Published in final edited form as:
Ann Neurol. 2010 February ; 67(2): 258–260. doi:10.1002/ana.21831.

Local IRB Review of a Multicenter Trial: Local Costs without Local Context

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Abstract

Multicenter clinical research involves parallel IRB reviews based on the premise that local review reflects aspects of the research environment. We examined the costs and effects of local IRB review of the consent and protocol in a multicenter clinical trial in Parkinson's disease. Seventy six percent of changes to the consent reflected standard institutional language, with no substantive changes to the protocol. The costs of this process exceeded $100,000. These findings support initiatives by the Office of Human Research Protections and NCI to facilitate centralized reviews. This may be an opportune time for NINDS to adopt a central review model.

Introduction

The Office for Human Research Protections (OHRP) is exploring a rule change to encourage institutions participating in multicenter studies to forgo review and rely upon the review of another qualified Institutional Review Board (IRB).1 The overall goal is to enhance the use of centralized review processes and improve the efficiency of review for multicenter studies. Federal regulations support the use of cooperative IRB review arrangements,2 but few institutions use them because of concerns about liability and oversight. Additionally, centralized or cooperative reviews might risk losing relevant aspects of local context, such as features of the local study population or research environment3. There are little data on this topic to guide the OHRP initiative. We therefore examined the impact of local review on the informed consent and protocol for a NIH/NINDS funded, phase III clinical trial in Parkinson disease, to determine how local context is reflected in these study documents.

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Statistical analysis: Ravina, Deuel
Obtained funding: Ravina, Dorsey
Administrative, technical, or material support: Deuel, Siderowf
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Methods

The trial was a randomized, double blind, phase III trial of coenzyme Q_{10} and vitamin E, conducted by the Parkinson Study Group, at 52 US sites. We compared the IRB approved template consent and protocol, developed by the coordinating center at the University of Rochester, to each sites' IRB approved version. We identified consent modifications that changed meaning and were relevant to local context. We measured Fleisch-Kincaid reading level of the consent and reviewed each site's approved protocol for changes. Three raters coded the changes (LD, BR, AS), including one active IRB member (AS); disagreements were resolved by consensus. We examined the time spent by site personnel on the IRB submission process and the direct costs of this process, using a standardized log and an hourly labor cost of $35 for study staff.

Results

Forty-five of the 52 sites (87%) participated in this study. Five used two central IRBs; all others used their institution's IRB. Review and approval time averaged 61.4 days (±39.2) from submission. Table 1 shows consent changes after local IRB review. On average, 5.2 (±2.1) local changes were made per site, and the most frequent change was for injury compensation. Most edits (76%) involved standard institutional language (e.g., HIPAA wording) or site-specific contact information. Sixty-five of the 270 changes (24%) were trial specific, and 55 (85%) of these were for recruitment expectations. Reviewed consents tended to be longer with a higher reading level.

There were no substantive changes to the protocol. On average, the site and coordinating center staff spent 13.7 hours (±12.6) submitting each sites' consent and protocol. The direct costs associated with local review and approval was $107,544: $82,610 in IRB fees and $24,934 in labor.

Discussion

In this study, local IRB review added little in terms of local context at considerable cost. Most changes to study-related documents after local IRB review, consisted of standard institutional language, unrelated to the study, with no meaningful changes to the protocol. Such changes may need only administrative review at the site level. Consistent with previous studies, reviewed consents tended to be longer and more complicated.[4, 5] Our findings are not surprising since most local issues pertain to the qualifications of the investigative team, facilities, recruitment plans, and study conduct, rather than the consent or protocol.[6] Centralized review of the consent and protocol may free overburdened IRBs and site study personnel to engage in more oversight of local conduct, thereby enhancing protections to research participants.

The institutional costs of supporting an IRB have been examined and may exceed $800,000 a year.[7] We examined the direct costs from the NIH/NINDS sponsor perspective, which were over $100,000 for this trial. NINDS is currently sponsoring 26 multicenter phase III clinical trials (personal communication, Dr. Scott Janis, NINDS). While our findings may not generalize to all neurology clinical trials, this trial is similar in overall design and risks to many other late stage trials in neurodegenerative diseases. Multiple clinical trials are needed to develop an intervention and demonstrate efficacy.

