Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations

Wendy R Galpern, Jacqueline Corrigan-Curay, Anthony E Lang, Jeffrey Kahn, Danilo Tagle, Roger A Barker, Thomas B Freeman, Christopher G Goetz, Karl Kieburtz, Scott Y H Kim, Steven Piantadosi, Amy Comstock Rick, Howard J Federoff

There have been several recent scientific advances in gene-based and cell-based therapies that might translate into novel therapeutic approaches for neurodegenerative disorders. Such therapies might need to be directly delivered into the CNS, and complex scientific and ethical assessment will be needed to determine whether a sham neurosurgical arm should be included in clinical trials assessing these agents. We have developed a framework of points for investigators to consider when designing trials that involve direct delivery of a therapeutic agent to the CNS. The inclusion of a sham neurosurgical arm will be guided in part by the objectives of the clinical study (preliminary safety, optimisation, and feasibility *vs* preliminary efficacy *vs* confirmatory efficacy) and the need to minimise bias and confounds. Throughout the clinical development process, the perspectives of researchers, ethicists, and patients must be considered, and risks should be minimised whenever possible in a manner that is consistent with good trial design.

Lancet Neurol 2012; 11: 643–50

Office of Clinical Research (W R Galpern MD) **and Neurogenetics** (D Tagle PhD), **National Institute of Neurological Disorders and Stroke, and Office of Biotechnology Activities** (J Corrigan-Curay MD), **National Institutes of Health, Bethesda, MD, USA; Movement Disorders Center, Toronto Western Hospital and the Edmond J Safra Program in Parkinson's Disease, Toronto, ON, Canada** (Prof A E Lang MD); **Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD, USA** (Prof J Kahn PhD); **Department of Neurology, University of Cambridge, Cambridge, UK** (Prof R A Barker PhD); **Department of Neurosurgery and Brain Repair, University of South Florida, Tampa, FL, USA** (Prof T B Freeman MD); **Rush University Medical Center, Chicago, IL, USA** (Prof C G Goetz MD); **Center for Human Experimental Therapeutics, University of Rochester Medical Center, Rochester, NY, USA** (Prof K Kieburtz MD); **Department of Psychiatry and Center for Bioethics and Social Sciences in Medicine, University of Michigan, Ann Arbor, MI, USA** (S Y H Kim MD); **Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA** (Prof S Piantadosi MD); **Parkinson's Action Network, Washington, DC, USA** (A Comstock Rick JD); **and Department of Neurology, Georgetown University Medical Center, Washington, DC, USA** (Prof H J Federoff MD)

Correspondence to:
Dr Wendy R Galpern, Office of Clinical Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 6001 Executive Blvd, #2225, Bethesda, MD 20892, USA
galpernw@ninds.nih.gov

Background

Randomised, double-blind, placebo-controlled trials are generally viewed as the gold standard in comparative clinical investigations. Application of this design to trials involving the direct delivery of therapeutic agents to the CNS introduces unique scientific and ethical issues because the control arm might involve a sham neurosurgical procedure—ie, a non-therapeutic surgical intervention. Many recent advances in gene transfer and cell transplantation might be applicable to the treatment of neurodegenerative diseases. As these findings are translated into clinical trials, questions arise regarding when and how a sham neurosurgical arm should be included in the trial design.

An international group of clinical trial researchers, neurologists, neurosurgeons, basic scientists, ethicists, and patient advocates have considered the complex scientific and ethical issues surrounding the decision to include sham neurosurgical procedures in clinical trials and have developed a framework of points for investigators to consider when designing a clinical study that involves direct neurosurgical delivery to the CNS. This Personal View is not a comprehensive review of the field but rather a synthesis of the authors' views.

Randomised, double-blind, placebo-controlled trials and alternative designs

Clinical trials are intended to establish the safety and efficacy of therapeutic interventions and, when designed well, will minimise confounding and bias. When studying neurodegenerative disorders, objective outcome measures or biomarkers of disease status are rarely available; thus, diligence is needed in the trial design to minimise bias and to address the placebo response.

In randomised, double-blind, placebo-controlled trials, eligible participants are randomly allocated to either an experimental or a control intervention (table). This design protects against investigator and participant bias in treatment assignment and controls for known and unknown influences on disease outcome. Double-blinding ensures that study investigators and participants are not influenced by knowledge of the intervention assignment. Additionally, the inclusion of a placebo intervention is intended to control for the so-called placebo effect, whereby a participant might experience a clinical improvement despite receiving an inert substance.[3] A sham neurosurgical procedure can produce a placebo response that differs from that seen with a so-called placebo pill. Our understanding of the physiological basis of the placebo response is limited and the duration and magnitude of the effect are unknown. Expectation of benefit underlies the placebo response;[4–6] thus, controlling for such effects is particularly important when studying disorders where the outcome measures may be susceptible to bias. The effect of these factors can be significant when there is a high expectation of benefit, as has been noted in some trials of new surgical therapies in Parkinson's disease,[7–10] and investigator expectation can also affect outcomes.

