Introduction. The time required to obtain Institutional Review Board (IRB) approval is a frequent subject of efforts to reduce unnecessary delays in initiating clinical trials. This study was conducted by and for IRB directors to better understand factors affecting approval times as a first step in developing a quality improvement framework.

Methods. 807 IRB-approved clinical trials from 5 University of California campuses were analyzed to identify operational and clinical trial characteristics influencing IRB approval times.

Results. High workloads, low staff ratios, limited training, and the number and types of ancillary reviews resulted in longer approval times. Biosafety reviews and the need for billing coverage analysis were ancillary reviews that contributed to the longest delays. Federally funded and multisite clinical trials had shorter approval times. Variability in between individual committees at each institution reviewing phase 3 multisite clinical trials also contributed to delays for some protocols. Accreditation was not associated with shorter approval times.

Conclusions. Reducing unnecessary delays in obtaining IRB approval will require a quality improvement framework that considers operational and study characteristics as well as the larger institutional regulatory environment.

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In addition, despite currently being neglected from methodological discussions, speed alone should not be the sole metric considered when seeking to improve IRB performance; in some cases, protocols require revision and delays could be entirely appropriate.

To obtain a new perspective on IRB processes and efficiency, the IRB directors and the University of California, Biomedical Research, Acceleration, Integration, and Development (UC BRAID) collaborated on a project to define and assess key metrics for IRB efficiency and set the stage for quality improvement efforts within and across 5 California campuses of University of California (UC). The IRB directors identified the main operational and study characteristics to be analyzed based on their collective experience. Each of the variables selected was then operationally defined (including supporting examples) to ensure data harmonization and interinstitutional comparability.

The goals are to identify (1) operational and study characteristics that affect administrative, committee, and total IRB approval times, (2) compare data between the 5 UC campuses for “lessons learned” that can identify practices associated with shorter approval times, and (3) begin developing a high-level quality improvement assessment framework.

Materials and Methods

Study Design

This study examines the relationship between the operational characteristics (the “institutional capacity”) of 5 UC IRB offices, the attributes of clinical trials (“nature of the task”) involving Food and Drug Administration (FDA)-regulated products and the time required to obtain IRB approval (“outcome”). Operational characteristics included frequency of IRB meetings, staffing ratios, volume of approvals, and type of accreditation. To calibrate performance drivers across campuses, analysis for this segment of the study was restricted to phase 3 multisite studies.

Study attributes included phase, funding source, authorship, and types of ancillary reviews, among others. Approval times were operationally defined as:

- The number of days between initial submission of a research approval application to the IRB and the submission being sent to Committee (Administrative Review),
- The number of days between initial IRB review and full Committee approval (Committee Review).

Eligible trials met all of the following three criteria: (1) they were designed to evaluate the safety, tolerability, or efficacy of an FDA-regulated device or drug; (2) they were received by an IRB on or after January 1, 2014; and (3) they obtained full IRB approval on or before December 31, 2014. Table 1 presents a detailed list of all data elements used in this analysis.

Quality Control Process

Data management and quality control adhered to ISO 8000-110:2008 standards and followed CRISP-DM guidelines [4, 5]. Each UC IRB Director received monthly quality control reports on the number of cases submitted that month, the number and type of potential data entry errors for review, and corrected or verified for specific cases. As a result, data entry errors were <0.01% exceeding ISO/ANSI 13606-3:2009 [6].

Statistical Analyses

Data Preparation and Analysis

Continuous data, such as approval times, were evaluated to determine their distribution type and variance homogeneity to help in the selection of the statistical measures. This included Tukey and Grubbs tests to identify statistically significant “outliers” and “extreme” cases. Continuous data not found to satisfy assumptions required for parametric analyses underwent either Mann-Whitney U test (with continuity correction), when examining interactions with a single dichotomous variable (e.g., commercially sponsored or PI initiated), or Kruskal-Wallis analysis of variance (ANOVA) when exploring multiple categories (e.g., study phase). Wilcoxon-signed rank test was used when the interactions of interest involved 2 continuous variables such as duration and number of ancillary reviews.