The direct costs and indirect costs of the IRB review process, such as delays in study conduct,[8-10] accrue over the course of these trials and contribute to the growing expenses of drug development.[11-13] Use of alternate review processes could result in considerable

savings for NINDS and other sponsors that could directly fund additional neuroscience research.

The oncology research community recognized the potential benefits of central review processes several years ago. The National Cancer Institute's (NCI) adopted a system of centralized IRB review, which allows for a focused review at the site level to address possible local concerns.6 NCI has a $3 million annual contract for its central IRB (personal communication, Jacquelyn Goldberg, JD, NCI), which reviews selected large multi-site adult and pediatric studies for hundreds of participating centers.14 NINDS has a smaller volume of multicenter studies and could operate a similar central IRB for substantially less money. A variant of cooperative review arrangements may be more cost efficient for NINDS than a central IRB. The coordination center or the Principal Investigator's institution for a study could also act as the central IRB. Participating institutions would conduct an administrative review by the local IRB chair or another member to ensure compliance with institutional language. The local IRB may conduct a more extensive review in specific cases. For example, studies that entail waiver of informed consent may require more extensive vetting of community acceptance. This model would not add central administrative costs and would markedly reduce direct costs and delays by eliminating full board reviews. However, this model relies on cooperation among institutions, which may not happen without incentives from NIH. Additional savings in time and effort could be achieved by harmonizing standard language among institutions, but this may be difficult to achieve practically.

Our findings support the proposed OHRP rules change and highlight the inefficiency of current IRB review practices. However, uptake of the NCI system and other cooperative review models has been limited because of local concerns about regulatory liability and relinquishing management of operations.3, 15 These concerns were recently heightened by findings of lax operations at a commercial IRB.16 The OHRP proposal would directly addresses concerns about liability and compliance with federal regulations; it would allow the Department of Health and Human Services to hold a central IRB or the organization operating that IRB directly accountable for compliance with federal regulations rather than the institution conducting the research.1 If the OHRP rule change is implemented, it would be an opportune time for NINDS to evaluate and foster alternate IRB review models.

Acknowledgments

The authors thank Drs. Robert Holloway and Scott H. Kim for their critical review of the manuscript, Amy Beimler for designing the study logs, and the Parkinson Study Group for their collaboration on this project. This study was supported by grants from the Michael J Fox Foundation and the National Institutes of Neurological Disorders and Stroke, NS05073-04. The authors have no conflicts.

Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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Table 1

Local Changes to Customize Model Consent Form

Category of change	Changes per document	Study specific changes	Examples of study specific changes
Compensation for injury	1.2 (0.9)	1/61 (2%)	Stated that site investigator would not compensate for injury
Expected enrollment at each site	1.0 (0)	52/52 (100%)	Number of subjects expected to enroll at site
Subject rights	0.9 (0.7)	0/47 (0%)	-
Confidentiality and HIPAA wording	0.6 (0.8)	1/32 (3%)	Timing of treatment assignment disclosure
Local standards and record retention	0.6 (0.7)	0/30 (9%)	-
Cost and payment	0.5 (0.6)	0/25 (0%)	-
Investigator qualifications, staffing, and conflicts of interest	0.2 (0.4)	5/9 (56%)	Investigator paid by NIH
Blood repository wording	0.1 (0.3)	1/4 (25%)	Contact information for the repository
Facilities and storage of study drug	0	N/A	-
Other	0.1 (0.4)	5/10 (50%)	Additional description of Parkinson disease; use of backup subject identification
TOTAL CHANGES	**5.2 (2.1)**	**65/270 (25%)**	
Final length of the main consent form (words) Template was 6011	6128 (869)		
Final Fleisch-Kincaid grade reading level Template was 10.6	10.8 (0.8)		

Values are mean (standard deviation)

Abbreviations: NIH, National Institutes of Health; PD, Parkinson's disease