When assessing agents delivered directly into the CNS, a randomised, double-blind, placebo-controlled trial would need to include a sham neurosurgical procedure in the control arm. The risks, potential benefits, and ethical implications of such procedures need careful consideration to decide which trials should include a sham control arm, how invasive the sham procedure will be (eg, partial burr hole or delivery of an inactive vehicle), and whether an alternative design without a sham procedure could reasonably achieve the trial objectives. The table summarises alternative trial designs, their ability to minimise bias and the placebo effect, and potential benefits and limitations. The amount of expectation, and its influence on the placebo effect, might vary between trial designs.

Scientific considerations for trials involving direct delivery to the CNS

In recent decades, several studies have investigated gene-based and cell-based neurosurgical interventions, notably adrenal medullary transplantation, fetal ventral mesencephalon cell transplantation, and gene transfer for the treatment of Parkinson's disease.[11–13] Rigorous assessment of these studies, with the benefit of hindsight, has highlighted the need for a thorough scientific rationale for the intervention and for proceeding to clinical trials and has identified important lessons regarding the design, implementation, and interpretation of studies with neurosurgical interventions.

Findings from initial studies suggested that grafting of adrenal medullary tissue was of benefit for the treatment of the symptoms of Parkinson's disease.[14] However, subsequent reports did not show sustained benefit, and the occurrence of significant adverse events resulted in this approach being abandoned.[11,15]

Early case reports of the transplantation of fetal dopaminergic cells into the striatum of patients with Parkinson's disease were encouraging.[16–21] The procedure seemed to be well tolerated, no significant safety issues were reported, and evidence of efficacy was suggested by graft survival, seen on imaging, and improved clinical outcomes. Subsequent open-label trials showed similar clinical benefit,[22–24] and long-term graft survival and clinical improvement have been noted in some participants.[25] However, trials of fetal dopaminergic cell transplantation that included a sham neurosurgical arm did not identify a clinical benefit between groups.[26,27] Similar scenarios of a reported benefit in open-label studies but limited or no benefit in controlled trials have been noted in cell and gene transfer investigations of other agents, including GDNF,[7,28,29] neurturin,[8,30] and retinal pigment epithelial cells.[9,31]

These discordant results raise several questions about the observations noted in the open-label studies. Was the reported benefit attributed to the intervention a true positive whereas those in the controlled trials were false negatives? In the case of fetal cell transplantation, this scenario is possible because there are substantial methodological differences between some of the open-label case reports and the controlled trials, including differences in tissue preparation, dosing, delivery, participant characteristics, immunosuppression regimens, and endpoints. Optimum cell preparation and delivery methods are not known, and to what extent these might have affected graft survival and clinical outcomes is difficult to conclude.[32] Was the reported improvement a placebo response? In the absence of a sham arm, differentiation between a placebo effect and a true benefit is difficult, and the expectations of the participants and investigators might have affected the outcomes. Also, only a subset of participants might be responders; however, post-hoc subgroup analyses cannot be relied upon to identify subgroups of responders. Could the benefits in the open-label studies

	Randomisation	Masking		Placebo arm	Additional considerations
		Participants	Rater		
Randomised comparison of active intervention arm to placebo arm (randomised, double blind, placebo controlled)	Y	Y	Y	Y	Gold standard Typically needs a large sample For neurosurgical intervention, a sham procedure is needed
Comparison of participants before intervention *vs* after intervention, with participants serving as their own control	N	N	N	N	Could the disease have progressed during the course of the assessment period?
Comparison of participants receiving active intervention *vs* historical data from similar participants (historical controls)	N	N	N	N	Are the participants sufficiently similar in terms of diagnostic criteria used, age, background treatments, and disease duration? Are the assessments done in an identical manner? Has the standard of care changed? Is there an effect of time that renders the comparability of the groups imperfect?
Randomised comparison of active intervention arm *vs* concurrent best medical management arm	Y	N	Y	N	Bias could be mitigated, but not removed, by incorporating masked raters Participant bias would probably persist because participants are not masked to treatment assignment
Within-participant comparison of active intervention *vs* placebo (crossover)	Y	Y	Y	Y	Advantageous for small sample sizes and heterogeneous disorders All participants receive active agent at some point during the study, which might improve recruitment Is the washout period between treatment arms of sufficient duration? Does the disease state vary over time? Cannot be easily used for time to event outcomes Cannot be used with irreversible interventions
Randomised-start design[1]	Y	Y	Y	Y	Can be useful when assessing disease modification[2] All participants receive active agent at some point during the study, which might improve recruitment Can be impractical if a second neurosurgical intervention is needed to maintain masking

Table: **Trial designs for comparative studies**

be secondary to bias in the outcome assessments or study management? Was there appropriate separation between the researcher who developed the therapy and the rater so that bias was minimised? Finally, did publication bias play a part—ie, were negative studies not published?

