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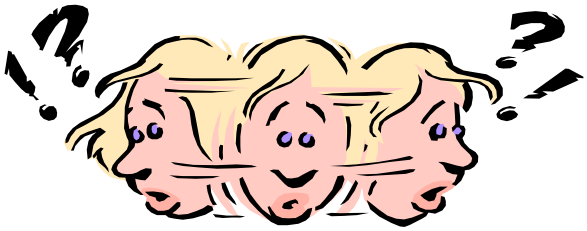
IRB Tools and Tips

Issue 5: Long-term Follow-up Protocols

This issue is a slight departure from the normal IRB Tools and Tips newsletter format, and it will not be applicable to all research support staff. This was developed in response to several questions and concerns that have arisen regarding the umbrella protocols created by the IRB to track those research base protocols that are essentially terminated, but for which there are subjects being followed for survival, in other words, the Long Term Follow Up protocols. If you do not work with research bases and/or these protocols, you can take a break and ignore this issue. Be sure to "tune in" for our next issue which will deal with the continuing review reporting forms.

Question: *I received a continuing review report for a "Long-Term Follow-Up Protocol." I don't understand what this protocol is or how to complete it. There aren't any patients being treated. What information does the IRB want? Help!*



Well, it may seem to confusing to have a protocol that's not really a protocol. (OK, it **is** confusing.) In order to explain these "umbrella" protocols, let's travel back a few years into IRB history to look at where they came from and how they were developed.

[*The following is a condensed version of the history of the development of long-term follow-up protocols.*]
The first correspondence the IRB has in its files related to long-term follow-up is dated July 1991 and is a memo from the National Surgical Adjuvant Breast and Bowel Project (NSABP) reminding investigators and coordinators that according to OPRR rules (the Office for Protection from Research Risks…the name of the federal agency currently known as OHRP or the Office for Human Research Protections), all Cooperative Group protocols must be reviewed by the full board IRB at least annually as long as patients are being treated. It further states that "when a protocol is closed to patient entry and all of your randomized patients have completed therapy, your IRB may provide expedited review of annual reapprovals" and "annual reapprovals are required as long as patients are being followed."

At that time, the IRB took the position that once a CCOP protocol was terminated by the research base and subjects were no longer being treated, these protocols would no longer need to be reviewed. There was nothing to suggest that, in some cases, subjects would be followed for life for survival analysis. These studies were terminated; end of story. Or was it?

About 2 years later, this issue resurfaced. In a memo to Tarit Banerjee, M.D., Diane Austin explains that in discussing the CCOP long-term follow-up of patients with representatives from OPRR, "it has become clear that these protocols will need to have an annual review." OPRR ruled that as long as patients were being contacted and data were being collected in regard to a particular study for survival analysis by the research base, then an annual review was necessary. Ms. Austin suggested "OPRR has indicated that it would be reasonable to review all CCOP protocols involved in long-term follow-up at the same time." Implementing this type of system would eliminate the need to keep all CCOP protocols active until the final patient was deceased (and would also eliminate the burden of needing an annual progress report for each individual protocol for which subjects were being followed for survival only.) It would also ensure that we were in compliance with Federal

regulations. So, the first long-term follow-up protocol was created. It was called "Long-term Follow-Up CCOP (Community Clinical Oncology Program) Protocol" and Dr. Banerjee was identified as the principal investigator. All studies that were part of CCOP, whether ECOG, RTOG, or NSABP, and were terminated but still followed patients for survival were collectively reviewed under that first umbrella protocol.

Several years later it became clear that each research base under CCOP would need its own long-term follow-up protocol. So, in 1998 that first umbrella protocol was replaced by long-term follow-up protocols for each of the individual research bases, including other research bases that were not part of CCOP. Currently the IRB has the following long-term follow-up protocols.

- CCOP-Children's Cancer Group (PI=Dr. Michael McManus);
- CCOP-Eastern Cooperative Oncology Group (PI=Dr. Banerjee);
- CCOP- MD Anderson Cancer Center (PI=Dr. Banerjee);
- CCOP- National Surgical Adjuvant Breast & Bowel Project (PI=Dr. James Hoehn);
- CCOP- Radiation Therapy Oncology Group (PI=Dr. Banerjee);
- GOG-Gynecologic Oncology Group – Minnesota (PI=Dr. Stuart Tipping); and,
- RTOG- Radiation Therapy Oncology Group (PI=Dr. Warren Olds).

So, what does all this mean for you?

Alright then, as interesting as all that is, what does it mean? To recap from above, if there were no long-term follow-up protocols for each of the research bases, it would mean that studies would need to remain active with the IRB until all local patients were deceased. That would mean that a continuing review report would need to be completed for each of those studies (69 in the case of the Children's Oncology Group) on a yearly basis, even though the only activity on the study would be to contact subjects for survival data. That's a lot of extra paperwork, not only for the IRB, but also for research coordinators. However, Federal regulations require that as long as subjects are being contacted or data are being collected, an annual review by the IRB is required. To simplify the process while still remaining in compliance with Federal regulations, the IRB created these umbrella protocols.

