

## The Cure Parkinson's Trust's response to Sham Surgery Survey of Neurologists in the context of NIH Meeting 30<sup>th</sup> June – 1<sup>st</sup> July 2010

The Cure Parkinson's Trust believes that our survey clearly demonstrates a wide diversity of opinions, including many excellent ideas, but with no consensus amongst leading neurologists on the central issues surrounding the use of sham surgery involving people with Parkinson's.

Accordingly, we strongly support the NIH's initiative to conduct an open discussion forum to consider scientific and ethical opinions from all stakeholders.

We believe there is a need for clear guidelines to be established which set out the following:

- The criteria upon which different levels of sham surgery are justifiable and warranted.
- Procedural aspects of clinical practice when conducting sham surgery.
- Guidelines for provision of appropriate information to patients involved in clinical trials with a sham surgery arm from enrolment through to the end of the study.

When considering the most appropriate criteria which comprise these guidelines, account should be taken of opinions from all stakeholders.

Clinical trials involving surgical procedures must balance inherent risks to the individual volunteers against the true value that statistical authenticity, with or without sham surgery, can provide, and how that relates to the likely therapeutic impact that each prospective proposed new surgical trial offers.

Furthermore, the justification for sham surgery must be put into the context of the consistency, reliability and accuracy of other means of outcome measurement, and the impact of any newly introduced effective biomarker(s) for PD. Therefore, we believe choices surrounding the utility and potential for adoption of sham surgery in any new surgical trial should be considered carefully in the light of these newly established guidelines within this evolving framework.

<p><b>Brief description of the Cure Parkinsons Trust and reason for survey</b></p>	<p>The Cure Parkinson’s Trust (CPT) was founded in 2005 by four people with Parkinson’s to direct funds into research towards a cure. The voice of the patient is central to the work of the charity.</p> <p>As part of its work, CPT has identified that the inadequacies and inaccuracies inherent within the current system of conducting clinical trials and in particular outcome measurement in Parkinson’s, are contributing to the slow progress being made in this arena.</p> <p>With a number of promising new surgical approaches in the pipeline, it is clear there is a need for an open debate on the issues surrounding sham surgery and its context in the wider issue of establishing accurate outcome measurement in Parkinson’s trials.</p> <p>CPT believes it is critical that people with Parkinson’s are sufficiently informed and are represented in this debate and continue to be consulted in any further initiatives on this emotive issue. The first stage of this process was to circulate a questionnaire to neurologists to ascertain their views about sham surgery.</p>
<p><b>Details regarding survey:</b></p>	
<p><i><b>Date survey sent</b></i></p>	<p>In December 2009, a preliminary questionnaire was sent as a draft to a small number of neurologists and neurosurgeons - this process led to the construction of the revised, final version of the questionnaire that was sent out on May 31st - June 1st 2010.</p>
<p><i><b>Number of individuals the survey was sent to</b></i></p>	<p>71</p>
<p><i><b>Criteria for Selecting Participants</b></i></p>	<p>Senior neurologists, well known on an international stage, with extensive experience of managing patients with Parkinsons Disease and who each also have a strong record of clinical research in PD published in leading journals</p>
<p><b>Who was the survey sent to (number):</b></p>	
<p><i><b>Neurologists</b></i></p>	<p>71</p>
<p><i><b>Other</b></i></p>	
<p><b>Location of recipients (number):</b></p>	
<p><i><b>UK</b></i></p>	<p>40</p>
<p><i><b>Europe</b></i></p>	<p>26</p>
<p><i><b>US</b></i></p>	<p>5</p>
<p><i><b>Other</b></i></p>	
<p><b>Respondents (number and percent)</b></p>	<p>30 (42%)</p>
<p><b>Location of respondents (number and percent)</b></p>	
<p><i><b>UK</b></i></p>	<p>22 (73% of 30)</p>
<p><i><b>Europe</b></i></p>	<p>7 (23% of 30)</p>
<p><i><b>US</b></i></p>	<p>1 (3% of 30)</p>
<p><i><b>Other</b></i></p>	<p>0</p>

Dear Participant,

The Cure Parkinsons Trust has been asked to explore issues surrounding the use of sham surgery in PD surgical trials. This brief 1 page questionnaire asks your views on current options, and on important future possibilities.

This questionnaire is being sent worldwide to leading neurosurgeons to see if we can find a way forward by logical consensus.

The results of this global questionnaire will be shared with the upcoming NIH conference on sham surgery, although your own specific responses will be kept absolutely confidential.

I would cherish to hear your responses, and any other helpful comments (however extensive you wish to write on how best to proceed), that you may wish to share about this important topic - an awkward conflict between ethics and scientific accuracy.

Kind Regards,

Richard Wyse  
Director of Research and Development  
The Cure Parkinsons Trust



## Cure Parkinsons Trust – Sham Surgery Questionnaire

### Invasive options for sham surgery in current clinical trials involving patients with Parkinsons Disease

**Is it possible to reduce surgical control numbers by a more thorough & accurate pairing of patients?** (26 respondents)

YES	NO	PROBABLY	UNSURE
65%	23%	4%	8%

#### **Additional comments :**

Neurologist 4

In most studies the lowest possible number for sham surgery is taken anyway. Rather, other options need to be focussed on.

Neurologist 13

You could alter randomisation schedule so that it is eg 2:1 active to placebo or 3:1 etc

Neurologist 22

This is possible for small trials

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**Under what circumstances do you think it possible to use an open label approach, thus avoiding sham surgery?**

(27 respondents)

Neurologist 2

Very difficult, as you would not be able to control for any placebo effect

Neurologist 3

Intravenous infusions of stem cells could be matched against sham IV infusions. It is harder ethically to justify sham invasive skull surgery

Neurologist 4

- If progression markers are better known. Then, it would be known how patients would have developed if they hadn't received a specific therapy.
- If subjects who receive the verum surgery were followed for a longer period before surgery to estimate the individual progression
- If results from verum surgery were compared with very large groups of controls – not undergoing sham surgery
- Few global control groups should be established. From the studies, that have taken place the results of controls with sham surgery should be used for further studies (no new sham surgeries).

Neurologist 5

The majority of circumstances - If patients are operated on using an open label approach, their response can be assessed by video ratings pre and post surgery by a rater who is blinded to the operative status of the patient. While this minimises bias using scores such as the UPDRS, this doesn't minimise bias from patient-reported questionnaires such as the PDQ-39, however it has been shown that disease progression in PD is most accurately assessed using physician rated scales such as the UPDRS rather than subjective patient-rated scales.

Neurologist 6

Ultimately comparison with sham is necessary unless the effect size is very great and exceeds that seen with placebo.

Neurologist 7

When a therapy is still in development and the delivery of that agent has not be optimised.

Neurologist 8

Pilot studies and/or involving a futility design

Neurologist 9

Every trial needs a control group. It might be possible to use historical controls if a large cohort of data could be obtained so people could be well matched.

Neurologist 10

I think the situation is different with DBS, where the stimulation can be either on or off. So I don't think sham surgery is necessary in DBS studies. I think that for gene therapy, GDNF and stem cell therapy we are not currently at a stage where double blind RCTs are necessary. It is also worth reflecting on the fact that the patient can have an implant on one side, so the other is the control. This could be randomized.

Neurologist 12

Only as part of a pilot study

**Neurologist 13**

**Pragmatic trials of treatment policy rather than efficacy eg PDSURG trial**

**Depends on multiple factors eg risks and cost of therapy, size of realistic treatment effect (if small then it is more important to exclude sources of bias), nature of outcome measures (ie susceptibility to bias) etc**

**Neurologist 14**

**None that are particularly meaningful**

**Neurologist 15**

**There is no way to avoid sham surgery to demonstrate the efficacy and safety of a novel treatment using a surgical approach. However, it is helpful to conduct a very preliminary proof of concept design, before the sham controlled study, to help assessing the dose to be tested subsequently and to be sure that there is a sufficient positive effect in the open trial to be assessed versus placebo as a second step of further development**

**Neurologist 16**

**Can rarely, if ever, use an open-label approach, due to the placebo effect. It may be possible at the level of a phase II study but not for a phase III trial**

**Neurologist 17**

**Pilot prove of concept trial**

**Neurologist 18**

**It depends how long you want to wait for answers. Without a control arm, given that we have seen many false dawns from early results that have not been borne out in longitudinal assessment, any study will have to have long-term follow-up prior to publication before any firm conclusion could be drawn on the results. With a control arm, more immediate direct comparisons are possible, even if they are not particularly wise.**

**Neurologist 19**

**When the related fundamental or translational research has been done before on animals**

**Neurologist 20**

**Never**

**Neurologist 21**

**I'm afraid I cannot think of any situation where we should avoid sham surgery by using an open label approach.**

**Neurologist 22**

**For assessment of acute / short / medium term effects of a treatment it might be worth performing the surgery but not activating the treatment eg dbs immediately, ie a delayed start trial. This would have the advantage of allowing isolation of the effect of the lesioning that accompanies any such surgery, as opposed to the effects of the real treatment + lesioning**

**Neurologist 23**

**Well designed quasi-experimental studies including control subjects (or stringent single-case designs) with well defined outcome variables and rigorous outcome measures that are solid representatives for those variables**

**Neurologist 24**

**It depends on the design and the type of surgery**

**Neurologist 25**

**Carefully controlled pilot/proof-of-principle/safety studies**

**Neurologist 26**

**I am inclined to say that you will be likely to always need to have an approach involving some sort of sham procedure. Placebo effects are really powerful and a misleading result can have major consequences.**

