

## SECTION III

### CLINICAL STUDIES: MANAGEMENT AND EVALUATION OF PERFORMANCE

#### Chairman

Dr. William Jenkins  
Texas A & M University

Initially let me say, I think on behalf of us all, a hearty congratulations are due to the Planning and Coordinating Committee, as well as the Planning Committee, as a subcommittee, for a job well done. This has been a well-organized, well-conducted and very provocative workshop. A special "thank you" for your efforts to date. I have derived particular pleasure from attending this meeting being from Texas A&M. It is the first AVPPT Meeting that I have been at that an Aggie joke hasn't been told by this time. I thought Dallas Horton was going to spoil that but fortunately he didn't, although I have no doubt that he has one ready.

Our program moves toward a crescendo as we go into Section III, entitled "Clinical Studies: Management & Evaluation of Performance." Once again as part of the whole theme of the symposium, three excellent speakers have been invited to participate. The first is Bill Kay, who needs no introduction really, but let me tell you (and those who may not know him that well) something of his background. He is a native of Massachusetts with a B.S. degree and then a D.V.M. degree received from Michigan State University (1963). After two years of practice in Rhode Island, he entered the Animal Medical Center as an intern. He subsequently undertook a double residency at AMC and then, a true success story, made his way up through the ranks so that today he is Chief of Staff of that very fine and well-known institution. He has been active in both the clinical as well as in the academic arenas and still maintains research interests. Of course, the reason he is part of this program is his involvement in the conduction of clinical trials. I think it is also important to recognize another aspect of Bill's background and that is his active participation in organized veterinary medicine, especially of the professional Colleges, such as Internal Medicine.

## Clinical Studies: The Investigator's Responsibilities

William J. Kay, D.V.M.\*

Good morning. Thank you for inviting me to speak at this very excellent meeting. When Dr. John Paul invited me to present a paper on "Responsibilities of the Investigator", I reviewed the clinical trials conducted during the last past 15 years by and at The Animal Medical Center. Arthur I. Hurvitz, DVM, PhD, the Center's Director of Research and I have conducted trials with many fine pharmaceutical companies on drugs developed for use in companion animals. Many of these companies and their representatives are at this meeting. I have some perspective on the problems and responsibilities of the investigator and the investigator's institution.

Let me try and answer a question asked yesterday (the question was asked of Dr. Charles Vail) "did Dr. Vail feel he could conduct a clinical trial?" I believe he answered yes. I admire his optimism.

We have been involved in about 50 clinical trials. It is not easy to conduct a clinical trial and to be perceived as successful. And what do I mean by successful? To satisfy the economic requirements of the sponsoring company, to satisfy our own ethical practice philosophy and economic requirements, to satisfy animal owners, to successfully treat pet animals, and to meet government standards. I have learned to be less critical of the approval process; even if I don't particularly like the steps required. The more you participate in the approval process, the harder it is to see good alternatives and we should constantly look for easier and better rules. Of all aspects of the investigators responsibility, probably the most difficult is to get everything done in the "hoped for" time frame. Murphy's Law is usually operative, for example "if it can go wrong, it will go wrong" and things always take longer than they should. So why do we at The Animal Medical Center continue to seek and accept new clinical trials? The public, the better health of animals, the veterinary profession and our institution need new and better products. Occasionally we experience a nice breakthrough. Very important for the Center was the creation of a culture, within our organization. Clinical trials are now a "thing" with meaning, merit and form, supported and accepted by the staff. The willingness to understand and to participate in this process is vital to our success. I recently read "In Search of Excellence" by Peters and Waterman. The recent best selling book on America's best managed companies. The authors found that to get anything done in an institution, you must create the right "culture". Which goes far beyond procedures, protocols and committees and orders. We have created a culture for clinical trials at The Animal Medical Center. Many of our staff look forward to participation in clinical trials.

