Systems approach to assessing and improving local human research Institutional Review Board performance

John Fontanesi1*, Anthony Magit1, Jennifer J. Ford1, Han Nguyen1 and Gary S. Firestein1,2

1 University of California at San Diego, San Diego, CA, USA
2 University of California Biomedical Research Acceleration, Integration & Development (UC BRAID), San Francisco, CA, USA

Received 10 October 2017; Revised 1 March 2018; Accepted 30 March 2018

Objective. To quantifying the interdependency within the regulatory environment governing human subject research, including Institutional Review Boards (IRBs), federally mandated Medicare coverage analysis and contract negotiations.

Methods. Over 8000 IRB, coverage analysis and contract applications initiated between 2013 and 2016 were analyzed using traditional and machine learning analytics for a quality improvement effort to improve the time required to authorize the start of human research studies.

Results. Staffing ratios, study characteristics such as the number of arms, source of funding and number and type of ancillary reviews significantly influenced the timelines. Using key variables, a predictive algorithm identified outliers for a workflow distinct from the standard process. Improved communication between regulatory units, integration of common functions, and education outreach improved the regulatory approval process.

Conclusions. Understanding and improving the interdependencies between IRB, coverage analysis and contract negotiation offices requires a systems approach and might benefit from predictive analytics.

Introduction

A central goal of the Clinical and Translational Science Awards (CTSA) initiative is to foster data-driven improvements in medical research infrastructure that “…increase the quality and efficiency of translational research, particularly of multisite trials.” [1] Local Institutional Review Boards (IRBs) have garnered much of this focus in numerous commission, federal agencies, and publications [2–11]. For example, a recent publication explored IRB performance across 5 University of California Schools of Medicine and proposed a model in which the interaction between operational conditions, study characteristics and proposal characteristics determines how quickly proposals are likely to be approved [11]. The multitude of studies have led to reform proposals have included centralizing IRBs [12], increasing federal oversight, credentialing, greater training [10, 13], and increasing resources for personnel and technology [14]. Furthermore, the time required to acquire IRB approval is now a core “common metric” for all CTSA-funded institutions [15].

However, local IRB’s do not operate in isolation but rather function within a larger regulatory environment (see supplementary Figure A) [11, 16–19]. For example, an IRB-approved informed consent form (ICF) must inform a subject about their potential financial liability. That financial responsibility is negotiated between the contracting unit, the investigator and the sponsoring agency. The terms of that contract are, in turn, reviewed by the institution’s Medicare billing coverage analysis unit to assure compliance with the Centers for Medicare and Medicaid Services regulations. All 3 units have different regulatory oversight for the same section of the consent form and must coordinate their respective language before the consent can be released and a study initiated.

Received 10 October 2017; Revised 1 March 2018; Accepted 30 March 2018

Key words: Common metrics, Institutional Review Board, best practices, clinical trials, quality improvement.

© The Association for Clinical and Translational Science 2018. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
The University of California at San Diego (UCSD) Altman Clinical and Translational Research Institute has prioritized improving the performance of the human research regulatory environment. This effort led to the creation of the Workflow, Outcomes and Quality Improvement Office, which collects and analyzes operational data, conducts data-driven quality improvement (QI) studies and modifies the workflows of regulatory offices. The present study is a novel approach through the systems analysis to explore the relationship between the various offices and identifies actionable data that can improve performance.

**Methods**

**Data Collection and Analysis**

This process adhered to the International Council on Systems Engineering Standards (INCOSE) QI [20]. Systems engineering is based on the fundamental principle that the world is composed of inter-related systems such that improvement in any one system requires understanding both the nature of that component and the environment within which it exists. INCOSE QI standards are highly detailed, incremental, iterative and flow through a series of prescribed steps from project planning, project assessment, project control, decision making, data analysis, through alternative strategy risk and opportunity assessment to data analysis/modeling, exploring alternatives to the “AS-IS” state, pilot testing and re-assessment.

Each stage begins with a declaration of the “customer’s” requirements, in our case—to understand and improve the regulatory environment for clinical research at UCSD. This methods and analysis are an example of how INCOSE QI methods can be used to improve the regulatory environment affecting human subject research with a specific focus on how data analysis can identify the actionable interdependencies between different elements of the regulatory environment.

