

Launching Invasive, First-in-Human Trials against Parkinson's Disease: Ethical Considerations

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Abstract

The decision to initiate invasive, first-in-human trials involving Parkinson's disease presents a vexing ethical challenge. Such studies present significant surgical risks, and high degrees of uncertainty about intervention risks and biological effects. We argue that maintaining a favorable risk-benefit balance in such circumstances requires a higher than usual degree of confidence that protocols will lead to significant direct and/or social benefits. One critical way of promoting such confidence is through the application of stringent evidentiary standards for preclinical studies. We close with a series of recommendations for strengthening the internal and external validity of preclinical studies, reducing their tendency toward optimism and publication biases, and improving the knowledge base used to design and evaluate preclinical studies.

1. Introduction

A major objective in Parkinson's disease (PD) research is the development of strategies to halt degeneration and/or restore the function of dopaminergic and other neurons.

Among the approaches being tested are various small molecule drugs,¹ trophic factors,² deep brain stimulation,³ cell transplantation, and gene transfer.⁴

Ethical discussion of translational PD trials has tended to center on sham surgery,^{5,6,7} quality of informed consent,⁸ subject selection,⁹ and the use of fetal tissues.¹⁰

Nevertheless, a perhaps more fundamental question remains uncharted: when is it ethical to initiate invasive first-in-human (FIH) PD trials? Decisions to launch such trials are often marked by controversy. To date, three gene transfer strategies have been reviewed by the Recombinant DNA Advisory Committee. All received full public review, signaling novelty and ethical concerns.¹¹ The first received a particularly skeptical hearing,¹² and when this trial was initiated, several researchers castigated the investigators as “crazy,” venturing into “terra incognita,”¹³ and “raising hopes in people with minimal evidence of benefits.”¹⁴

In November 2007, the Novel Neurotechnologies Ethics Research Group convened a workshop at McGill University to discuss the ethics of initiating invasive FIH PD trials. What follows is analysis and recommendations stemming from this meeting.

2. Methods

Two of us (JK and AJL, both ethicists) drafted a statement outlining objectives of the workshop. We then sought input from a preclinical researcher (MEE). After refining our statement, we invited another preclinical researcher (AF), a neurologist clinician / researcher (BR), an epidemiologist (TR), a neurosurgeon / researcher (MB), and a neuroscience historian (FS). Participants were selected on the basis of their interest in neurology translational research ethics. To ensure focused discussions, the pre-workshop statement was refined by invitees. The workshop was held on November 9, 2007; after a series of presentations and discussion, areas of consensus were identified. Except where noted, participants were in agreement about the analysis and recommendations presented here.

3. The Central Ethical Challenge of When to Initiate Trials

The core ethical challenges surrounding the initiation of invasive PD studies derive from the nature, probability, and indeterminacy of study risks. PD trials present a difficult risk problem in part because they target the brain. As “*the organ of our personhood,*”¹⁵ adverse events have the potential to disrupt those features that make us who we are: language, memory, cognition, and identity.

Surgical Risk and PD Trials

The probability of harms is also somewhat unusual because of surgical risks. Whereas administration of small molecule drugs involves minimal risk, invasive PD studies involve inoculations to the brain. Based on studies examining complication rates

associated with analogous surgical procedures in similar brain regions, risk of surgery-related permanent neurological deficits are on the order of 0.5 - 1% per inoculation.¹⁶¹⁷¹⁸¹⁹²⁰ This might appear modest when compared against phase 1 oncology studies (these involve 14% risk of grade 4 adverse events),²¹ but two additional factors must be considered. First, many PD protocols involve multiple injections; assuming somewhat conservatively that permanent neurological deficit risk is 0.5% per inoculation, four injections present almost 2.0% risk (in comparison, risk of irreversible adverse events in phase 1 oncology studies is approximately 1.5%²¹). Second, these represent baseline levels of risk that are present before investigational agents are even received (contrast this with phase 1 cancer studies, where study risk normally derives from the study drug itself).

