Time to institutional review board approval with local versus central review in a multicenter pragmatic trial

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Abstract
Background/aims: Central institutional review board (IRB) review will be required for National Institutes of Health–funded multisite human subjects research as of January 2018, with similar requirements extending to most US multisite human research in 2020. Nonetheless, little is known regarding the relative efficiency of central versus local IRB review for multicenter studies. We compared the amount of time required for central versus local IRB review and approval for sites in one ongoing multicenter randomized trial.

Methods: The REGAIN Trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture; clinicaltrials.gov number: NCT02507505) is an ongoing randomized trial comparing standard-care spinal anesthesia to standard-care general anesthesia for patients undergoing hip fracture surgery. After approval of the protocol by the sponsor IRB, each participating US site opted either to submit the protocol for local IRB review or to designate the sponsor IRB as the IRB of record (i.e. central IRB) via an authorization agreement after a limited local review. For each US REGAIN site approved through 18 April 2017, we assessed (1) the time in calendar days from protocol receipt to IRB submission, (2) the time in calendar days from IRB submission to IRB approval, and (3) the total time in calendar days from protocol receipt to IRB approval (i.e. time from protocol receipt to IRB submission plus time from IRB submission to IRB approval).

Results: The main study protocol was submitted to the sponsor IRB on 25 May 2015 and approved on 8 July 2015 (44 days). Out of 34 sites, 9 received initial approval from the central (sponsor) IRB; 25 sought initial approval via local review. The median time from protocol receipt to IRB submission was 39 days for sites approved by the central IRB (interquartile range: 35–134) versus 58 days for sites approved via local review (interquartile range: 41–105; p = 0.711). The median time from IRB submission to IRB approval for sites approved by the central IRB was 27 days (interquartile range: 14–32) versus 66 days (interquartile range: 29–138) for sites approved via local review (p = 0.026). The median total time from protocol receipt to IRB approval was 100 days (interquartile range: 71–148) for centrally approved sites versus 132 days (interquartile range: 87–209) for locally approved sites (p = 0.191).

Conclusion: While central IRB review was associated with a shorter time from IRB submission to IRB approval compared to local IRB review, the total time from protocol receipt to IRB approval varied markedly across sites.

Keywords
Central institutional review board review, pragmatic trials, aging

Introduction
Beginning in January 2018, central institutional review board (IRB) review will be required for National Institutes of Health (NIH)-funded multisite human subjects research.1 in 2020, similar requirements will apply to US multisite human research more generally under recent Federal regulations.2 Past empirical research has shown local IRB review of multicenter
studies to be associated with inconsistencies in ethics review processes and delays in study initiation.3–6 Increasing use of central IRB review for multicenter studies is intended to increase the efficiency of multicenter studies while also promoting consistency of ethics review across participating sites.7,8 Nonetheless, little is currently known regarding the relative efficiency of central versus local IRB review for multicenter studies.7–11 Here, we compared the time required for central versus local IRB review and approval for sites in an ongoing multicenter randomized trial. We hypothesized that the time from IRB submission to IRB approval would be shorter under central versus local review.

Methods

The design of the REGAIN Trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture; clinicaltrials.gov number: NCT02507505) has been described elsewhere.12 After providing written informed consent, participants are randomized to receive standard-care spinal anesthesia or standard-care general anesthesia for hip fracture surgery; the primary outcome is recovery of independence in walking at 60 days after randomization.

After initial approval of the protocol by the sponsor IRB (University of Pennsylvania, Philadelphia, PA), each US site chose either (1) to submit the protocol for review and approval by their local IRB or (2) to agree to rely on the sponsor IRB as the IRB of record (i.e. central IRB) via an authorization agreement following a simplified local review. Upon joining the study, each site received an email from the coordinating center with the approved protocol, a template informed consent form, other documents for IRB submission, a draft IRB authorization agreement and a table delineating the specific responsibilities of the central (sponsor) IRB, the relying IRB, and the local investigator under the authorization agreement. Copies of the draft IRB authorization agreement and the provided table appear in the online Appendix.

Sites were permitted to modify the informed consent document to add site information and to adhere to local formatting and content standards. Sites were also permitted to opt out of enrolling, via proxy consent, individuals who could not provide their own consent. Other protocol modifications were not permitted.

For US sites approved through 18 April 2017, we assessed three time intervals: (1) the time in calendar days from protocol receipt to IRB submission, (2) the time in calendar days from IRB submission to IRB approval, and (3) the total time in calendar days from protocol receipt to IRB approval (i.e. time from protocol receipt to IRB submission plus time from IRB submission to IRB approval; Figure 1). We obtained hospital characteristics data from the 2015 American Hospital Association Survey and 2016 NIH funding data from the NIH Research Portfolio Online Reporting Tool (https://report.nih.gov/). For centers with two or more hospitals overseen by a single IRB, hospital characteristics data were analyzed for the largest network hospital by bed count. Analyses compared characteristics and outcomes for centers approved via local versus central review using Fisher’s exact test for categorical variables; for continuous variables, we used the Wilcoxon rank-sum test as we anticipated that the distribution of times required for IRB submission and review could be skewed. We considered $p < 0.05$ to indicate statistical significance. This analysis was exempt from IRB review.

