How Is It Decided When to Conduct a Large-scale Caries Clinical Trial?

W. W. BRINER

The Procter & Gamble Company, 11511 Reed Hartman Highway, Cincinnati, Ohio 45241

J Dent Res 63(Spec Iss):715-717, May, 1984

First, I will give a relatively simple answer to this question, then expand upon it, and finally evolve criteria which should be helpful in making the decision when to conduct a large-scale clinical trial.

Considering that the purpose of a large-scale clinical trial is to make a decision on the anti-caries efficacy of something, it is proposed that an investigator needs two things:

(1) something to test (called a "Product" in this discussion), and

(2) a means to test the Product clinically (called a "Clinical Trial").

Expanding upon these, the decision to proceed with a large-scale clinical trial can be based upon answering two fundamental questions:

(1) Is there sufficient evidence of anti-caries efficacy, safety, etc., of the Product to merit a decision to proceed with the Clinical Trial? and

(2) Is the mechanism for conducting a Clinical Trial available so that an accurate estimate of the anti-caries efficacy of the Product can be made?

I will now discuss each of these questions – Product and Clinical Trial – in general terms and suggest some criteria for making the decision to proceed, realizing, of course, that it is impossible to cover every conceivable facet in so short a discussion.

There are at least seven criteria worthy of consideration concerning the product to be tested. All should be evaluated in the process of making the decision to proceed. These are:

- Anti-caries efficacy – The product should possess sufficient efficacy for testing.
- Safety assessment – The product should pose minimal safety concerns.
- Benefit/risk assessment – The anti-caries benefit should far outweigh any safety concern.
- Acceptance of product by subjects – The subjects should be willing to use the product throughout the trial.
- Manufacturing – A long-term supply of raw materials sufficient to last throughout the study should be assured, and feasibility of manufacturing the product should be established.
- Supply and distribution – Adequate plans should have been laid.
- Cost-effectiveness – The product should be within the financial reach of the intended consumer.

Let us now discuss how each of these is related to the decision to proceed with a clinical trial:

(1) *Anti-caries efficacy.* – First of all, there should be on hand *in vitro* and *in vivo* experimental evidence showing that the product compares well with respect to similar products in anti-caries efficacy. It stands to reason that without substantial evidence of this kind, there is little justification in proceeding further. The nature of the experimental evidence will vary from product to product. However, it would probably be unwise to go to a clinical trial without meaningful evidence of anti-caries efficacy in some sort of animal model(s), because many of these models simulate the human experience. Of these models, the rat has been shown to be of great value, especially in the case of fluoride-containing products.

(2) *Safety.* – The product should be safe for the duration of the trial, which will probably be several years. Safety, indeed, covers a wide range of topics, since the product will usually be used in the oral cavity and, therefore, will have the potential to be ingested. Among the topics for consideration should be safety in the mouth for hard and soft tissues, safety upon acute and chronic ingestion, and so forth. In reality, the safety profile of the product will probably be reviewed by several agencies at the national (in the U.S., the FDA), state and/or local (Human Safety Committee) levels, depending upon the nature of the product and the nature of the clinical trial. Failure of the product to meet the standards set forth by any of these reviewing bodies would, of course, preclude a decision to proceed. From a practical standpoint, it is wise to consult a toxicologist early in the development of a product in order to minimize pitfalls in safety.

(3) *Benefit/risk assessment.* – Since dental caries is not a life-threatening disease, and the results of caries can usually be treated with little risk in a dental office, it stands to reason that little risk should be associated with caries prevention. Data from the efficacy and safety assessments above should be used for a benefit/risk assessment. It follows that the ideal anti-caries product would give virtually complete protection against caries, with minimal safety concern. Conversely, a product with a discernible safety negative(s) and moderate anti-caries efficacy might be deemed unworthy of a large-scale trial.

(4) *Acceptance.* – The aesthetics (flavor, aftertaste, appearance, etc.) of the product should be such that it will be used readily by the subjects during the trial. An aesthetically unacceptable product carries with it the risk that it will not be used by subjects in the manner desired, or – even worse – the subjects drop out of the study because of the unacceptable nature of the product. The aesthetics of the product should be researched carefully before a decision to proceed is made. In practice, evidence from home-use trials is used at least in part to obtain data on product acceptance and compliance.

(5) *Manufacturing.* – The product will usually consist of components which must be processed to make the product that is actually tested. Before the decision is made to proceed with the trial, it should be established that the raw materials necessary to make the product are available, and that the manufacturing capabilities can meet the demands of the clinical trial. It is also prudent to make trial runs of any scaled-up manufacturing process, to assure that the scale-up has not affected product performance. If several batches of the product are made during the trial, provisions should be made so that the necessary raw materials and facilities are in place to make each batch. Assurance that these needs are met should be sufficient to warrant a decision to proceed.

(6) *Supply and distribution.* – The means for supplying each subject with his/her own individually-coded product

should be in existence. Each unit of the product should be individually coded to blind the trial for all concerned or to verify product usage. Provisions should be made to break the code without compromising blindness in case of emergency. This appears to be a trivial point, but in reality it is of extreme importance, because sometime during the trial it is usually desirable to ascertain that subjects are actually using the product or control as specified. If this cannot be verified, then the trial might be compromised.

