Patient Numbers Required In Clinical Endpoint ANDA Trials

Clinical Endpoint ANDA Program Optimization
White Paper Series

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Introduction

The first question that invariably gets asked when planning a clinical trial is, “How many patients do I need?” Just as often the first answer is, “For what?” This discourse usually follows with “How many patients do I need in my trial so that I am 100% sure that I will be successful?” To which the Statistician answers, “You will need all of them.”

This exchange of questions and answers is not very useful, but it is correct for both parties involved. The Sponsor wants a successful trial and wants to include an adequate number of patients to insure this outcome. The Statistician realizes there is truth to the old maxim that nothing is certain in life except taxes and death.

Much of statistics deals with uncertainties and the estimation of the degree of uncertainty that exists for a given situation. The fact is that the only way to be 100% certain of anything concerning a population of patients is to study all of them. If we could do so, we would then be able to “describe” the characteristics that we studied. Anything less than looking at all patients (current and future ones) will involve some uncertainty.

From a practical standpoint, all we can do is take a certain number of patients (a sample), study them, and then make, with some level of confidence, statements about the characteristics of the general population of all patients. In the context of a clinical trial, the characteristic of primary interest is how patients respond to one treatment relative to their response to another.

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The number of patients required in a trial is one of the cornerstones of the trial design. This number is calculated by using statistics, but the validity of any estimated number is totally dependent on certain assumptions. So before the estimates can begin, there are some key questions that need to asked and answered. As the above conversation continues and the Statistician starts asking some concrete questions, it becomes clear that some questions should be answered by the sponsor while a multidiscipline trial design team is needed to complete the entire set of design considerations. The participants on such a team might include:

Business Representatives, such as:

- A Business Executive, who is responsible for making final trade off and risk assessment decisions; and
- Business Development Professionals, who are responsible for business-oriented decisions that impact the product development program; and

A Trial Design Team, including:

- A Statistician, with responsibility for framing the information about trial design, endpoint and clinical significance into the probability assessments required to calculate the appropriate patient numbers;
- A Clinician, responsible for in-depth knowledge of the disease, its treatment and the practical aspects of studying patients within "the specific trial territory";
- A Scientific Analyst, responsible for extracting information from the literature, regulatory guidance and actions, product labeling, prior trials, etc. and
- A Regulatory Affairs Professional, to determine the applicable regulatory venues and the requirements within those venues.

The likelihood of a study's success is significantly increased when members of the team, or at least most members, have worked successfully before on similar drug development programs.

The Questions and Answers Process

As the team is assembled and the questions and answers developed, they will likely look similar to what is shown in the following table. Note that this table presents a high level summarization of the process and that some of the following topics and issues will be discussed in greater detail later in this paper.

Typical Question	What The Answer Impacts	Team Members Responsible for Answer
What is the purpose of the trial?	Study Type	Bus Executive, Bus Dev, Reg. Affairs
What disease state is involved?	Endpoint Determination	Bus Dev, Clinician, Analyst, Statistician
What Statistical tests will be run?	Statistical Methods	Statistician, Clinician
How good is the Test Product?	Test-to-Ref Assumption	Operations, Clinician
Desired certainty of Success?	Power of Trial	Business Executive
What is anticipated dropout rate?	ITT-to-PP difference	Analyst, Clinician

Let's take a look at how this Q & A process works for CE ANDA trials in particular.

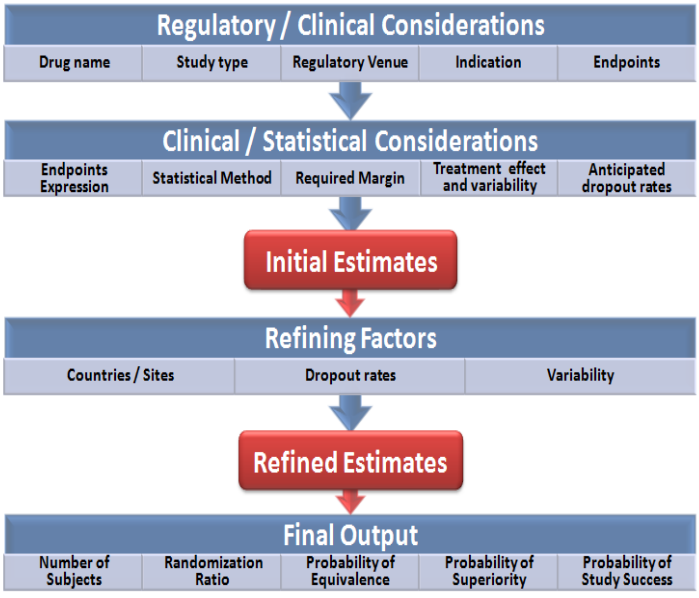
Clinical Endpoint ANDA Studies

Clinical Endpoint ANDA trials, commonly called Clinical Equivalence or Therapeutic Equivalence trials focus on demonstrating bioequivalence of locally acting drugs. In these trials, there is an investigational product (Test), an active comparator (Reference) and, usually, a negative control (Placebo). The Test and Reference products are evaluated as to how comparable they are to one another, usually by confidence interval methods.

