CLINICAL MONITORING - THE SPONSORS RESPONSIBILITY

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I have been asked to discuss the sponsor's responsibilities, as defined by the Code of Federal Regulations, when conducting a clinical trial using an unapproved animal drug. Rather than just reading the regulations, what I would like to do is to walk you through a clinical study from start to finish. Let me begin by first giving a few definitions.

"Sponsor" is the person, agency or corporation who initiates a clinical investigation, but who does not actually conduct the investigation.

"Investigator" means an individual who actually conducts a clinical investigation and under whose immediate direction the test article is administered or dispensed.

"Monitor" means a designated individual selected by the sponsor to oversee the progress of a clinical investigation.

My responsibilities at Bristol are to both initiate and monitor our clinical studies. The first step in any clinical study is to design a protocol, that will test both the safety and efficacy of the investigational drug under field conditions. A case report form is then designed to collect the necessary information. It has been our practice at Bristol, to review protocols with FDA before initiating clinical trials.

Once a protocol has been finalized, clinical supplies are manufactured and labeled according to the CFR with the following:

"CAUTION: CONTAINS A NEW ANIMAL DRUG FOR USE ONLY IN INVESTIGATIONAL ANIMALS IN CLINICAL TRIALS. EDIBLE PRODUCTS OF INVESTIGATIONAL ANIMALS ARE NOT TO BE USED FOR FOOD UNLESS AUTHORIZATION HAS BEEN GRANTED BY THE U.S. FOOD AND DRUG ADMINISTRATION OR BY THE U.S. DEPARTMENT OF AGRICULTURE.

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Needless to say, we proceed differently if we are working with food producing animals vs. non-food animals. In the former, milk discard and slaughter withholding times are established and authorization received from FDA prior to initiating any studies.

Now the recruiting of clinical investigators is ready to begin. Contact is made by phone or letter to set up the initial site visit. The first thing I do on an initial visit, is explain to the practitioner what his or her responsibilities will be as a clinical investigator. I discuss the following eleven requirements:

1. That he or she must keep a written patient record for each animal treated regarding diagnosis, clinical signs, exam dates, treatment dates, drugs administered, and quantity administered or dispensed.

2. To send in case reports as soon as they are completed - this enables us to keep track of any trend in adverse reactions, should there be any. Investigators are instructed to call in the event of serious or unexpected adverse reactions.

3. That investigators are required to maintain an accurate drug inventory record and must account for all clinical supplies.

4. That all unused clinical supplies must be returned at the end of the study.

5. That periodic checks of case reports against patient records will be carried out by the study monitor.

6. That it will be necessary to have certified laboratories conduct any required tests.

7. That any deaths occurring during the treatment period must be documented regarding cause and a statement included as to whether or not the investigator feels the death was drug related. I request investigators to submit necropsy reports when available.

8. I inform the investigator that FDA has the right to inspect patient records and drug inventory records pertaining to the study.

9. That records pertaining to the study must be maintained until notified by Bristol that they may be destroyed. I notify all investigators by letter regarding the date on which they may discard records.

10. That it will be necessary to obtain written consent from the owner of the animal to be treated. When dealing with horses, we allow the agent who is responsible for the horse to sign the consent form.

11. I inform the investigator that the investigational supplies should be maintained in a secure location. If we are working with a controlled substance, investigators are instructed to keep the supplies in a securely locked enclosure. I also obtain the investigator's DEA number.

Now, after all this has been explained to the investigator and he or she is still interested in conducting the study, I proceed to detail the investigational drug, discuss the protocol, and describe what should be recorded on the "Source Documents" or patient records. I ask the investigator to show me the type of patient records that he or she maintains. Usually in the small animal practices, record keeping is adequate to document diagnosis, exam and treatment dates, and amount of drug administered or dispensed. However, in large animal practices, record keeping isn't as extensive. Records usually consist of invoices or day books that are primarily maintained for billing purposes. When recruiting large animal practitioners, I try to get them to record the following on their invoices or day books:

1. Diagnosis
2. Clinical signs
3. Exam and treatment dates
4. Drug and quantity administered or dispensed
5. Dates and results of follow-up visits

If a practitioner does not maintain the kind of records we require and if he or she is truly interested in conducting the study, I help them devise some form of record keeping that will meet regulatory requirements. For example, provide a farm workbook that can be used to collect the necessary data and from which data can be recorded on the case report forms, at a later date. The farm workbook would then serve as "Source Documentation".