**Neurologist 27**

**In the development phase, before an optimal procedure has been achieved, open-label trials will be important in small numbers of patients. However, in order to become a proven therapy, clinical trial with a control group is necessary. In PD, a suitable control group for a surgical intervention is DBS (best available surgical procedure).**

**Neurologist 29**

**My prejudice is that I think all surgical treatments for PD should have placebo control/ sham surgery. They should have the most robust evidence of efficacy as they have the highest risk. DBS has now been through this process.**

**Neurologist 30**

**Placebo effects in PD are huge, so for a good clinical trial, sham surgery cannot be replaced**

**Do you feel it is justified in control subjects receiving sham surgery (DBS, gene or stem cell therapies) to use :-**

**a) Partial thickness burr holes?** (27 respondents)

<b>YES</b> 81%	<b>NO</b> 15%	<b>POSSIBLY</b> 4%
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**b) Full burr holes?** (27 respondents)

<b>YES</b> 56%	<b>NO</b> 44%
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**c) Full burr holes with insertion of probe?** (27 respondents)

<b>YES</b> 41%	<b>NO</b> 59%
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**d) Full burr holes with insertion of probe and procedure simulation (such as infusion of saline)?** (26 respondents)

<b>YES</b> 34%	<b>NO</b> 62%	<b>POSSIBLY</b> 4%
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**Additional comments from three responding neurologists:**

I am not sure the question applies in a global manner to all different types of surgery. For example, I think it is much preferable for an infusion technique to implant everybody with the catheter and to pump, and then randomly decide who will receive saline or active therapy during the first months of assessment, so that if the result is positive, everybody can be switched without novel surgical intervention to active treatment. Same comment for DBS. On the other hand, this cannot apply for cell therapy or for gene therapy, where those who will have received sham surgery will have to be re-operated if they are supposed to be treated actively afterwards. In that condition, the less aggressive procedure for sham surgery is reasonable, although not inserting the probe may not induce the same placebo effect than implantation (although this reduces the risk of bleeding)

Burr holes can be felt through the skin so effective “blinding “ needs a burr hole

The main thing here is blinding so that the patient is unaware whether they have had the real or sham procedure. If this can be done with only partial thickness burr holes then great but one issue would be that the insertion of the probe and procedure may itself have an effect outside of the DBS, or stem therapy so in this case you need to reproduce the procedure minus the active ingredient.

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**Choice of potential ways to reduce requirements for the numbers of PD patients receiving sham surgery**

**Do you feel it appropriate to try to find ways to reduce the overall number of control subjects used in neurosurgically-based PD clinical trials?**

(27 respondents)

<b>YES</b> 85%	<b>NO</b> 15%
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**If so, how you feel it might be possible to reduce the level of sham surgery in control subjects?**

**(24 respondents)**

**Neurologist 1**

Careful review of historical sham controls

**Neurologist 2**

The idea of a global standardised surgical PD control reference group is appealing

**Neurologist 3**

We need to develop better biomarkers of what stem cells, gene therapy and DBS actually do. In the case of DBS, techniques such as high field MRI and magnetoencephalography may achieve this.

**Neurologist 4**

Have some global control groups and take the results of subjects, who already have undergone sham surgery. Other suggestions concerning replacement of sham surgery should also be suggested.

**Neurologist 5**

If patients are operated on using an open label approach, their response can be assessed by video ratings pre and post surgery by a rater who is blinded to the operative status of the patient. While this minimises bias using scores such as the UPDRS, this doesn't minimise bias from patient-reported questionnaires such as the PDQ-39, however it has been shown that disease progression in PD is most accurately assessed using physician rated scales such as the UPDRS rather than subjective patient-rated scales.

**Neurologist 6**

One could explore whether a bank of representative sham control surgeries would be acceptable for authors to draw upon and derive an appropriately matched sample. However, I suspect the best approach is to have patients act as their own control, with DBS electrode and stimulator implanted, but used in a cross-over design.

**Neurologist 7**

By keeping data on natural history of patients with PD, and matching patients to a well studied group of patients that have not been operated on

**Neurologist 8**

Yes, it is possible

**Neurologist 9**

By obtaining a very large cohort of control patients and outcome measures that are more responsive and fit for purpose.

**Neurologist 10**

Certainly in DBS there could be more use of 'on' v off paradigms, delayed switch on parallel design, and N of one studies

**Neurologist 11**

Whilst accepting that patients cannot be blinded (the stimulator being switched on is felt), an approach could be adopted where all assessments are undertaken remotely on pre-recorded video recordings by a truly blinded assessor. A video could be produced on each operated/non-operated patient, and the standardised UPDRS can be undertaken "on" and "off". Additionally, a blinded assessment can be undertaken of diaries with dyskinesias pre and post-procedure.

As highlighted in the questionnaire, a cohort of patients having best medical care can be used as a comparator, but I think there is some virtue in randomizing subjects to surgery and medical care (or Apomorphine infusions/Duodopa via enteral tube) where there is genuine uncertainty on what best to do. We believe that remote assessment by a truly blinded third party offers the best means forward.

**Neurologist 13**

One could alter randomisation schedule so that it is eg 2:1 active to placebo or 3:1 etc

**Neurologist 14**

By having multiple 'active' treatment conditions, e.g. 3 different vector doses plus 0 vector control, which could then be only approx 25% of all subjects enrolled

**Neurologist 15**

This is a laudable objective. But from a scientific perspective, there is not much to be offered. This is obviously possible for surgical approaches like DBS where each patient is his/her own control in a cross over design. On the other hand, it is difficult to envision in a parallel group design to really improve the pairing of the patients in a manner that will substantially reduce their numbers if the principle of randomisation is maintained. Otherwise, this would mean to limit the inclusion criteria to a point that will not allow generalising the results.

**Neurologist 16**

Use the minimum required and ensure appropriate sharing of data for meta-analyses using standardised criteria. The optimum ratio in any RCT is 1:1 i.e. for every treated subject you have one control so there is no need to have more controls. You can increase power further by saying having 2:1 ratio of treated to controls so if we wanted to treat 80 patients you would only recruit 40 controls. This is better than 40 treated 40 controls but not as good as 80 treated and 80 controls.

Neurologist 17

Accuracy of selection and objective measurements

Neurologist 18

2:1 study designs and crossover studies might be one way to achieve this

Neurologist 19

Abandoned altogether, or coalesced into one (or just a few) global standardised surgical PD control reference group(s) that would be applicable for neurosurgeons worldwide to use in their future surgical trials.

Neurologist 21

I think it would be entirely appropriate to try and find ways to reduce the overall number of control subjects, but I'm afraid I cannot think of a sensible way forward here myself

Neurologist 22

Possibly by linking trials so that comparable patients are randomised between more than one active treatment and the controls shared between studies.

Neurologist 23

Well designed quasi-experimental studies including control subjects (or stringent single-case designs) with well defined outcome variables and rigorous outcome measures that are solid representatives for those variables –

Learn from the behavioural sciences where placebo controls often are impossible but scientifically valid alternatives have been developed

Neurologist 24

By accurate pairing of patients

Neurologist 25

Better matching of groups and procedures, but still sufficiently powered

Neurologist 30

The most important thing here would be to develop an objective and reliable biomarker, that would be independent of placebo effects

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**Do you feel the value of neurosurgically-based PD clinical trials would be compromised if control groups were :-**

A) **minimised?**

(27 respondents)

YES 37%	NO 52%	POSSIBLY 11%
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B) **abolished?**

(27 respondents)

YES 81%	NO 15%	UNSURE 4%
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C) **replaced with internationally-agreed 'standard' control reference group(s)?**

(27 respondents)

YES 52%	NO 44%	UNSURE 4%
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**How do you think it might be possible to form one or more 'standard' pre-agreed control groups for widespread repeated use in neurosurgically-based PD clinical trials that would meet worldwide acceptability amongst clinical/surgical researchers, and editors of leading neurological journals?**

(24 respondents)

**Neurologist 1**

Arrange a meeting of experts with a view to producing a 'consensus' document on 'standard control groups'

**Neurologist 2**

Control group, assembled prospectively, should be representative of different disease stages, different ethnic groups etc

**Neurologist 4**

- a) All existing controls with sham surgery should be comprised into one database (with all the evaluations, these people received). The database should be made accessible for all trials that need sham surgery.
- b) From the existing studies data should be collected on the time of study and outcome measurements. If a new cohort is to be investigated the time frame of these studies and outcome measurements should be considered.

**Neurologist 5**

By better collaboration of neurologists/neurosurgeons undertaking DBS both nationally and internationally, via trials such as PD SURG for example and standardised data set collection/video rating.

**Neurologist 6**

One could explore whether a bank of representative sham control surgeries would be acceptable for authors to draw upon and derive an appropriately matched sample. However, I suspect the best approach is to have patients act as their own control, with DBS electrode and stimulator implanted, but used in a cross-over design.

**Neurologist 7**

I think every trial requires its own control group and that there should not be universal central core set to refer all therapies to, as I think each trial can generate its own biases. I think that control groups vary with each trial as it depends where in the development pipeline that therapy is.

**Neurologist 8**

Yes, this is an intelligent approach. Anticipating an explosion of such studies, they should all be linked to share control data. But there are issues of procedure etc across trials. Standardising everything is best avoided.

**Neurologist 9**

Possibly patients need to be matched accurately.