Investigational Agents, Risk, and Uncertainty

Uncertainty presents another important challenge for PD FIH studies. Experimental agents employed in invasive PD studies often have characteristics (e.g. potential vector immunogenicity) that limit the reliability of animal models for risk determination.²²²³ Impairments in brain processes such as cognition are also difficult to model preclinically. Furthermore, though nonhuman primate toxicology studies play a crucial role in risk assessment, sample sizes and time horizons enable the detection of only high frequency, immediate, and catastrophic events. Our review of five well-known gene transfer and neurotrophic factor trials²⁴²⁵²⁶²⁷²⁸ found that, on average, investigators used 20 nonhuman primates in preclinical studies; two of these trials appear to have been based on preclinical studies for which the last time point was eight months (**Table 1**).²⁹

The Ethical Approach to Uncertainties

How does this high uncertainty affect the appraisal of risk? We believe it translates to a presumption that study risks exceed numeric “best-estimates” provided by preclinical studies. This position is justified on the grounds that risk estimates from preclinical studies will tend, at best, to have wide confidence intervals and, at worst, will have limited predictive value. A cautious human protection policy would tend to operate on the assumption that the full range of adverse events is not known, and that their probability might be higher than anticipated. Such precaution is consistent with approaches used by U.S.³⁰ and European³¹ drug regulatory authorities.

Volunteers entering such studies are often motivated by the prospect of therapeutic benefit.³² They might argue that this precaution is unduly restrictive in that it presumes a greater level of risk than indicated preclinically. Nevertheless, the primary rationale for FIH studies is to collect generalizable information about the properties of an intervention. As captured in the notion that trials should begin with an “honest null hypothesis” (according to which at the outset of a study, new interventions are assumed to have no advantage over standard care), assumptions about possible benefits should be conservative.

We believe that it is consistent with sound medical practice and policy that a novel agent with uncertain properties be considered unacceptably risky as a therapeutic modality until

clinical evidence indicates otherwise. Together, the character, probability, and uncertainty surrounding risk for invasive PD intervention studies translate to a presumption of unusually high risk by the standards of most clinical research.

4. The Ethical Basis for Risk in FIH, Novel Intervention Studies

Numerous influential statements on research ethics underscore the importance of preclinical studies.³³³⁴ For example, the CIOMS guidelines state “clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk.”³⁵ This suggests that safety is an insufficient condition for launching human studies; study interventions must also have shown evidence of promise in laboratory studies. However, there is no consensus on either the quantity or quality of preclinical evidence necessary to justify a human study.

Evidentiary Standards

We believe that the risks of invasive PD FIH studies create exacting demands on the quantity and quality of preclinical evidence. This position is rooted in the requirement that risks and benefits be favorably balanced in clinical research. Accordingly, when administering riskier interventions, a research team should have a higher degree of belief (hereafter termed “confidence;” this is not to be confused with the concept of confidence used in biostatistics) that trials will produce corresponding benefits either to the volunteer or to society. In contrast, where study risks are moderate or minor, evidentiary standards need not be as stringent.

Many would question whether interventions used in FIH PD trials can be plausibly viewed as presenting a prospect of direct medical benefit. Granting for the moment that they do, it is nevertheless axiomatic within medicine that potentially harmful and difficult to reverse interventions should be undertaken only where there is a reasonably high degree of confidence that they offer therapeutic benefit. This favors stringent evidentiary standards for preclinical studies.

Risks in clinical trials are also ethically justified by the prospect of producing generalizable knowledge. With greater risk comes the obligation that studies present proportionately greater probability of producing knowledge benefits. We contend that trials founded on a sound evidence base will tend to have stronger claims to scientific value than those supported by weak evidence.

This claim rests on the following logic: the value of an experiment is partly a function of the confidence in the veracity of a hypothesis that an experiment engenders in the expert community. Experiments that can exclude competing explanations for results will produce greater confidence in the veracity of a study hypothesis than those that exclude fewer. For example, clinicians interpreting randomized controlled trial results tend to form stronger beliefs about a drug's efficacy if treatment allocation during the trial is concealed, because this excludes a competing explanation—that observer bias explains a “positive” trial result.

