

IRB Committees: Balancing Medical Policy, Ethics and Statistics

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Introduction

The underlying premise of an ethical clinical study involving human subjects is that the study is reasonably safe, and that participants fully understand and consent to the procedures or treatments they will receive. Subjects must be free (e.g., without coercion, deceit, duress, fraud, or force) and competent (e.g., do not manifest impaired decision-making ability, or lack of maturity due to age, disease, or fetal/embryo status) to choose whether or not to participate, and may opt to withdraw from the study at any point without prejudice, financial loss, or embarrassment. Patients must be informed of any potential or expected risks or discomforts known or believed to be associated with the study, and be advised of any appropriate alternatives to the study. Prior to enrolling in the study, a patient must be clearly and completely informed of remedial medical treatment and compensation, if any, available to them, if complications should arise during the course of the study, or following the completion of the study (if they are believed to be consequent to the study). The confidentiality of a patient's medical condition and care must be respected at all times by attending staff in their communications with outside individuals (e.g., friends, classmates), groups (e.g., insurance agencies, employers), the press, or anyone not directly involved in the care of the patient. Patient charts and computerized medical records must also be securely maintained to protect the privacy of participants in the study and their immediate families. Should tissue samples or bodily fluids be extracted from patients in the study, they must be informed of and agree to their intended use, whether now or in the future, and be told of the study policy regarding when and if test results will be made available to them.

Mandate and Tasks of a Institutional Review Board

The primary mandate of an Institutional Review Board (IRB) is to assure the ethical behavior of clinical studies conducted at their facility or under their auspicious. This includes, but is not

limited to, reviewing the overall safety of the study (with respect to both study participants and attending staff), assuring that a patient's decision to participate in the study is informed and voluntary, and protecting the confidentiality of a patient's medical information. The fundamental responsibility of the IRB is to minimize the risk associated with a study. Even when reasonable and appropriate precautions are taken to minimize risk, a non-trivial likelihood of complications or injury potentially exists in any study involving human subjects. Accordingly, the IRB must justify the perceived level of risk in terms of potential benefit to the patient and/or medical knowledge/scientific advancement. Given the task of achieving an acceptable risk/benefit balance for a clinical study, the IRB is authorized to impose special restrictions on the length, scope, size, and monitoring of a study.

The Role of the IRB Statistician

The exact role of a statistician on the IRB is contingent to a certain degree on whether or not the institution at hand has a separate committee that reviews the scientific merit and design of clinical studies conducted under their authority. When this is the case, the IRB statistician will typically function in a secondary capacity, serving to cross-validate (e.g., "second pair of eyes") the recommendations of the scientific review committee. Often, however, institutions do not have a separate scientific review committee and simply absorb this function into the IRB. Regardless of whether the statistician serves on the IRB or scientific review committee, the ethical and human subject concerns remain the same. The study must be designed in an efficient manner. The risk to patients must be minimized. The study must have sufficient power and analytic structure to assure that solid scientific data will result from the process. For example, a study should enroll enough patients, per a pre-specified level of statistical confidence, to achieve the analytic objective of the study. Depending on the study design, this may entail demonstrating the statistical equivalence or superiority of an experimental drug or procedure with respect to a control regimen. When too few subjects are enrolled, little or no useful information will be

obtained, while unnecessarily exposing patients to risks, regardless of how trivial they may be. On the other hand, enrolling too many patients in a clinical study is inefficient and has equally dire ethical consequences in terms of unnecessarily exposing patients (whom otherwise would not be enrolled) to the risks of the study.

Determining the proper sample size for a clinical study depends on many issues. These include the study design (e.g., cross-over, randomized block, sequential), whether the outcome of interest is discrete or continuous, the event rate, the required number of covariates, the magnitude of effect necessary or clinically meaningful to detect, the set level of statistical certainty established by regulatory agencies, and the anticipated dropout or non-compliance rate. When the event rate is difficult to estimate in advance, or there is uncertainty about how many patients may be withdrawn from the study prematurely, the IRB statistician may recommend early stopping rules (usually based on group sequential methods), or advise that the study be periodically reviewed by a Data and Safety Monitoring Board (DSMB), typically attended by an outside statistician.

The IRB statistician must also be attentive to possible unblinding and study biases (e.g., selection, recall, detection, surveillance, consequential) that may impair the integrity of the study, or dilute the ability to detect a real study effect, should one exist. Equally important, the IRB statistician brings general analytic and computer knowledge to the table, and is thus well positioned to critique data management, monitoring, and validation of the study.

Summary

The statistician plays an important team role on IRB committees. Their responsibilities include assessing the overall adequacy of study design, determining if a study is sufficiently powered, and recommending, when necessary, the inclusion of a study DSMB. The IRB statistician may also alert the board to fatal problems during an ongoing study, such as differential biases, unblinding, an excessive number of premature terminations, or an unusually high adverse event profile, in comparison to historical data. Ultimately, the IRB statistician may recommend the length of time between reviews of a study, and request a list of medically serious adverse events by treatment arm, or a detailed breakdown by reason of patients whom have been terminated from the study prematurely.

References

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