Published in final edited form as:

Am J Emerg Med. 2013 June ; 31(6): 967–969. doi:10.1016/j.ajem.2013.03.003.

Variations in Institutional Review Board reviews of a multi-center, Emergency Department-based genetic research protocol

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Keywords

genetic testing; institutional review board; multi-center

Introduction

In the United States, the Department of Health and Human Services and the Food and Drug Administration have jurisdiction to develop and implement regulations that empower local committees to approve and monitor all forms of medical research. These committees are Institutional Review Boards (IRBs) which oversee the scientific, ethical, and regulatory aspects of research conducted on human subjects. With the increasing complexity of medical research, there have been increasing federal regulations governing these studies. This is especially true concerning the conduct of studies collecting genetic data[1-4]. Institutional variation in the interpretation and application of these regulations can have significant impact on the implementation of such studies.

In the present investigation, we assessed variability in IRB review at institutions participating in the Project CRASH Research Network. This network was formed to conduct Project CRASH, a large NIH-funded (AR056328) multi-center ED-based study examining genotypic and phenotypic predictors of pain and psychological outcomes after minor motor

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vehicle collision (MVC). This is one of the first multi-center genetic research protocols based solely in the Emergency Department (ED).

Material and Methods

Project CRASH enrolls patients who present to the ED after minor MVC. Consenting patients complete initial interview evaluation in the ED, and a blood sample is obtained in the ED for subsequent genetic analyses. The purpose of these analyses is to examine alleles associated with patient recovery characteristics. Patient outcome information is subsequently obtained 6 weeks, 6 months, and 1 year after MVC via telephone and/or web-based self-report survey.

We performed an observational study looking at variability in the IRBs reviewing the Project CRASH protocol. Initial research network institutions include XXX (n=7). Three of the sites are academic university-based institutions, and four sites are community hospitals with strong academic affiliations. All sites have an emergency medicine residency training program.

During the preparation phase of the study, the principle investigator (PI) at each institution in the research network used a uniform Project CRASH study protocol to prepare their local IRB application. Each of these sites has a full time, professional research staff, including a study coordinator who supervises and assists with IRB submissions. In addition, site PIs also used a prototype IRB application, which contained responses to commonly asked IRB application questions. Following completion of the IRB approval process at each site, each site PI was asked to complete a standardized questionnaire which collected information on the IRB process at their site. This questionnaire collected data including information regarding institution demographics, original IRB application characteristics, subsequent IRB correspondence, and time interval between submission and approval.

Descriptive statistics were used to compare IRB approval process characteristics across participating sites. If initial questionnaire responses were unclear, copies of the original IRB application and/or correspondence were obtained and reviewed to determine appropriate categorization.

Results

PIs from all 7 institutions participating in the research network completed the questionnaire. Characteristics of participating institutions are displayed in Table 1. Among institutions, the time interval in receiving IRB approval varied between 20-760 days (see figure 1). One site appeared to be an outlier with time delay to approval of 760 days. After removing this site from analysis, the median time delay was 101 days (IQR 20-192).

Table 2 describes the number and type of IRB requests for revisions. The most commonly requested changes were changes to the consent form. No IRB required a separate signature for use of genetic data or genetic banking on the consent. Again, there were multiple outliers amongst the IRBs in various topics. Two sites required more than ten changes on the protocol while the majority of sites requested three or less changes. One IRB required eight changes on the protocol due to ethical issues while the rest required two or less changes.

Discussion

In the past several decades, the number of genetic studies has exponentially increased. IRBs have increasingly searched for guidance to aid in the discussion and regulation of these studies. In 2009, the Infectious Disease Society of America addressed the regulatory burden

on research and called for a clearer federal guidance and greater use of a centralized IRB system. This would remove some of the duties of "overloaded" local IRBs.[1]

Compared to other similar studies, our study had a much greater mean time to IRB approval. In 2003, McWilliams and colleagues reported variations in the IRB approval process among the thirty-one sites in their multi-center genetic epidemiology study on cystic fibrosis. In their study, the mean time for approval after full IRB review was 81 days (range, 13-252). Our study had a mean 201 days (range, 20-760). Although McWilliams study had a shorter time interval to approval, there were a far greater number of changes and issues that were raised during the implementation of their study. This may in part be due to the fact that the McWilliams study included children.[3]

Other multi-center ED studies have had much shorter time intervals to IRB approval. In 2006, Mansbach and colleagues reported their difficulties in their multi-center observational pediatric study investigating bronchiolitis. In their study, the mean time for approval was 42 days (range, 27-61). Again, there were a far greater number of changes and issues as compared to our study.[2] In 2001, Stair and colleagues reported a median time of delay of 38 days (IQR 26-142) in their randomized, placebo-controlled, interventional study investigating asthma treatment.[5]

Limitations

One confounding factor is the relatively small number of study sites (seven). In our study, all sites that agreed to participate in the CRASH study obtained IRB approval. Other similar studies reported a greater "drop-out" rate and those sites were not included in their respective final analyses.[2, 3] This may have inflated our mean time to approval since we did not have any sites "drop-out". The first three sites that entered into the research network had a much longer time interval to approval as compared to the last four. We do not know whether the various IRBs discussed this project amongst themselves.