Methodological review of these studies highlights important issues for the design, implementation, and interpretation of studies that involve neurosurgical interventions. The small preliminary studies were often designed to assess feasibility and were exploratory in nature; the primary objective was not to assess efficacy. When only a few participants are studied, there is a likelihood of missing by chance clinically important adverse events, and conclusive statements regarding safety cannot be made on the basis of a small sample. Furthermore, although some of the early-phase studies were not designed to assess efficacy, conclusions were drawn regarding clinical benefit.[14,33] Because participants had received an irreversible intervention, their clinical response could be assessed over time, whereas in a drug trial the investigational drug is usually discontinued after a prespecified period and any associated effect is likely to wane. However, conclusions regarding efficacy should not be drawn from trials that were not designed to determine efficacy. A further issue in the early studies is the inclusion of multiple efficacy outcome measures. Although obtaining as much information as possible from each study participant might be of interest, discipline in design, management, analysis, and reporting is important to minimise erroneous conclusions.

Ethical considerations for trials involving direct delivery to the CNS

To justify proceeding to a clinical trial of an investigational agent in human beings, there must be a very strong scientific rationale, because exposing participants to potential risks without adequate scientific justification is unethical.[34] Similarly, from both scientific and ethical perspectives, the study design should ensure the question under investigation will be answered.[34] These standards are crucial when the trial involves direct delivery of an agent to the CNS and a sham procedure is being considered.

The inclusion of a sham neurosurgical arm in clinical trials has been strongly debated and requires adherence to the highest standards of research design and ethics.[35–41] A sham surgical procedure entails higher risk than a placebo in a medical trial; in the USA, federal regulations require that risks to participants be minimised and be reasonable in relation to anticipated benefits, if any;[42] regulatory agencies and ethics review committees in other jurisdictions follow a similar approach.[43] As such, substantial consideration must be given to the rationale for the inclusion of a sham arm. Moreover, one must bear in mind that investigators and participants might have different perspectives on the significance of the risks and potential benefits of a study.

If a sham arm is to be included, the procedure used should have the absolute minimum risk necessary while maintaining the scientific integrity of the trial. Although reporting of adverse events has varied across studies, use of a partial burr hole has a favourable safety profile, with associated serious adverse events reported rarely[8,9,44,45] compared with the higher risks associated with a trajectory into deep brain nuclei.[46] One must assess, with patient input, whether the study objectives are of sufficient value to warrant the potential risks, and must ensure that the study design will allow the study objectives to be met. Does the sham procedure substantially increase the ability to interpret the results, or could an alternate design answer the question? Parameters of the intervention, such as dose, delivery method, and formulation, will ideally be optimised before the inclusion of a sham arm. If optimum parameters are not yet defined, a sham controlled study can only eliminate one of many possible suboptimal regimens. Optimisation of parameters for a surgical intervention in human beings involves the careful consideration of providing at least a possibility of benefit given the surgical risk entailed.

There are further ethical considerations for trials that involve special populations. In studies that include a participant who might be cognitively impaired, the capacity of the participant to give informed consent needs to be carefully considered, and there might be cases where consent by a caregiver or participant assent can be obtained.[47] Research involving paediatric populations may involve additional safeguards; for example, in the USA, for research that poses more than a minor increase over minimal risk, there must be the prospect of direct medical benefit to individual participants.[48] If there is no such prospect, then additional review is required by the Department of Health and Human Services regulations.[48]

The issue of limited resources is also relevant. For example, in some health-care systems, operating room and staff availability is limited, highlighting one of the ethical issues of use of resources for sham neurosurgical procedures, because the use of resources for sham procedures might reduce the availability for other operations.

Patient considerations and perspectives on trials involving direct delivery to the CNS

The views and concerns of patients and family members must be considered, respected, and addressed throughout all stages of a trial. Although the goals of investigators might be focused on scientific advancement, patients might be interested primarily in the opportunity to improve their disorder. Additionally, patients and investigators might define the risks of a procedure and the value of a trial differently, and the trial design, implementation, and closure and the consent process must address these differing viewpoints to the greatest extent possible.

The systematic, published data regarding patient viewpoints on the use of sham neurosurgical controls are

limited but suggest that the individual patient perspective might differ from that of the investigator or ethicist. For example, when surveyed about a hypothetical trial assessing a novel surgical intervention, most Parkinson's disease researchers favoured a sham controlled study,[49] whereas patients with or without Parkinson's disease more strongly supported an open-label study despite finding sham surgery ethically acceptable.[50] Although patients are concerned about false negative results,[51] Parkinson's disease clinical researchers have expressed concern about false positives if a study does not include a masked control.[49,52] Additionally, interviews with patients with Parkinson's disease who participated in clinical trials involving sham procedures have identified various viewpoints.[53] Many participants initially viewed the inclusion of a sham arm negatively, although about the same number viewed it neutrally. However, most participants understood the purpose of a sham arm and the difference between sham and experimental procedures. Most participants expressed optimism that the experimental intervention might be of benefit to them. With progressive neurological disorders for which there are no effective disease-modifying treatments, the hope of receiving individual benefit might influence a patient's choice to participate in a study. This point emphasises the importance of discussing the scientific rationale and uncertainty inherent to clinical investigation during the informed consent process in an effort to maximise patient understanding.