Scientific Value and “Positive” Findings

Whether a FIH PD study has a reasonable prospect of producing valuable generalizable knowledge will depend on whether both positive outcomes (that is, an intervention seems reasonably safe and hints at biological activity) and negative outcomes (an agent proves unsafe, or shows no biological activity) are informative. Insofar as the FIH study is designed and executed with scientific rigor, positive outcomes will tend to be informative and allow the clinical community to move from a state of total uncertainty to one in which a particular hypothesis can be tested in controlled clinical trials.³⁶

Scientific Value and “Negative” Findings

However, novel interventions rarely translate smoothly into clinical applications.³⁷ Some epidemiologists argue that “most published research findings are wrong” in “hot” research fields.³⁸ Rates of attrition are striking in CNS disorders.³⁹ For example, numerous randomized trials aimed at slowing PD progression have been conducted; none show conclusive modification of disease course.⁴⁰⁴¹ There are similar results in stroke⁴²⁴³ and other neurodegenerative diseases.⁴⁴⁴⁵ A central question in deciding whether invasive PD trials strike an appropriate risk-benefit balance is whether negative outcomes will be informative. Here, a critical ingredient in appraising the value of a null result is whether obvious competing explanations can be excluded. Thus, for example, if observer bias may have produced exaggerated treatment effects in preclinical studies, a null human result will be less informative.

In conclusion, preclinical researchers should reduce uncertainty where it is feasible to do so. Where preclinical studies can either limit uncertainty surrounding the properties of an intervention or weaken the plausibility of competing explanations for observations, FIH studies can make a stronger claim to producing scientifically meaningful outcomes. Preclinical data thus become an essential feature in deciding the risk-benefit balance of FIH trials.

5. Towards A Compelling Supporting Evidence Base in Invasive PD Studies

What practices should investigators use in preclinical studies to enhance the scientific and/or therapeutic promise of FIH studies? When reviewing proposals, what elements should IRBs, funding agencies, and policy-makers expect? The remainder of our analysis is directed towards describing methodologies and practices in preclinical research that we believe would greatly enhance the ethical justification for initiating invasive FIH studies (**Table 2**).

Maximizing Internal Validity

Clinical research has evolved a series of methodological practices aimed at maximizing internal validity. As extensively documented in stroke research, these practices have permeated preclinical research to only a limited degree.⁴⁶⁴⁷ The first is *a priori* power calculation. These are almost never reported in PD preclinical studies. Though expense and burden severely constrain sample size for non-human primate studies, the absence of power calculations seems harder to defend where studies involve lesioned rats. Stating

an *a priori* hypothesis, and powering a study accordingly, helps discourage researchers from expanding their samples sizes or manipulating definitions of efficacy to attain a “significant” results.

PD preclinical studies also rarely report the use of random treatment allocation. Of 22 published preclinical studies used to support human GDNF and/or gene transfer studies against Parkinson’s, only four reported randomization. This is lower than reported in other preclinical literatures.⁴⁸⁴⁷ In a systematic review of 290 animal studies, non-randomized studies had a 3.4 times higher odds of showing a positive treatment effect compared with studies that used randomization.⁴⁹ We acknowledge that simple randomized treatment allocation may not always be the best strategy in PD: it will often be more useful to balance groups on the basis of pre-treatment performance on key outcome measures, and then assign treatment randomly within these groups.

Blinded treatment allocation is also necessary to avoid subtle differences in the handling of animals. In one meta-epidemiological study involving preclinical studies of stroke interventions, studies that did not mask investigators to allocation produced significantly larger treatment effects than those that did.⁵⁰ However, another procedure—blinded or automated outcome assessment—seems almost universally accepted in PD preclinical research (only three of 22 preclinical studies did not report using either).

Another crucial variable is the treatment of missing data. Given the small sample size in many preclinical studies, how missing data are managed can significantly alter the outcome of statistical tests.