The comparison between the Test and Placebo and the Reference and Placebo use hypothesis-testing methods. These are geared toward detecting differences between treatment responses in order to demonstrate the superiority of the active treatments over the Placebo. The Series Introduction White Paper provides more information on these types of drugs and CE ANDA trials. In this paper, our objective is to provide a path for determining the number of patients that will provide some agreed upon level of probability of demonstrating both the bioequivalence of the Test and Reference and the superiority of both of these over the Placebo.

The Design Road Map

The design team has been assembled, and the task has been defined as calculating the number of patients required for a given Clinical Endpoint ANDA trial. The following diagram provides a road map for our journey toward completing this task. As can be seen in the chart below, the design team will go through a set of decisions, assumptions and calculations divided into several major steps.



Road Map Overview

We'll begin by examining the Design Road Map at its highest level. The design team normally gets initial input from the Sponsor. This may be just the name of the reference drug and required regulatory venue, but more commonly it also includes some information about the type of study required as well as some initial clinical information. At this point, the team is ready to go to work.

They first must scour the available literature for as much information as possible. The Scientific Analyst works closely with the Statistician, Regulatory Expert and Clinician to collect the information needed regarding the regulatory pathway, the disease, the drug, and prior studies.

For purposes of simplifying our journey, we have divided the overall initial process of gathering information and creating assumptions into two distinct categories:

1. Regulatory/Clinical Considerations
2. Clinical/Statistical Considerations

While every task clearly resides in one of these groups, they need not be performed sequentially. In fact, tasks from each group are commonly addressed in parallel

Initial and Refined Estimates

Often, by just using the available literature to obtain answers to the issues and questions, we can do a preliminary analysis of the required number of patients. But it is important to go beyond this initial point and make several more refined estimates as to what the optimal number might be.

The initial estimate provides the Sponsor with needed information for making an informed decision on the potential (feasibility, cost-to-benefit ratio, etc.) of the drug development program. This estimate, based purely on high level data, can influence such actual trial variables as geographic venue, number of sites, PIs, project management considerations, etc.

At this point, the initial patient number estimates are preliminary and designed to simply help move the program from concept worthy of consideration.
If the Sponsor decides to move the program forward, then a more precise second estimate is required. Now the design team moves into a refining process and considers factors such as the venue of the trial in order to tweak the assumptions that were based on general considerations and scientific literature.

This refining process can be repeated several times as additional trial details become available. The output of each of these refinements is normally presented in the form of a table linking the number of patients (enrolled, ITT, and PP) to the probabilities of a study's success. This helps the Sponsor to make a decision about the number of patients for the upcoming trial.

Now let's examine the Design Road Map processes in more detail. So you can more easily follow these discussions, we will be referencing our map from top to bottom and from left to right.

Regulatory / Clinical Considerations				
Drug name	Study type	Regulatory Venue	Indication	Endpoints

Regulatory/Clinical Considerations

Drug Name and Study Type. The purpose of the trial and the filing strategy largely dictate the Study type. All phase II-III clinical trials deal with safety and efficacy assessments in a patient population, but the intensity of focus between these two types of assessments depends on whether the filing is a 505(b)(1) NDA, a 505(b)(2) NDA, or an ANDA. The emphasis of the specific trial is a decision that the Sponsor must make with guidance from the design team. For the purposes of this paper, we will confine our discussions to generic products (ANDA pathway or its EU counterpart) that require a clinical endpoint trial to establish bioequivalence.

Regulatory Venue. In most cases, the Sponsor will provide the design team with the name of the drug and the regulatory pathway to pursue. Let's say that the drug is a topical dermatological product for which the Sponsor is planning on obtaining approval as a generic product. The drug might be intended to move through the ANDA regulatory path at FDA or in the European Approval path at EMEA, or both. In either case, it is the sponsor's decision to make and is often based on the design team's recommendations.

Indication and Endpoint. The appropriate endpoint is determined not only by the disease involved in the trial, but also by the trial design. The proper endpoint for a new drug filing is not necessarily the correct one for a generic drug filing. The proper endpoint for filing in the U.S. may not be the most appropriate one for the EU. Endpoints must have clinical relevance for the disease (Clinician input), but also need to be expressed in a way that permits statistical evaluation (Statistician input).