If a sham arm is included, the reasons for selection of such a design, the procedure-associated risks, and the possibility that a sham procedure might preclude enrolment in future trials should be discussed during the consent process. Some studies might include an open-label extension period wherein all participants receive the experimental agent if prespecified criteria are achieved. This design can allow all participants the prospect of early access to a new treatment, which might improve enrolment and participant satisfaction, but the circumstances under which the investigational agent will be available must be clearly specified in the consent form and investigators must ensure that they are understood by participants. Furthermore, because participants might experience a placebo response, the potential psychological effect of learning treatment allocation should be discussed at the time of enrolment and study conclusion. Moreover, allowing participants the option of remaining masked after trial completion might be appropriate.

Various viewpoints on the placebo effect and alternatives to sham neurosurgery have been suggested by patients. Some patients have proposed that extended follow-up of participants could obviate the need for inclusion of a sham arm because the placebo response might wane over time, allowing a true benefit to be identified.[54] Another suggestion was that the apparent benefit of a placebo might potentiate a therapeutic effect in those receiving the active agent and need not be controlled but rather viewed as part of the treatment effect.[41] Also, concern has been raised by patients that a profound and prolonged placebo effect, as has been noted in several neurosurgical studies in Parkinson's disease,[8–10] might mask a true benefit of an intervention, resulting in an agent incorrectly being deemed ineffective.[51] As an alternative to a sham arm, patients have suggested subtracting the amplitude of the placebo effect from the reported treatment effect; however, the magnitude of the placebo response is variable,[55] which precludes such use of historical data.

Patients have also expressed interest in the randomisation ratio, suggesting that more participants could be enrolled in the active intervention arm and that masking could be maintained after study completion.[54] They have also expressed concern that receiving a sham procedure might preclude them from future trials because previous neurosurgery is often an exclusion criterion. An additional issue of importance to patients in some health-care systems is the potential financial burden that might be incurred if they experience a trial-related adverse event.[54,56]

Points to consider for trials that involve delivery to the CNS

Given the aforementioned scientific and ethical issues, we present a framework of points to consider when designing trials that involve delivery of an agent to the CNS where a sham neurosurgical arm could be considered (panel).

Preliminary safety, optimisation, and feasibility studies

As is typical in any therapeutic development process, initial studies will probably focus on optimisation of the intervention as well as assessment of safety and tolerability. Animal studies, including relevant disease models, can probably be used to inform these clinical studies. The utility of preliminary animal and human studies might be limited by the irreversibility of the treatment, the inability to adjust or optimise treatment parameters in individual patients (unlike for deep brain stimulation), and the inadequacy of most animal models to reliably predict outcomes in human beings.

When feasible, the earliest investigations should be aimed at optimisation of preparation and delivery of the investigational agent and at showing that the therapeutic agent is transported within the brain and is able to reach the desired target. Pharmacokinetic parameters can be assessed, and the longevity and durability of the agent, for example cell or vector survival or transgene expression, can be assessed when methodologically feasible. Initial studies can also address dose finding where biological activity is assessed. Although safety assessments cannot be conclusive in such small, early studies, preliminary safety assessments can be informative by showing either little risk or unexpected events.

Once delivery parameters have been optimised, safe dosing paradigms and the maximum tolerated dose are generally identified. An adequate number of participants must be included to obtain a meaningful assessment of safety. For example, if no clinically significant adverse events are reported in a trial with 20 participants, adverse event frequencies as high as 15% could be missed because they still fall within the (exact binomial) 95% confidence bound.[57]

The study protocol should clearly define a primary outcome measure as well as any secondary or exploratory outcomes. If any efficacy measures are included in these initial studies, they must be prespecified and secondary to safety. Within the publication, the primary outcome should be clearly identified and reported. Because such studies are not designed with efficacy as the primary outcome, efficacy outcome measures must be interpreted and reported with caution.

For the earliest trials in human beings, when safety and feasibility are not yet established, inclusion of a sham neurosurgical arm might be difficult or inappropriate. However, a sham control design might be justified in some early trials if initial data regarding dose, delivery, and feasibility are available and if a sufficient number of participants are included and the emphasis of the study is on assessment of measures of biological activity and efficacy. Moreover, if preliminary efficacy results are intended to guide so-called go–no go decisions, then a sham control design might be warranted.