Yesterday, we spoke about "getting together". I would appeal to institutions, companies, practitioners and other groups performing clinical trials to insist on an early meeting. In project design, implementation and follow-up. Technological advances are many and increased specialization often creates an

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investigator who is "leading the charge" in an area, procedure or disease. Occasionally, the company and the government may not be aware of his/her state of the art. The earlier we get together, to plan the study, the better we do. This is true with involvement of FDA too. The earlier we meet with the FDA to get their sense of where they are, the less heartache we have later. And, generally, the Center for Veterinary Medicine is very helpful.

Conduct of initial meetings--The initial meeting should result in a clear statement of the project's objectives: What are we trying to prove or demonstrate: In what time frame? Can we safely and effectively treat clinical cases with the proposed protocol? What concomitant therapy is needed: Can we "get by" without concomitant therapy? and so forth. I guess we are optimists. Occasionally in our desire to accept a clinical trial we may agree to do a more difficult task. There are inherent setbacks in conducting most clinical trials. Inadequate numbers of clinical cases may seek care at the clinic, many cases are rejected for various reasons, the protocol has changed, the product did not arrive from the company, the animal died (usually from another cause), healthy disease free-symptom free pets are not returned often enough to satisfy most protocols, etc. The case may be lost to follow up. It is axiomatic that the better the product, and therefore the more successful the treatment, the more difficult the follow up. Clients do not return if the pet is perceived to be cured.

Selection of a project team--You need to determine initially whether there is a high or low staff interest in the project. If it is a breakthrough product - a super new or real hot project, there will be real interest. Examples of this include a breakthrough in antibiotic therapy, a nonsteroidal, anti-inflammatory or a new anticancer drug. Such clinical trials will be received by the faculty or staff as an intellectual challenge. If the trial is a redo of topical dermatologic or a generic "me too" which has been around for 20 years, it may not generate strong interest. The form and amount of compensation will be important.

We feel a real responsibility to provide the best institutional skill we have in terms of satisfying the needs of the project. It is easy to choose the wrong person for the right project and vice versa. There may be a high degree of interest by a particular person. The person best qualified may not be interested or available. This is certainly true in training institutions where residents desire to participate in a project. For promotion, to satisfy the boss, and for money. They may not have the level of experience to properly conduct the trial. The AMC routinely uses additional senior staff support when residents are involved.

Dosages--I don't know the dosages on most drugs. The approved clinical dosage of most compounds will change. Sometimes the clinical trial creates evidence for new and better dosage, time of administration, etc.

Proper timing of trials--If we expect a project to be completed on time, be careful to evaluate the required time carefully. For example, a study with an industrial company, may realistically, take four years to complete. The company wants you to do the study in two years. You do not want the industrial/pharmaceutical company to leave the table saying "gee, we would like to do business with you (Mr. AMC) but we can't afford to take four

years". Do you tell it like it absolutely really is or do you agree to complete the project in less time. Is the glass of water half full or is the glass of water half empty? This is a very important consideration. It may be better to use a variable time table. Using worse case, likely case, and best case analysis. We now negotiate more realistic time frames.

Compensation--Your institutional policy for compensation has a great deal to do with the level of interest exhibited. The Center routinely shares the revenue. Payment is usually direct. Occasionally it is deferred. I remember listening to Dr. Thomas Keith of Beecham Laboratories many years ago. Tom suggested that the Center consider a different compensation plan. I would use emotional and logical appeals to our investigators. I discussed compensation with veterinarians at other institutions. Clinical trials may be good for promotion, career advancement, etc. Trials teach about industry and government and so on and so forth. This is true. And money talks. Let's use an example. Currently The Animal Medical Center is contracted to evaluate a well known companion animal product sold by a well known company. It is a good product and a good study. We are not doing very well in meeting our requirement. The cases are not being entered with sufficient frequency to meet our agreed upon time frame. We therefore sweetened the pot and awarded \$15.00 to each clinician for a completed case. We sent out memos and our staff agreed to identify, evaluate and treat selected cases. Very few cases were entered. After several meetings we determined that the \$15.00 wasn't enough compensation. We raised the compensation to \$50./case. The study is now doing better. I know this may strike some academic types in the heart. It strikes me, harder in the heart, when the work doesn't get done. When we compensate our investigators adequately, the trial usually goes along quite well. Everyone is always more than busy and the clinical trial may not be a top priority.