Consistent with current recommendations for conducting quality improvement assessment, we report descriptive statistics using median, standard deviation, upper and lower quartiles, and percent outliers (Tables 2 and 3). The combination of upper and lower quartiles is used in quality improvement to identify how “in control” a particular process is as well as whether there might be subprocesses or special causes associated with “outlier” and “extreme” cases identified by the Tukey and Grubbs tests that require special attention and additional analysis [7, 8].

Table 1. Data collected for analysis

| Study characteristics | Outcomes |
|-----------------------|----------|
|                        | Days between first reviewed and approved | Days between first reviewed and approved |
| Total number of clinical trials reviewed | Total number of FTEs | FTE to protocol ratio |
| Number of committees | Frequency of committee meetings | Proportion of FTE holding CIP certification |

Study phase

- Federally funded
- Investigational device exemption
- Biosafety review required
- On behalf of the IRB, the Institutional Review Board; PI, principal investigator.

- Private foundation funded
- Oncology/hematology
- Conflict of Interest Review required

- PI-authored
- Number of ancillary reviews required
- Scientific Review Committee

- Commercial sponsored
- Radiation safety review required
- Medicare Billing/Coverage Analysis

- Investigational drug
- Table 1 presents a detailed list of all data elements used in this analysis.
Eight hundred seven protocols met criteria for inclusion into this study of which 205 were phase 3 multisite studies. Results presented in this section are restricted to variables with statistically significant results \( \leq 0.01 \).

## Operational Characteristics

### Operational Characteristics and Administrative Review Times

Staff workload, as measured by the number of protocols per FTE \( (p = 0.0047) \) negatively impacted administrative review time whereas staff training, as measured by percent of certified IRB professional staff \( (p = 0.0029) \) had a positive effect. Interestingly, there was also suggestion of a queuing effect where more frequent IRB Committee meetings was associated with shorter administrative review times \( (p = 0.0249) \).

### Operational Characteristics and Committee Review Times

Dramatic differences in median time to complete reviews between individual committees were observed within each university. Of the 15 individual IRB committees contributing to this study, 3 accounted for 82% of all the committee review outliers though only represented 30% of the studies included in the analysis \( (p = 0.019) \). The median committee review time for these 3 committees was 57 days \( (\text{interquartile} = 34–71) \) compared with 28.5 \( (\text{interquartile} = 14–55.5) \) for the other 12 committees.

### Operational Characteristics and Total Times for Approval

Operational characteristics affecting total approval times reflect those of administrative and committee review times. Specifically, higher staff workload was associated with longer total approval times \( (p = 0.0026) \) while certified IRB professional-certified staff were associated with shorter total approval times \( (p = 0.0006) \).

## Study Characteristics

### Study Characteristics and Administrative Review Times

The most striking influence on time required to complete administrative reviews was the number and type of ancillary reviews by other

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regulatory committees ($p = 0.0063$). In particular, Biosafety Review (median = 28, SD = 34.6, interquartile = 15–49), Scientific Review (median = 27, SD = 36.6, interquartile = 15–48), and Coverage Analysis (median = 23.0, SD = 32.3, interquartile = 15–38) were most notably associated with longer approval durations. Indeed, all phase 3 multisite administrative review outliers (100%) implicated Coverage Analysis as a driver. In addition, investigator-initiated studies (median = 29, SD = 36.1, interquartile = 18–49) and multisite studies (median = 24, SD = 53.1, interquartile = 16–38) also required significantly longer time for administrative review.

Conversely, private foundation funded (median = 15, SD = 31.9, interquartile = 14–27) and commercially sponsored studies (median = 22, SD = 31.4, interquartile = 14–34) required significantly less administrative review time, as did studies involving investigational drugs (median = 22, SD = 38.4, interquartile = 15–36) or oncology studies (median = 21, SD = 38.4, interquartile = 14–36).