Preliminary efficacy studies

After the preliminary optimisation and safety studies, subsequent studies will probably be aimed at assessment of both efficacy and safety. There are several prerequisites for this stage of development. An unbiased research team must be established, with appropriate independence from the basic science researcher, treating investigator, and outcome rater. Also essential is that participating investigators are uncertain about the effectiveness of the intervention because clinical benefit has not yet been reliably shown. The primary outcome measure needs to be clearly defined and must show an improvement that is clinically meaningful to a patient so that the risk of a neurosurgical procedure is reasonably balanced by the potential clinical benefit and the value of the generalisable knowledge. When validated, a surrogate outcome can be used; while there are no validated markers of disease progression for neurodegenerative disorders, inclusion of exploratory markers of bioactivity might be of interest in such studies. At this point in development, consideration of a staged trial design with interim efficacy or futility and safety analyses is often worthwhile so that a study can be terminated at the earliest evidence of futility or failure and participants are not exposed to any unnecessary risks.

Because one of the objectives at this stage of development is to show signs of efficacy, sham surgical controls can be considered. Alternative designs might be appropriate, keeping in mind the need to minimise bias and control for the placebo effect through randomisation and masking, while also balancing patient interest in increasing the likelihood of receiving the investigational agent. If a historical control is proposed, several questions need to be addressed (table). How recent are the control data and how reliable is their use for the present disorder?

***Panel:* Points to consider for trials involving direct delivery of an investigational agent to the CNS**

Preliminary safety, optimisation, and feasibility studies

Study objectives

- Optimisation of intervention, feasibility, and preliminary safety and tolerability

Points to consider

- What is the primary outcome?
- What are the secondary outcomes?
- Are there sufficient data regarding the following to justify the inclusion of a sham procedure: safety, feasibility, dose, delivery, and participant numbers?

Preliminary efficacy studies

Study objectives

- Efficacy and safety

Points to consider

In addition to the above

- Is the research team unbiased and uncertain about the effectiveness of the intervention?
- Is the effect size clinically meaningful?
- Have interim analyses for safety, efficacy, and futility been considered?
- Is the comparator arm appropriate?
- Should a sham procedure be considered, or is there an alternative design that can adequately minimise bias and control for the placebo effect?
- Has patient interest in receiving the investigational agent been considered?

Confirmatory efficacy studies

Study objectives

- Efficacy and safety

Points to consider

In addition to the above

- Has the research team remained uncertain about the effectiveness of the intervention despite findings of preliminary efficacy?
- Are treatments randomised and double-blind to ensure masking of the investigators, assessors, and participants? Does this require a sham procedure, or is there a comparable control?

All studies where a sham neurosurgical procedure is considered

Points to consider

- Is the rationale for the study scientifically and ethically sound?
- Is risk to the subject minimised?
- If a sham procedure is included, is it the most minimally invasive that can generate uncertainty and answer the question under study?
- Have all potential biases been minimised?
- Does the informed consent process address the following: scientific rationale for the study, uncertainty of benefit, possibility that a sham procedure might preclude enrolment in future trials, and circumstances under which open-label access might occur?
- Has an external advisory committee been considered?
- Has a data and safety monitoring board been considered?

Search strategy and selection criteria

References for this Personal View were identified through searches of PubMed through December, 2011, with no date limits set, with combinations of the following terms: "ethics", "fetal cell transplantation", "GDNF", "gene therapy", "Huntington's disease", "neurotransplantation", "neurturin", "Parkinson's disease", "placebo", and "sham surgery". When more than one paper had similar conclusions, the initial publication on that topic or an appropriate review was cited. Only papers published in English were included.

How does this design address the placebo response? Is there a mechanism to control or mitigate investigator bias? If a concurrent standard care arm is included, is the placebo response still a potential factor? Other trial designs might include an active surgical control. For example, deep brain stimulation could be an active comparator in a surgical trial in Parkinson's disease, but masking of the participants would be difficult. In such designs, one must ask whether the comparator population is appropriate. How equivalent is the comparator intervention to the investigative intervention? Are the participant populations similar in terms of disease severity and other eligibility criteria? As with other designs, one must assess whether the design addresses the placebo response, investigator bias, and participant bias.

Confirmatory efficacy studies

If the preliminary efficacy trial does not show evidence of failure or futility, then a definitive trial will probably be needed to reliably show efficacy. Even though these studies are probably supported by encouraging pilot data, investigators should remain uncertain regarding the effectiveness of the intervention. The study should be designed for a clinically meaningful effect size, especially given the risks of surgical delivery. To minimise bias and control for the placebo response, treatment assignments should be randomised and double-blind. This design can be achieved by the inclusion of a sham arm or a comparable control that effectively masks the investigators, assessors, and participants to the treatment allocation.