**Parameters Selected for Study**

In the data collection process, we identified 18 entities at UCSD with direct influence on the approval of clinical research studies (see supplementary Figure A for an organizational flow chart). Based on interviews with the unit directors, we selected the 2 units perceived to have to most frequent interactions with UCSD IRB: Office of Coverage Analysis and Office of Contract Analysis (see supplementary Figure B for a high-level flow chart).

We then interviewed and directly observed researchers applying for regulatory approval, analyst reviewing these applications and faculty IRB committee members reviewing new proposals.

Based on this preliminary work and review of the literature, we then selected data fields from the IRB, Office of Coverage Analysis and Office of Contract Analysis data management systems for analysis, using ISO 9004:2000 for process and productivity measures, ISO/IEC 15504 for technology measures and ISO 2859-1 and ANSI/ASQC Z1.9-1993 for sampling procedures [21, 22]. This amounted to 110 data fields contained in 8200 IRB, 4200 Coverage Analysis and 350 new contracts submitted between 2013 and 2016. We constructed and verified data dictionaries for the data fields followed by data cleaning, verification, and validation using Cross-Industry Standard Process for Data Mining (CRIP-DM) methodology [23].

**Data Analysis**

Following data cleaning, verification, and validation procedures, the next step in analyzing interdependencies is to explore the distribution characteristics of the data elements. This is an often overlooked but critical QI step or, when done, non-normally distributed data are “normalized” by removing outliers. INCOSE QI uses the distribution family to select appropriate statistical techniques and explores “outliers” as “special cause” or “assignable cause” of undesirable performance variation requiring separate analysis and interventions [24]. As part of our QI effort, we developed predictive models of outliers using 2013-2015 data to predict 2016 performance data to assess the stability of the factors creating “outliers” to help determine the feasibility of, first identifying new proposals likely to become outliers and, then, providing a more interventional path to help the investigators address likely challenges in achieving regulatory approval in a timely manner.

**Statistical Methods**

Following INCOSE methodology, non-normally distributed data are reported using quintile regression, such as Kruskal-Wallis ANOVA, and predictive analytics [25, 26] with the direction and dispersion of the data best represented as medians, 25th and 75th percentiles [27]. “Outliers” were analyzed using K-Means and Tree Clustering data mining techniques. Both data mining techniques can be used when there is a mixture of Gaussian distributions.

**Results**

**Time Required for IRB Approval**

In total, 3389 new human subject research protocols, including 618 commercial sponsored studies, submitted to the UCSD IRB Regulatory Environment (IRB environment) between January 2013 and December of 2014 were used for baseline analysis and modeling characteristics affecting time to approval. The first step in the INCOSE methodology was to determine the distribution family, which proved to be a bounded Johnson Distribution with a highly skewed right-sided tail for IRB approval times (Fig. 1). The highly skewed right-sided tail is composed of statistically significant “outliers” identified using Tukey one-sided test \( p = 0.0001 \). Further analyzing outliers creates an opportunity to identify variations affecting performance that might benefit from a change in the workflow [28-31]. Outliers were independently identified for 2 key phases of the approval process: (1) administrative review by staff; and (2) IRB committee review (see below).

**Contribution of Ancillary Reviews to Delays**

Both the type and number of ancillary reviews affect the time required to receive IRB regulatory approval (Fig. 2) \( p < 0.0001 \). Ancillary reviews also added a median of 36 days (interquartile = 19–64) post IRB committee approval for release of the consent form. Of interest, UCSD proposals undergo more ancillary reviews than many comparable institutions [11]. For example, UCSD phase III multisite studies had a median of 3 ancillary reviews (interquartile = 2–4) whereas data from the previous UC-wide study showed that other UC campuses operating under the same university policy had a median of 0.9 reviews (interquartile = 0.2–1.5). The most commonly co-occurring ancillary reviews at UCSD during the initial review period were Radiation Safety Committee (50% of the time) and Scientific Review Committee (35% of the time). The ancillary reviews associated with the longest approval times were the Scientific Review Committee (median = 120 days, interquartile = 62–147), Biosafety Committee (median = 118 days, interquartile = 70–148), and Radiation Safety (median = 116 days, interquartile = 83–147).

**Contribution of Study Type and Study Misclassification**

Unexpectedly, non-interventional applications such as anonymized registries, retrospective chart reviews, or observational studies had
longer approval times than interventional clinical trials. In exploring where delays occurred, the administrative review had a median duration of 23 days while committee review required a median of 104 days (p = 0.0018). This counter-intuitive observation is similar to findings from other investigators [29]. Focus groups conducted with researchers suggested that the explanation related to researchers not understanding the criteria and documentation requirements non-interventional studies. This led to requests for expedited reviews or requests for exemptions when full IRB review was required. In addition, 63% of non-interventional studies indicated in the submission documentation that the protocol was a clinical trial, which also created administrative delays.

