of more educated patients who better understand the nature and outcomes of the trial and might have more realistic expectations of anticipated improvements. However there is an important counter argument that those who are selected for the trial should be representative of the real population and that access to trials should not be discriminatory on demographic criteria falling outside of the trial inclusion and exclusion criteria.

In 2012 the National Institute for Health Research Clinical Research Network identified that 82% of patients in the UK thought it important for patients within the National Health Service to be offered the opportunity to be involved in research and that one of the key findings was that 'patients rely upon their doctors to 'open the door' to opportunities to take part in clinical research' [8]. Indeed physicians are often

described as ‘gatekeepers’ to clinical trials as it is their initial decision whether to recruit a patient to a trial. It is clear though that despite being part of the recruitment process, clinicians do not enrol all eligible patients into trials. For example 79% of oncologists responding to a UK survey said that they would enrol less than 50% of eligible subjects into trials [9].

The question that follows is how do physicians decide which patients to enrol? In terms of physician attitudes towards patient suitability for trials, focus groups with Clinical Research Associates in the United States identified many factors including logistics, physician beliefs regarding patient preferences and the perceived ability of patients to retain trial information [10]. In the UK, it has been reported that 33% of surveyed oncologists identified intelligence level as the major factor helping communication about trials [9]. In our study both higher educational level and better cognitive status were seen in those patients enrolled in TRANSEURO compared to eligible PD controls, despite all controls meeting the same cognitive criteria applied to the TRANSEURO population (see box 1).

Not only are educated patients more likely to be offered enrolment into clinical trials by physicians, they are also more empowered to request change and participate in decision making surrounding their care [11, 12]. In our cohort this may be a key factor in explaining why the TRANSEURO cohort have better UPDRS scores *on* medication (a reflection of their therapeutic optimisation), as patients with higher levels of education have been shown to have greater expectations for treatment success with a correlation between lowered expectations of success and worse UPDRS scores [13].

Another factor affecting enrolment is that physicians who spend more time in an academic setting are more likely to recruit their patients into clinical trials [4]. This selection bias is reflected here in the high percentage of patients recruited by the academic principal investigator in TRANSEURO, although of course these patients may have elected to see this physician in the first place for the purpose of being enrolled into trials of this type. There may have been additional barriers to other physicians recruiting patients into TRANSEURO including ethical dilemmas related to the use of foetal tissue or lack of knowledge regarding the trial as well as lack of time in the clinic which is often identified as a key factor preventing clinicians from enrolling patients into trials [14].

There is another important angle with regards to the disparity in cognitive status between the two groups. Although somewhat counterintuitive, it has

been shown previously that PD patients with preserved cognition are more prone to risky behaviours as measured by the Iowa Gambling Task [15]. This raises the possibility that in the enrolled group high levels of cognitive function may be leading them to seek out trials with high risk procedures such as TRANSEURO. These are aspects that we plan to explore in the future looking specifically at executive function and impulse control disorders within this population.

The main limitation to this study is the difficulty in obtaining a truly population representative sample of patients for comparison as PD controls. Most were enrolled in population based incident cohorts, which whilst being highly representative of PD in the community nevertheless fails to capture every patient. Another significant limitation was the lack of a record of patients who had been offered the opportunity to participate but had declined. In future trials it will be important to maintain these records to allow for more detailed analysis of factors affecting enrolment.

Overall this study has shown that there are many barriers to clinical trial participation (at least with regard to a new cell based treatment) among patients with PD. It is only by identifying and reporting those barriers that we will be in a collective position to overcome them and move forward to improve the robustness of recruitment methods and ensure parity of access to clinical trials in the future. Immediate ways to improve this include wider dissemination of information about clinical trials locally and the education of physicians to identify factors that have previously caused potential discrimination in access to trials of this type.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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