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The effects of local review on informed consent documents from a multicenter clinical trials consortium

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Abstract

There is increasing controversy about the appropriate role of the local institutional review board in the review of multicenter clinical studies. We evaluated the effects of the local review process at 25 study sites on the consent forms from two studies of the Tuberculosis Trials Consortium, a multicenter trials group. Two independent reviewers classified all changes made in the centrally approved consent forms; a third reviewer evaluated those changes if the two initial reviewers disagreed. The median time to initial local approval was 104.5 days (range 31–346). There were no changes in the study protocols as a result of local review. Consent forms became longer and less readable after local review, with a mean increase in grade level of 0.9 ($\pm$0.9) reading grade levels ($p < 0.001$). A median of 46.5 changes (range 3–160) were made in the centrally approved forms. Most changes (85.2%) involved altering wording without affecting meaning. Errors were commonly introduced (11.2% of changes), and 33 of 50 (66%) locally approved consent forms contained at least one error in protocol presentation or a required consent form element. Local approval of two multicenter clinical trials was time-consuming and resulted in many changes in centrally approved consent forms. These changes frequently decreased readability and introduced errors.

Keywords: Institutional review board; Consent form; Human subjects protection; Reading level; Multicenter clinical trials

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Introduction

The local institutional review board (IRB) is the focal point of the human subjects protection system. All federally sponsored studies involving humans and studies using drugs or devices regulated by the Food and Drug Administration (with a few strictly defined exceptions) must be evaluated by an IRB. Medical practice increasingly emphasizes evidence-based decision making, resulting in many and large clinical trials. In order to obtain the required number of study subjects in a timely manner, many human studies are carried out at multiple sites. Although independent IRBs provide centralized review of some multicenter trials, particularly industry-sponsored trials [1], many institutions require that all studies be reviewed by a local IRB. Local review has been retained for multicenter protocols and consent forms because it is thought that the local IRB has specific knowledge of local conditions that make it uniquely qualified to judge the appropriateness of the research and to assure that the informed consent document is written in a manner appropriate for the local population [2].

Local IRBs have come under increasing scrutiny and criticism [3,4]. The workload at many local IRBs has increased dramatically [5], and federal regulatory officials have warned or suspended an increasing number of IRBs because of their inability to monitor and adequately evaluate the large number of studies under their purview [6]. Clinical investigators have become increasingly concerned about the time and volume of paperwork required to obtain local IRB review [6–9]. Despite the controversy over the appropriate role for local IRBs in the oversight of multicenter clinical trails, there has been very little empirical research in this area. Little is known about the effect of local review on the consent forms for multicenter clinical trials. We performed an in-depth study of the impact of local review process on the protocol and consent form from two multicenter clinical trials.

Methods

The Tuberculosis Trials Consortium (TBTC) is funded by the Centers for Disease Control and Prevention (CDC) to carry out research on the treatment of tuberculosis. Protocols and consent forms are developed by local investigators, research nurses and CDC staff members. During the time period included in this study, the CDC required a dual system of protocol and consent form review, first by an IRB at the CDC and then by local IRBs at study sites in the United States and Canada. After initial local approval, the consent forms were then sent back for review by the CDC IRB. If there were substantive differences between the changes requested by the CDC and local IRBs, additional changes in the consent form might be required. Before enrollment could occur, both the CDC IRB and local IRB had to approve of the final consent form language.

We evaluated the local review process for two trials of tuberculosis treatment, one that is evaluating currently approved drugs and doses in a standardized regimen for the treatment of isoniazid-resistant tuberculosis (TBTC Study 24) and one that evaluated two investigational doses of an approved drug, rifapentine (TBTC Study 25) [10]. The local review process includes activities of the study site (protocol submission, responses to the local IRB, submission back to the CDC) and the local IRB. In the analyses for this study we could not distinguish changes in the consent form made by local study site versus changes required

by the local IRB. Similarly, among study sites in which more than one local IRB (e.g., a university IRB and a health department IRB) had to review and approve sequentially a specific consent form, we could not distinguish changes made by one IRB from those required by another.