**Neurologist 10**

I think this would be extremely difficult and perhaps not achievable. Historically the behaviour of PD control groups have changed.

**Neurologist 13**

Not possible

**Neurologist 14**

Not a good idea to pursue this; controls change as a function of decade, location, covariates etc. Each trial should have its own optimally matched controls.

**Neurologist 15**

Any intervention has to be tested in a rigorous manner. Historical control groups have been tried for drug assessments and abandoned because of the many biases this strategy has. The problem is the same for surgery, and it would be VERY UNETHICAL to expose our patients to a surgical process that has not been rigorously assessed in a comparative manner. One should consider the opinion of the regulatory drug agencies also and not simply be concerned by editors' opinions. This is designed to establish the benefit-risk ratio of a treatment for the good of our patients before the matter of a scientific publication, although I agree it is important to publish to inform the scientific community. Views from patients, methodologists, professional treatment developers and regulatory agencies are also important to collect, otherwise it will look like neurosurgeons are making the decisions.

**Neurologist 16**

I am not sure this is possible as most of the outcome measures are self-reported and hence would have socio-cultural differences. Even video-rating scales may differ due to the role of the researcher who will give instructions and may affect performance. We have a bad track record of trying to make comparisons using historical controls which has not proved valid. There is a danger that we may repeat this mistake here. Given the marked benefit seen with sham surgery, the potential harm of taking part is to some degree offset by this benefit.

Neurologist 17

Agree on standard procedures and selection criteria

Neurologist 18

I don't think that is achievable. There are too many differences between sites for a start and studies would be criticised. In addition, medical therapy advances and historical controls are out of date as soon as they are created.

Neurologist 19

These could be patients that will be operated later anyway. They would be subjected to one day in the surgery room and to false burr holes that would be used for the true surgery after follow up.

Neurologist 20

Impossible. Must have concurrent control groups.

Neurologist 21

I don't think this would be possible

Neurologist 22

I would not favour a control reference group

Neurologist 23

Probably not yet possible due to need for rating scale based data and the lack of rigorous rating scale based measurement in PD – there is a great need to first put efforts into this area to ensure measurement validity and cross-cultural equivalence, which is virtually non-existing today (yes, I am aware of the work on, eg the new MDS-UPDRS but given what has been presented so far, that does NOT represent an advancement but exemplifies poor rating scale practice and ignorance regarding the fundamental issues)

Neurologist 25

Characteristics of controls groups & placebo response varies according to chronological time frame and trial design

Neurologist 26

I don't agree that it would be wise to go down this route. I think you need to have a placebo controlled matched control group for each individual trial, be it surgical or non-surgical

Neurologist 28

I don't think a single control group can be relevant at all.

Neurologist 29

Using a single group loses the ability to randomize and therefore match treatment groups. I think control group(s) need to be contemporaneous rather than historical since rate of change of disability changes from one decade to the next.

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**If one could secure widespread agreement from leading journal editors that they would find it acceptable for a pre-defined global standard surgical control group(s) to be used by all neurosurgeons when performing and analysing their patient surgical trials, what control groups do you think would be needed?**

**One pre-defined control group would cover all surgical research situations?**

**(20 respondents)**

**YES  
20%**

**NO  
75%**

**PROBABLY  
5%**

**If so, how many control patients should comprise this group?**

Neurologist 2  
200

Neurologist 4

This is dependant on age, sex, duration of the disease and concomitant medication.  
If all needs are accounted for - between 50 and 80.

Neurologist 9

Ideally thousands

Neurologist 24

Need a powerful calculation to answer this

**Would a separate control group be needed for surgical trials involving DBS?**

(19 respondents)

**YES**  
68%

**NO**  
32%

**Additional comments from responding neurologists:**

**Neurologist 10**

Patients could receive DBS surgery but stimulation could be delayed

**Would a separate control group be needed for surgical trials involving gene therapy? ?**

(19 respondents)

**YES**  
63%

**NO**  
37%

**Would a separate control group be needed for surgical trials involving stem cell therapy?**

(19 respondents)

**YES**  
63%

**NO**  
37%

**If in your view separate control groups are needed, how many patients should comprise these groups?**

(10 respondents)

**Neurologist 5**

An equivalent number to those undergoing the intervention in a cross-over study design, ie 1 group gets active treatment, 1 gets control/placebo and then the second group gets the treatment intervention. Assessment is done using video rating by blinded assessors.....

**Neurologist 6**

Bank of ~40 to enable selection for matching

**Neurologist 7**

This depends on what you are trying to show

**Neurologist 10**

This varies with the predicted statistical power of the study design

**Neurologist 14**

Depends on estimated effect, size etc; such determinations are the basis of the critical role of biostatistical expertise in the design of quality clinical research

**Neurologist 16**

Depends on statistical power; there is no off-the-shelf answer to this

**Neurologist 17**

It depends upon statistical methods and measurements used....

**Neurologist 23**

Impossible to tell without knowledge of the data to be collected; depends on, eg the measurement properties of the outcome measures. In relation to the questions above: the crucial issue is not necessarily the investigated intervention per se, but the patient population that that is tested – control samples should be representative of the same populations as the intervention samples.

**Neurologist 25**

Depends on power calculations

**Neurologist 26**

You would need to evaluate this for each individual trial, based on power calculations using likely effect sizes from appropriate sources. It is also crucially important to involve capable trialists/statisticians right from the beginning, so that work is adequately powered, both to show benefit or lack of efficacy.

**How many years would such a pre-defined control group(s) be usable before needing replacement?**

(8 respondents)

Neurologist 4

This is only depending on the study design. If much longer study designs would be developed, then new control groups must be established. If not, one may stay with the old control group.

Neurologist 6

Would only need changing if drug therapy should change dramatically in the future, or the type of patient selected for surgery change

Neurologist 7

This depends on what research question is being asked

Neurologist 9

Need longitudinal data anyway

Neurologist 16

Impossible to say as there may be secular changes in natural history

Neurologist 23

Depends on development of PD management/treatment, and other related factors of relevance for how representative the group would be of the respective study samples

Neurologist 25

2 years ?

Neurologist 25

Not relevant. I don't think the control group should be predefined.

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**Do you think it better (or possible) to compile relevant global control groups by astute selection of data from previous surgical control sham-operated patients, or should we prospectively compile a new control patient group(s)?**

(24 respondents)

Neurologist 2

Prospective

Neurologist 3

Compile prospectively under agreed guidelines

Neurologist 4

It will be more difficult to get the data needed from previous trials – but this should be the first step.

Neurologist 6

Prospectively, in a defined and agreed fashion

Neurologist 7

Each trial should ultimately have its own control group built into it

Neurologist 8

The former is an option, but only as a prelude to prospective material, i.e. there would be no harm in compiling data on prior studies. But there are issues over historical controls. It depends if one is studying a new agent a Phase II (to get a dose right) or definitively at Phase III

Neurologist 9

Yes

Neurologist 10

No

Neurologist 13

I don't think this is sensible. Astute selection can never match randomisation. This may not be what people want to hear but I am afraid it is true.

Neurologist 14

No

**Neurologist 15**

Not appropriate. Management of patients change over years, and such a control group would be soon out-dated anyway, and would never apply across countries with different cultures, differences in patient management from place to place, changes in clinical practice over time, changes in health care systems, etc....\_

**Neurologist 16**

Without doubt new control groups would be needed, but I am not convinced yet by the argument that we can use universal control groups.

**Neurologist 17**

It may be necessary to develop a new control group

**Neurologist 18**

I'm afraid I really do favour prospective recruitment

**Neurologist 19**

It depends how different are these sham operations

**Neurologist 20**

Disastrous suggestion. Please talk to a PD trial statistician before this gets any further.

**Neurologist 21**

I don't this would be possible

**Neurologist 22**

Neither

**Neurologist 23**

Both would be possible but, again, the issue is how representative the group(s) is(are) of the intended population(s). However, in general prospective groups are preferable

**Neurologist 24**

New patient group

**Neurologist 25**

Yes, prospectively compile new patient control group(s)

**Neurologist 26**

I do not think it is valid to use historical controls. You need appropriately matched patients and controls, and a prospective, placebo controlled study.

**Neurologist 28**

I don't think a single control group can be relevant at all - we need to have randomised control trials in which a single group are randomized between treatment and non-treatment arms. the question is what happens to the non-treatment arm and how that can control for the very large neuro-psychological effects of an operation.

**Neurologist 30**

One will need new controls

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**Can you please share your overall additional views on how best in future to tackle any of the issues raised here?**

(17 respondents)

**Neurologist 1**

Write paper covering expert views surrounding sham surgery, and some press coverage

**Neurologist 4**

It is a good first step to try to get as many opinions as possible from different experts

**Neurologist 6**

Difficult area, with consensus being critical before action is taken

**Neurologist 9**

Need better longitudinal data using more robust measures

**Neurologist 10**

For DBS there are many ways around sham surgery, which in my view is not necessary.  
For GDNF, gene therapy and stem cells implantation, sham surgery may be more necessary, as therapy cannot be turned on or off. However, I would like to see more pilot data on outcome from these therapies first.

In addition for unilateral implantations the patients other side offers a comparator, and sides could be randomized.

**Neurologist 11**

Remote assessment by a truly blinded third party offers the best means forward

**Neurologist 13**

This is too complex to cover simply. The degree to which blinding needs to be achieved depends on multiple different issues. Providing the patient has given fully informed consent and is prepared to be randomised ie accept they may end up in either active or sham arm, then it is not unethical to do these trials. However, recruitment will never be easy.