Maximizing External Validity

External validity issues center on the models used in PD studies. Although spontaneous rodent models of PD are now available,^{51,52} researchers have typically relied on various injury-induced models, which mimic nigrostriatal dopamine deficiency but do not recapitulate the slow, progressive degenerative or pathophysiological nature of PD. Thus, a typical PD neuroprotection study administers a putative neuroprotective agent before or at the same time as inducing an acute PD-like lesion. In contrast, human trials administer interventions in the context of a disease that is progressed and chronic.⁵³ The difference in disease states severely constrains the external validity of preclinical studies. A number of different animal models and clinical outcome measures are available for PD preclinical researchers,⁵⁴ and transgenic models should be given serious consideration when designing preclinical studies. At a minimum, investigators should justify their selection of models and outcome measures.

Preclinical studies should also correspond as much as possible with the methods used in clinical studies. For example, clinical studies should be performed without departing from delivery techniques, agent composition, or inoculation sites validated in preclinical studies.

Control of Optimism and Publication Biases

Optimism bias refers to an often unconscious tendency for researchers to present or interpret their data in a favorable light.⁵⁵ Optimism bias might pose particular challenges to translational research, because at the point where preclinical studies are underway, investigators have devoted many years to a research program . Though personal identification with a therapeutic strategy can fuel perseverance, it can also interfere with dispassionate appraisal of study findings.⁵⁶

Publication bias (that is, a tendency to withhold reporting of unfavorable findings) presents yet another challenge to the credibility of preclinical study claims. By showing strong relationships between small sample sizes and large treatment effects, several meta-analyses of neurological preclinical studies show high rates of publication bias.⁴⁷⁵⁷⁵⁸

Preclinical research should therefore build mechanisms to check optimism and publication biases. Trial protocols should include critical reviews that place animal studies within a broader clinical context. Similar to a systematic review but broader in scope, a critical review should seek to comprehensively summarize all existing literature that may be relevant to the results being reported. In contrast to a systematic review, the search strategy should be open-ended rather than rigorously pre-specified. This is because preclinical animal studies that replicate a given study exactly are relatively rare. Rather, researchers should search for all possible studies that may be relevant, whether they are

based on the same treatment in different animal models, related treatments in the same animal model, or even related treatments in different animal models. Given a propensity for optimism bias, critical review should aim at finding dissenting evidence (as opposed to supporting evidence). Preclinical reports and trial proposals should discuss competing explanations for observed treatment effects. Reports should disclose limitations of a study by discussing the weaknesses of animal models and rating scales.

One last counter to optimism bias is transparency. Publication of preclinical toxicology studies is hardly the norm. Such non-publication might have understandable commercial motivations, but it frustrates the ability of assessors to form independent judgments about the safety and promise of an intervention. Researchers should make good faith efforts to publish all preclinical studies before proposing human trials; public and private funding agencies might also establish public databases of preclinical studies. One promising model that might be employed would be the National Gene Vector Laboratory toxicology database.⁵⁹

6. Further Measures Beyond Single Protocols

The practices described above provide a non-exhaustive list of measures that research personnel, funders, and IRB members should expect from preclinical data. Though we recognize that each entails burdens, budgets, and in some instances, proprietary liabilities, we find the counterargument—that these sources of bias remain unchecked—

untenable. Our recommendations only address what we consider to be the most tractable problems confronting individual PD FIH studies.

Nevertheless, just as clinical practice is best judged on the basis of community standards, so too should research practices be evaluated. To that end, we suggest two further measures designed to foster the development and articulation of quality standards and practices surrounding FIH studies.