On the initial site visit, I inspect any hospital facilities that might be pertinent to the conduct of the study. For example, if hospitalization is required during the study, I want to be sure that adequate facilities are available for study animals.

If the practitioner is willing to conduct the study, he or she is required by Bristol procedures to sign two forms. The first is an agreement form regarding investigational drugs and contains the following:

1. Brief curriculum vitae of the principal investigator.

2. The states in which investigator is licensed to practice.

3. Location where study is to be conducted.

4. A description of the sponsor's responsibilities under the CFR.

5. A description of the investigator's responsibilities under the CFR.

6. Names and CV's of co-investigators.

7. The investigator certifies that the drug will be administered only to animal subjects under his or her personal supervision or under the supervision of licensed veterinarians responsible to him or her.

8. The dated signature of the principal investigator.

The second is a protocol acceptance form. This is a simple form indicating that the protocol has been explained to the investigator and that he or she is willing to conduct the study in accordance with the protocol. This form also states that the protocol may be amended by Bristol Laboratories. If ammendments are made by Bristol during the course of study, they must be signed by the Director of Research and the Study Monitor. The ammendment is then sent to the investigator for his or her signature. A carbon is retained by the investigator and the original returned to Bristol for our files. This procedure assures us that all concerned parties are aware of any protocol changes. FDA is notified by letter of any protocol amendments.

Following the initial site visit, the monitor completes a "pre-investigational visit" check list.

This provides further documentation for Bristol management and FDA that:

1. The protocol was explained to the investigator.

2. That lab work will be conducted in an approved facility.

3. That the requirements of a clinical investigator as set forth in the CFR have been explained to the investigator.

4. That there will be adequate drug accountability and source documentation.

On page two of the form, the laboratory facility to be used is specified and the study monitor gives a brief description of the investigator's practice and facilities.

We select clinical laboratory facilities as follows: "If the clincal laboratory facility being used by the investigator is licensed or accredited to perform the desired tests by the Clinical Laboratories Improvement Act, or by another body recognized by the Center of Disease Control, is part of a licensed school of veterinary medicine, or is licensed or accredited by the state in which it operates, it is concluded that licensure or accreditition under these conditions is an acceptable measure of the adequacy of the clinical facility."

We do not allow the investigator to conduct any laboratory tests that are pivitol to the study.

Now that the necessary prerequisites have been fulfilled, drug shipments are made. Prior to shipment, the clinical monitor must complete a "Clinical Monitor's Checklist".

This is another reminder and form of documentation that the requirements of the sponsor as set forth in the CFR have been met. Specifically the following:

1. Protocol explained in detail to investigator.

2. Arrangements made for laboratory work to be done in an approved laboratory.

3. That FDA has been notified that drugs are being shipped to a clinical investigator.

The other items on the checklist are reminders to insure that all Bristol procedures have been fulfilled.

We notify FDA of the shipment of investigational drugs as follows:

1. INAD Number
2. Name of Drug
3. Date of authorization letter (food animals)
4. Proposed use
5. Approximate dates of trial
6. Name and address of investigator
7. Location of trials

8. Approximate number of animals to be treated
9. Number of animals previously used
10. Species
11. Size or type of animal
12. Maximum daily dose and duration
13. Method of administration
14. Withdrawl period
15. Labeling information supplied to investigator

Now that the FDA has been notified and the drug has been shipped, the study is underway. All shipments are accompanied by a shipping form that the investigator signs and returns to Bristol upon receipt of the investigational supplies. This assures us that the supplies have been received. If the form is not returned within 10 days, the investigator is contacted to determine the status of the shipment.

When I first visit prospective investigators I ask them how many cases of a particular indication that they would normally see in a month's time. Most will usually say "Oh!, I see 20 to 30 of those each month". However, once they have received the drug and studied the protocol with all the exclusion criteria and requirements for post-treatment evaluation, this number drops down to 2 or 3 cases per month.