**Neurologist 14**

Recruit only subjects who understand the need for controls and accept that their contribution to helping others with disease may occur through their randomised assignment to receive a placebo treatment/active procedure

**Neurologist 15**

Accept the idea that sham surgery is an inevitable, unpleasant, but inevitable burden, and teach doctors and patients about the reasons why it is better (or not as bad) as other options.

**Neurologist 16**

I fully understand why we want to limit controls in RCTs especially for neurosurgery. I would point out however that there are plenty of examples in the medical literature where the control group had a better outcome than the active treatment group. Usually the same doctors before the trial considered that they were depriving the controls of a useful therapy until the true results were observed. Given the dangers of producing a biased control group which could lead to misleading results and the potentially harmful or useless expensive treatment of many thousands of PD patients in the whole world, it is important to get this correct for the benefit of all. These patients who altruistically volunteer for RCTs make a major contribution to all patients and are to be applauded. Trying to limit controls and taking short cuts could be a very well intentioned but dangerous path to tread. Without FDA or other regulatory authority acceptance this route will not help license or approve new therapies for PD.

**Neurologist 19**

I again say that upstream research in primate models is more than necessary in many occasions

**Neurologist 20**

It is clear the placebo effect is large in PD surgery trials (Goetz paper). Without a concurrent control group, the study is open to performance bias. Using historic controls was a major problem in the US NET-PD trials and more recently in the Multiple Sclerosis Disease Modifying Therapy Risk Sharing Scheme. We have only just established the practice of good quality surgery trials in PD. Please do not allow a slip backwards.

**Neurologist 21**

I fully appreciate that this is a hugely difficult topic. However, on balance I think it would be more questionable from the ethical point of view to introduce treatment into routine clinical practice which has not been tested to the most rigorous standards.

**Neurologist 22**

Whilst there are many possibilities, most do not really get around the primary statistical problem of a truly comparable control group, and ultimately, at least for definitive studies that will convince the medical community and healthcare purchasers, we still need proper RCTs. It may be possible to try the above methods for preliminary explorative studies. I wouldn't support the development of control groups as I think randomisation remains key. Linking trials is possibly the best option.

**Neurologist 23**

Better defined study objectives, samples/populations, outcome variables and outcome measures implemented in rigorous quasi-experimental designs

**Neurologist 26**

I am very aware of the huge problems that arise with open label trials that show modest benefit. Such trials do not I think do anyone any favours. You need properly conducted, randomised, placebo controlled trials. If a positive result from such a trial is obtained, one has much more confidence in taking that forward with potential for more patient benefit in the long run.

**Neurologist 30**

Biomarkers for disease progression are the most important here. We need to develop an objective and reliable biomarker, that would be independent of placebo effects.



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**From:**

**Sent:** Wednesday, June 16, 2010 5:03 PM

**To:** Office of Biotechnology Activities (NIH/OD)

**Cc:** j.e. Burns

**Subject:** revised Patient comments for Sham Neurosurgical Procedures.... Meeting

Please use these comments:

1. Current FDA laws require well controlled studies BUT NOT PLACEBOS
2. DBS was approved **without** any placebo studies.
3. DBS may provide a templat for study design without sham.
4. Please review the UK's PD-SURG trial which did not require sham surgery
5. UK doctors believe sham brain surgery for PD is unethical - do any other countries use sham surgery?
6. Please do not look for ways to 'improve' sham surgery - it needs to be discontinued.
7. i have participated in 10+ clinical trials/studies, but i draw the line at a sham surgery trial. I will not participate. It is unethical. I will urge others to carefully consider before they join such a trial.

sincerely,

Jean Burns patient & advocate



**Sent:** Thursday, June 24, 2010 2:12 PM  
**To:** Office of Biotechnology Activities (NIH/OD)  
**Subject:** sham surgery workshop

To Whom it May Concern

I am submitting the attached file -- a survey of PD patients views on sham surgery as a public comment in regard to the wokshop being held next week -

**Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases:  
Scientific and Ethical Considerations.** It was compiled and written on behalf of the Parkinson Pipeline Project

Linda Herman

Amherst, NY

## **2010 Survey Report on SHAM SURGERY in Parkinson's Clinical Research.**

### **INTRODUCTION**

As more Parkinson's treatments involving surgery move into phase II and III clinical trials (such as gene therapies and growth factors), we can expect increased use of sham surgery as a placebo control in clinical trial designs. However, there continues to be controversy about its use among those who consider placebo controlled clinical trials to be the gold standard (namely, researchers, regulatory agencies, and doctors) and the clinical trial participants. Participants might become more hesitant about volunteering for trials that involve drilling into their skulls and possibly entering their brain tissue.

Recognizing the need for a thorough review of the ethical, scientific, and medical issues; the NIH will be conducting a 2-day conference on June 30 - July 1, 2010, "Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations." There have been few studies focusing on patients' perceptions of sham surgery (1), and many questions remain. In 2007, the Parkinson Pipeline Project (PPP) conducted an informal survey on the views of People with Parkinson's (PWP) on sham surgery (2), and in June 2010, we conducted an updated survey.

Both the 2007 survey and the current one were small and non-scientific. However, both provide a range of opinions about sham surgery from a sub group of PWP who are educating themselves about their disease by reading, researching, communicating and sharing information online. Likewise, many are active in PD organizations and advocacy. Fifty percent of those who responded to this survey had participated in clinical trials, while less than 1 % of the general population of PWP have actually done so.

#### **How were survey participants recruited?**

The survey was posted during June 2010 on a number of Parkinson's online forums/discussion groups and mailing lists including: The Parkinson List (PIEN), Neurotalk, PDF Clinical Research Learning Institute (CRLI) graduates (composing about 25 % of the respondents), the Parkinson Pipeline Project, Young Onset Forum of NPF, and the Patients Like Me PD forum.

#### **Who participated in this survey?**

Thirty-five PWP's responded during the two weeks allotted for the survey. Ages of survey participants ranged from 43 to 78 years. The average age was 61.4 with about equal number of men and women. They ranged from 1 – 25 years since diagnosis, the average being 8.5 years.

Significantly over half of these respondents (51.4 %) reported that they have participated in PD clinical trials (2 were in surgical and 16 were in medical trials), while the national participation rate is estimated to be less than one percent. These respondents' perceptions and opinions should be of interest to all stakeholders in the clinical trial and drug development process.

## **What is sham surgery?**

For the purposes of this survey sham surgery as a placebo control was described as including the following elements:

“A control group of randomly selected trial participants will be surgically prepped, be placed on IV solutions, undergo anesthesia and have burr holes drilled into their skulls and possibly enter into brain tissue, but they will not receive the experimental therapy.

“They may also receive immunosuppressants and/or antibiotics following the sham surgery.

“All surgical procedures and possible risks must be explained to and agreed to by the patient as part of the informed consent process.

“These trials are usually double-blinded – neither the patient nor the trial staff, except for the neurosurgeon knows if they received treatment or a sham procedure.”

Alternative trial designs are being developed, but are not yet widely accepted by consensus of the North American scientists and the FDA.

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## **The Survey Questions and Responses**

2010 Survey Report on Sham Surgery in Parkinson’s Clinical Research (3 year update) and comparison with 2007 responses are as follows:

“Some questions will be asked twice. Answer the first in regard to sham surgery that involves drilling into the skull, but does not penetrate any brain tissue. Answer the second in regard to sham surgery that involves drilling into the skull and penetration of the brain tissue (e.g. inserting a brain catheter; needle passing through the brain, implanting a delivery device - such as a pump, etc) (3)

1. Before taking this survey, did you know that some clinical trials use sham surgery as a placebo control? (Y or N)

**YES** 29 (83%)

**NO** 6 (17%)

**In 2007 survey 74% answered YES**

2. Is the scientific information gained by clinical trials worth any risk to trial participants who receive sham surgery (burr holes drilled into the skull only) ? (Y or N)

**YES:** 8 (23%)

**NO:** 26 (74%)

**NA** 1 (3%)

*In 2007 survey 34% answered Yes to any type of sham surgery*

3. Is the scientific information gained by clinical trials worth any risk to trial participants who receive sham surgery (burr holes drilled into the skull and brain tissue penetrated?) (Y or N)

**YES:** 1 (0.3 %)  
**NO:** 31 (88%)  
**NA** 3 (9%)

*In 2007 survey 34% answered Yes – scientific information gained was worth the risk to volunteers who receive sham surgery*

4. Would you volunteer for a trial knowing you could receive sham brain surgery in which your skull would be drilled into? (Y or N)

**YES:** 6 (17%)  
**NO:** 29 (83%)

*In 2007 survey 37% said they would volunteer for trial that involved sham surgery (type not specified)*

5. Would you volunteer for a trial knowing you could receive sham brain surgery in which your skull would be drilled into and your brain tissue penetrated? (Y or N)

**YES:** 1 (3%)  
**NO:** 34 (97%)

*In 2007 survey 37% said they would volunteer for a trial that involved sham surgery (type not specified)*

The remaining 2 questions were open-ended:

6. Are there any guarantees from scientists and trial sponsors that would make the risks acceptable to you? Open-ended question.

**Responses - The most requested guarantees were :**

1. Guarantee that they would receive the treatment once trial was over, should it proved to be successful
2. Any medical expenses for adverse events caused by the treatment would be covered.

3. More transparency. Patients should be given more information about the trial and the treatment, and there should be more patient input into the decision-making process.