(7) *Cost-effectiveness.* – If the product is quite costly, even though there is evidence of significant efficacy, then there may exist a risk that even though it is efficacious, its high cost may preclude its use, and the clinical trial will have been for naught! Thus, it would seem prudent to establish before starting the trial that if, indeed, the product proves efficacious, it can be placed into the hands of its potential user(s) at a reasonable cost. If the product is not cost-effective, then a decision should be made as to whether the trial should proceed, and whether the money required to conduct the trial might be used more productively elsewhere.

Once these criteria, and/or others deemed necessary for a particular product, are met, then it is feasible to assess the criteria for the clinical trial to determine whether the mechanism for conducting it is sufficient to make a determination of the anti-caries efficacy of the product.

To conduct the trial, it is necessary to have a scientifically valid and ethically valid plan. This plan is called a "Protocol". The protocol should specify the nature of the product to be tested, the qualifications of subjects who will use the product (and how these subjects will be recruited), the length of time the subjects will use the product, and how the progression of caries will be assessed during the trial. The assessment of caries is done by an Examiner, and this will result in data which must be processed and analyzed in order to reach a decision on efficacy.

Thus, the criteria for assessing whether the mechanism for conducting the trial is ready to proceed are:

- Protocol – a clear statement of the hypothesis [including control(s)] should be on paper;
- Subjects – an available pool of subjects who meet the requirements to test the hypothesis;
- Examiner – a competent examiner should be available for the entire study;
- Data processing – This should be in place before the study begins; and
- Money – Funds to complete the study should be available.

A decision to proceed with a clinical trial should be based upon whether the above components are sufficient to estimate the efficacy of the product. Let us now look into the criteria necessary to accomplish this:

(1) *Protocol/hypothesis.* – The protocol provides the vehicle for testing a hypothesis concerning anti-caries efficacy of the product. Execution of the protocol results in acceptance or rejection of the hypothesis. Prior to the start of the trial, certain decisions should be made concerning the statement of the hypothesis. That is, the hypothesis should be stated in its null form – Product = Control (whose efficacy is known from previous clinical evidence) at a specified caries rate. This topic will be addressed in much greater detail by Dr. Fertig.

The nature of the control should be clearly defined in the protocol. Furthermore, since the hypothesis is stated in the null form, then it must be established what will be accepted as a "meaningful difference" from the control in anti-caries efficacy. Selection of a meaningful difference between product and control is of great importance, because in reality this establishes how many subjects in each group are needed in order to detect the meaningful difference at a given caries rate. The meaningful difference should also state the probable levels of risk associated with Type I and Type II statistical errors. I'm certain these points will be covered in detail by others, so I shall not pursue them further.

The selection of a control may pose a dilemma. An historical control is not acceptable because of the body of evidence showing that the caries rate has decreased across time, and a basic assumption of the trial is that product and control groups face the same challenge. From an ethical viewpoint, the use of a placebo or "no treatment" control is not usually justifiable, with the exception of a non-fluoride product whose anti-caries efficacy would be additive to that of fluoride. An example of this could be a trial of an anti-caries vaccine in which one group was vaccinated and the other not – both groups continuing to use their usual oral hygiene, including use of fluoride. It would also seem prudent in the selection of a control to compare within-delivery systems (mouthrinse *vs.* mouthrinse) rather than across-delivery systems (mouthrinse *vs.* prophy paste). However, if the object is to determine the anti-caries benefit of a second fluoride delivery system added to that of a first, it would seem prudent that the trial provide adequate control over both systems.

Thus, to assess the benefit of a fluoridated mouthrinse added to that of a fluoridated dentifrice, a design worthy of consideration would normally be a 2 x 2 factorial in which the test population would be subdivided into four groups:

(1) placebo dentifrice – placebo mouthrinse,
(2) placebo dentifrice – fluoridated mouthrinse,
(3) fluoridated dentifrice (of known anti-caries activity) – placebo mouthrinse, and
(4) fluoridated dentifrice – fluoridated mouthrinse.

Since use of a placebo dentifrice is not justifiable, one might consider omitting the two placebo dentifrice groups entirely. This design should permit the added benefit of the fluoridated mouthrinse to stand out clearly. Alternately, an option to consider might be to maintain the fluoride dentifrice groups (with placebo and fluoridated rinses) and replace the placebo dentifrice groups with groups that would continue using their "usual" dentifrice. The latter ("usual" dentifrice) alternative often raises more questions than it answers because of the uncertainties around the kinds of fluoridated or non-fluoridated dentifrices used by the subjects and the interactions of the various dentifrices with the fluoridated mouthrinse. Certainly the latter ("usual" dentifrice) alternative should never be run without including the fluoridated dentifrice groups because of the vagaries of interpretation. These examples may serve to illustrate the dilemma of choosing a control. Finally, if there is a heirarchy of efficacy among possible controls, the most efficacious should be selected, so that acceptance of the null hypothesis would carry with it evidence of anti-caries benefit. Dr. Fertig will pursue this further in his paper.