**Contribution of Staffing Ratios**

Our previous study across the University of California identified IRB staffing ratios were critical determinants of approval times [11]. This finding was confirmed with the larger UCSD data set, where static full-time employee (FTE) staffing over time in the face of increasing number of new applications changed the ratio of new applications per FTE from 69:1 in 2013 to 72:1 in 2016 (see supplementary Table C). The increasing ratio of new protocols to FTEs was accompanied by a rise of median administrative time from 13 days (interquartile = 6–34) in 2013 to 25 days (interquartile = 15–50) in 2016 (p < 0.0001). Increased administrative review times meant overall approval times remained essentially static with a median of 75 days (interquartile = 42–122) in 2013 to a median of 86 days (Interquartile = 53–126) in 2016 (Fig. 3). The increased durations were accompanied by an increase in the number of withdrawn applications, largely due to delays for commercial sponsored studies when deadlines passed. For example, 9 IRB and 23 contracts were withdrawn in 2013. That number increased to 43 IRB and 68 contract withdrawals in 2014 (p < 0.001, p = 0.0182, respectively).

**Contribution of Individual Committee Performance**

The second operational issue was statistically significant difference between IRB committees. Comparisons were restricted to Phase III multisite commercially sponsored clinical trials to control for study type (see supplementary Figure D). The median time for review and approval for one committee at 53 days (interquartile = 42–122) in 2013 to a median of 86 days (Interquartile = 53–126) in 2016 (Fig. 3). The increased durations were accompanied by an increase in the number of withdrawn applications, largely due to delays for commercial sponsored studies when deadlines passed. For example, 9 IRB and 23 contracts were withdrawn in 2013. That number increased to 43 IRB and 68 contract withdrawals in 2014 (p < 0.001, p = 0.0182, respectively).
Commercial clinical trial sponsors frequently use contract research organizations (CROs) to negotiate contracts and launch a study. Contract delays are translated into delays in IRB ICF release and are typically viewed by the research unit as an "IRB delay." One of the most striking finding was that individual CROs varied dramatically in terms of timeliness of contracting despite the fact that they all work with the same university contracting office. Fig. 4 shows that there is wide variation in contract execution for various CROs, typically related to responses to queries and contract terms. In addition, Fig. 3 shows how improved staffing and training significantly decreased overall timelines for contracting.

**Contribution of Outside Entities and Contract Office Staffing**

Commercial clinical trial sponsors frequently use contract research organizations (CROs) to negotiate contracts and launch a study. Contract delays are translated into delays in IRB ICF release and are typically viewed by the research unit as an “IRB delay.” One of the most striking finding was that individual CROs varied dramatically in terms of timeliness of contracting despite the fact that they all work with the same university contracting office. Fig. 4 shows that there is wide variation in contract execution for various CROs, typically related to responses to queries and contract terms. In addition, Fig. 3 shows how improved staffing and training significantly decreased overall timelines for contracting.

**Contribution of Coverage Analysis**

A coverage analysis for protocols that could involve third-party payers, like defined contract language, is required before the ICF is released. Although the early days of centralized coverage analyses created significant delays, improved staffing ratios and training led to a dramatic decrease in the time for completing coverage analyses (Fig. 3).
An additional policy change at UCSD delegated authority to the coverage analysis office rather than the research unit to assign a procedure as billable to third parties or the sponsor. This change minimized prolonged negotiations with most research units, which can decline a study if the approved coverage analysis is not acceptable to that unit. An additional finding is the number of study arms within a proposal affects the time required to complete coverage analysis ($p = 0.0006$). Each arm requires a separate coverage analysis, which accounts for the longer timelines (see supplementary Figure E).

**Identifying Outliers to Improve Regulatory Performance**

Analysis of study characteristics for outliers, defined as observations which fall more than 1.5 times the interquartile range, shows some of the key distinguishing features, including principal investigator (PI)-initiated studies, radiation safety review, and testing devices (Fig. 5). We further explored study characteristics associated with the 2 major initiated studies, radiation safety review, and testing devices (Fig. 5).