### **IN THEIR OWN WORDS:**

“Maybe if they took over all my health-care costs forever, and if I would receive the actual surgery the instant it was shown to be safe and effective.”

“Proof of outcome”

“Given the potential risks associated with neurosurgery, there are NO guarantees that would induce me to participate in a clinical trial in which "sham surgical" procedures are utilized. “

“Guarantee of honesty. For me to consider it, I would need access to data such as history of complications and cure rate. In addition, each of these studies should have several patient advocates that would raise issues that the patient may overlook. In other words, the patient must have the same level of information AND equivalent sophistication in order to make a truly informed decision. Of course, the study must guarantee that any needed medical care will be provided free of charge.”

“If I was desperate and they guaranteed the real treatment.”

“If the surgery on the actual patients was successful and that I would be eligible for free surgery after the trial was completed.”

“Yes, if the real surgery were successful that the surgery would be performed on me.”

“If we had better diagnostic biomarkers, and knew more about the chemical changes that occur in brain surgery, I would feel better about the risks. More patient input into the decision-making process would help, also.”

“NO, BECAUSE I DON'T BELIEVE THEY KNOW ENOUGH TO GIVE PROPER GUARANTEES”

“YES, pay for my care and support indefinitely IF something went wrong during surgery, such as a stroke, bleeding on the brain, etc. OR after the surgery IF the device implant (be it real or sham) caused any problems.”

### **7. Do you have any other comments? (open-ended question)**

The most common responses were:

1. Disbelief that sham surgery is necessary – “There must be another way.”
2. Only the most “desperate” patients would agree to sham surgery.
3. We do not know enough about the placebo effect to justify use of sham surgery.
4. It is “unethical.”

### **IN THEIR OWN WORDS**

“Surely there are other models for trials of new surgeries. Can’t the surgery be compared to no surgery?”

“It is unethical to submit trial participants to sham brain surgery; there are other means to obtain reliable data to support the results of clinical trials, and better models for these need to be developed. Ignoring patients’ feelings on this inevitably will lead to a low uptake by potential participants. In order for studies to be larger and give clearer results, this issue needs to be addressed.”

“Surely there must be other methods of determining whether an experimental treatment results in authentic positive effects or placebo effects. Or until these exist, give all trial patients the experimental treatment and record the markers for the endpoint determinations. Once there is a method to separate placebo effect from true clinical effect, then a differentiation can occur. Just what do other countries utilize? I cannot believe sham neurosurgery is wide-spread in clinical trials throughout the rest of the world. “

“Any physician who plans a clinical trial should aggressively counter an FDA suggestion that the only way that the study can be "adequate and well-controlled" is through the use of sham surgery as a control. See 21CFR314.126”

“There are no circumstances under which sham surgery is ethically acceptable. The idea of anyone giving informed consent is ludicrous. It would only be out of desperation that anyone would participate in experimental brain surgery.”

“We are humans - the placebo effect in humans is called "Faith" and faith is a belief in an honorable G-d”

**“APPEARS TO NOT FOLLOW INSTITUTIONAL REVIEW BOARD STANDARDS NOR BELMONT REPORT FOR ETHICAL RESEARCH”**

“As my condition progresses I might feel more open to sham surgery where the skull is penetrated, but not the brain.”

“You volunteer for a trial knowing you could receive sham brain surgery in which your skull would be drilled into? (Y or N) no but I would not volunteer for a trial for an untested compound, either - not worth the risk at this point - perhaps if I were more desperate, I would feel differently.”

“Answers will depend on severity of disease”

“As my condition progresses, I might feel more open to sham surgery where the skull is penetrated, but not the brain.”

“I had DBS surgery in 2007 and at that time the surgery was worth the risk to me because "I would have rather died than continued to live the 'shut in' life I was living. Fortunately for me... the surgery gave me my life back! I suppose if, or when, I reach that point again I would be willing to volunteer for brain surgery, be it sham or the real thing! “

“More research is needed on placebo effects to justify sham BEFORE I would consider participating in a sham trial. The burden of proof is on the scientists, not on the patients.”

“IF THE DESIGN SUCKS ... AND RESULTS ARE INCONCLUSIVE BECAUSE OF THAT, THEN NO. Or, if they are studying something we already know, like the recent DBS trial that showed that DBS is effective in advanced (read: at the end of the levodopa road) PD, then no (I know that trial had no sham arm, it is just an example that fit my needs but happened to involve brain surgery) - difficult to answer yes or no, in other words.”

“There is too much ambiguity about positively diagnosing PD to risk sham surgery. Also, science has been working with a dopamine replacement model for over 40 years. Maybe we have been totally wrong in our approach. In my opinion, PD is both a movement and a mood disorder with the same neural pathways used. This could be inflating the already inflated placebo effect even more and longer than we think. It is time for a new model to help solve this mystery. “

“I AM ALWAYS HUMBLLED BY THE COURAGE OF FOLKS WHO PARTICIPATE IN THESE TRIALS.”

“WHY NOT ASK THE SCIENTISTS AND THE FDA WHO ARE NOT READY TO ACCEPT ALTERNATIVES TO TAKE THE SURVEY”

“ I would say as comment: Let’s enjoy the placebo effect and not risk lives just to measure it.”

## **CONCLUSIONS AND RECOMMENDATIONS**

**The acceptance of sham surgery as a placebo control and willingness to participate in such a trial has decreased among survey respondents since 2007, as shown by questions 2-5.**

It is instructive to compare the results of the 2007 and 2010 surveys and see what has changed and what has not over the last three years. Although more people are aware of its use in 2010, the current survey respondents are less likely to believe its use is worth the risks to individual PWP. Almost unanimously, they replied that they would not volunteer for a trial that utilized sham surgery (37 % would volunteer in 2007, but only 17 % and 2 % in 2010. )

Compare these results to a 2005 online survey of 103 investigator members of the Parkinson's Study Group. Ninety percent said drilling burr holes in the heads of sham control group members was justified. Twenty-two percent said penetration of brain tissue in a control group member is justified if it leads to a definite answer. (4) Yet only 1 out of 35 of our survey respondents would agree to participating in such a study. Based on the comments we received, that patient is likely to agree because they believe they have run out of options and are desperate for any treatment that might help them

There appears to be a huge disconnect between how scientists perceive patients' opinions on the issue of sham surgery and what patients really think. We need to reconnect through two-way communication and education.

It is also interesting to read patients' comments from three years ago, and realize they haven't changed very much. It appears few of the recommendations were addressed, and little discussion of the issues has taken place.

A number of the comments dealt with "therapeutic misconception" This is a commonly held belief among scientists and some medical ethicists that patients should not volunteer for trials believing they will benefit medically from the experimental treatment. Yet many of our respondents stated they wanted to be guaranteed they would receive the experimental treatment, as soon as the blind was lifted. Considering the many failed and terminated trials in the last three years, those assigned to the control groups who received sham surgery are unlikely to ever get the real thing.

Clinical trial participants are told that patients should volunteer for the good of future generations only and not to expect medical benefits for themselves. These researchers do not seem to realize how desperate many PWP actually are - even the most altruistic participant still hopes for some therapeutic effect. Indeed a number of respondents commented that they would only consider joining a sham surgery trial if they had reached the point of desperation. There appears to be a huge chasm between researchers

and patients on this issue. We believe this can only be bridged by honest and equal communication between all stakeholders. Though the opportunity for patient feedback is limited in the upcoming NIH workshop, we hope this conference will open up a much-needed dialogue.

### **RECOMMENDATIONS:**

Our recommendations are essentially the same as stated in the 2007 survey report.

The Parkinson Pipeline Project believes that the use of sham surgery in PD clinical trials raises safety and ethical issues that should be investigated further, and that patient input should be sought and considered.

Larger, scientific studies of patient viewpoints are needed.

Better understanding of the placebo effect in PD is crucial.

As part of the informed consent process, the researchers and sponsors should explain how the value of the data gained from the placebo group outweighs the risks to the participants. They should provide evidence that alternative study designs were considered and explain why they chose to use sham surgery.

The Parkinson Pipeline Project thanks all PWP who participated in this survey, and especially thanks to all who seek to accelerate PD research progress by volunteering for clinical trials.

### **NOTES:**

(1) Frank, SA, (et al). Ethics of Sham Surgery: Perspective of Patients. *Movement disorders*. 23, 1, 2008, 63-68.

(2) The 2007 survey with results available online at:  
[http://pdpipeline.org/whatsnew/shamsur\\_survey.htm](http://pdpipeline.org/whatsnew/shamsur_survey.htm)

(3) In the 2007 survey the types of surgery (burr holes drilled in skull only or brain penetrated).were not asked or answered separately as they were in 2010

(4) Kim SY, Frank S, Holloway R, Zimmerman C, Wilson R, Kieburtz K. Science and ethics of sham surgery: a survey of Parkinson disease clinical researchers. *Archives of Neurology*, 2005;62:1357–1360.