The issue of how to adequately cost account clinical trials--Clinical drug trials are interesting. Let's make a contract. If you receive a federal grant, there is, usually a very strict application process, a very detailed formal way to obtain a grant or contract. There is an overhead factor built in, very detailed forms, etc. That may not be the case, or least it has not been my experience, in conducting companion animal clinical trials. Whether dealing with a big company or a small company, the contractual process is one of negotiation. Sometimes we trade dollars for time: we can do a study for more dollars in less time or we can do a study for less dollars in more time. We trade time for dollars. It is difficult to properly cost account clinical trials. If we use standard cost accounting/cost stepdown techniques including overhead, our contracts might be different. Whether we cover expenses or experience an excess of revenue over expenses, or break even doing clinical trials is a difficult question. It is hard to determine if clinical trials are financially "legitimate". The bigger the institution, the easier it becomes to hide a piece of the puzzle. This is not a complaint. I'm mentioning a reality in that some studies are ultimately financed by your institution.

Competant therapy--This is an area where institutions and clinicians must make a hard choice. Especially in treating critical diseases. I will contrast two disease states. Topical (cutaneous) pathology and treatment with a topical compound and a parenteral (systemic) compound for congestive heart failure.

In one case, you might be able to treat the dermatologic condition with a topical compound without concomitant therapy. In congestive heart failure, however, treatment without concomitant therapy may be very difficult. I am gratified by my colleagues refusal to withhold accepted and excellent treatment in the conduct of clinical trials. The FDA supports this position too. Our staff will not permit animal patients to suffer or be treated without competent care. We are gratified that our pharmaceutical company colleagues support the delivery of the best care. The issue of competent and concomitant therapy complicates our clinical trial design and implementation. I do not have an easy answer. Additional (concomitant) therapy should be carefully evaluated and justified. We have a responsibility to design studies with good science, and good care.

Organizing the staff--Unless the project director, associate project director, project supervisor or unit leader responsible for the studies is committed to getting it done and is willing to monitor the study, it will quickly go astray. Problems can be corrected if discovered early and if rapport between industry, the institution, and FDA is there. Our memorandum of understanding includes important ground rules.

An institution can do clinical trials--In the context of performing clinical trials, look at several parameters. Veterinary institutions often become involved without a formal, structured process adequate to design and administratively manage clinical trials. These studies may be "tag on" issues. If the project is a tag on do not be surprised if the project doesn't get properly handled. Some studies can not be performed by some institutions. For example, I know the difficulty of identifying twenty clinical cases afflicted with particular and sensitive microorganism in the evaluation of an antimicrobial. I sympathize with all of us trying to complete trials without a better alternative. We have a real responsibility to grapple with the issue of better and easier protocol design.

Dose selection--Institutions and practitioners need to be aware of the shifting sands of dosages. I know the government is aware of this. In the future, more veterinarians will narrow their professional focus. Veterinary medicine has about five or six percent certified specialists. The context and content of diseases will change and specialists will take leading edge positions. They will know more about effective dosages. These specialists are in possession of new information. And a certain amount of time is required to get this information in the professional world. We might initiate a study only to learn about a better, more effective dose before the study is complete. Even well established dosages are changing.

Summary--In summary, it is fun, productive and rewarding to be involved with clinical trials. Especially when new products reach the marketplace. Institutions that keep an eye towards the marketing needs of industry area step ahead. As institutional investigators, we can be very valuable to industry if we are sensitive to the demands of the market place and careful in structuring our institution to respond to the challenge of clinical trials. Without a rigorous interested investigative force, the approval process and the data available for those compounds approved, will be inadequate.