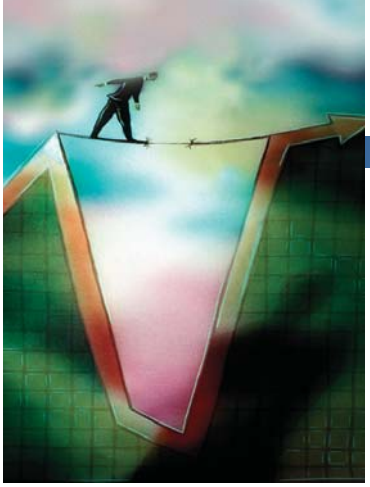

Projecting Realistic Enrollment Rates

Principles and Methodology

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Determining a realistic enrollment potential for a given site . . . has a significant bearing on site selection and subject recruitment planning activities.

Introduction

Determining and projecting realistic enrollment rates is one of the most challenging aspects of conducting a clinical trial. According to industry statistics[1]

- Recruitment timelines represent 22.3 percent of the entire clinical development timeline.
- Some 70 percent of studies fail to recruit on time.
- Most U.S. clinical trials must extend enrollment by at least 1 month beyond the study completion period.

Given that so many clinical trials are faced with enrollment challenges and delays, it is important to consider these challenges early on in the study planning process. Determining a realistic enrollment potential for a given site, based on access to the patient population of interest within a community and within the site's own practice, has a significant bearing on site selection and subject recruitment planning activities. **Figure 1** outlines some common questions typically asked during the study planning phase.

This article describes a simple methodology for addressing the questions in Figure 1 and will outline an approach for projecting realistic enrollment rates and determining realistic timelines for meeting enrollment goals. The methodology draws on various data sources to determine the potential opportunity to enroll subjects within a given community and an expected rate of enrollment for a given site. It encompasses the following building blocks:

- U.S. Census Data and community population data
- disease incidence and prevalence rates
- the number of cases of a given condition seen in an investigator's practice each year
- the projected or actual randomization: screen ratio for a given study
- enrollment period

Due to readily available census data, the scenarios depicted will reflect U.S. examples; however, the core methodology can be applied globally. Further, this approach is not intended to account for all variations within a clinical trial setting (e.g., acute vs. chronic conditions; practicing sites vs. research-only investigative sites), but provides a framework for discussing which aspects of the methodology are appropriate and relevant for a given clinical trial.

Determining Community Enrollment Potential and Rate

As disease incidence and prevalence rates are one of the core building blocks, it is important to establish an understanding of these concepts. Incidence is defined as

Figure 1. Enrollment Planning Checklist

1. How many potential suitable, willing, and able candidates are available within the investigator's community per month?
2. Assuming that there are no other competing studies in the community, can the investigator meet the enrollment goal by drawing upon candidates within the community should his within-practice recruitment efforts fall short?
3. Realistically, how many subjects is the investigator expected to enroll per month? _____ Total during the X month enrollment period? _____
4. Realistically, will the investigator be able to meet his enrollment commitment without additional recruitment support?
5. If no additional recruitment support is provided, how long will it take the investigator to reach the enrollment target?

the rate at which new cases occur in a population during a specified period (e.g., 49/100,000/year, or 49 cases per 100,000 individuals per year). Incidence is sometimes confused with prevalence, which refers to the proportion of a population that currently has the disease or condition (e.g., 3% of the population). Both incidence and prevalence are different measures of a disease's occurrence. There are challenges and problems associated with capturing and reporting disease frequency statistics that are discussed frequently by experts in the field of epidemiology.

As the intent of this article is to describe a simple methodology to help determine a more realistic enrollment projection, this article adopts the convention used by www.wrongdiagnosis.com. This Web site is one of many excellent resources that provide disease incidence and prevalence data.[2] This Web site attempts to manipulate prevalence and incidence data via rates of incidence/prevalence calculations to report more relevant data on the number of people affected with a given condition or the odds of developing a given condition in a 1 in 1,000 format. Hence, the prevalence rate data reported by www.wrongdiagnosis.com serves as a useful benchmark for our calculations. These data will be combined with community population data derived from the U.S. Census (http://www.census.gov/main/www/cen2000.html).

Before projecting the enrollment rate for a given *site*, it is first necessary to project the prevalence rate of a disease within a given *community* (the community of patients from which one can draw to fulfill the enrollment goal). This is calculated as follows:

[prevalence rate] × [community population]

The case study of a fictitious investigator, Dr. Will Recruit, an endocrinologist based in Dallas, Texas, illustrates this calculation. Dr. Recruit is being considered for participation in a study of Type II diabetes. The prevalence rate and population data for Dallas are as follows:

Condition	Prevalence rate
Type II diabetes	0.06 (1 in 17)
City	**Population**
Dallas, Texas	1,188,580

Therefore, the prevalence of Type II diabetes in Dallas, Texas, would be

$$0.06 \times 1{,}188{,}580 = 71{,}315$$

To determine the calculated *potential* number of clinical trial candidates per community per year, the community prevalence is multiplied by the overall expected or known randomization: screen ratio for a specific clinical trial. For this case study, it is assumed that the randomization:screen ratio, based on past experience, is approximately 0.33 (1 patient randomized for every 3 patients screened). This is calculated as

[community prevalence] × [randomization:screen ratio]
$71{,}315 \times 0.33 = 23{,}533$

Based on this calculation, it appears that there is a reasonable population of patients with Type II diabetes in Dallas to draw upon for recruiting patients into this study. To determine the *potential rate of enrollment*, the potential number of candidates is divided by the enrollment period (months). For our case study, we'll assume the enrollment period is 9 months, therefore