### Study Characteristics and Committee Review Times

The number, rather than the type of ancillary reviews, associated with a given study proved to be the dominant influence on Committee Review times ($p = 0.0027$). Funding source also affected the time required by an IRB Committee to approve a new proposal, often in the opposite direction from that found with administrative review times. For instance, private foundation funded (median = 60, SD = 67.7, interquartile = 36–100) and commercially funded studies (median = 42, SD = 56.7, interquartile = 20–71) required significantly longer committee time. Yet, federally funded (median = 23, SD = 57.5, interquartile = 6–48), PI initiated (median = 30.5, SD = 53.0, interquartile = 15.5–64), and multisite studies (median = 33, SD = 53.1, interquartile = 15–57) required less committee review time.

### Study Characteristics and Total Times for Approval

Consistent with both administrative and committee review times, the number and types of ancillary reviews significantly influenced total review time or duration. Biosafety Review (median = 81, SD = 67, interquartile = 48–119), Scientific Review (median = 77, SD = 65.8, interquartile = 47–116), and Coverage Analysis (median = 73, interquartile = 38–115) again feature prominently but total number of reviews ($p = 0.0001$) dominated as a mediator of total time required to receive IRB approval (Fig. 1).

Funding source also was related to total approval time, with federally funded studies (median = 60, SD = 68.8, interquartile = 34–83) approved significantly faster than privately funded studies (median = 84, SD = 73.1, interquartile = 57–123). Finally, multisite studies (median = 63, SD = 62.3, interquartile = 40–96) also required significantly less time to receive IRB approval.

### Discussion

The present study of over 800 clinical trials is one of the largest multisite efforts to understand variables that affect IRB performance...
adding to the emerging body of literature [2, 3, 9–13]. Uniquely, this study was created by and for IRB directors from multiple campuses working under the same institutional policies in meeting those institutional polices as efficiently as possible. This allowed us to not only focus on issues identified as involved with the regulatory process but also to compare procedures and begin formulating best practices. The findings both support previous published results as well as identify new factors affecting IRB approval time.

Consistent with previous findings [2, 3], ancillary reviews increased the time required to receive IRB approval. Three campuses reported only 15% of their clinical trials required 3 or more ancillary reviews whereas 50% of the clinical trials at the other 2 campuses had 3 or more ancillary reviews. The median time to receive IRB approval between the 2 groups was 58 and 85 days, respectively. The difference between campuses was true even for phase 3 multicenter studies, suggesting a difference in policy interpretation at the 2 groups of campuses. This underscores the importance of not simply writing policies but also providing clarifying use cases to help calibrate decisions about when the IRB can review and make recommendations that might otherwise be the responsibility of a separate ancillary committee.

A new factor identified is the impact of workload (number of protocols per FTE) on administrative review time. There was no attempt to identify optimal ratios in the tradeoff between cost of IRB employees and the opportunity costs of delayed IRB approval.

The study highlights the value of frequent feedback in improving performance in 2 different domains: data quality and response time. Using ISO/ANSI 13606-3:2009 standards to provide monthly feedback and data entry errors reduced the rate of errors from 6% during the first month to <0.01% by the ninth month. Equally striking was the reduction in median total duration from 103 days during the first quarter of this study to a median of 62 days by the third quarter of data collection. There is enormous potential for improvement by including quality improvement such as Statistical Process Control and Pareto Charts to monitor both durations and factors associated with improvement such as Statistical Process Control and Pareto Charts to improve the speed and efficiency of the review process.

Finally, this study suggests that while there are categories of study and operational characteristics that impact approval times, the pattern of critical variables is likely to vary from one IRB to the next. Rather than focus on a single outcome measure such as total duration time, it is more productive to develop a quality improvement framework that individual IRBs can use to identify challenges at their respective campuses. Doing so would permit the development of a common problems-common solutions matrix. Such a framework would minimally be composed of 4 dimensions (see Table 4).