Results

The main study protocol was submitted to the sponsor IRB on 25 May 2015 and approved on 8 July 2015.
Out of 34 sites, 9 received initial approval from the central (sponsor) IRB; 25 sought initial approval via local review. Compared to sites undergoing local IRB review, sites approved via central review were more often under governmental, non-federal ownership versus private, not-for-profit ownership (33% vs 4%, p = 0.048); sites approved via central versus local review did not differ significantly in terms of membership in the Association of American Colleges Council of Teaching Hospitals (7 of 9 (78%) vs 22 of 25 (88%), p = 0.591), receipt of any fiscal year 2016 NIH funding (9 of 9 (100%) vs 21 of 25 (84%), p = 0.554), or the fraction with hospitals of 500 beds of more (7 of 9 (78%) vs 20 of 25 (80%), p = 1.00).

Among all sites, the median time from protocol receipt to IRB submission was 57.5 days (interquartile range (IQR): 36–115), the median time from IRB submission to IRB approval was 27 days (IQR: 14–32), and the median total time from protocol receipt to IRB approval was 122 days (IQR: 87–197). There was substantial variation in the duration of all three intervals across sites, with a greater than twofold difference between the 25th percentile value and the 75th percentile value for each measure (Figure 2).

Table 1 compares the study outcomes for sites approved via local versus central review. The median time from protocol receipt to IRB submission was 39 days for sites approved by the central IRB (IQR: 35–134) versus 58 days for sites approved via local review (IQR: 41–105; p = 0.711). The median time from IRB submission to IRB approval for sites approved by the central IRB was 27 days (IQR: 14–32) versus 66 days (IQR: 29–138) for sites approved via local review (p = 0.026). The median total time from protocol receipt to IRB approval was 100 days (IQR: 71–148) for centrally approved sites versus 132 days (IQR: 87–209) for locally approved sites (p = 0.191).

Discussion

In this multicenter trial, central IRB review was associated with a shorter time from protocol submission to initial approval compared to local IRB review. At the median, the time from protocol submission to IRB approval was 39 days shorter for sites approved via central review than for sites approved via local review. Neither the time from protocol receipt to IRB submission nor the total time from protocol receipt to IRB approval differed between sites approved via central versus local review. For sites approved via central IRB review as well as those approved via local IRB review, we observed marked variability across sites in terms of the overall time from protocol receipt to IRB approval, with a more than twofold difference in the number of days required for a site in the 25th percentile compared to a site in the 75th percentile in each group.

Our study builds on prior work in this area. A 2010 mailed survey of oncology study coordinators and IRB staff regarding their experiences with the National Cancer Institute (NCI) Central IRB found central IRB review to be associated with reported review times that were 34 days shorter on average than those reported in the literature. The median time from protocol receipt to IRB submission for sites approved via central IRB was 39 days (IQR: 35–134) versus 58 days for local review (IQR: 41–105), a difference that was not statistically significant (p = 0.711). Similarly, the median time from IRB submission to IRB approval was 27 days (IQR: 14–32) versus 66 days (IQR: 29–138) for central versus local review, respectively, with a statistically significant difference (p = 0.026). The median total time from protocol receipt to IRB approval was 100 days (IQR: 71–148) for centrally approved sites versus 132 days (IQR: 87–209) for locally approved sites (p = 0.191).

Table 1. Study outcomes by route of initial IRB approval.

<table>
<thead>
<tr>
<th></th>
<th>Sites receiving initial approval via central IRB review (N = 9)</th>
<th>Sites receiving initial approval via local IRB review (N = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in days from protocol receipt to IRB submission, median (IQR)</td>
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<td>0.711</td>
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</tbody>
</table>

IRB: institutional review board; IQR: interquartile range.
for local review. Our findings confirm this work and extend it in at least two important ways. First, by using dates obtained directly from site IRB submission and approval records, our analysis avoids potential recall biases that may occur with survey response data. Second, prior to 2012, the NCI Central IRB used a "facilitated review" model in which the NCI Central IRB did not serve as the IRB of record; our work thus provides new data of relevance to contemporary models of central IRB review, including the approach used by the NCI Central IRB since 2012, in which participating sites authorize a central IRB to serve as the IRB of record.

Our data come from a single multicenter trial and examine one model of central IRB review; as such, our findings require confirmation in other contexts. As sites were not randomly assigned to central versus local IRB review, we cannot draw causal conclusions regarding the effect of the route of initial IRB review on study approval times. Finally, given the limited sample available for analysis, our study may have underpowered to detect significant differences between sites approved via central versus local IRB review in terms of the time from protocol receipt to IRB submission or the total time from protocol receipt to IRB approval.

Nonetheless, this work offers important insights for policy and practice. First, it suggests that broader use of centralized IRB review may increase the efficiency of future multicenter trials overall. Second, given the variability in approval times that we observed across sites in our study that used central IRB review, our findings suggest that adoption of a central IRB model alone may not be sufficient to eliminate delays in study initiation related to human subjects review processes. While not formally evaluated here, variations in approval times across centrally approved sites in our study may have stemmed from differences across study teams in workflows related to preparation of IRB submissions; differences across sites in organizational requirements for administrative protocol review prior to IRB submission; or differences across site IRBs in the time required to complete required local reviews and to finalize IRB authorization agreements. Additional research is needed to evaluate the degree to which these or other factors may contribute to variations in the time required for central IRB approval across institutions and to define organizational best practices that may support the overall efficiency of centralized models of IRB review.

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Declaration of conflicting interests

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The sponsor had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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