Substantive Criteria

Decisions concerning trial initiation would be greatly enhanced if the field were to articulate clear standards for producing and evaluating preclinical evidence. Questions include the types of cellular and molecular evidence that should be available before initiating studies, effect sizes and consistency of effects in animal models, length of follow-up, clinical and subclinical toxicity testing in animals, and appropriate functional rating scales or other outcome measures with clinical impact. Given the great difficulty encountered in translating PD interventions into clinical applications, guidelines might have limited utility for predicting if a candidate intervention is likely to prove clinically useful. Nevertheless, guidelines might be used to cull agents that do not meet minimum criteria. The Stroke Therapy Academic Industry Roundtable established guidelines in 1999 for the design of preclinical studies.⁶⁰ Although these guidelines are not “fail-proof,”^{61,62} they provide a framework for designing and evaluating preclinical studies. PD research sponsors might consider whether similar substantive standards might be established for preclinical researchers and referees.

Identifying Best Practices and Research Needs

As noted above, several PD preclinical models are available for preclinical testing. Some members of our workshop questioned whether PD preclinical models had any predictive value whatsoever. This view echoed concerns recently expressed by some Amyotrophic Lateral Sclerosis, Alzheimer's disease, and Huntington's disease researchers.⁶³

Accumulated evidence supports the value of preclinical research for neurological disorders when appropriate models and hypothesis-driven experimental designs are utilized.⁶⁴ A thorough understanding of the models, their differences and their limitations is nevertheless needed to match the model to the question at hand. This knowledge is also needed to select appropriate outcome measures (functional, anatomical, cellular or molecular) that will provide accumulated evidence of the effects of a therapy.⁵⁴⁶⁴

Recently, Alzforum hosted a discussion of animal models to discuss shortcomings in mouse models used for neurodegenerative disease research; representatives from the Michael J. Fox Foundation participated.⁶⁵ A similar forum might be established for non-human primates, and for articulating research needs with respect to alternative models.

PD preclinical models will be among the many topics discussed in detail on PD Online Research, which is being built by Michael J. Fox Foundation as a web-based, "large-scale self-organizing community of basic and clinical scientists, industry professionals, grantmakers, and financial investors involved in PD research."⁶⁶

7. Conclusion

In summary, the nature and degree of risk for invasive PD FIH studies puts particular pressure on the requirement that risks be favorably balanced against benefits for human studies. A critical factor in assuring favorable benefit profiles—whether this involves direct, therapeutic benefits or knowledge benefits—is the requirement that preclinical studies be designed and executed with scientific rigor. Toward that end, we have offered several recommendations that center on strengthening internal and external validity, while managing or reducing optimism and publication biases.

Though our workshop centered on PD, our analysis and recommendations could conceivably extend to any research area involving novel and complex agents delivered to the brain. Our recommendations are thus consistent with others aimed at improving the scientific utility and predictive value of experimental neurological interventions. In 1992, for example, PD researchers established the core assessment program for intracerebral transplantation, which aimed at enhancing the interpretability and value of open-label transplant studies.⁶⁷ This framework was subsequently extended to Huntington’s Disease,⁶⁸ and an analogous framework has been devised for surgical treatments of PD.⁶⁹ In 1999, the Stroke Therapy Academic Industry Roundtable convened a working group to “optimally preclinically assess neuroprotective and restorative drugs for acute ischemic stroke.” The group issued a series of recommendations on preclinical⁷⁰ and clinical⁷¹ study design.

We nevertheless acknowledge that several additional issues will need to be addressed, perhaps in future workshops, to assure that FIH studies have a favorable risk-benefit balance. These include standards for study design, best practices for reporting and disseminating findings, and how barriers to high quality preclinical research might be overcome. Our recommendations on preclinical study methodology would also be complemented by the development of substantive criteria for initiating studies and procedural guidelines for establishing acceptable risk. At the minimum, our recommendations should stimulate reflection and debate within the wider PD research community.