The first, most obvious and seldom mentioned in the literature, is IRB staff workload. This domain has 4 major components:

(1) Staffing levels for the volume of work,
(2) the mix of trained analysts and support staff,
(3) the adequacy of infrastructure such as electronic tracking systems, and
(4) the skills and training of the staff.

The second potential dimension for assessment is committee-to-committee variation in workflow, expertise and guidance provided by staff and the chairperson. For example, 3 of the 13 Committees included in this study accounted for the majority of “outlier” cases even though they reviewed only 30% of the protocols. Potential causes include:

(1) Committee workload (the number of new, renewal, deferred, addendum, violation, adverse event, and safety reports assigned to each committee member per meeting);
(2) The knowledge and expertise of committee members relative to the content of the IRB application (e.g., a committee member unfamiliar with standard of care for a given discipline—may not be comfortable in determining risk levels and will ask for additional information from an applicant); and
(3) The internal dynamics of a committee. There may be times in which competition develops between committee members to identify errors in the study design.

The third dimension is the quality of submitted protocols. Regulations affecting IRB determinations are both dynamic and complex. Timing and context matter: what may have been considered a complete and adequate application 5 years ago might no longer meet regulatory review requirements. Conversely, advances in complex adaptive clinical trial designs or in personalized medicine research pose challenges to current guidelines. Drivers of these issues are:

(1) Current regulatory knowledge of the investigator submitting a protocol,
(2) The degree to which that investigator is able to articulate the risk and benefits of the proposed protocol.

Table 4. Suggested analytic framework for Institutional Review Boards quality improvement efforts

| Dimension                  | Potential contributors                                      | Potential solutions                      |
|----------------------------|-----------------------------------------------------------|-----------------------------------------|
| Staffing workload          | Inadequate staffing                                       | Benchmarking                            |
|                            | Wrong mix                                                 | Develop business case                   |
|                            | Training                                                  | Identify key content knowledge and work ethics |
|                            | Inadequate infrastructure                                 | Explore options for supportive technology |
| Committee workload         | Meeting frequency                                          | Benchmarking                            |
|                            | Volume and types of reviews X meeting X committee member   | Feedback/policy/education               |
|                            | Member training/understanding                              | Explore options for supportive technology |
|                            | Member knowledge and expertise                             |                                         |
|                            | Committee dynamics                                        |                                         |
|                            | Infrastructure                                            |                                         |
| Application quality        | Researcher knowledge of current regulatory requirements    | Training/concierge service              |
| Regulatory environment     | Number of other regulatory units                          | Supportive templates and use cases      |
|                            |                                                            | Institutional policy on sequential or parallel processing |
|                            |                                                            | Harmonized requirements and application forms |
|                            |                                                            | Supportive templates and use cases      |
The last dimension is the regulatory environment within which the IRB functions. This analysis corroborates previous studies [3] suggesting that much of the delay in IRB approval processes is driven by ancillary reviews from other regulatory units such as Medicare Coverage Analysis or Radiation Safety. Examples of such issues include:

1. Campus policies determining if ancillary reviews are conducted in parallel or in sequence to IRB review.
2. The degree of communication and harmonization between the different regulatory units.
3. The overall culture of the larger regulatory environment within which the IRB functions.

The present study has a number of potential limitations. First there was no attempt to define what quality of IRB administrative or committee review means. The rapid risk-benefit analysis for a study does not mean it is done well. This is an essential element of analysis that must be considered in any future iteration. Second, it is possible that important trial characteristics such as enrollment of vulnerable populations or research involving Veterans Administration (VA) facilities have been overlooked. Third, we did not attempt to control for the uneven volumes of human subjects research activity across the 5 campuses. These differences may operate to influence approval times in yet unknown ways. The 807 clinical trials that met criteria for inclusion into this study represented only a portion of the human subjects research portfolio at the participating UC campuses. As such, review and approval times may not reflect the levels of efficiency for a given campus. Finally, the time to approval analyzed in the present study did not include the time from approval to the time of release nor enrollment of the first patients into a trial, an important factor considered by many in industry to be representative of an institution’s regulatory efficiency.

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Disclosures

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