IRB *EasyEd™* - For IRB Members Volume 2 Number 3

Topic: Controverted Issues

Overview of the Topic

The minutes of IRB meetings must include all the information stipulated by the regulations, including a summary of the discussion of **controverted issues** and their resolution (45 CFR 46.115(a)(2); 21 CFR 56.115(a)(2)). What a controverted issue is and how it is documented is an issue that many IRBs struggle with. OHRP *Recent Compliance Oversight Determinations* (2009) lists inadequate IRB minutes, including "failure to include a written summary of the discussion of controverted issues and their resolution," as a common non-compliance finding. Likewise, a finding that "IRB minutes fail to include a summary of the discussion of controverted issues" was listed over 40 times in FDA Warning Letters. Many OHRP and FDA letters note the complete absence of controverted issues in minutes.

The dictionary defines "controvert" as *to dispute or oppose by reasoning*. Thus, a controverted issues is one that is debated. Applying this to IRBs, OHRP defines a controverted issue as an issue that causes controversy and dispute among the IRB membership during a convened meeting. In most IRBs, IRB Members like to debate the issues. In fact, it has been said that if your IRB is not arguing the issues, it is not doing its job (anonymous but widely held belief). So these types of debates are not only common, they are an important part of the review and approval process.

To drill down further, a controverted issue is a debate that comes up within the discussion of a research protocol prior to the final vote for approval. Research projects may be controversial by their very nature, for example sham surgery or research on criminal activities, and there may be debates about what steps should be taken to protect the subjects. Of course, the final vote will determine the ultimate disposition of the project. But there are also issues within a research project, for example should pregnant women or children be included in a particular clinical trial, or what should the age cutoff be for treadmill exercise study, or should a particular outcome be listed as a risk in the consent form. The resolution of these issues usually influence the final vote on the project, but they themselves must be decided upon within the discussion.

Let's delve into some of the examples given above to illustrate the discussion and documentation of a controverted issue within the IRB minutes:

A clinical trial may be straight forward and destined for final approval, but the inclusion criteria includes women of child-bearing age. Someone should ask, if not already addressed, "should pregnant women be allowed to participate?" "Historically, women have been excluded from clinical trials to the detriment of information about women's health and effects in women." On the other side, "the intervention may have negative effects on a pregnant women or her fetus." Even if it's a benign intervention, "the physiology and endocrinology of pregnancy may complicate interpretation of the results." These are all issues which need to be addressed and debated by knowledgeable people. "Okay, we decided to exclude pregnant women – so how do we do that? Ask them, urine test, blood test?" Again, these are all questions which need to be asked, debated and decided upon, and documented.

The second example is "what should the age cutoff be for treadmill exercise study?" The age at which exercise becomes risker for older people may be discussed. "But some people in their 70s run marathons. How should people be screened?" "What emergency equipment should be readily available due to the increased risk in older subjects? Should a physician be involved, or present?" What may have seemed like a simple question can raise many issues, each of each needs to be discussed, resolved and documented.

The third example is a disagreement if a particular outcome should be listed as a risk in the consent form. "Well it may be rare but this is an important risk which people should be aware of." "There's a test to determine if someone is susceptible to the risk, should that information be included?" "Look, consent forms are too long already." "This will only needlessly worry people." Knowledgeable and reasonable IRB Members should come up with an appropriate decision. IRBs have to make such decisions at every meeting and should always do their best to inform, debate and decide. Note that if the proposed consent change is acceptable without debate, this is not a controverted issue.

A controverted issue may be settled by a vote on that specific issue or by consensus. That said, a controverted issue may not be resolved or agreed upon because of different and strongly held opinions of IRB Members and the way

forward determined by the final vote for approval or disapproval of the protocol.

Remember that anyone who later reads the IRB minutes (perhaps even years later) should be able to recreate the history of the review and know what decisions were made and why. For example, why were pregnant women included or excluded from a clinical trial or why the specific age range was approved for the treadmill study. These may become important issues to know at continuing review. In the future these decisions may be reconsidered due to changing information or circumstances, but the knowledge of the original decisions are an important part of that discussion. Thus, the documentation of converted issues in the IRB minutes is of vital importance, both because the regulations require it and the knowledge related to the decisions must be recorded. The IRB minutes should include:

1. A description of the controverted issue that is being debated.
2. A description of the various sides or points of view related to the controverted issue.
3. A summary of the essence of the discussion of the issues.
4. Documentation of the specific final resolution of the controverted issue including the vote, if taken.

It is a best practice to have a template for your IRB minutes which includes a list for controverted issues and their resolution. Some may be entered prior to the meeting and some during the meeting. A controverted issue may be raised at various points in the review process. Primary or secondary reviewers may raise questions during their review. Other members may raise questions during their reading of the protocol. In some instances, pre-review by the IRB Staff may spot a questions which needs to be resolved. Regardless of the source, each controverted issues should be relayed to the IRB Chair and individually discussed and resolved at the convened meeting. The resolution of controverted issues is a key component of the review of protocols at IRB meetings, usually results in changes required as a result of the discussion, and thus, is important to the final approval of the research and protection of subjects.

Questions for the IRB to Consider

Questions your IRB Members may ask about the controverted issues:

1. When you are a primary or secondary reviewer do you raise controverted issues and relate them to the IRB Chair or Staff?
2. When you receive the materials for an IRB meeting and review the protocols do you find controverted issues and bring them up for discussion at the IRB meeting?
3. When a controverted issues is discussed at an IRB meeting, do you provide your opinion on the issue and its resolution?
4. When you approve the minutes, are you satisfied that the documentation of controverted issues and their resolution are complete and accurately reflect the discussion at the meeting?

Case Studies

Case 1. A primary reviewer questions whether a blood draw, for research purposes only, of 80 ml per week for eight weeks from young women is appropriate. Is this a controverted issue? What should the reviewer do? How should it be resolved? What should be documented?

Case 2. During their review of the material in preparation for an IRB meeting, an IRB member thinks that certain survey questions may cause emotional distress in subjects and the issue is not included in the consent form or dealt with by the investigator. Is this a controverted issue? What should the IRB member do? How should it be resolved? What should be documented?

Case 3. At the IRB meeting, an IRB Member raises the question of whether the requested sample size for the research is too large. Is this a controverted issue? How should it be resolved? What should be documented?

Case 4. During the IRB review of a protocol, there is a debate of whether children under 18 should be included as subjects. After much discussion there is no consensus on the resolution of the issue. How should the IRB proceed?

Prospective Thinking: At the end of an IRB meeting, retrospectively look over the review of the protocols from that meeting. Critically discuss whether all controverted issues were raised, debated, resolved and documented. Discuss ideas on how controverted issues can be better handled by the IRB and documented in IRB minutes.

Next Month's IRB EasyEd: ***The Definition of Human Subject Research***