

SECTION II

CLINICAL TRIALS--EXPERIMENTAL DESIGN

Chairman

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Statistical View of Clinical Trials: Academia

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As I was thinking about what I was going to talk about today, I thought maybe the best thing to do is to go back and try to find the first reference of a clinical trial that I could find. I am sure you are not surprised that that reference came from the human side but you might be surprised at how far it went back. I think it is very pertinent to some of the discussions we were having this morning about are controls needed or are they not needed? This first reference to a clinical trial goes back to Nebuchadnezzar. He had decided that the diet of choice, the best diet that he could feed to young men, was wine and meat. So he went out into the community, got the most virile of the young men and put them under the care of a eunuch. This eunuch was instructed to feed them nothing but wine and meat. This trial was to last for a full year. Among these most virile of young men was Daniel. Daniel soon decided that he did not like eating only wine and red meat so he persuaded the eunuch to feed him and three of his pals some vegetables and pasta. He did this for three weeks. At the end of the three weeks, it was very clear that Daniel and his three friends were in much better state of health than the rest of the young men. However, Nebuchadnezzar was very upset about this because Daniel and his friends had ruined his clinical trial which was to have shown the people that, indeed, red meat and wine was the best kind of diet they could have. Without these four recalcitrant young men, how would we have known that indeed wine and red meat is not the best diet. Thus Daniel and his friends represent the control group in this first clinical trial.¹

The whole world was shocked with some of the "clinical trials" that we became aware of after World War II. As a result of these atrocities, in 1947 the Nuremberg Code was developed. This code presents 10 points which should be followed by any medical investigation involving humans, Table 1.

Today the medical community is acutely concerned with animal welfare as well as human welfare. Thus with the appropriate modifications in the statements this code also applies to the conduct of veterinary clinical trials. In particular, item 3 is applicable not only to clinical trials but to all investigations involving living subjects. The anticipated results justify the experiment. Whether it is basic research, a clinical trial or other applied research this is of primary importance. Are the results justified in doing the experiment at all! Of equal importance is item number ten. The investigator must terminate the experiment, if its continuation may be detrimental to the patient. The veterinarians first and foremost responsibility is to the welfare of the patient. Adherence to protocol must always be secondary to this responsibility.

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Table 1--The Nuremberg Code

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1. The subject must give his or her voluntary consent, knowing the nature, direction, purpose, inconveniences, and hazards of the experiment.
 2. The experiment should be necessary both in yielding fruitful results for the good of society and in the sense that the information cannot be gained without the experiment.
 3. The anticipated results justify doing the experiment (see section 3.3.2, Clinical Research Combined with Professional Care and Nontherapeutic Clinical Research).
 4. All unnecessary physical and mental suffering must be avoided (see The Use of Sham Operations, section 3.8.3).
 5. There should be no a priori reason to believe that death or injury will occur.
 6. The degree of risk shall not exceed the humanitarian importance of the problem (see section 3.1 and the discussion on reasonable).
 7. Preparations should be made and adequate facilities provided against the remote possibility of adverse effects.
 8. Those who conduct the experiment shall exercise the highest degree of skill and care and be scientifically qualified.
 9. The subject must always be free to bring the experiment to an end.
 10. The investigator must terminate the experiment if its continuation may be detrimental to the patient.
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After the Nuremberg Code was laid down in 1947, the next historical reference to the conduct of clinical trials was in 1964. The World Medical Association at a meeting in Helsinki thought this 1947 code should be updated so they laid down a series of statements, essentially along the same lines as the Nuremberg Code. A man who had been there, Sir Bradford Hill, did not like the generalities of the Helsinki statement so he developed a list of his questions, Table 2. These questions incorporate the same ideas and principles which we are addressing in this symposium. "Is the proposed treatment safe" or in other words, is it unlikely to do harm to the patient. "Is it ethical to use a placebo or dummy treatment." We are back to what kind of controls should we have. Is it proper for the doctor not to know the treatment being administered to the patient. This brings us to the question of should we do blind studies? Double blind studies? I leave it to you to formulate your answers to these questions.

Table 2--Bradford Hill's Questions

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1. Is the proposed treatment safe or, in other words, is it unlikely to do harm to the patient?
 2. Can a new treatment ethically be withheld from any patients in the doctor's care?

Tuberculous meningitis was a universally rapidly fatal condition and when the first case reports revealed that streptomycin treatment had resulted in the patients' recovering, this fact was conclusive evidence of the effectiveness of the new treatment. It was then not ethical to perform a clinical trial of streptomycin in tuberculous meningitis. However, respiratory tuberculosis runs a more viable course and it was ethical to perform the randomized controlled trial of streptomycin in this condition. Moreover, only a limited amount of streptomycin was available at that time (1947) and as all cases could not be treated, it can be argued that it would be unethical not to have performed the trial.