Linda Herman,  
On behalf of the Parkinson Pipeline Project

June 2010

Influence of Review of Baseline Video on Global Ratings 12 Months after  
Double-Blind Placebo Surgery for the Treatment of  
Parkinson's Disease

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A double-blind sham surgery-controlled trial was conducted to determine the effectiveness of implantation of human embryonic dopamine neurons into the putamen of patients with advanced Parkinson's disease (PD). Forty persons participated in the parent study; 20 patients received neural implantation and 20 patients received sham surgery. Thirty patients participated in the related quality of life (QoL) study. A videotape of each participant performing UPDRS Motor activities off medications was made at baseline and was archived for review at the 12 month assessment before the double-blind was lifted. The primary outcome variable was a one item Global Rating Scale (GRS) ranging from -3 (much worse since surgery) to +3 (much improved since surgery). Upon admission for the 12 month evaluation, patients rated themselves on the GRS before and after viewing the archived video. This investigation determined whether patient scores on the GRS changed as a result of watching the videotape. Because previous research with this unique sample showed a strong placebo effect, differences in scores between actual implant and sham groups, as well as perceived groups, were examined.

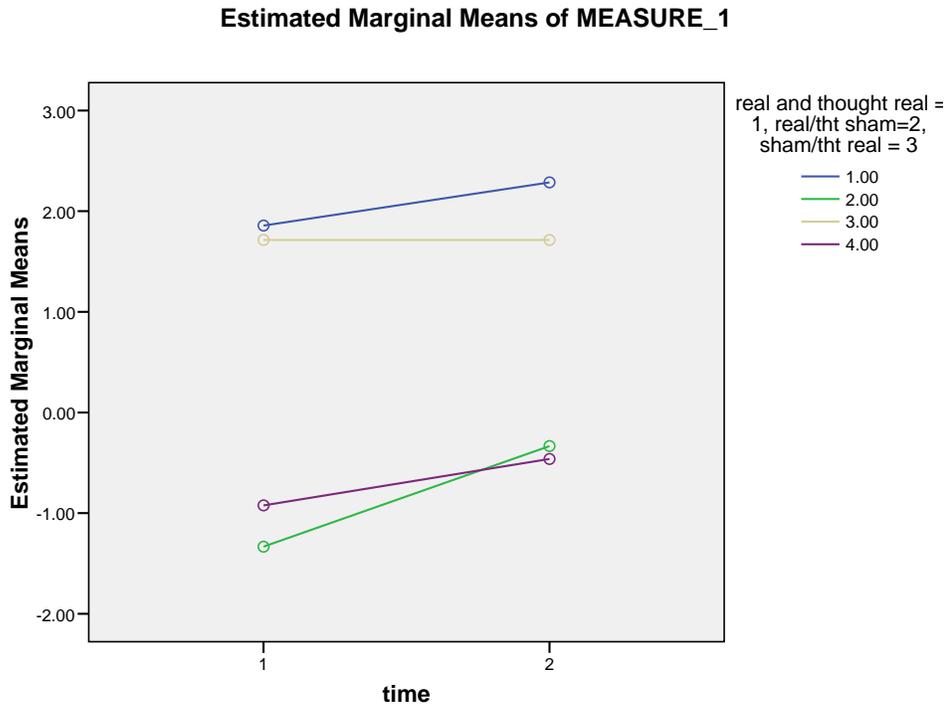
Results revealed that scores on the GRS improved for the total sample after viewing the videotape ( $P = .001$ ). Although there were no differences in ratings between the actual implant and sham groups before or after the video, there were differences between those who *thought* they received the neural implant and sham surgery at both times, regardless of type of surgery they actually received ( $P < .001$ ). Based on the pattern of change in scores from before to after the video in the actual and perceived groups, we divided the sample into four subgroups of patients (i.e., 1. Received implant/perceived implant, 2. Received implant/perceived sham, etc.).

Based on repeated measures analysis of variance, results indicated that the two groups who thought they received the implant (Groups 1 and 3) reported higher scores (about +2) both before and after the video than the two groups who thought they received the sham surgery (about -1 to -.5; Groups 2 and 4;  $P \leq .001$ ), regardless of type of surgery they actually received (see Figure 1). The only group that improved significantly as a result of watching the video was Group 2 ( $t = -3.07$ ;  $P = .011$ ), who received the implant but thought they received sham surgery at 12 months. Viewing the baseline video apparently affected the group's perception of degree of change in their condition since surgery, with the average score moving from -1.33 before the video to -.33 after the video. Using the same logic, we wondered why scores for Group 3 did not decrease since they had received the sham surgery but *thought* they received the implant. However, as a group their scores remained exactly the same before and after the video.

In addition to the many interesting directions for further investigation this research study has already provided, results of the present investigation seem to suggest the following:

1. In addition to investigating actual and perceived treatment groups, it may also be important to examine subgroups of actual implant/perceived implant, etc.
2. While we can explain why Group 2 improved (ceiling effect/ room to change), we cannot explain why Group 3 did not change. What made Group 3 different and unwavering on the GRS in spite of whatever they must have seen on the video? One long-time consultant on this grant said, "They must have been resistant to objective data" while another said, "Well, I don't know, but whatever it is, we'd better bottle it up and sell it!"

**Figure 1.** Plots of pre- and post-video GRS scores for four groups



## “Failed” Clinical Trials Using Sham Brain Surgery Controls

By Perry D. Cohen, Wilson H. DeCamp, Linda Herman, Arnold M. Kuzmack, Stan Planton, Carolyn Stephenson, Peggy Willocks and Paula Wittekind  
 Parkinson Pipeline Project, Washington, DC  
 ASENT Annual meeting March 10, 2009, update Oct. 10, 2009, update June 25, 2010

This paper examines three failed clinical trials for promising new Parkinson’s therapies. All have similar designs that require surgical intervention to deliver the treatment and utilize sham brain surgery as a placebo control. It relates common reasons for their failure and gives scrutiny to evidence on the benefits vs. risks of placebo brain surgery. Much of this paper was displayed as a poster at the ASENT annual meeting in March, 2009. Background information can be found in our “ethics” paper<sup>1</sup>

Phase II of all three trials were multicenter, randomized, double blind, sham surgery controlled studies All three showed favorable results in the open label Phase I trials, but did not meet their primary endpoints in pivotal Phase II studies. All three trials were conducted using the dopamine replacement theory as treatment by either viability of available dopamine (GDNF), production of dopamine from transplanted cells (Spheramine), or genetic alteration for the production of dopamine (CERE 120).

**Table 1. Summary of Design Characteristics of Failed Clinical Trials**

Therapy Name Description	GDNF	Spheramine	NTN
Sponsor	Amgen	Titan	Ceregene
Other Backer	Medtronic	Bayer/Schering	Genzyme
Phase 1 Design	Open label, 2 sites	Open label, unilateral for worst side	Open label
# pts./duration	14/4 years	6/6+ years	12/36+ months
Improved UPDRS (off score)	39% to 57%p	48% after 1 year; 44% after 4 years	40% up
Other evidence	Autopsy		Autopsy
Phase 2 design	All multicenter, randomized, double blind, placebo surgery control		
Sample	34 pts. (50% control)	78 pts. (50% control)	51 pts (33% control)
Blind for placebo	Install equipment w/saline solution	Sham, did not pierce dura	Sham, did not pierce dura
Duration	6 months	12 months	12 months
Improved UPDRS	Ave. 10%	Ave. 22%	Ave. 18%
Placebo	Ave. 4.5%	Ave. 21%	Ave. 18%

<sup>1</sup> Ethical Issues in Clinical Neuroscience Research: a Patient’s Perspective” PCohen, et.al.. *Neurotherapeutics*, vol 4#3 (July, 2007), pages 537-544. available online at <http://www.pdpipeline.org/whatsnew/neurotherapeutics%20art%20july%202007.pdf>

## **GDNF (Neurotrophic factor) – recombinant GDNF by pump infusion method**

Amgen sponsored two open label phase I safety trials of GDNF in 15 patients. The studies were initially for six months, with some patients treated for up to 3 1/2 years. Based on the clinical endpoint of reduction in the UPDRS motor "off" score, the efficacy ranged from 39 to 57%.

Randomized, double blind, placebo controlled, parallel group phase II trials were initiated in 34 patients. The clinical endpoint was the Change in UPDRS motor score in the practically defined off condition at 6 months.

The sponsor (Amgen, Inc.) terminated the phase II trials in September 2004. The rationale given was that, "Six months of treatment with GDNF delivered to the putamen failed to improve UPDRS scores compared to placebo." There was "evidence of alteration of brain function," a likely reference to changes on neuroimaging, but improvement on UPDRS scores did not meet the primary endpoint of the trial. However, a participant from the Bristol (UK) study died of an unrelated cause, and, upon examination of his brain via autopsy, neural sprouting was noted (the first report of its kind).

Open label extension studies began to resolve differing trial results. But in Sept. 2004, Amgen sent letters to clinical investigators halting further clinical studies, due to safety concerns – development of lesions in the cerebellum of 4 test monkeys and "anti-r-metHuGDNF neutralizing antibodies found in two of the study participants to date."

## **Spheramine [Retinal Pigmented Epithelial (RPE) Cells]**

In 2000, Titan Pharmaceuticals in a Phase I open label trial consisting of six participants with advanced disease (3 3.5 or greater on the Hoehn & Yahr scale) received unilateral treatment (for their "worst" side) transplanting RPE cells (without the use of immunosuppressant), using a donor eye from a cadaver. (One eye can be used to treat hundreds or patients.) At 12 months, an average improvement of 48% in the UPDRS M (off) outcome measure was realized, along with improvements seen in other measures of motor function and quality of life. One participant dropped out because of a later diagnosis of Parkinson's Plus. Participants continued to be followed through 48 months, maintaining a 44% average improvement and continue to be followed. It was reported, "The data also demonstrate a very good preliminary safety profile for Spheramine. There has been no evidence to date of any significant side effects in any of the patients . . . a reduction in dyskinesias for most patients and . . . no 'off state' dyskinesias . . . observed." (Titan handout, April 2002)

In 2003, a phase II study was initiated with a randomized, double blind; placebo controlled (sham surgery) trial of 71 patients (78 were actually recruited) receiving treatment bilaterally, and received fast track approval by the FDA. Titan was joined with the U.S. Berlex sponsor, which is also Schering AG (Germany), and was later acquired by Bayer (Bayer Schering/Titan). In July 2008, Titan announced that Phase II did not meet its primary or secondary endpoints and Bayer Schering AG withdrew as a sponsor. The sponsors (Bayer Schering / Titan) announced that they had discontinued development of Spheramine in July 2008.