We determined the time (days) from the date the centrally approved protocol and consent form was sent from the CDC to local sites to the date the locally approved consent form was submitted back to the CDC for review. We could not determine how much of the time required to obtain local approval was needed for the local IRB review versus the time spent by the local study site to prepare the IRB submission and submit the completed review back to the CDC. Study sites also estimated the number of hours local site personnel devoted to the process of obtaining local IRB approval for TBTC Study 24. The remainder of the analysis deals with the changes present in the initial locally approved consent forms (i.e., we did not analyze the consent form wording that was eventually agreed upon after rereview by the CDC IRB).

The initial locally approved consent form from each site was entered into a word-processing program (Word 97, Microsoft, Renton, Washington), manually checked for accuracy, and all site-specific information (name of the institution and investigator, telephone numbers, patient remuneration) was removed. We identified all changes made from the standard, centrally approved consent form and subdivided these into small changes (changes involving less than one sentence) and large changes (involving one or more contiguous sentences).

The Flesch-Kincaid reading grade level in the word-processing program was used to evaluate the effect of changes on consent form readability [11]. Federal regulations require that the consent form be written "in language understandable to the subject" [12]. In a recent large randomized trial of tuberculosis treatment 56% of subjects enrolled had less than a high school education and 35% were born outside the United States and Canada [13]. Therefore, the TBTC and CDC IRB decided that the maximum allowable grade reading level for consent forms for tuberculosis studies should be the eighth grade. For this analysis, we defined any consent form with a Flesch-Kincaid score >8.0 as having inappropriately complex language. To evaluate the effect of local IRB requirements on consent form readability, study sites sent their local IRBs suggested or required language for consent forms. These required sections were evaluated for readability as above.

Two independent reviewers categorized all changes from the centrally approved consent form using a system developed for this study. The categories included: a change in location within the consent form without a change in wording, a change in wording without a change in meaning, a change to fit local conditions, a grammatical or spelling error, an error in protocol presentation or a required consent form element, or a change with potential relevance to all sites. When the two reviewers categorized a change differently, the final categorization was determined by a third independent reviewer. The reviewers evaluated consent forms after all identifying information had been removed. All reviewers are experienced clinical investigators; two are or were chairpersons of an IRB.

Results

Of the 25 TBTC sites and subsites, 14 (56%) used one local IRB, eight (32%) used two, and three sites used three local IRBs. The process of local review took a median of

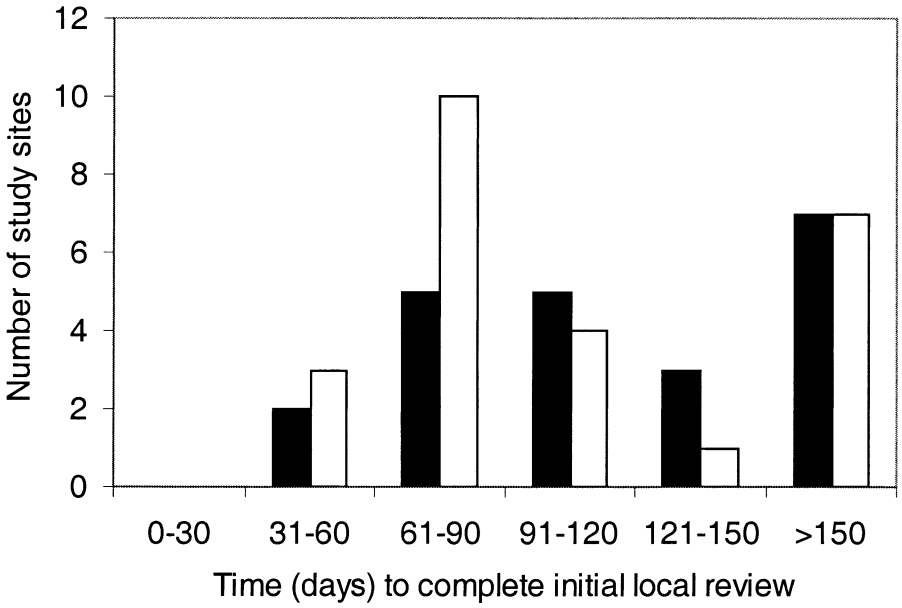

Fig. 1. Time in days from the release of TBTC Studies 24 (filled bars) or 25 (open bars) to local sites to the completion of the initial local review.