Committee outliers were disproportionately comprised of unfunded studies, PI-initiated studies with protocols requiring radiation, scientific and conflict of interest reviews. An example would be a PI-initiated cancer study in which the investigator had a potential conflict of interest, where treatment of metastatic disease was guided by genomic data and included radiation therapy.

**Algorithm to Identify Outliers**

The outlier data were used to develop an algorithm $\left(1 - a \cdot b \right) \frac{3}{2} \sum (a_i - b_i)^2$ to identify studies with a high probability of significantly delayed approval. To confirm the approach, we used K-Means and Tree Clustering to identify subgroupings that were in turn used to create Random Forest predictive algorithms. Table 1 shows the key elements that contribute to outlier status for administrative review, committee review, and total time for approval. The predictive algorithms were then tested against 3828 study protocols submitted to the IRB in 2015–2016. The predictive algorithms identified 88% of the administrative outliers and 93% of the committee outliers (see Fig. 6).

**Overall Impact**

While it is difficult to ascribe overall improvement to any one initiative, improved education, staffing ratios, and policies together contributed to significant improvement in the performance of the UCSD IRB environment between the 2013–2014 baseline compared with 2015–2016. The impact was particularly evident in contracting and coverage analysis timelines (Fig. 3). However, IRB approval times have modestly increased. This was largely due to the increase in applications per FTE discussed earlier (Contribution of Staffing Ratios section) and has recently been addressed by increasing the staffing for the IRB administrative office.

**Discussion**

In this study, we evaluated IRB performance in the context of a larger regulatory environment that not only includes the IRB but also ancillary reviews, clinical trial contracting and research billing coverage analysis. The interactions between the various regulatory units and the researchers trying to navigate them are dynamic and subject to

---

**Table 1. Random Forest accuracy in predicting 2015–2016 Institutional Review Boards administrative outliers and committee review outliers**

| Variable                              | Predictor importance |
|---------------------------------------|----------------------|
| Response: outlier                     |                      |
| Rank                                  | Importance           |
| Institutional Review Boards administrative outliers |                      |
| Scientific Review Committee required | 100                  | 1.000               |
| Junior faculty                        | 99                   | 0.987               |
| Vulnerable population                 | 97                   | 0.965               |
| Reliance                              | 32                   | 0.315               |
| Medicare billing/coverage analysis required | 21                   | 0.208               |
| Biosafety Review required             | 18                   | 0.177               |
| PI-authored                           | 7                    | 0.0666              |

| Committee review outliers             |                      |
| Number of ancillary reviews required  | 100                  | 1.000               |
| Conflict of Interest Review Required  | 58                   | 0.581               |
| Unfunded                             | 57                   | 0.573               |
| Medicare billing/coverage analysis required | 52                   | 0.516               |
| Biosafety Review required             | 46                   | 0.463               |
| Scientific Review Committee required | 16                   | 0.157               |
| Oncology/Hematology                   | 15                   | 0.153               |
| Radiation Safety Review required      | 12                   | 0.115               |
| PI-authored                           | 2                    | 0.0244              |

| Predicted                              |                      |
| Actual                                 | Yes (%) | No (%) |
|----------------------------------------|----------|--------|
| Yes                                    | 88.1     | 11.90  |
| No                                     | 14.75    | 85.25  |
| Overall accuracy                       | 85.98    | 85.98  |

| Variable                              | Predictor importance |
|---------------------------------------|----------------------|
| Response: outlier                     |                      |
| Rank                                  | Importance           |
| Committee review outliers             |                      |
| Number of ancillary reviews required  | 100                  | 1.000               |
| Conflict of Interest Review Required  | 58                   | 0.581               |
| Unfunded                             | 57                   | 0.573               |
| Medicare billing/coverage analysis required | 52                   | 0.516               |
| Biosafety Review required             | 46                   | 0.463               |
| Scientific Review Committee required | 16                   | 0.157               |
| Oncology/Hematology                   | 15                   | 0.153               |
| Radiation Safety Review required      | 12                   | 0.115               |
| PI-authored                           | 2                    | 0.0244              |

| Predicted                              |                      |
| Actual                                 | Yes (%) | No (%) |
|----------------------------------------|----------|--------|
| Yes                                    | 100.00   | 0.00   |
| No                                     | 100.00   | 0.00   |
| Overall accuracy                       | 93.90    | 93.90  |

PI, principal investigator.