23,533 potential patients/9 months
= 2,615 patients/month

However, this doesn't take into consideration the likelihood that a given potential candidate will actually agree and consent to participate in the study. Conservative industry figures estimate that only 6 to 12 percent of potential candidates actually participate in clinical trials.[3] Thus, if it is estimated that only 10 percent of the potential subjects approached in a given month will actually agree to participate, this leaves us with a more realistic enrollment projection of

2,615 patients/month × 0.10
= 261 suitable and willing subjects/month

Sponsors typically perform this calculation during their site selection process to determine if a site is located in an area where the potential for identifying suitable candidates for the study is reasonable. Such an exercise also helps sites determine what the potential for recruiting suitable subjects is within their community. Should it be determined that a site cannot meet the enrollment goals through traditional within-practice recruiting methods, then knowing the potential population within the community helps to outline the possible pool of candidates that can be reached through external recruitment efforts (such as outreach programs, physician referrals, advertising).

Determining Site Enrollment Potential and Rate

To determine the expected enrollment rate for a given site, the same princi-

Table 1. Calculations Summary				
Disease Prevalence Rate	×	City (community) Population	=	Prevalence per City (community)
0.06	×	1,188,580	=	71,315
Prevalence per City (community)	×	Randomization:Screen Ratio	=	Potential Candidates per Community
71,315	×	.33	=	23,533
Potential Candidates per Community	÷	Enrollment Period (months)	=	Potential Candidates/Month
23,533	÷	9 months	=	2,615 patients/month
Number of Potential Subjects/Month	×	Percentage Likely to Consent	=	Number of Suitable and Willing Subjects/Month
2,615	×	.10	=	261

ples are applied, using the sites' subject population as a starting point. For example, assume Dr. Recruit's practice includes some 1,200 type II diabetics. The potential site-specific pool of candidates would be calculated as follows:

[site population] × [randomization:screen ratio]
1,200 × 0.33 = 396

The projected enrollment rate for Type II diabetic patients for this site would be

396 potential subjects/9 months
= 44 subjects/month

If Dr. Recruit's commitment is to enroll 30 subjects, it appears, based on the above calculations, that it is realistic for the site to meet the enrollment goal, given the access to the appropriate patient population and the expected randomization:screen ratio.

If the likely percentage of subjects who would be willing and able to participate (10%) is factored in, then a truer estimate of the enrollment potential can be projected as

[site potential candidates/month] × [conservative consent proportion]
44 × 0.10 = 4 subjects/site/month,
that are likely to be suitable candidates
and willing to participate in the trial

This calculation presents a different picture regarding the site's ability to meet the enrollment goal, but it still suggests that the potential to meet the enrollment goal of 30 subjects within 9 months is feasible.

Table 2. Summary of Calculations Used in the Case Study for Dr. Recruit				
Site Population	×	Randomization:Pre-screen Ratio	=	Potential Candidates
1200	×	0.33	=	396
Potential Candidates	÷	Enrollment Period (overall)	=	Number of Potential Subjects/Month
396	÷	9.0	=	44
Number of Potential Patients/Month	×	Percentage Likely to Consent	=	Number of Suitable and Willing Subjects/Month
44	×	.10	=	4
Number of Suitable and Willing Subjects	×	Enrollment Period (remaining)	=	Number of Suitable and Willing Subjects likely to enroll during remaining enrollment period
4	×	2.0	=	8
Enrollment Goal	–	Number of Current Randomized Subjects	=	Number of Subjects Needed to meet goal
30	–	10	=	20
Number of Subjects Needed to meet goal	–	Number of Suitable and Willing Subjects likely to enroll during remaining enrollment period from physician's own pool	=	Number of Additional Subjects Needed
20	–	8	=	12
Number of Additional Subjects Needed	÷	Number of Suitable and Willing Subjects/Month (from own practice)	=	Additional Months Needed to Meet Goal
12	÷	4	=	3.0

Monitoring Enrollment Progress for Recruitment Contingency Planning

The methodology used to determine how a site is doing in terms of meeting their enrollment goal can be used throughout the course of the study. At any point, one can look at the remaining enrollment period to determine how many additional subjects the site is likely to get from within its own practice, which again may help to prioritize the need for additional study awareness building activities.

For the purpose of this case study, the assumption is that the enrollment has been open for 7 months and Dr. Recruit has enrolled only 10 of the 30 required subjects. This may have been due to a number of factors, such as unplanned staff changes, competing studies within the community and within the practice, and delayed study startup and ethics approvals, all of which impact the enrollment period. With only two months remaining, Dr. Recruit would likely be able to enroll, at a rate of four suitable and willing candidates per month, for two months, an additional eight subjects within the remaining enrollment period from within his own practice. Thus, he still needs an additional 12 subjects to meet the enrollment commitment. To achieve this goal, Dr. Recruit will require either

- recruitment support to identify additional subjects from sources external to his own pool of subjects or
- an additional three months to meet the enrollment goal, relying on his own subject population.

Summary

Many unforeseen factors can impact enrollment rates. Information, resources, and tools are available to enhance the predictability of enrollment success. This article has outlined a simple approach for calculating the enrollment potential within a given site and within the community surrounding that site. By considering these parameters up front, sponsors and sites can better plan where and how to focus their subject recruitment efforts.

References

1. Food and Drug Administration, Centerwatch.
2. http://www.epibiostat.ucsf.edu/epidem/epidem.html includes a comprehensive library of epidemiology references and links to many epidemiology references.
3. National Institutes of Health and Institute of Medicine, www.nih.org.

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