104.5 days (range 31–346) and was similar for Studies 24 and 25 (Fig. 1). There was a trend toward more time being required to obtain local approval if more than one local IRB reviewed the protocol (median time to approval of 96, 109, and 131 days for sites using one, two, or three IRBs, respectively, $p = 0.34$). Study sites estimated that the process of obtaining initial local approval required a median of 30 hours of staff time (range 10–48 hours).

No changes were made in the two study protocols as a result of local review. However, a median of 46.5 changes were made per consent form (range 3–160). Most of these were small changes (less than one sentence), with a median of 26 per consent form, as compared to a median of 10 large changes per consent form (Table 1).

With these changes, the locally approved consent forms were somewhat longer but had fewer sentences than the centrally approved consent forms, more words per sentence, and a higher proportion of sentences in the passive voice (Table 2). These changes increased the

Table 1. The number of changes per consent form made in centrally approved consent forms after local review

	Study 24	Study 25	Total
Small changes,[a] median (interquartile range)	25 (5–42)	29 (14–45)	26 (8–45)
Large changes,[b] median (interquartile range)	9 (5–19)	11 (5–21)	10 (5–21)
All changes, median (interquartile range)	37 (10–67)	47 (20–59)	46.5 (11–62)

[a] Changes involving less than one sentence.
[b] Changes involving one or more contiguous sentences.

Table 2. Summary of the effects of local review on readability of the consent form for TBTC Study 24 and 25

	Study 24		Study 25	
	Centrally approved consent form	Locally approved consent forms, median (interquartile range)	Centrally approved consent form	Locally approved consent forms, median (interquartile range)
Words	2188	2231 (2140–2320)	2218	2323 (2271–2412)
Sentences	137	130 (112–137)	135	134 (105–170)
Words per sentence	13	17 (16–18)	15.8	17 (13–22)
Sentences in the passive voice	13%	20.0% (10–20%)	9%	12% (10–20%)
Reading grade level	7.4	8.0 (8.0–9.0)	7.2	8.0 (8.0–9.0)

reading level by a mean of 0.9 ($\pm$0.9) reading levels ($p < 0.001$). Of the 50 locally approved consent forms, 21 (41%) had an inappropriately high reading grade level (above the eighth grade).

There was no relationship between the total number of changes per consent form and the reading grade level ($p = 0.47$), but a strong linear correlation between the number of large changes and reading grade level for both Studies 24 and 25 ($p = 0.001$, $r^2 = 0.54$) (Fig. 2). There was no relationship between the number of IRBs per site and the number of changes made (data not shown).

The local IRBs of 12 sites had suggested or required language (the IRBs at the other 13 sites had general guidelines for consent forms, but no suggested or required language). The median reading grade level for the suggested or required language was 10.8 (range 8.6–12.0).

Of the 2347 changes categorized, the two primary reviewers agreed on the classification of 1999 (85%). After the final categorization by the third reviewer, 85.2% of the changes were classified as being changes in wording that did not change the meaning of the consent form (Table 3). Relatively few changes ($n = 36$, 1.5%) were thought to represent a need to fit specific local conditions. Most of the changes to fit local conditions dealt with differences in local policies regarding health care and compensation for research-related injury (particularly at Veteran's Administration and Canadian sites). There were also few changes ($n = 39$, 1.7%) of potential relevance to all study sites. However, errors were commonly introduced (264 changes, 11.2% of all changes) during local review. Approximately half of the errors were errors in protocol presentation or required parts of the consent form (117 changes) and the remainder were grammatical or spelling mistakes (147 changes). Of the 50 consent forms from the two studies, 40 (80%) had at least one error; 33 (66%) had an error of protocol presentation or a required consent form element.