I make it a practice to phone all investigators every 4-5 weeks. All phone conversations are logged in the investigator's file in regards to the following: name of investigator, number of study, date of the conversation and what was discussed.

A contact form is also used when site audits are conducted. All investigators are audited at least twice during the course of the trial. Investigators that I have not worked with before are monitored more frequently. If I am working with a new investigator, I try to conduct an audit after the first 5-7 cases have been submitted. This serves to correct any minor errors before they become major problems.

When case reports are received, they are date stamped, reviewed, signed and dated by the reviewer. Case reports are assigned numbers and entered into a master log and into an individual investigator log. Adverse reactions are recorded in both logs so that a rapid assessment can be made by individual investigator and for the total study. The study monitor alerts the Director of Research of any unexpected or alarming adverse reactions. The Director of Research will notify FDA and investigators if either the type or frequency of adverse reaction poses a significant hazzard. Investigators are instructed to call the study monitor if there are any unexpected adverse reactions or any problems with the study.

Each case report is reviewed for completeness and adherence to the protocol. If there are major discrepancies, the investigator is immediately notified by phone and a contact form is completed regarding the conversation. If there are omissions on the case report forms, they are noted for the investigator to correct. This is done in one of two ways. The form is xeroxed, the copy maintained by Bristol, and the original returned to the investigator for correction. Or, at the time of the next visit, the case reports are taken to the investigator for correction.

If case reports are complete, they are entered into a computer so that we always have up-to-date summaries of each clinical study.

As I mentioned earlier audits are conducted at least twice during a study and more frequently if an investigator is new or very active. When I conduct an audit, I set up an appointment with the investigator and have him or her pull all the patient records pertaining to the study, so that they are available when I arrive. I compare the data on the case reports with the information on the patient records regarding the following: patient indentification, diagnosis, clinical signs, exam dates, sample dates, drug given and quantity administered or dispensed, concommitant therapy, wash-out times for other drugs, adverse reactions, and adherence to protocol requirements.

If a protocol calls for a wash out time of 7 days for antibiotics, I go back into the patient records to be sure none were given during that period. If I find discrepancies between the case reports and the patient records I discuss them with the investigator. Any changes on the reports are made by the investigator and initialed by the investigator. During the audit, the investigator's drug inventory record is checked to be sure that it is current. When the audit is complete, I fill out a monitoring form detailing what records were audited and any significant findings. Any reports that do not meet protocol criteria or cannot be substantiated by source documents are excluded from our final evaluation. All adverse reactions are reported!

Every 18 months I am audited by the Bristol Corporate Technical Evaluation Division. TED, as we refer to them, also make unannounced audits.

They audit the records for all the clinical studies that we have conducted in the last 18 months. This is to insure that the clinical studies conducted by Bristol are in compliance with the CFR. These audits usually last a week. When the audit is complete, TED conducts field audits on the clinical investigators that are pivotal to the studies.

When the clinical trial is completed, I conduct a final audit on all investigators. Any records not previously audited are reviewed in the same manner as the previous audits. Any case reports that do not meet protocol criteria or do not have adequate source documentation, are excluded from final evaluation. Any unused clinical supplies are returned to Bristol for destruction. The investigator returns the signed drug inventory form to the monitor. The monitor, then conducts an accountability audit comparing the amounts of drug shipped, administered, and returned.

If there is a significant shortage or any magnitude or overage, Bristol procedures require that the monitor investigate the discrepancy and file a report regarding the findings. Once the study has been completed, the investigators receive xerox copies of all the case reports submitted to Bristol, along with instructions regarding the length of time that the records be maintained.

Some final notes regarding clinical monitoring are as follows: If an investigator tells you he or she can get 20 cases expect 5; expect $\simeq$ 2% of cases to be excluded because of poor source documentation; and expect $\simeq$ 12% of cases to be excluded because of protocol violations or losses to follow-up.

We feel that by conducting clinical trials in the manner I have described, that we fulfill all the responsibilities of the sponsor as setforth in the CFR. But equally important is the fact that adequate monitoring is both good science and good business.