General principles regarding sham neurosurgical arms

On the basis of both science and ethics, the following principles should guide the decision for and implementation of a sham neurosurgical arm. At all times, risk to the participant should be minimised. When selecting the sham procedure, a minimally invasive procedure that can generate uncertainty regarding the actual participant treatment assignment should be used. Recent experiences suggest the sham procedure might not need to be more invasive than a partial burr hole; a more invasive procedure must be deemed essential for answering the research question. Also, the choice of anaesthesia or sedation should keep risk to a minimum. All potential biases must be minimised; such efforts are relevant not only to investigator assessments but to the participant, their family members, and the involved clinical staff. Standardisation of masking and surgical procedures and training of personnel will help to avoid inadvertent unmasking.

Given the complex considerations inherent in a sham arm as well as the diverse perspectives that must be taken into account, establishment by the study leadership of an independent external committee to provide advice throughout both trial design and implementation can be beneficial. This committee could include investigators, statisticians, ethicists, and patients. Additionally, a data and safety monitoring board with a similar representation might be warranted.

Finally, participants who receive a sham neurosurgical procedure in a clinical trial should not be precluded automatically from enrolling in a subsequent trial that uses a neurosurgical procedure to deliver an investigational agent or from a more standard non-surgical trial.

Conclusions

When designing clinical trials of new therapeutic agents for neurodegenerative disorders, mitigating bias and controlling for confounding variables are paramount. The disease process cannot be directly observed, and the function-based and symptom-based assessments typically used can be susceptible to observer bias. When the trial includes a sham neurosurgical arm, the risks to participants can be increased, and a careful risk-to-benefit analysis is essential. The framework described here is a guide to the issues that should be considered during the therapeutic development process. There might be additional disease-specific and practical factors to consider, such as the capacity to consent and the availability of resources. As objective markers of disease progression are developed, trial designs will become more streamlined, and some features such as a sham control arm might not be necessary. However, throughout each stage of clinical development, the scientific and ethical issues must be thoroughly re-assessed to ensure that the research question remains relevant and the trial design is ethical and scientifically sound.

Contributors

All authors were involved in drafting or critically reviewing and revising the manuscript, or both, and all authors reviewed the final submitted version.

Conflicts of interest

AEL is an adviser for Abbott, Allon Therapeutics, AstraZeneca, Avanir Pharmaceuticals, Biovail, Boehringer-Ingelheim, Cephalon, Ceregene, Eisai, GlaxoSmithKline, Lundbeck, Medtronic, Merck Serono, Novartis, Santhera, Solvay, and Teva; has received grants from Canadian Institutes of Health Research, Dystonia Medical Research Foundation, Michael J Fox Foundation, National Parkinson Foundation, and Ontario Problem Gambling Research Centre; has received publishing royalties

from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry. TBF is a consultant for SanBio, SpineGuard, Synthes Spine, Medtronic, Alnylam Pharmaceuticals, and Signus; Medical Director for Saneron CCEL Therapeutics; scientific advisory board member for NeuralStem; Founding Scientist, President, Chairman of the Board for Ciracell; receives fees for consulting for all the aforementioned companies; holds stock options for NeuralStem, Saneron, and Ciracell; has a licensing agreement with Medtronic Neuromodulation; and holds patents and provisional patents, numbers 7896889, 7981120, 7963980, 8012159 B2, 7699854, 7416885, and 6528245. CGG receives honoraria for consulting and advisory board membership from Addex Pharma, Asubio, Biovail Technologies, Boston Scientific, Cleveland Medical Devices, Decision Resources, Dixon Group, ICON Clinical Research, Impax Pharmaceuticals, Ingenix (i3 Research), Intec Pharmaceuticals, Kenes International, Motac Neurosciences, Oxford Biomedica, United Bioscience Corporation, and UCB; grants or research funding from the National Institutes of Health (NIH) and Michael J Fox Foundation; honoraria from the Movement Disorder Society, American Academy of Neurology, University of Pennsylvania, Washington University, and University of Michigan; and royalties from Oxford University Press, Elsevier Publishers, Wolters Kluwer Health, and Lippincott, Wilkins and Williams. CGG directs the Rush Parkinson's Disease Research Center, which receives support from the Parkinson's Disease Foundation, and directs the translation programme for the MDS-UPDRS (Movement Disorder Society unified Parkinson's disease rating scale) and UDysRS (unified dyskinesia rating scale), for which he receives funds from the Movement Disorder Society. KK is a consultant for the National Institute of Neurological Disorders and Stroke (NINDS), The US Food and Drug Administration, The US Veteran's Administration, Abbott, Acorda, Aptiv, Biogen Idec, Biotie, Biovail, Boehringer Ingelheim, Ceregene, Civitas, Clintrex, Cynapsus, EMD Merck Serono, Genzyme, Impax, Intec, Ipsen, Isis, Knopp, Lilly, Link Medicine, Lundbeck, LZ Therapeutics, Merz, Novartis, Orion, Otsuka, Pharm2B, Phytopharm, Schering-Plough, Siena Biotech, Synosia, Solvay, Synagile, Teva, UCB Pharma, Vaccinex, Vectura, and Xenoport; receives grants or research support from Medivation, Michael J Fox Foundation, National Eye Institute, NINDS, National Institute on Aging (NIA), National Institute of Child Health and Human Development, Neurosearch, and Pfizer; and does legal consulting for Pfizer, Thompson Hine, and welding rod litigation defendants. HJF is founder, equity participant, and scientific advisor for MedGenesis; founder and equity participant of Socratec; board member for the American Federation for Aging Research and Biomedical Research and Education Foundation; adviser for Oxford University Parkinson's Disease Center; and has received grants from NINDS, NIA, and the Department of Defense. All other authors declare that they have no conflicts of interest.