The most common errors of protocol presentation or required consent form elements (Table 4) were minor errors in the description of study procedures (e.g., the omission of the need for a urine sample) or in required parts of the consent form (e.g., incorrectly stating that the manufacturer of rifapentine would have access to study records). However, a substantial proportion of errors, 27.4% (32 of 117), were more substantive: deletions of significant side

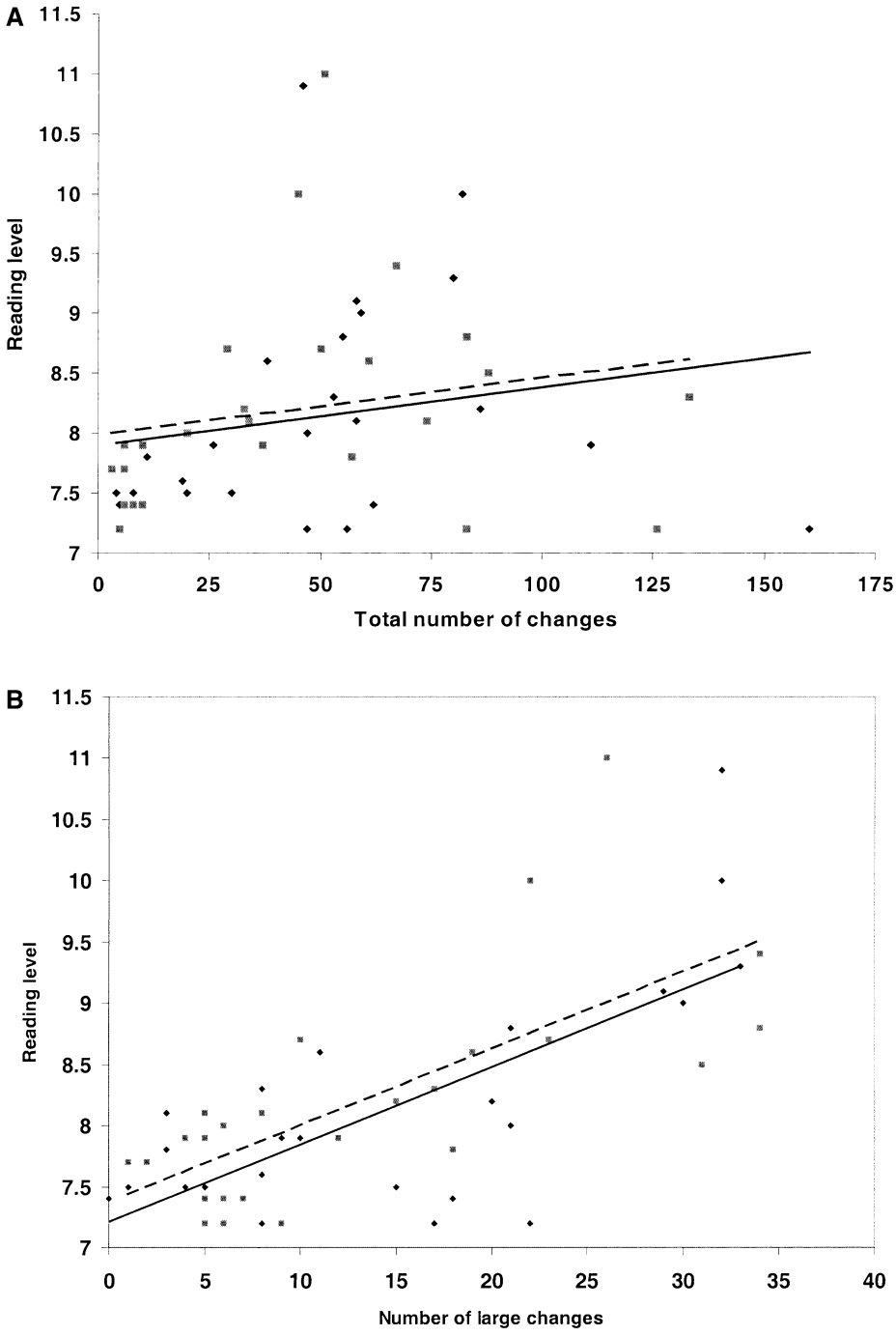

Fig. 2. The relationship between the number of changes made in the local review process and the reading grade level of consent forms (Study 24, dotted line; Study 25, solid line). There was no statistically significant relationship between the total number of changes (**A**) and reading grade level ($p = 0.47$), but there was a relationship with the number of large changes (**B**) and reading grade level ($p = 0.001$, $r^2 = 0.54$).

Table 3. Final categorization of changes made in centrally approved consent forms (TBTC Studies 24 and 25) after local review

Classification	Small change (n = 1649)	Large change (n = 698)	All changes (n = 2347)
Sentence or section moved, but not otherwise changed, n (%)	2 (0.1)	6 (0.9)	8 (0.3)
Change in wording without a change in meaning, n (%)	1461 (88.6)	539 (77.2)	2000 (85.2)
Change to fit local conditions, n (%)	9 (0.5)	27 (3.9)	36 (1.5)
Grammatical or spelling mistake, n (%)	129 (7.8)	18 (2.6)	147 (6.3)
Error in protocol presentation or required consent form element,[a] n (%)	33 (2.0)	84 (12.0)	117 (5.0)
Potentially relevant for all study sites, n (%)	15 (0.9)	24 (3.4)	39 (1.7)

[a] Study procedures, risks, benefits, alternatives, confidentiality, compensation for research-related injury, contact information, voluntary nature of research and the right to withdraw, conditions under which the subject can be removed from the study, costs to the subject, new findings communicated to the subject [12].

effects (e.g., the possibility of hepatotoxicity from rifampin and/or pyrazinamide), major errors in the description of study procedures (e.g., incorrect information on study duration), or the complete removal of a required section of the consent form (e.g., the right to withdraw from the study).

Discussion

We evaluated the local review process of two protocols from a multicenter clinical trials group. Local review was a time-consuming process, requiring a median of 30 hours of work by the local study site and more than 3 months of calendar time to complete. During this process many changes were made in the centrally approved consent forms. The resulting consent forms were generally longer, more complex (i.e., had an increased reading grade level), and often contained errors.