Conclusion

Institutional interpretation of regulations regarding our ED-based genetic study was highly variable. Although the majority of our results are consistent with other similar published studies, the mean time interval for approval for this genetic study is far greater than other reported studies. We hope that the process of IRB approval will become more efficient as institutions become more familiar with genetic and multi-center ED based studies.

Acknowledgments

This study was presented at the annual Society for Academic Emergency Medicine meeting in Phoenix, AZ in May 2010.

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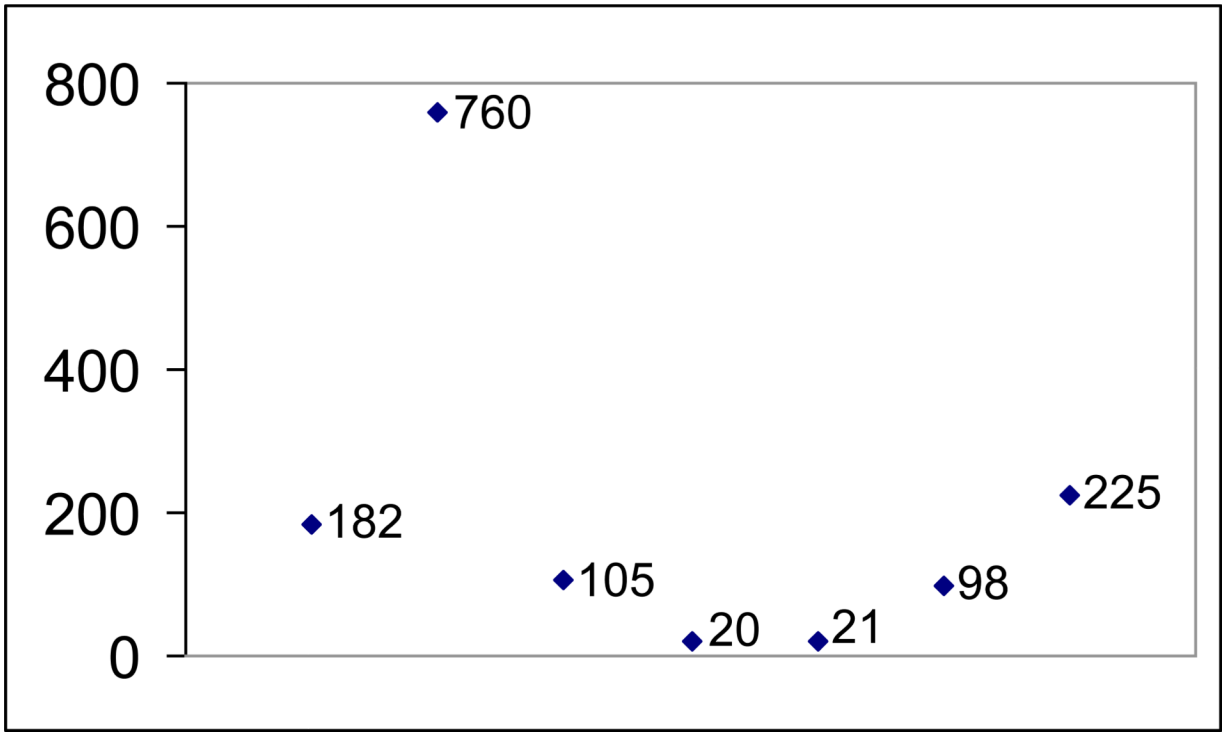

Figure 1.
Number of days to final IRB approval

Table 1

Hospital characteristics (median and interquartile)).

Number of hospital beds	Number of members on the IRB committee	Number of pages in final consent form	Number of required signatures from the subject	Number of days between initial receipt of IRB application and final IRB approval
731 (529-900)	30 (20.5-63.5)	8.0(7.0-10.0)	3.5 (2.0-8.2)	105 (21-225)

Table 2

IRB requests for revision (median and interquartile)

Total number of changes	Changes to methodology	Changes to consent	Changes to eligibility	Changes to statistics	Changes to funding	Changes due to ethical issues	Changes due to genetic testing
2.0 (0.0-11)	1.0 (0.0-2.0)	2.0 (0.0-4.0)	1.0 (0.0-1.0)	0 (0.0-1.0)	0 (0.0-0.5)	0 (0.0-3.5)	0 (0.0-4.0)