Office of Intramural Research
Office of Human Subjects Research Protection

IRB Member Update | December 2019

Updates on the NIH IRB membership

We currently have 157 members of the NIH IRB! All of the previous IRBs in the Intramural Research Program have now held their last meeting, so we look forward to meeting some new members in the upcoming NIH IRB meetings.

Reviewing amendments and Continuing Reviews (CRs)

When reviewing amendments and CRs, the IRB is evaluating a very focused question. For and amendment, the question is "given this change to the research, does the protocol still meet the criteria for approval". For continuing review, the question is "given the events that have occurred over the past year, does the protocol still meet the criteria for approval".

Continuing Review is not a repeat of an initial review. OHRP guidance on continuing review specifically states:

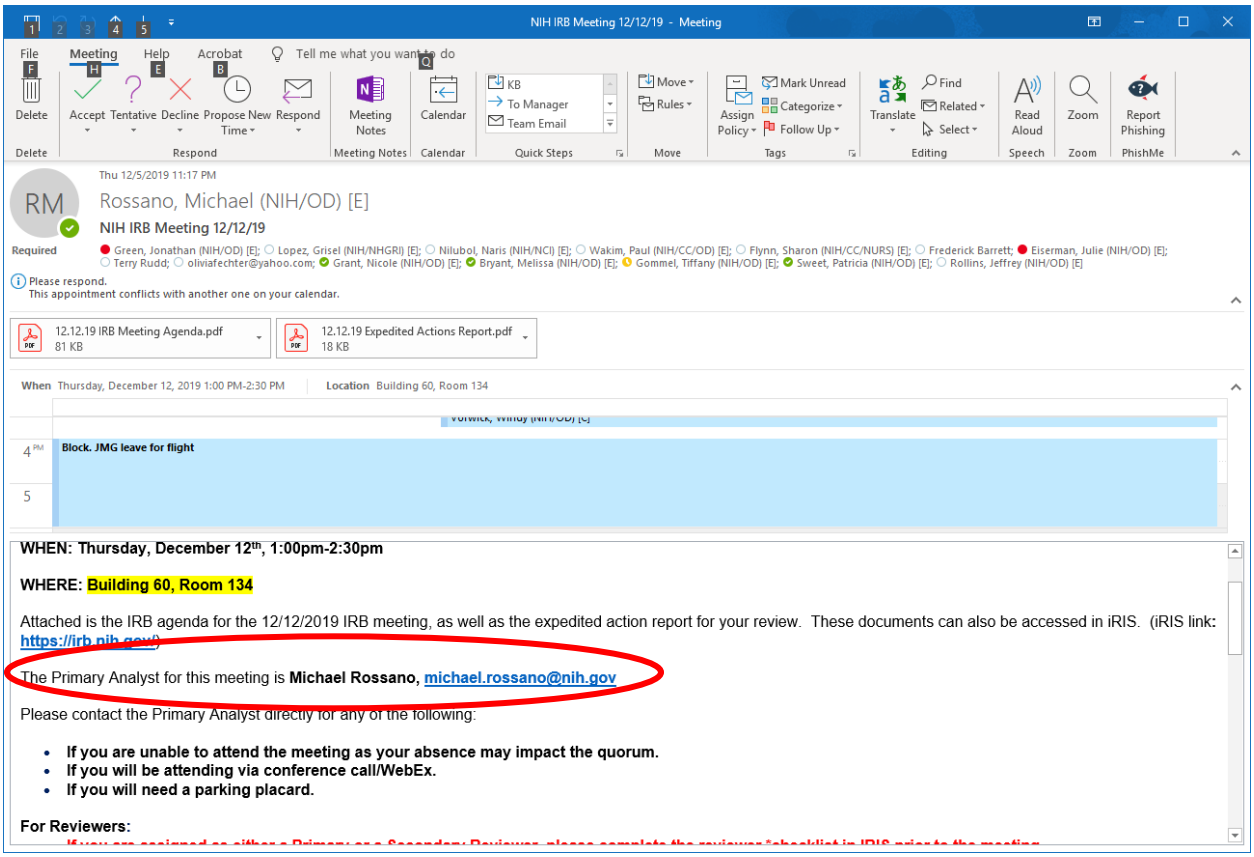
> When conducting continuing review, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the above criteria. The IRB should focus on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document.

Therefore, presentations and discussions for amendments and CRs may be brief, unless of course there are regulatory concerns. If the events of the last year do not alter the approvability of the study, that is all the reviewer needs to state. Similarly, for an amendment, after a brief description of the change(s), if in the reviewer's assessment the change(s) does not alter the criteria for approval, that should be stated and the motion made by the chair.

Communicating with the analyst before the meeting

As you conduct your reviews prior to the meeting, please be certain to communicate any problems or concerns that you may have with the protocol to the primary analyst for the meeting. It is essential that the analyst be aware ahead of time. They may be able to help address the concern or get additional information so it can be resolved. They also may need to share the information with the rest of the committee.

The primary analyst and their contact information is identified in the outlook email invitation sent to you with the agenda. This is the person to contact.



Remember, the meeting is the time to make decisions, not the time to get answers. Resolve your questions and concerns prior to the meeting date.

Device Determinations

A number of amendments are being reviewed by the full board that would otherwise be able to be reviewed expedited except for the need to make a device determination. FDA regulations require that the full board make the determination that a device study is a non-significant risk (NSR) study. This cannot be done by expedited review. The staff can determine that a device is exempt, and the FDA issues the IDE if the device is significant risk. But the NSR determination has to happen at the convened IRB.