Titan stated that its "potential cell based treatment for Parkinson's Disease failed to meet its primary and secondary endpoints in a Phase IIb study, and likely won't be continued by partner Bayer Schering Pharma... Initial analysis of results from the 71 patient study of Spheramine designed to test the safety, tolerability and efficacy of the treatment found that it had no significant differences from sham surgery arms after 12 months of follow up." (Company press release dated 7/2/08)

Phase II data have not yet been published, but the phase II study was presented at a conference (13<sup>th</sup> International Congress of Parkinson's Disease and Movement Disorders, Paris, France, June 7-11, 2009).

The STEPS trial: A Phase 2b study evaluating Spheramine® in patients with advanced Parkinson's disease. RL Watts, RE Gross, RA Hauser, RAE Bakay, H Reichmann, Weisner, NP Stover, E Reissig, H Steiner-Schulze, K Fichte . Abstract LB-18

The primary endpoint was change in UPDRS III (motor) off score at 12 months

	OFF		ON	
	Baseline	12 months	baseline	12 months
Spheramine	48.8	38.3	18.4	19.7
Sham	48.8	38.7	18.1	17.8

Conclusions:” There was no statistically significant difference between Spheramine- and sham-implanted patients at 12 months in the off state. There were also no differences in secondary outcomes, including on-state UPDRS III, time spent in off or on state, levodopa reduction, or UPDRS ADL score.

“The study failed to show efficacy of cellular implants of human retinal pigmented epithelial cells beyond a remarkable placebo effect,” the authors concluded. “Preliminary long-term results in part of the study patients suggests that the placebo effect persists even longer than 12 months.”

### **CERE 120 (neurturin) – Gene therapy**

CERE 120, a gene therapy product in development for the treatment of Parkinson's disease, was administered to the putamen with adeno associated virus carrying the gene for neurturin (NTN), a growth factor related to GDNF and shown in experimental models to protect dopaminergic neurons from degeneration. Six patients received a low dose and six a high dose (1.4 x 10<sup>11</sup> vs. 5.7 vector genomes). Neurturin was well tolerated and appeared to reduce symptoms by approximately 40% (p<0.001), as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) motor “off” score, in an open label Phase 1 study in 12 patients with advanced disease. (Company press release dated 10/10/2006)

The sponsor (Ceregene) announced the phase II trial failure in Nov. 2008. Analysis of the phase II trial data did not demonstrate an appreciable difference between patients treated with CERE 120 versus those in the control group. Both groups showed an approximate 7 point improvement in the protocol defined primary endpoint (Unified Parkinson's Disease Rating Scale motor off score at 12 months), relative to a mean at baseline of approximately 39 points. Both groups had a substantial number of patients

who demonstrated a meaningful clinical improvement from baseline. CERE 120 appeared to be safe and well tolerated."

A company spokesman stated "...we are stunned by the results of this trial and will continue to analyze the data in order to gain greater insight into the factors that may have contributed to this negative outcome, not only to build upon this insight for our Parkinson's program, but also to help assure continued successful development of our product candidates for other diseases." (Company press release dated 11/28/08)

In an in depth interview with the Michael J. Fox Foundation, Raymond T. Bartus, PhD, executive vice president and chief scientific officer of Ceregene, reported that they are attempting to redesign the CERE- 120 trial to expand the delivery target area and increase dosage. Two trial participants died from unrelated causes, providing the opportunity to view the progress of the neurturin through autopsies. Discoveries were made that may enable research to continue in the near future.

[http://www.michaeljfox.org/research\\_viewpoints\\_newsInContext\\_article.cfm?ID=11](http://www.michaeljfox.org/research_viewpoints_newsInContext_article.cfm?ID=11))

In May 2009, Ceregene reported that based on additional analyses of data from "30 subjects who continued to be evaluated under double-blind conditions for up to 18 months, there were increasing effects of CERE-120 over time. There was a "clinically modest but statistically significant treatment effect in the primary efficacy measure (UPDRS motor off;  $p=0.025$ ), as well as similar effects on several more secondary motor measures ( $p<0.05$ ), were seen at the 18 month endpoint." (Ceregene press release)

In July 2009, "The Michael J. Fox Foundation agreed to fund a long-term (48 months), open-label analysis of data from Ceregene's Phase 2 trial of CERE-120...The funding will allow Ceregene to collect and analyze data from trial enrollees for another 48 months. While the study will be unblinded, the goal is to gather as much data on safety and efficacy as possible in an open-label setting, while looking for suggestions of a longer-term neuroprotective effect. " (press release)

In September 2009, recruitment began for a new phase I/II trial --

**Phase 1/2 Trial Assessing the Safety and Efficacy of Bilateral Intraputaminial and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) in Subjects With Idiopathic Parkinson's Disease.**

"Approximately sixty patients with Parkinson's disease will participate in this study. The first part of the study is designed to evaluate the **safety** of two different doses of CERE-120. Six subjects will participate in this part of the study, all of whom will receive CERE-120. The second part of the study will provide more information about the **safety** of CERE-120 and also evaluate if it is beneficial in the treatment of Parkinson's disease. In this portion of the study, half of the subjects will receive CERE-120 and the other half will undergo a "placebo" surgery (or sham surgery) where no medication will be injected. Participants in both **phases** of the study will be followed for three years after surgery."

(see: clinicaltrials.gov record at:

<http://clinicaltrials.gov/ct2/show/NCT00985517?term=Ceregene+safety+phase&rank=1>

Some of the differences between the two trials are:

The earlier trial targeted delivery of CERE120 to the putamin. The new one adds the nigral area as a target.

There are differences in outcome measures – The first phase II trial's primary outcome measure was the score on the UPDRS Part III while OFF. The Time Frame: was 12 Months.

New phase II trial's Primary Outcome Measures are safety issues, while the Secondary Outcome Measures include:

“Changes from baseline in clinical laboratory tests, vital signs, weight, and examination findings and **clinically significant changes from baseline in brain imaging results.**”

**The Time Frame has been increased to 36 months**

## RESEARCH FINDINGS ON PLACEBO BRAIN SURGERY

The Placebo Response is based on conditioned expectations from the social context of the intervention for a reward. It is a well known concept in social science including the Hawthorn effect from industrial engineering in studies of worker motivation showing the power of an experiment, and the Pygmalion effect in education documenting the subtle bias from the expectations of teachers (authority figures). The greater the saliency from the risk and other stimulation the more powerful the effect. The effect is reinforced by conditioning and medical ritual No wonder experimental brain surgery produces such a dramatic effect.

The mechanism of the placebo effect for PD is release of endogenous dopamine in the brain using the same channels that are used by humans for movement. This makes the placebo effect indistinguishable from and directly confounded with the most prominent features of PD.

- Dilution of placebo effects in randomized experiments. In the treatment group confounding placebo effects may be diluted by the less than 100% likelihood that the patient is on the “real” treatment, and in the control group the chance that the patient is on the “real” thing elevates expectations. In addition, unlike real medical practice where both doctors and patients want patients to improve, the experimental situation tendency to dampen hope for fear of biasing results also may dampen treatment effects. Attempts to mitigate the hopes and expectations of patients who's primary, if not only, reason for taking the significant risks of experimental brain surgery are those very hopes and expectations, will not succeed and may further bias results due to placebo effects.
- False negative (Type 2 errors) bias. Our observation is that in placebo brain surgery controlled trials that placebo effects are so strong that they overwhelm the power of the study and introduce type 2 errors. The assumption that blinding neutralizes this bias to allow measured improvements to be attributed to the

treatment does not fit the findings that both treatment and control groups improve. Instead, by randomizing the very strong placebo effect you dilute treatment group effects that may be masked by placebo response, and increase placebo response in the control group. For Ceregene both treatment and control improved (!) for 70% of subjects; in other studies treatment groups did better than control groups but both IMPROVED so differences were not statistically significant.

- Triggering effects in pain control. Experiments with pain control show the necessity of letting the patient know s/he is getting pain medicine, and placebos work well if the patient expects that s/he is receiving the medicine.

## DISCUSSION

Based on the design of the three studies described above, we suggest two possible reasons for the unanticipated failures in phase II.

1. Selection bias resulted in different types of PD patients being enrolled.

Examples of such bias are:

- tremor dominant vs. rigidity dominant symptoms
  - responders vs. non responders to standard therapy
  - responders vs. non responders to placebo
  - optimized on medications vs. non-optimized
2. Sham brain surgery as placebo may be so powerful that it overwhelms treatment effects for a time (maybe up to 2 or more years).

Such an effect could force type 2 errors when the interim study results are analyzed after a shorter time.

## CONSEQUENCES OF “Failed” Pivotal Trials.

Development of new therapies by industry sponsors is extraordinarily high risk and high cost. It not only requires great understanding and knowledge to identify targets for intervention, but it also requires flawless execution of complex protocols to get it right.