Fig. 6. Correlation between predicted and actual times for IRB approval. The algorithm to predict outliers (Table 1) was tested against an independent dataset and showed a significant correlation.
misinterpretation of data. The IRB often bears the ultimate “blame” for delays in the eyes of the investigator even though the committees often are awaiting ancillary reviews, contracts, and coverage analysis simply because the final common pathway for all delays is ICF release.

One important caveat is that “speed” is not always the optimal outcome. In some cases, serious contract issues need to be resolved or the protocol might not incorporate sufficient power or scientific rigor. These situations might require a pause or delay in order to assure compliance or an improved risk/benefit profile. However, operational inefficiencies, such as improper staffing ratios or training, duplicate reviews, or unnecessary ancillary reviews are clearly areas that can be addressed. Collaboration between regulatory units and incorporation of simple solutions like proper staffing, training, project management, and sharing information between regulatory units can overcome some of these barriers.

We have also developed an algorithm for predicting outliers, which can be used to remove those protocols from the normal workflow. Key study characteristics, including multiple ancillary reviews for IRB, multiple study arms for coverage analysis (especially in cancer) and specific CROs for contracting, can be proactively identified. Ultimately separate workflows could be developed for these protocols, which could improve the timelines for other protocols because the outliers will not consume as much resources. Similarly, the causes of administrative delays can be addressed by maintaining adequate staffing and assuring research unit education to improve the initial submission.

This systems engineering approach, in which the processes are broken into individual components, interactions explored and performance drivers identified, involve exploring methods for improving IRB and the entire regulatory process. Unfortunately, centralize control management principles that work in a manufacturing plant are unlikely to work in a human research regulatory environment. Traditional systems are managed to minimize cost while human research should be managed to maximize value. A focus on the efficiency and productivity of the regulatory units is, as noted above, an important value but not at the cost of quality, including patient safety.

Rather than mandate a set of interventions or specific outcomes, our data suggest that a focus on managing complexity by monitoring and influencing the system state might be more beneficial. The organizing principle that promotes understanding and/or appreciation of the role each unit contributes to human research is also required.

A productive approach would be to integrate processes and seek to learn from each protocol and each delay. For example, minor changes in protocols (e.g., same protocol with a different drug in a clinical trial) could be “fast tracked” to assess the safety of the drug rather review the entire protocol as if it had never been seen before by the IRB or other offices. Table 2 provides a matrix for exploring the interdependencies and well as identifying some potential solutions. The challenges outlined will also be true for a centralized IRB.

### Conclusion

We identified and reviewed issues and delays associated with the regulatory environment, with an emphasis on IRB processes in the context of a larger regulatory universe. Relatively simple steps can have a significant impact on timelines and, ultimately, on researcher satisfaction and patient access to novel therapies. The next steps will entail analyzing the impact of these steps on timelines and quality.

### Acknowledgments

The authors thank the staff of the Office of Coverage Analysis Administration, Office of Clinical Trial Administration and the Human Research Protection Program at UCSD for their kind assistance and providing access to the data required for this analysis.

### Financial Support

This paper was partially supported by the National Institutes of Health grant UL1TR001442. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

### Disclosures

The authors have no conflicts of interest to declare.

### Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/ccts.2018.24

### References

1. **NCATS.** Clinical and Translational Science Awards Program. Opportunities for Advancing Clinical and Translational Research, Chapter: 3, Leadership CTSA Fact Sheet [Internet], 2013 [cited July 2017]. (https://ncats.nih.gov/files/CTSA-factsheet.pdf)

2. **United States.** President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research; Implementing human research regulations. United States Code Annotated United States 1982; Title 42 Sect.

3. **United States Department of Health and Human Services.** Office of Inspector General, Institutional Review Boards: Promising Approaches (OEI-01-97-00191) [Internet], 1998 [cited July 2017]. (https://oig.hhs.gov/oei/reports/oei-01-97-00191.pdf)

4. **United States Department of Health and Human Services.** Office of Inspector General, Institutional Review Boards: A System in Jeopardy “DRAFT”; A Time for Reform (OEI-01-97-00193) [Internet], 1998 [cited July 2017]. (https://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf)
5. United States Department of Health and Human Services. Office of Inspector General, Institutional Review Boards: A Time for Reform (OEI-01-97-00193) [Internet]. 1998 [cited July 2017]. (https://doi.org/10.1017/cts.2018.24)

6. United States Government Accountability Office. Human Subjects Research: HHS Takes Steps to Strengthen Protections, But Concerns Remain (GAO-01-775T) [Internet]. 2001 [cited July 2017]. (http://www.gao.gov/products/GAO-01-775T)

7. Institute of Medicine (US). Committee on assessing the system for protecting human research participants. In: Federman DD, Hanna KE, Rodriguez LL, eds. Responsible Research: A Systems Approach to Protecting Human Research Participants. Washington, DC: National Academies Press, 2002, pp. v-vi.