Acknowledgments

The National Institutes of Health (NIH) convened a meeting of international experts to discuss the complex issues surrounding the decision to include sham neurosurgical procedures in clinical trials at a workshop entitled *Sham Neurological Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations* (June 30–July 1, 2010). The deliberations at this meeting were used in the development of this manuscript, and the authors acknowledge the contributions of the meeting participants. Authors were selected by the Organising Committee (WRG, JC-C, AEL, DT, and HJF) to represent the areas of expertise and opinions represented at the meeting. Authors include the members of the Organising Committee and a subset of meeting participants with expertise in clinical trials, neurology, neurosurgery, basic science research, ethics, and patient advocacy. A participant roster, slide presentations, written public comments, and a webcast are available online. The meeting was funded by the NIH. We also thank the following staff from the Office of Biotechnology Activities, NIH, for their contributions in bringing together this symposium: R Jambou, E Rosenthal, M O'Reilly, M Montgomery, and L Gargiulo. We also thank Perry Cohen for his contributions in the development of this symposium. The points described should not be interpreted to represent a consensus statement or the opinions of any individual or the NIH.

References

1 Leber P. Slowing the progression of Alzheimer disease: methodologic issues. *Alzheimer Dis Assoc Disord* 1997; **11** (suppl 5)**:** S10–21.

2 Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; **361:** 1268–78.

3 Beecher HK. The powerful placebo. *J Am Med Assoc* 1955; **159:** 1602–06.

4 de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 2001; **293:** 1164–66.

5 McRae C, Cherin E, Yamazaki TG, et al. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. *Arch Gen Psychiatry* 2004; **61:** 412–20.

6 Lidstone SC, Schulzer M, Dinelle K, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. *Arch Gen Psychiatry* 2010; **67:** 857–65.

7 Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol* 2006; **59:** 459–66.

8 Marks WJ Jr, Bartus RT, Siffert J, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2010; **9:** 1164–72.

9 Gross RE, Watts RL, Hauser RA, et al. Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2011; **10:** 509–19.

10 Hauser RA, Watts RL, Freeman TB, et al. A double-blind, randomized, controlled, multicenter clinical trial of the safety and efficacy of transplanted fetal porcine ventral mesencephalic cells versus imitation surgery in patients with Parkinson's disease. *Mov Disord* 2001; **16:** 983–84.

11 Hallett M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. *Neurology* 1999; **53:** 1910–21.

12 Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. *Mov Disord* 2005; **20:** 523–39.

13 Wakeman DR, Dodiya HB, Kordower JH. Cell transplantation and gene therapy in Parkinson's disease. *Mt Sinai J Med* 2011; **78:** 126–58.

14 Madrazo I, Drucker-Colin R, Diaz V, Martinez-Mata J, Torres C, Becerril JJ. Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. *N Engl J Med* 1987; **316:** 831–34.

15 Goetz CG, Stebbins GT 3rd, Klawans HL, et al. United Parkinson Foundation Neurotransplantation Registry on adrenal medullary transplants: presurgical, and 1- and 2-year follow-up. *Neurology* 1991; **41:** 1719–22.

16 Lindvall O, Brundin P, Widner H, et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. *Science* 1990; **247:** 574–*77.*

17 Lindvall O, Widner H, Rehncrona S, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: one-year clinical and neurophysiological observations in two patients with putaminal implants. *Ann Neurol* 1992; **31:** 155–65.

18 Sawle GV, Bloomfield PM, Bjorklund A, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: PET [18F]6-L-fluorodopa studies in two patients with putaminal implants. *Ann Neurol* 1992; **31:** 166–73.

19 Lindvall O, Sawle G, Widner H, et al. Evidence for long-term survival and function of dopaminergic grafts in progressive Parkinson's disease. *Ann Neurol* 1994; **35:** 172–80.

20 Peschanski M, Defer G, N'Guyen JP, et al. Bilateral motor improvement and alteration of L-dopa effect in two patients with Parkinson's disease following intrastriatal transplantation of foetal ventral mesencephalon. *Brain* 1994; **117:** 487–99.

21 Freeman TB, Olanow CW, Hauser RA, et al. Bilateral fetal nigral transplantation into the postcommissural putamen in Parkinson's disease. *Ann Neurol* 1995; **38:** 379–88.