Clinical / Statistical Considerations				
Endpoints Expression	Statistical Method	Required Margin	Treatment effect and variability	Anticipated dropout rates

Endpoint Expression. Let's say that it is generally agreed that the Physician's Global Assessment is the appropriate primary endpoint for a given study. So the question to be answered becomes, "Should this outcome be expressed as the mean change from baseline, or is it better to express it as the proportion of patients who meet some particular level of change from baseline (e.g. score ≤ 1 for a 0-5 severity rating)?" The Clinician, Scientific Analyst and Statistician must work closely together to insure that the correct decisions are made on this choice as well as the correct expression of the proper endpoints. The proposed endpoints and their presentations should be agreed on as reasonable and appropriate by the entire design team.

Statistical Method. The choice of statistical method is not just the domain of the Statistician. While the Statistician must use a method appropriate to the purpose of the trial (in-equivalence, equivalence, non-inferiority, superiority), there are generally multiple ways to evaluate an endpoint. An endpoint such as change-from-baseline, as in the above example, may be expressed in different ways (Clinician and Scientific Analyst input), which will generally influence the choice of the statistical method.

The proper evaluation method (Statistician input) must permit the results of the analysis to be expressed in a clinically relevant way to Clinicians within the discipline involved. In some clinical disciplines (diseases) the convention may be to analyze the change after transforming it from baseline to percent change, in which case the statistical method would be Analysis of Variance. In another discipline, this same endpoint may be evaluated without transformation by a statistical method such as Analysis of Covariance, which incorporates an adjustment for the influence of baseline. Again, the understanding and concurrence of the entire design team in making this choice is useful.

Required Margin. The required limits for Equivalence (Test vs. Reference) must be known prior to estimating patient numbers. These limits have been standardized for generic drug ANDA submissions in the U.S. For new drug submissions (NDAs), and submissions for generic drugs with clinical endpoints in the EU, they have not been standardized, so regulatory guidance from the authorities is a very important input.

Such limits, referred to as the "margin," are ideally the smallest differences that are considered to be clinically relevant. For U.S. generic ANDA trials, this margin is set at 20% (i.e. ±20% on a difference, 0.80 and 1.25 for a ratio). In all other trials, this margin must be chosen and justified in the trial.

Treatment Effect and Variability. Estimates of treatment means and standard deviations for continuous clinical endpoints (e.g. percent reduction in lesion counts) or for proportions of patients with treatment success for the dichotomized clinical endpoint (e.g. proportion of patients with lesion clearance) are best obtained from the scientific literature by the Scientific Analyst and Statistician.

Several important decisions about treatment differences must be made as well. We need to know how good we think our Test (investigational) treatment is relative to those treatments to which it will be compared. Specifically for the Clinical Equivalence trial, we need to decide on an estimate of the "true" Test-to-Reference, and Active-to-Placebo, relationships. Some care needs to be taken in this assessment, as a difference between products in an in-vitro evaluation (such as potency) does not often lead to the same magnitude of difference in a clinical endpoint.

This is where input from both the Operations Manager and the Clinician is important. An overestimation in the true clinical difference between products could lead to a large overestimation of the required patient number, but an underestimation of the difference can lead to an underpowered trial with too few patients to meet the trial objectives. While the former is a costly mistake, the latter is a disaster.

Dropout Rates. The anticipated dropout rates during the trial must be addressed. In a clinical equivalence trial, it is common to look at the Per-Protocol (PP) population as the primary one for the comparison between active treatments (e.g. 90% confidence interval on Test-to-Reference ratio or difference, for a U.S. generic submission, 95% confidence interval for a EU submission).

The Intent-to-Treat (ITT) population, or some slightly restricted modified ITT (mITT) population, is typically the primary one for the superiority comparisons (Test vs. placebo, Reference vs. Placebo). In terms of patient numbers the following is true: Enrolled > ITT > mITT > PP. For a proper patient number calculation, both PP and ITT (mITT) numbers must be considered. The estimate of the proportion of ITT patients expected to qualify for inclusion in the PP population is an assumption that greatly influences the statistical calculations for subject number.

Refining Factors		
Countries / Sites	Dropout rates	Variability

Refining Estimates

We are now at the point where the information and assumptions discussed above are sufficient to permit the calculation of the number of patients required. The Statistician goes to work and provides the team with that number. But before we discuss the format of that calculation, it is natural to ask, "Is this the best calculation we can develop?"