8. Institute of Medicine (US). Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington, DC: National Academies Press, 2010.

9. Institute of Medicine (US). Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary. Washington, DC: National Academies Press, 2012.

10. National Academies of Sciences, Engineering, and Medicine. Optimizing the Nation’s Investment in Academic Research: A New Regulatory Framework for the 21st Century. Washington, DC: National Academies Press; 2012.

11. Caligiuri M, et al. A multi-site study of performance drivers among Institutional Review Boards. Journal of Clinical and Translational Science 2017; 1: 192–197.

12. Sobol ski GK, Flores L, Emanu el EJ. Institutional review board review of multicenter studies. Annals of Internal Medicine 2007; 146: 759.

13. Anderson EE. A qualitative study of non-affiliated, non-scientist institutional review board members. Accountability in Research 2006; 13: 135–155.

14. Steinbrook R. Improving protection for research subjects. New England Journal of Medicine 2002; 346: 1425–1430.

15. Rubio DM, et al. Developing common metrics for the Clinical and Translational Science Awards (CTSAs): lessons learned. Clinical and Translational Science 2015; 8: 451–459.

16. Dils DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. Journal of Clinical Oncology 2006; 24: 4545–4552.

17. Dils DM, et al. Steps and time to process clinical trials at the Cancer Therapy Evaluation Program. Journal of Clinical Oncology 2009; 27: 1761–1766.

18. Strasser JE, Cola PA, Rosenblum D. Evaluating various areas of process improvement in an effort to improve clinical research: discussions from the 2012 Clinical Translational Science Award (CTSA) Clinical Research Management workshop. Clinical and Translational Science 2013; 6: 317–320.

19. Rosenblum D, Alving B. The role of the Clinical and Translational Science Awards program in improving the quality and efficiency of clinical research. Chest 2011; 140: 764–767.

20. Walden D, et al. INCOSE Systems Engineering Handbook: A Guide for System Life Cycle Processes and Activities, 4th edition. Hoboken, NJ: Wiley, 2015, pp. 7.1.3–7.3.6.

21. United States Department of Commerce. NIST/SEMA TECH e-Handbook of Statistical Methods, Section 1.3.5.17 [Internet], 2012 [cited July 2017]. (http://www.itl.nist.gov/div898/handbook/).

22. Burnham KP, Anderson DR. Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach, 2nd edition. New York, NY: Springer, 2002.

23. Chapman P, et al. CRISP-DM 1.0 Step-By-Step Data Mining Guides, SPSS Inc., 2000 [Internet] [cited July 2017]. (ftp://ftp.software.ibm.com/software/analytics/spss/support/Modeler/Documentation/14/ UserManual/CRISP-DM.pdf)

24. International Organization for Standardization. Statistical interpretation of data — Part 4: Detection and treatment of outliers. ISO 16269-4:2010(en) [Internet]. 2010 [cited May 2018]. (https://www.iso.org/obp/ui/#iso:std:iso:16269-4:ed-1:v1:en).

25. Zarin D. Newsmaker interview: Debora Zarin. Unseen world of clinical trials emerges from U.S. database. Science 2011; 333: 145.

26. Koenker R, Hallock KF. Quantile regression. Journal of Economic Perspectives 2001; 15: 143–156.

27. Freedman DA. Statistical Models: Theory and Practice. New York, NY: Cambridge University Press; 2009.

28. Nahar A, et al. Quality Improvement and Cost Reduction Using Statistical Outlier Methods. Lake Tahoe, CA: Computer Design, 2009, pp. 64–69.

29. Hodges VJ, Austin J. A survey of outlier detection methodologies. Artificial Intelligence Review 2004; 22: 85–126.

30. Xu S, et al. An improved methodology for outlier detection in dynamic datasets. Process Systems Engineering, The American Institute of Chemical Engineers 2015; 61: 419–433.

31. Shoenbill K, et al. IRB process improvements: a machine learning analysis. Journal of Clinical Translational Science 2017; 1: 176–183.