Only a few studies have examined the effects of local IRB review on multicenter protocols. The median time for local review in an evaluation of 100 multicenter protocols in Spain was 85 days [8]. Studies of local review of single multicenter trials have shown median times to approval of 46–102 days [9,14,15], the higher figure coming from a recent multicenter study in the United States [16]. In our study there were marked differences in the consent forms from different sites after local review, with some having only minimal changes from the standard and others having up to 160 changes. Similar variability has been found in the few studies that have formally evaluated the effects of local review on multicenter protocols and consent forms [7,16–18]. In a study of local review of a randomized trial comparing different strategies for mechanical ventilation, one IRB waived the need for informed consent, some allowed telephone consent, while others required written informed consent of a family member [18]. Among the IRBs requiring consent, the informed consent documents differed substantially. Only 3 of 16 (19%) approved informed consent documents contained all elements required by federal regulations [18].

Table 4. Summary of the types of errors in consent forms after local review

Type of error	Study 24	Study 25	Total (%)
Error in background information	7	7	14 (12.0)
Minor error in description of study procedures	11	22	33 (28.2)
Major error in description of study procedures[a]	5	8	13 (11.1)
Minor error in side effects section	4	11	15 (12.8)
Major error in side effects section[b]	8	5	13 (11.1)
Error in another required section	10	13	23 (19.7)
Complete deletion of a required section	3	2	5 (4.3)
Addition of exculpatory language[c]	1	0	1 (0.9)
Total	49	68	117

[a] Incorrect information on duration of treatment ($n = 5$), incomplete information on contraception ($n = 2$), deletion of the statement that study therapy would be directly observed ($n = 1$), deletion of the statement that the highest experimental dose would only be evaluated after the demonstration of the safety of a lower dose ($n = 1$), need for follow-up after completing treatment ($n = 1$), deletion of the statement that therapy would be prolonged if the study regimen was not effective ($n = 1$), errors that made sentences nonsensical ($n = 2$).