Dr. Stanley Fahn of the Columbia University Medical Center has stated:

*“A negative trial result does not necessarily mean that the compound in question is of no therapeutic value – especially when that compound has demonstrated promise in animal studies and earlier, smaller, human trials. There could have been a problem with the study design or lack of optimum dosage of the experimental compound. A variation in the study design (e.g., different duration, different dosage, different patient selection criteria, and a change in method of drug delivery) may yield different results, and should be explored before any particular approach is abandoned.”*

**Business Decisions.** The science, however, is only part of the decision to continue development of a new treatment. The economy, patent life, and competitive factors as well as the capital reserves and cash flow of the company weigh in heavily on what is primarily a business decision. Even when money was readily available enormous capital

investments (close to \$1B ) to carry the development more than 15 years for neurology before receiving any return, and even then many treatments fail in late stages of development, after most of the money is spent. To make matters worse, most of the innovative therapies are sponsored by small entrepreneurial firms with little revenue and investment capital that are betting the whole company on the outcome of the study. These entrepreneurs are usually committed to their idea, so want to give it every chance to succeed, but once a pivotal trial fails. Decisions about further development pass to the responsibility of a dispassionate large company executive or other investors who are not likely to be very familiar with the promise of the science or with patients that have done well on the treatment. Thus, the real consequence of a failed study is most often a termination of the program, and often the closing of the business, such as Titan Pharmaceutical described earlier. Table 2 lists seven more PD therapies that have terminated in late stages

**Table 2. Other Therapies recently terminated in late phases**

Therapy	Sponsor	Clinical Endpoint	FDA Action: NA = not approvable	Company Action
CEP-1347	Cephalon	disability requiring dopaminergic therapy		phase 2/3 trial discontinued, 5/2005
Tesofensine (NS 2330)	Neurosearch			phase 3 canceled, 1/2006
GPI 1485	Symphony	brain uptake of [ <sup>123</sup> I}Beta-CIT		phase 3 terminated, 3/2006
Perampanel	Eisai	reduction in "off" time		phase 3 trials terminated, 10/2007 and 4/2008
Sarizotan	Merck			phase 3 terminated, 6/2006
Vadova	IMPAX	alternate tapping of keys	NA, 3/2006 & 1/2008	terminated development, 4/2008
Istradefylline	Kyowa	reduction in "off" time	NA 2/2008	suspended phase 3 in North America, 6/2008

## KEY QUESTIONS

Our analysis of the three recent failed trials points to questions that need to be addressed in order to justify what many consider to be unjustified risk to ask patients to take in a blinded, placebo brain surgery controlled clinical trial, even given expectations that even if they do not benefit personally science will advance.

1. What adjustments in the design of statistical controls are necessary to account for the impact of the context of an experimental protocol that alters expectations of participants by blinded randomization into treatment and control groups?

2. What scientific criteria are used to determine efficacy or the lack of efficacy of a treatment?
3. What assumptions are made about the interaction effects between a treatment response and a placebo response?
4. What factors should be considered when selecting samples from a heterogeneous populations as the evidence grows that some endpoints may be achievable only for patients (responders) with certain genetic variants or clinical sub types of the disease or are influenced by other factors including the method of delivery?

This presentation adds urgency to the need for these discussions, because trials are failing, and promising therapies are being shelved in what has been called the “tyranny of the type 2 error.”<sup>2</sup>

## **CONCLUSION**

The above failed phase II studies were for therapies that were known to work for some people over extended periods. The members of the Parkinson Pipeline Project have analyzed possible explanations for this poor record of accomplishment. We have suggested hypotheses that fit the pattern of results seen in these studies. Our goal is to present a clear and convincing argument that these are plausible hypotheses that merit further study and such a study is a very high priority.

There is considerable research on pain, depression and the mechanism of the placebo effect. These studies suggest that an experimental protocol that views placebo surgery as a "bias" to be minimized may in fact undermine the validity of the study. Key questions are raised that researchers and regulators need to answer in order to prevent type 2 (false negative) errors. Based on the research literature, alternative design features and methods that are more rigorous are needed to reduce error. Particularly valuable would be acceptance of un-blinding patients (not raters) in comparison to best medical practice as was for DBS (a surgical intervention and the most important new therapy for PD in the 40 years since Levodopa was introduced 40 years ago).

Given the number of new, promising, surgically delivered, treatments in the PD pipeline, policy discussions among FDA officials, scientists and knowledgeable patient advocates (including patients that volunteer for experimental treatments) on both the scientific and ethical issues about what constitutes adequate control in the study design must be a high priority to provide guidance to sponsors. The topic needs to be addressed fully before other promising therapies are shelved based on faulty assumptions about human behavior and the response to medicines.

The authors wish to acknowledge the support of the Parkinson's Disease Foundation to the work of the Parkinson Pipeline Project.

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<sup>2</sup> M. Hutchinson, S. Gurney and R. Newson. GDNF in Parkinson disease: An object lesson in the tyranny of type II. *Journal of Neuroscience Methods*. 163, 2, July 2007, 190-92

My name is Peggy Willocks, from Johnson City, TN. Let me thank those involved in planning this workshop, with special thanks to Dr. Federoff, who initiated this event at the request of my colleague, Dr. Perry Cohen. My sincerest appreciation to the scientists and patient advocates who have dedicated themselves to helping improve quality of life for those living with Parkinson's.

Noting symptoms as early as my late 30's, I was diagnosed with young onset Parkinson's 16 years ago. Because I was young, I was told a cure, or better treatments, would be found before I got worse. I am not here to say sham surgery is unnecessary, nor that it should be banned. No one wants to find a cure more than I do. However, we have an obligation to those risk takers - participants in neurosurgical trials - to ensure that benefits outweigh risks using this design.

My disease advanced rapidly, and my neurologist referred me to a movement disorder specialist at Emory. With bilateral symptoms and medications optimized, more than half my waking hours were spent in a debilitated state. When unpredictable "off" time occurred lasting 2-3 hours, I could not dress or feed myself, had difficulty swallowing, and could not walk across this room unassisted. This led to early retirement as a school principal - a job that I loved. I had no trouble getting Social Security disability the first time I applied, which is somewhat of a miracle in itself.

Then I learned of a promising study at Emory. The Phase I open-label trial required neurosurgery to transplant dopamine-producing cells from the retina of a donor eye - one eye able to treat thousands. The decision was easy; my family and I agreed to participate. Potential "adverse events," included a brain bleed, infection, rejection of the cells, and even death. The cells would be delivered stereotactically, drilling burr holes and injecting these cells into our brains. We reasoned it was worth the risk if it did no more than slow the progression and contribute to science. Knowing we were getting the cells, under general anesthesia six of us became the first humans to receive these cells unilaterally with no immunosuppression necessary.

The morning of surgery, my family encircled me, and we held hands and prayed. My youngest daughter later confessed to thinking that would be her last time to see me.

The first stop was where the halo was to be attached - a metal stereotactic frame used to "map" your brain for cell delivery. There was only one nurse who gave an explanation, injected the local anesthesia, and screwed the four screws into my skull, all simultaneously. Then it was back into the "tunnel" for one of many MRI's, which would be repeated after surgery.

Entering the operating room, I saw the walls covered with "maps" of my brain. My head was prepped, shaving my hair and sterilizing the field. My two daughters are nurse anesthetists, so I knew what was to come - intubation. From this point on, I only remember being lulled to sleep.

I awakened to a new hairdo, a head full of staples and about a 6-8" incision across the top of my head. Small burr holes were drilled into my skull and the catheters, or long hollow needles, were meticulously manipulated to inject the cells into the needed area, with no room for marginal error.

Let me stop here. Up to this point, I have described the very same protocol followed for sham surgery participants. Attaching the halo, general anesthesia (or having a machine to breathe for you), making the incision, and even drilling the burr holes are all done in the sham operation - and it is all for show. The sham patient also awakens to find staples across the top of his head, and burr holes are drilled, though usually not penetrating the dura, or outer covering of the brain. No catheters are inserted, and no cells are delivered; with, supposedly, only the neurosurgeon knowing who receives the "real" treatment.

Ten years later, my story is on-going. At 48 months Phase I participants showed an average improvement of more than 40%. Phase II unpublished results, however, which included a sham neurosurgical arm, was surprisingly halted almost a year ago after failing to meet its endpoints. There was no statistical difference between those receiving the real cells and the sham group.

I have questions. How does the neurosurgeon "pretend" to be inserting catheters in sham surgery without unblinding the trial? Do staff who care for these patients recognize physical differences in patients, such as facial swelling?

Bottom line - I have improved since the surgery, actually reversing some symptoms, but still have disabling times, keeping in mind that PD is progressive. Is the placebo effect strong enough to improve me that much time? How can we use that to our advantage?

The placebo effect remains a mystery. Studies indicate the brain releases natural pain-killing endorphins after a sugar pill placebo. And although penetration of the dura does not usually occur with sham neurosurgery, the brain may still undergo actual chemical changes.

During the informed consent process, I was never asked to consider that I probably will never qualify for another trial, nor will I be having my other side done, as was promised. So where do I go from here?

Did we wait long enough for results? Is this another potential treatment to sit on the shelf and collect dust?

Fortunately, I received benefit from the treatment; but I have concern for those who underwent the sham operation. The final question for them is . . . did the benefits outweigh the risks?

Thank you.

6/7/2010 Peggy Willocks