Here's the process for terminating projects and transferring them to a long-term follow-up protocol

1. To qualify for termination and transfer to long-term follow-up status, a project must be closed to accrual with no subjects being actively treated under protocol.
2. If these criteria are met, the "other" box under "Current Status" on the continuing review report should be checked and a comment should be entered stating that the project should be "terminated to long-term follow-up." The number of subjects being followed for survival should be indicated on the report.
3. The project will then be added (in the database) to the list of studies being followed under the appropriate long-term follow-up protocol for the indicated research base.
4. Then, on an annual basis, a request for continuing review will be sent to the principal investigator for each of the long-term follow-up protocols. That request will include a database report which lists all of the individual protocols being followed under the long-term follow-up protocol.
5. The investigator (or Research Coordinator) is responsible for completing the report and returning it to the IRB office. On the list of individual studies, the investigator/coordinator should indicate the number of subjects being followed for each study. When there are no subjects being followed, the individual study will be terminated and removed from the long-term follow-up protocol.

Special IRB Review Issues/Concerns

While this process outlined above seems reasonable and less burdensome than keeping each individual project active until subjects are no longer being followed for survival, it has created some problems for both coordinators and the IRB. One issue the IRB has struggled with is the expectations associated with reviewing these long-term follow-up protocols. The continuing review reports often contain very little information beyond how many subjects are being followed under each individual study. At times the IRB has tabled these reports and asked the investigators for more information on issues such as whether any long-term adverse effects are occurring in patients being followed. This has caused a problem for investigators/coordinators because some of the research bases really don't

provide such information. (A few research bases do provide survival data for these terminated long-term follow-up studies.) Correspondence from one of the research bases has indicated that they do continue to monitor any adverse event reports, however, they do not routinely circulate information on long-term side effects. In the rare cases where long-term risks which could have an impact on all previously enrolled subjects (such as Tamoxifen and endometrial cancer), the information on those risks are circulated to the research base membership.

Another issue that arose in the past was a concern that not all studies terminated to long-term follow-up were being tracked appropriately. This issue was raised by an investigator when his studies were audited and the auditor wanted documentation that all studies were being reviewed on an annual basis. The report from the database which accompanies the continuing review request should address this concern, as it lists the SP code and title of each protocol that has been transferred to long-term follow-up status.

So how can you ensure that these continuing review reports are complete and avoid having them tabled? First, check the list of studies against your own records to ensure that the information is accurate. If your records indicate a study should be followed for long-term follow-up and it's not included on the list, please call the IRB office so we can check our records. Alternately, if a study is on the list that should not be, let the IRB office know. For each study on that list, indicate the number of subjects being followed. (You can write these numbers directly on the database report.)

Next, check with the research base to determine whether they have any information on adverse events or other long-term data for these terminated long-term follow-up studies. If available, request a copy of that information and submit it with the report. If no information is available, please indicate that in answer to the questions asking for a summary of results, and/or significant findings. In particular, be sure to provide an answer to the question about adverse events which asks whether any unexpected long-term effects have been reported, even if your answer is that no data is currently available. (See the highlighted box for information regarding the reporting of adverse events or amendments for long-term follow-up studies.)

Finally, as with all other correspondence to the IRB, ensure that the report is complete and accurate, realizing that some of the questions will not apply in the case of long-term follow-up studies. For example, the section of the report dealing with numbers of subjects is not exactly applicable; however, you can comment "see numbers on attached report." Depending on the number of studies being followed, you can either answer the question about the number of subjects who have ceased to be involved, or you can again refer to the attached report. However, if you refer to the report list, be sure that you have indicated the numbers on that report list.

If you have any additional questions regarding long-term follow-up protocols, please feel free to contact IRB staff.

Adverse Event Reporting in Long-term Follow-up Protocols

IRB policy states that Adverse Events occurring **after a project has been terminated or occurring after all subjects have completed study treatment** should not be reported and will not be accepted or reviewed by the IRB **unless** the principal investigator determines that the event could have implications for the long-term health/safety of subjects. **If** the investigator determines the event could have such implications, then a process for informing subjects of the event must be developed and explained on the reporting form.

"But the IRB asks us about adverse events during the continuing review of these long-term follow-up protocols. Isn't that contradictory to the policy?"

Actually, no it's not. The adverse event reporting policy **does** ask that events be reported **if** they affect the long-term health or safety of subjects. Therefore, events **should** be reported if they meet this criteria. In fact, one of the most important things the IRB is looking for in these long-term follow-up protocols is whether there is any information on the long-term effects of the treatment.

Reporting Amendments

Amendments to studies that have been placed in long-term follow-up should not be submitted unless the amendment would have an affect on the subjects or if the information contained in the amendment somehow needs to be shared with the subjects (such as if some type of long-term toxicity was discovered, or there will be additional follow up, beyond what was originally conveyed to subjects.)