[b] Deletion of hepatoxicity from rifampin or pyrazinamide ($n = 4$), deletion of drug interactions from rifapentine ($n = 3$), incorrect information about contraception ($n = 2$), deletion of arthralgias from pyrazinamide ($n = 1$), deletion of neuropathy from isoniazid ($n = 1$), addition of side effects from a drug not in the protocol ($n = 1$), nonsensical statement ($n = 1$).

[c] Language "through which the subject or the representative is made to waive or appear to waive any of the subjects' legal rights" [12].

Readability of consent forms is an important aspect of obtaining written informed consent. Therefore, it was disconcerting that many consent forms became less readable after local review. Indeed, "boilerplate language" from a number of local IRBs required that consent forms become less readable. Studies over the past 25 years have consistently found that local IRBs approve consent forms having overly complex language. In evaluations of 1086 consent forms reviewed by 166 local IRBs, the average reading grade level of approved consent forms ranged from 11.1 to 16.2 [19–24], including, remarkably enough, assent forms for children [25].

Our study was an in-depth evaluation of the effects of local review on consent forms. As such it provides fine detail of the kinds of changes made to the written document, but it also has clear limitations. We evaluated two consent forms submitted to a relatively small number of local IRBs (compared to the 3000–5000 IRBs thought to exist in the United States alone) [5]. We did not evaluate the effects of local IRB review on industry-sponsored research, nor did we evaluate the review process by an independent IRB. In addition, the two consent forms we evaluated had been prepared by a research group with specific concerns about readability and had been approved by a central IRB. We are unsure whether our conclusions apply to consent forms from multicenter clinical trials that have not gone through this process. However, the 25 TBTC study sites include academic medical centers, Veteran's Administration Medical Centers, and public health departments chosen in large part for their experience in clinical research. Thus, this study includes local sites and IRBs that are likely to be representative of large institutions oriented toward clinical research. Finally, our study did not evaluate other ways in which the local IRB may affect the conduct

of multicenter clinical trials (education of investigators, determining the suitability of local study sites, etc.).

Additional research is needed to characterize more fully the impact of local review on multicenter clinical trials. However, our results support the findings and recommendations of two recent comprehensive reviews, by the National Bioethics Advisory Commission [26] and the Institute of Medicine [27], of the human subjects protection system in the United States. The Institute of Medicine concluded that duplicative review of multicenter protocols by the IRB of each study site does not add to human subjects protection and that the resultant variability in the research protocol and consent "actually detracts from participant protections" [27]. Both reviews noted that review of multicenter protocols has overloaded the local IRB system and both called for evaluation of alternatives to the present system.

Current federal regulations allow an IRB to cede oversight to another IRB [12]. Using this feature of the regulations, the National Cancer Institute has undertaken a pilot project of having local IRBs cede oversight for phase III multicenter trials to a specialized central IRB [28]. The Tuberculosis Trials Consortium, working with an IRB at the CDC having expertise in ethical issues in studies involving tuberculosis, is also initiating such a system. Other institutions have cooperative agreements allowing review of multicenter clinical trials by a single IRB in the consortium, rather than having the IRB of each institution undertake a full review [27].

Perhaps the most important result of our study is that of illustrating the value of doing research on the process of research oversight. Many areas of the human subjects protection system would benefit from careful quantitative study, including alternative methods for writing consent forms and obtaining informed consent [29], different systems for reporting and evaluating of possible adverse events, and alternative forms of IRB review.

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