In order for a clinical trial to proceed, there should be in existence a protocol which, if executed properly, will result in a valid decision concerning the efficacy of the product. It follows that the finalized protocol should be reviewed by appropriate bodies to ascertain its scientific and ethical integrity prior to a decision to proceed.

(2) *Subjects.* – A pool of subjects should have been identified which meets the requirement for caries rate as

stated in the protocol. This implies first-hand knowledge of the expected caries rate in the subject pool. It is desirable that the subject pool reside within a single, albeit large, community. If this be the case, then concerns about pooling of data from several widely-dispersed communities fail to arise. Also, within that pool of subjects, it is desirable to have minimal mobility so that the "dropout rate" will be low. The pool of subjects should be selected in order to minimize dental "noise" from unwanted sources. Obviously, a community in which another trial is planned or is in progress should be avoided. Likewise, the selection process should exclude communities which plan to initiate projects affecting dental health during the trial. Thus, a community which was planning to implement water fluoridation would be excluded, as would a community in which a new dental center was planned.

A mechanism for recruiting the subjects should also be in place. A strategy for recruiting should include mechanisms to inform the community of the trial and the potential health benefits and risks from it. (In the process of recruitment, the nature of the trial must be made crystal clear to the potential subjects, so that they understand the risks and benefits accruing from participation in the trial. Once the subjects understand the nature of the trial, a statement of informed consent should be obtained in which the subjects agree to participate under the conditions of the trial.) In order to make a decision to proceed, researchers should establish access to the required pool of subjects.

(3) *The examiner.* – The examiner determines the progression of caries during the trial by examining each subject for caries. This is done using methods specified in the protocol, and usually visual-tactile and radiographic examinations are included. The examiner must be available for the duration of the trial. In the selection of an examiner, it would seem prudent to select one who in the past has shown the ability to detect the difference stated in the hypothesis. If this aspect is disregarded, it is conceivable that the protocol could have a built-in bias toward false acceptance of the null hypothesis. In other words, selection of an examiner who was unable to detect the difference stated in the hypothesis could result in the generation of data which would indicate that control and product have similar efficacies when, in fact, the product was actually either more or less effective than the control.

A minor, but often troublesome, corollary to the selection of an examiner is a place for the examiner to work. This could also serve as a distribution site for the product. Plans should be made so that the examiner can function smoothly with a minimum of interference.

(4) *Data processing.* – The examiner generates data which must be processed and analyzed statistically so that the hypothesis stated in the protocol can be tested. The data processing element should be in place so that acceptance or rejection of the hypothesis can occur without a question related to data handling.

(5) *Money.* – Need we say that a clinical trial that may last years and involve thousands of subjects costs a lot, perhaps in the millions, even excluding the R&D costs of the product. Before a final decision to proceed can be made, an estimate of the cost of the trial should be made, and it should be established that the probability of success of the trial is commensurate with the amount of money to be expended upon it. If this cost estimate is in order, then the decision to proceed can be made with reasonable assurance that a valid trial will be conducted.

In summary – If the product meets the criteria below, then the product should be deemed worthy of clinical trial:

- Anti-caries efficacy,
- Safety,
- Benefit/risk assessment,
- Acceptance by subjects,
- Manufacturing,
- Supply and distribution, and
- Cost-effectiveness.

The clinical trial mechanism should be deemed ready when the following criteria have been met:

- Protocol/hypothesis,
- Subjects,
- Examiner,
- Data processing, and
- Money.

Once it has been established that the above criteria are met, then a decision to proceed is in order. Fulfillment of the stated criteria should carry with it reasonable assurance that a valid estimate of the anti-caries efficacy of the product will be obtained.

How Is It Decided When to Conduct a Clinical Trial?: Discussion of Dr. Briner's Presentation

J. P. CARLOS

Director, National Caries Program, National Institute of Dental Research, Bethesda, Maryland 20205

J Dent Res 63(Spec Iss):717-718, May, 1984

The process of deciding whether and when to begin a clinical trial can be examined from several perspectives. Dr. Briner has enumerated some of the practical considerations which are involved in this decision. I agree that every point he mentions ought to be explicitly addressed before a trial is undertaken, and, since I am not going to engage in nit-picking, I shall generally let his suggestions stand unchallenged, although I have a few amendments to some of his remarks.

I would like to approach the question from a slightly different standpoint, and suggest that, when the time has come to think about a clinical trial, we really ought to concentrate on three major questions:

- Is it likely that a trial can be carried out which will provide an unequivocal answer to the question of interest?
- Is the answer to the question worth having?
- Is it ethical to conduct a trial to get the answer?

I will comment briefly on each of these points.

- *Is it likely that a trial can be carried out which will provide an unequivocal answer to the question of interest?* – This question refers to the design of the trial, and it subsumes most of the criteria of which Dr. Briner spoke. What needs emphasis, however, is that the design of a clini-