For more on the **NIH meeting** see http://oba.od.nih.gov/rdna_rac/rac_sham_con.html

22 Freed CR, Breeze RE, Rosenberg NL, et al. Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease. *N Engl J Med* 1992; **327:** 1549–55.

23 Wenning GK, Odin P, Morrish P, et al. Short- and long-term survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease. *Ann Neurol* 1997; **42:** 95–107.

24 Hauser RA, Freeman TB, Snow BJ, et al. Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease. *Arch Neurol* 1999; **56:** 179–87.

25 Politis M, Wu K, Loane C, et al. Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci Transl Med* 2010; **2:** 38ra46.

26 Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* 2001; **344:** 710–19.

27 Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol* 2003; **54:** 403–14.

28 Gill SS, Patel NK, Hotton GR, et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nat Med* 2003; **9:** 589–95.

29 Slevin JT, Gerhardt GA, Smith CD, Gash DM, Kryscio R, Young B. Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminal infusion of glial cell line-derived neurotrophic factor. *J Neurosurg* 2005; **102:** 216–22.

30 Marks WJ Jr, Ostrem JL, Verhagen L, et al. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. *Lancet Neurol* 2008; **7:** 400–08.

31 Stover NP, Bakay RA, Subramanian T, et al. Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers in advanced Parkinson disease. *Arch Neurol* 2005; **62:** 1833–37.

32 Brundin P, Barker RA, Parmar M. Neural grafting in Parkinson's disease: problems and possibilities. *Prog Brain Res* 2010; **184:** 265–94.

33 Surgical treatment for Parkinson's disease: neural transplantation. *Mov Disord* 2002; **17** (suppl 4)**:** S148–55.

34 Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 2002.

35 Freeman TB, Vawter DE, Leaverton PE, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. *N Engl J Med* 1999; **341:** 988–92.

36 Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med* 1999; **341:** 992–96.

37 Albin RL. Sham surgery controls: intracerebral grafting of fetal tissue for Parkinson's disease and proposed criteria for use of sham surgery controls. *J Med Ethics* 2002; **28:** 322–25.

38 Miller FG. Sham surgery: an ethical analysis. *Am J Bioeth* 2003; **3:** 41–48.

39 Horng SH, Miller FG. Placebo-controlled procedural trials for neurological conditions. *Neurotherapeutics* 2007; **4:** 531–36.

40 Alterman RL, Tagliati M, Olanow CW. Open-label surgical trials for Parkinson disease: time for reconsideration. *Ann Neurol* 2011; **70:** 5–8.

41 Katsnelson A. Experimental therapies for Parkinson's disease: Why fake it? *Nature* 2011; **476:** 142–44.

42 US Food and Drug Administration. Code of Federal Regulations: 21 CFR 56.111(a)(1,2). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.111 (accessed Dec 15, 2011).

43 Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000; **283:** 2701–11.

44 Frank S, Kieburtz K, Holloway R, Kim SY. What is the risk of sham surgery in Parkinson disease clinical trials? A review of published reports. *Neurology* 2005; **65:** 1101–03.

45 LeWitt PA, Rezai AR, Leehey MA, et al. AAV2-*GAD* gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol* 2011; **10:** 309–19.

46 Kimmelman J, Duckworth K, Ramsay T, Voss T, Ravina B, Emborg ME. Risk of surgical delivery to deep nuclei: a meta-analysis. *Mov Disord* 2011; **26:** 1415–21.

47 Appelbaum PS. Consent in impaired populations. *Curr Neurol Neurosci Rep* 2010; **10:** 367–73.

48 US Food and Dug Administration. Code of Federal Regulations:21 CFR 50.50-50.54. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50 (accessed Dec 15, 2011).

49 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. *Arch Neurol* 2005; **62:** 1357–60.

50 Frank SA, Wilson R, Holloway RG, et al. Ethics of sham surgery: perspective of patients. *Mov Disord* 2008; **23:** 63–68.

51 Cohen PD, Herman L, Jedlinski S, Willocks P, Wittekind P. Ethical issues in clinical neuroscience research: a patient's perspective. *Neurotherapeutics* 2007; **4:** 537–44.

52 Prehn AW, Vawter DE, Gervais KG, et al. Studying neurosurgical implants for Parkinson disease: a question of design. *Neurology* 2006; **67:** 1503–05.

53 Kim SY. National Institutes of Health. Research studies on patient perspectives. http://oba.od.nih.gov/rdna_rac/rac_sham_con.html (accessed Oct 28, 2011).

54 National Institutes of Health. Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations. http://oba.od.nih.gov/rdna_rac/rac_sham_con.html (accessed April 12, 2012).

55 Goetz CG, Wuu J, McDermott MP, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. *Mov Disord* 2008; **23:** 690–99.

56 Moral science: protecting participants in human subjects research. http://bioethics.gov/cms/node/558 (accessed April 12, 2012).

57 Piantadosi S. Clinical trials: a methodological perspective, 2nd edn. Hoboken, NJ: John Wiley and Sons, 2005.