END

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Research Project: (Initial Conception: JK; Design: JK, AJL, MEE, BR, TR; Organization: JK; Data Collection: JK, MEE; Execution and Content of Workshop: All)

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Table 1:

	Species (PD agent)	Sample size		max. last time pt (mo.)	sex	Blinding			<i>a priori</i> power	published before trial	Reference
		total	active			allocation	outcome assess.	random- ized			
AAV-GAD (Kaplitt 2007)	Rat (OH)	49	30 ^a	2	m	1	0	0	0	1	Kaplitt 1994
	Rat (OH)	20	8	4	m	0	0	0	0	1	Luo 2002
	Rat (OH)	47	23	4	m	0	0	0	0	1	Luo 2002
	Rat (OH)	48	24	1	m	0	1	1	0	0	Lee 2005
	Monkey (M)	20	7	12	f	0	1	0	0	0	Emborg 2006
AAV-NTN (Marks 2008) ^b	Rat (OH)	34	24	1	m	0	1	0	0	0	Gasmi 2007
	Rat (OH)	39	15	7	m	0	1	0	0	0	Gasmi 2007
	Rat (N)	120	80	12	m/f	0	1	0	0	0	Gasmi 2007
	Rat (N)	90	60	3	m/f	0	1	0	0	0	Gasmi 2007
	Monkey (N)	13	9 ^c	3	m/f	0	1	0	0	0	Eslamboli 2005
	Monkey (OH)	18	12 ^c	6	m/f	0	1	0	0	0	Eslamboli 2005
	Monkey (M)	20	5	10	m	0	1	0	0	0	Kordower 2006
	Monkey (A)	3	3	8	f	NA	1	0	NA	0	Herzog 2007
AAV-AADC (Eberling 2008)	Monkey (M)	4	2	2	NA	0	0	0	0	0	Bankiewicz 2000
	Monkey (M)	8	4	72 ^d	m	0	1	0	0	0	Bankiewicz 2006
GDNF (Nutt 2003) ^e	Monkey (M)	13	6 ^f	1	f	0	1	1	0	NA	Gash 1996
	Monkey (M)	9	6 ^g	3	f	0	1	1	0	NA	Gash 1996
	Monkey (M)	30	25	3	f	1	1	1	0	NA	Zhang 1997
GDNF (Gill 2003) ^h	Monkey (A)	8	4 ⁱ	3	f	0	1	0	0	1	Kordower 2000
	Monkey (M)	20	5 ⁱ	3	NA	0	1	0	0	1	Kordower 2000
	Monkey (N)	2	2 ⁱ	8	NA	NA	1	0	NA	1	Kordower 2000
	Monkey (M)	13	8 ^f	4	f	0	1 ^j	0	0	NA	Grondin 2002

Table 1: Methodologies, Samples Sizes, and Practices for Preclinical Studies Leading to PD Trials Involving Trophic Factors and Gene Transfer. References to preclinical supporting studies were obtained from published clinical studies of first-in-kind invasive PD interventions. Whether preclinical studies were published before trial initiation was inferred by comparing publication dates with press reports of trials being initiated or being published. All data were extracted independently by two authors (JK and MEE). Abbreviations: M=MPTP model; A=Aged model; OH=OHDA model; N= normal animals; NA= Not applicable or not available; m= male; f= female. Notes: a- Active treatment was AAV-TH; b- References Huges et al, 1992 and Starr et al, 2002, that focused on PD diagnoses and DBS targeting for STN respectively, were excluded from this table; c-Active treatment was AAV-GDNF; d- Necropsies timeline: control animals: 24 mo. (n=4): active treatment: 36 mo (n=2), 72 mo. (n=2); e- Reviews by Gash et al., 1998 and Bjorklund 1997 were excluded from this table; f-Active treatments included intraparenchymal and ICV injections; g-Two ICV monkeys treated with active treatment and 3 controls were also part part of experiment; h-Review by Gash et al., 1998 was excluded from this table; i-Active treatment was lenti-GDNF; j-Defined as "coded" tapes.

Table 2: Practices That Help Establish Ethical Basis for Initiating First-in-Human Trials

Concern	Practices
Internal Validity	A priori hypothesis stated A priori power calculations Randomization Blinded treatment allocation Blinded outcome assessment Discussion of missing data
External Validity	Explanation for selection of animal model Explanation for selection of rating scale Correspondance of trial with preclinical conditions
Optimism and Publication Bias	Critical review of preclinical data Full publication of preclinical studies

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