



## **Unanticipated Closing of a Clinical Trial**

(How to properly conclude a clinical trial that has been terminated unexpectedly)

A sponsor may stop the investigation of a new compound before studies are complete. There are many reasons for this, both positive and negative. When this occurs, clinical trials may be stopped prematurely. Some of the reasons for these early terminations are:

1. The drug has been shown to be so beneficial that it would not be ethical to continue a trial where subjects might not receive the drug (for example, subjects could be receiving placebo).
2. Overall trial enrollment was met, so all sites are being closed, even if some sites have not completed their enrollments.
3. The sponsor finds that the investigational drug (device, etc.) presents an unreasonable and significant risk to subjects. In this case, the sponsor must discontinue the investigation as soon as possible, and not later than 5 working days after making the decision. When this happens, the sponsor must notify the FDA, all IRBs, and all investigators who have participated in trials of the investigational drug. (21 CFR 312.56)
4. The treatment was not effective, so there is no reason to continue the trial.
5. The sponsor finds that they are unable to manufacture the drug appropriately for marketed use (can not obtain needed materials, formulation problems, etc.).
6. The sponsor determines that they are unable to continue the investigation for a business reason, such as lack of funds, lack of adequate market potential, competing drugs have received marketing approval ahead of the test compound, etc.

Although early terminations of clinical trials do not happen very often, they often catch clinical sites and study subjects unaware. Sponsors often do not inform sites of the possibility of closure in advance; they wait until the decision has been made. This means that sites must perform closure activities within an unexpectedly short time frame.

There are two very important things that the clinical site must know when a study is terminated early:

1. Is the study being closed for safety reasons?
2. Do the subjects currently on the study need to have their study medication tapered, or can it be withdrawn abruptly?

If the study is being closed for safety reasons, it means that there is a significant risk to subjects. In this case, subjects must be contacted immediately, told to stop their drug, and scheduled for a visit to return their unused drug and complete the necessary final evaluations, lab tests, etc. The sponsor will inform the investigator of the proper procedures to follow to ensure that the safety of subjects is maintained.

Some drugs need to be tapered off at the end of their use. This situation is drug-dependent, and needs to be addressed without regard for the reason the study is being stopped. All subjects taking the study medication will need to be scheduled for a visit to explain and start the taper period. Again, the sponsor should inform the investigator of the timing and tapering schedule that must be followed.

The impact of early trial terminations is significant for both the study site and the study subjects. For the study site, early closure means having to handle activities for all study subjects within a short time period,

which can be difficult in terms of time and logistics. It also means that the site may lose anticipated study revenues. For study subjects, there is the inconvenience of having to complete the study early, the potential loss of a beneficial treatment for the diagnosis under study, and the worry of safety concerns if the drug has been found to be unsafe. (As a hint, before a subject enters any trial, the site personnel should explain that, although it happens rarely, the sponsor may stop the trial early for any reason, including safety concerns, efficacy situations, business or manufacturing problems, etc. It is very important that every informed consent document contains a statement that the trial may be stopped early by the sponsor.)

To minimize the impact and work involved in the early termination of a trial, sites should have a checklist of things that need to be addressed when this situation arises. A basic checklist is given here, but remember that it may need to be adapted for your specific site and/or study situation.

### **Site Checklist of Activities for Unanticipated Clinical Trial Discontinuation**

- Ask the sponsor:
  - Why the trial is being terminated.
  - Is it for safety reasons?
  - Determine the need for any long term safety follow-up.
- Determine if subjects can have the drug stopped abruptly or does it need to be tapered.
- Arrange for the necessary time and personnel to handle the subject discontinuation visits.
- Contact (telephone) each study subject:
  - Explain that the trial is being stopped, and why.
  - If there are safety concerns, explain to the subject what they are, and what is being done to ensure the subject's safety.
  - Explain the process for tapering the drug, if applicable.
  - Explain the need to come in for a final study visit, and for any tests, etc. that need to be done.
  - Reassure the subjects that their safety is paramount, and that the investigator and study staff will do everything possible to make this procedure go smoothly.
  - Schedule the discontinuation visit(s) for each subject.
- Complete the necessary study visit(s) for each subject.
  - Be sure to answer any questions the subjects might have about the study and/or the termination.
  - Thank the subjects for participating.
- Complete the final case report forms according to the sponsor's instructions.
- Stay in contact with the sponsor throughout the closure process to ensure that all activities are completed and that any subject-specific concerns are addressed.
- Remember that all the usual study closure activities must also be completed, including:
  - Completion of case report forms (CRFs), including error corrections and data queries.
  - Appropriate review, filing, and storage of all study documents, including CRFs, consent forms, regulatory documents, etc.
  - Return of any unused study materials, including study drug, to sponsor.
  - Submission of a final report to the sponsor and to the IRB.

Overall, good communication between the investigative site and the sponsor, and good communication from the site to the study subjects is the best way to ensure a reasonable resolution to an unexpected clinical trial termination.