3. What patients may be brought into a controlled trial and allocated randomly to different treatments?
 4. Is it necessary to obtain the patient's consent to his inclusion in a controlled trial?
 5. Is it ethical to use a placebo or dummy treatment?
 6. Is it proper for the doctor not to know the treatment being administered to his patient?
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Before conducting a clinical trial, the investigator must have informed consent. Whether you are doing clinical trials with humans or with animals, you have to have informed consent. I always wonder about the word "informed." Does the lay client or patient really understand the possible side effects and/or possible lack of effect? The investigator must tell either the patient or the client the nature of the treatment, the objectives of the trial, duration, what it involves, what are the possible benefits, possible hazards to the treatment, what to do if the patient becomes ill, if the patients runs out of tablets, etc. Now I think many of you, specifically those of you who have been associated with a human clinical trial, are aware of Marvin Zellan's idea of informed consent. His idea is that we do not have to get informed consent from everyone. What we do is randomly assign our patients to either the treatment or to the positive control. If a patient is assigned to positive control, Zellen says we do not have to get informed consent from him, because you are treating that patient with the treatment of choice so why do you need informed consent. It is an issue that not many people have been willing to endorse.

The next issue to be addressed is what are typical inclusion criteria. If you are conducting a trial, what kind of patients are suitable for entry into this trial. Are you going to select them on the basis of age, breed, case history, sex, current physical condition, this list could go on and on. These are but a few of the typical inclusion criteria. Now, let us look at some of those typical of exclusion criteria: age, breed, sex, current physical condition. They are the same! What does this tell us? This tells us that the objectives and the end point, the reason for doing the trial must be very well defined. It must be a unique definition. We have to know what kind of patients we want in the trial and why, because the same kind of criteria can be used for either inclusion or exclusion.

At this point we have informed consent and we know whether a particular patient will or will not be entered in the trial. What about terminating the trial? Are you ever justified in ever terminating a clinical trial? There are two reasons for terminating a clinical trial. One, the patients are exhibiting adverse affects. Secondly, significant benefits are observed.

At times the clinicians, the biological academicians, will be heard to say, "It is the statisticians who tell us that we have to have 30 cases" or "it is you statisticians that are increasing the number." A case in point is one of the human clinical trials was terminated recently. The trial was supposed to have continued on for several more years but because the evidence at that point in time was so overwhelming that the new treatment was superior to the treatment of choice, the decision to stop was forthcoming. Whenever, in any kind of clinical trial, the evidence is clear that there are significant benefits, I do not believe the statistician is going to say, "The protocol says you have to have 63 patients and you only have 59. You must get 4 more patients."

As we design a clinical trial, what are some of the things that the statistician keeps in mind.

Unique measurable end point--What are you going to measure? And is it unique. When two clinicians look at the same animal, will you both say that this particular patient has reached a given end point? This end point must be unique and must be measurable.

Biological versus statistical significance--This is an issue familiar to all investigators. A statistician has only to increase sample size, until even very small differences are statistically significant. Statistically two groups might be different but biologically the difference is meaningless. As the statistician and clinician design the clinical trial, let us make sure that we are designing it in such a way that significant differences have a biological meaning.

Comparability of control and treated groups--If two groups do not start out from the same physiological point at the beginning of a trial and if they end up at different points, you really can not say very much. Thus the only distinguishing factor of the two groups is the treatment.

Randomization--Is it always best to randomize? Overall randomization is not always in the best interest of good design. The statistician has other alternatives available, for example matching and/or stratification. Either of these techniques is quite effective when the characteristic being measured has a lot of variability.

Bias--Whenever a measurement is subjective, bias can be present. Subjective measurements are not the only source of bias, geographical location, time of year and the measuring device are only a few of other potential sources.

Repeatability of results--Can someone in a different setting repeat your trial and get similar type results?

These are some of the things that you must be aware of and take into consideration as you put your experimental design together. However before discussing specific designs, one point must be made. It is unethical to specifically design a study, to detect toxicity. Once in a while a toxic response is observed, but it is unethical to design a trial which deliberately elicits toxic responses.

In the broad sense, experimental designs are of two basic types: 1) Those in which each subject receives one and only one treatment and 2) Those designs in which each subject receives more than one treatment, possibly all treatments. Within each of these broad classifications a subject may be measured or observed once or more than once. The particular design chosen dictates the type of analysis and hence the specific hypotheses which can be tested. Only cooperative relationship between the statistician and the investigator will maximize the probability of success of the overall endeavor.

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