The fact is that although these initial calculations use all of the information required by our Road Map, most of that information was obtained from literature and typically does not take into consideration important specific details of the trial to be run. Optimization requires a "Refining Stage" where the team deals with issues directly related to the way a specific trial will be conducted. And this is where having team members who are experienced with the specific populations, sites, and PIs is imperative.

Trial Geographic Venue. A design team with experience in running similar trials at specific sites with access to patient populations that will be used in a given trial can provide important adjustments to the assumptions derived from the literature. Even moving the trial to different areas of North America or to the Caribbean, such as is common for dermal studies, may significantly change some parameters. The influence of moving the trial to different continents will generally have an even more pronounced impact on some of the key assumptions.

Dropout Rates. The initial or preliminary calculations as to dropout rates have been based on average numbers available in the literature. At this stage, we can refine those estimates by using information from the design teams' site-specific experience.

Variability. While initial means and standard deviation estimates were extracted from the literature, how and where the trial is conducted can greatly influence the variability estimates. The larger the variability in measuring the primary efficacy endpoint, the greater will be the required patient number. Reduction of trial variability will lead to an increase in the trial's probability of success using the same patient numbers calculated for the larger variability estimate. Alternatively, by reducing trial variability, we can reduce the number of patients while still maintaining the same success probability. And, there are some powerful ways to reduce trial variability. A discussion examining the issue of reducing trial variability is planned for a future Whitepaper in this series.

Final Output				
Number of Subjects	Randomization Ratio	Probability of Equivalence	Probability of Superiority	Probability of Study Success

Typical Output

At last we can take a look at the output. Standard statistical sample size estimation programs or more versatile simulation methods are used to obtain patient number estimates based on the values for key assumptions. Sample size estimates are made, more often than not, based on properties of the standard normal distribution curve, better know as the bell curve.

The results of the statistical calculations will generally be presented in a summary table such as that shown below. Some of the primary assumptions used in the calculations will also be presented in the form of a commentary on the table.

Most commonly the table will provide several scenarios for the number of patients, each accompanied by the probabilities of trial success. The table will also address one additional important parameter of the proposed study – the randomization ratio.

Enrolled Subjects [a]	mITT Subjects [b] (T:R:P)	PP Subjects [c] (T:R:P)	Probability of Bioequivalence	Probability of Superiority	Probability of Study Success
636	169:169:169	135:135:X	0.89	0.94	≥0.80
696	185:185:185	148:148:X	0.92	0.95	≥0.85
771	205:205:205	164:164:X	0.95	0.97	≥0.90
882	235:235:235	188:188:X	0.97	0.98	≥0.95

[a] - Assuming 25% dropout rate, and round up to allow 1:1:1 randomization;
[b] - A mITT subject is one who is properly randomized, receives at least one dose of study medication and has at least one post-baseline efficacy evaluation;
[c] - Number of PP for Vehicle Treatment is not critical to primary superiority evaluations

The choice of the randomization ratio, the proportional allocation of subjects between Test, Reference and Placebo, is determined by both statistical and practical concerns. If the clinical effect of the active treatments (Test and Reference) is not very much greater than that for the placebo, then an equal allocation of subjects to the three treatments (1:1:1; Test:Reference:Placebo) will generally be required. Sometimes when this difference is even smaller, a 1:1:2 ratio may be appropriate. If the active treatments are anticipated to be much more effective than placebo, then a 2:2:1 (i.e. twice as many subjects randomized to Test and Reference as to Placebo) may be appropriate.

Even a 3:3:1 may statistically be an appropriate randomization ratio, but this allocation may not be practical if we have many sites involved in the study. It is important to have some Placebo representation at every site, and the 3:3:1 randomization ratio could lead to too few Placebo patients at the sites. In such a case, the 2:2:1 may be needed, based primarily on practical considerations.

Since we can never be 100% certain that our trial will be successful, we need a decision on what level of certainty is desired or required. This decision is always one of evaluating the benefit/risk ratio. Because of its impact, The Business Executive of the Sponsor, with guidance from the design team, must be responsible for this decision.

For example, it will require a substantially greater number of patients to have a probability of 0.90 than for a power equal to 0.80 (80% certainty of success on the primary endpoints). The greater the patient number, the more expensive will be the trial and, generally, the longer it will take to complete. The number of patients will also influence the number of sites and sometimes geographic locations for the trial, which in turn might influence the trial regulatory acceptance and the level of service provided to the Sponsor by the trial team.

Conclusions

With the right preparation, proper decisions on values for the key assumptions, and the right design team, the next time you need an answer to, “How many patients do I need?” you can obtain a straightforward, and correct, answer. It is an answer that will go a long way toward not only increasing the probability of trial success and acceptance, but also one that will lower costs and decrease trial time.

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