We have found that several of the prior IC specific IRBs either did not make or did not document NSR determinations. Therefore, to ensure we are in compliance with FDA regulations, we are sending these to full board. These have been vetted by the IRBO staff, so the analyst may inform you at or ahead of the meeting that the reason this is going to FB is solely for the device determination. All that is needed, in addition to reviewing the amendment, is to voice that the study is an NSR device study (if you agree it is), as it does not meet the definition of a significant risk device.

Evaluating equitable subject selection

What does "equitable subject selection" mean?

> *Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. §45 CFR 46.111(a)(1)(3)*

When the IRB evaluates a protocol, the regulatory criteria for approval require the IRB to determine that subject selection is equitable. The Belmont report provides an excellent description of how subject selection flows from the principle of justice. It states:

> "Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

In evaluating a protocol for equitable subject selection, the IRB should be certain that no group of people are either unfairly targeted nor unfairly excluded from participating in research. The goal is to assure that both the benefits and burdens of research are distributed fairly. Groups of people that have no potential to benefit from the research should not bear the burdens, and conversely, those who may benefit should not be excluded.

The primary driver of subject selection for any protocol is the scientific question. The population enrolled should be that which is best able to address the scientific question being asked, with the least numbers of subjects and with the lowest likelihood of experiencing harm.

How does race/ethnicity/gender distribution play into equitable subject selection?

Diversity in clinical trials is important to assure that the results are broadly applicable. However, this *does not* translate into that the IRB must assure that all research protocols

enroll a population that reflects the local or national distribution of race/ethnicity or gender. Underrepresentation of certain groups in research is a complex problem and the NIH and regulatory agencies have independent policies addressing this. These policies are not the responsibility of the IRB to monitor and enforce.

The IRB should evaluate whether the recruitment and enrollment of participants reflects populations that are burdened by the disease or condition under study. For example, if an investigator is studying a condition that disproportionately effects African Americans, then the IRB should evaluate whether the investigator is making appropriate efforts to recruit and enroll from this population. This makes sense not only from a fairness standpoint, but also a scientific one. If a disease is equally distributed across all races and ethnicities, then as long as the investigator is not unfairly excluding or unfairly targeting anyone, then the IRB should not require that the investigator enroll a population that mirrors the local community.

Enrolling pregnant women, human fetuses and neonates in research

Pregnant women, human fetuses and neonates are a federally defined category of vulnerable subjects and additional regulations are in place to protect these persons. Subpart B of 45 CFR 46 spells out the additional regulatory requirements for enrollment of this population.

In addition to the determinations the IRB makes under subpart A (the common rule), the IRB must make a number of additional determinations, spelled out at 45 CFR 46.204. Without going through them all, I want to point out a few key points.

Similar to the regulations for the enrollment of children, the IRB must determine if the proposed research poses a prospect of direct benefit to the mother and/or the fetus, as well as whether the risk to the mother and/or fetus is minimal or greater than minimal. Depending on the answer to these questions, the inclusion of this population may or may not be approvable, and the consent signature requirements may differ.

Presuming all other requirements are met:

1. If there is prospect of direct benefit to the mother, then research in which the risk to the fetus is minimal or greater than minimal (even if no prospect of direct benefit to the fetus) is approvable. Only the mother must provide consent.
2. If there is prospect of direct benefit to ONLY the fetus and not the mother, the research is approvable even if risk is greater than minimal to the mother and/or fetus. Both parents must provide consent.
3. If there is prospect of direct benefit to the mother AND fetus, the research is approvable even if risk to mother and/or fetus is greater than minimal. Only the mother must provide consent.
4. If there is NO prospect of direct benefit to mother OR fetus, then the research is only approvable if 1) the risk to mother and fetus is no more than minimal and 2) the purpose of the research is important biomedical knowledge that cannot be obtained by any other means. Only mother must provide consent.

This 4th category is the one that provides the greatest challenge for IRBs to approve research. If applied literally to all studies, then a pregnant woman would not be allowed to enroll in a study conducting only surveys on a completely benign topic, unless the enrollment of pregnant women was scientifically necessary to answer the research question.

The IRB only needs to apply the subpart B regulations when the study is specifically targeting pregnant women as an included population. The regulations do not need to be applied if enrollment of pregnant women may occur entirely incidental (such as in a survey study).

This is independent of an assessment of whether pregnant women should be excluded for safety reasons, such as in an investigational drug study with teratogenic potential.

Therefore:

1. For a greater than minimal risk study:
    a. Determine if pregnancy should be an exclusion criterion for safety reasons. If so, it should be listed as such in the protocol.
    b. If pregnant women are to be specifically included, then it must be justified by a prospect of direct benefit to the mother and/or fetus.
    c. If pregnancy may occur incidentally during the course of the study (for example in a long-term longitudinal study), then either:
        i. the pregnant women should be withdrawn from the study, or
        ii. if the pregnant woman is to remain enrolled, then any intervention that poses greater than minimal risk to the mother and/or fetus should not be performed during the pregnancy unless it provides a prospect of direct benefit to the mother and/or fetus. The investigator should submit an amendment to the IRB to provide a justification for why the continued inclusion of the pregnant woman is scientifically justified and why the information cannot be obtained by other means. For example, it might be important to understand if the natural history of the disease under study changes with pregnancy.

2. For a minimal risk study:
    a. If the study is not about pregnancy and is silent on enrolling pregnant women, this is fine, and no action or determinations are needed by the IRB.
    b. If the study is specifically targeting pregnant women (indicated in the inclusion criteria), then the investigator must provide a justification in the protocol as to why the information cannot be obtained by other means.