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Metrics for Faster CLINICAL TRIALS

Almost half of clinical trials run late, year after year. Why does this happen? The biggest delaying factor is finding enough patients, and the delay starts with the clinical trial protocol. The protocol includes the inclusion and exclusion criteria that define the patients who are eligible for the study. Criteria are growing in complexity, and the sponsor may not find the patients needed because too few meet the criteria. If the patients do exist, it is difficult to find the clinical trial investigators who treat them. This article examines the trends in delay and available solutions.

Causes and Trends in Trial Delays

Recently, clinical trial protocols have had a sharp increase in eligibility criteria, which is reducing the number of available patients. As the criteria grow, study designers start to deal with unknowns. It is hard to estimate how many patients are lost without an objective statistical source. As shown in Figure 1, the number of major inclusion and exclusion criteria is up for Phases II and III in drug testing. Phase III, often the most difficult, has had a 23% increase in major criteria, measured between 2005 and 2009. A study by the Tufts Center for the Study of Drug Development looked at all criteria, not just the major ones, and the trends are worse. Total eligibility criteria are up 58%, to a new high of 49 in the 2004 to 2007 period.

More criteria result in fewer qualifying patients, making patient recruitment harder. Figure 2 shows the resulting delays. In an analysis of more than 1,300 trials in 2009, 45% of trials were late. Worse yet, 10% were more than 100% late, which means they took more than twice the originally allocated time.

The Right Questions and the Right Answers

The creators of the protocol should begin with these questions:

- » Are inclusion/exclusion criteria overly restrictive?
- » Are there specific changes that could improve patient availability?

- » How do changes affect investigator availability, those who have matching patients?

Answering these questions allows for the identification of unrealistic protocol criteria and for the planning of more sites when the patient counts are low.

To determine patient availability, trial planners send feasibility questionnaires to physicians who might become investigators. While questionnaires are necessary, the estimates of available patients are usually inaccurate. To assess all of the many criteria correctly, investigators would need to review the medical chart of each possible patient, and there is not enough time. Instead, investigators guess. My company compared insurance claims with one set of questionnaires, and the analysis proved the investigators guessed that there were 10 times more eligible patients than existed. When we presented our findings to a large group of clinical trial managers at an industry conference, there was an audible gasp. The gasps told us that there is far too much dependence on the questionnaire, and that we were messengers with bad news.

Small objective data sets, such as electronic medical records from a group practice or network, can provide better answers than questionnaires. But these still lack enough patients for good answers.

The best answers come from large sets of insurance claims. The biggest one has recent and usable medical claims information from more than 40 million lives in the United States. The data include claims made with commercial insurance programs and the major government insurance programs, Medicaid and Medicare.

Creating a Statistical Analysis with Insurance Claims

A large insurance claims database can count how many patients exist at the individual physician level as well as nationally. Every insurance claim has codes — diagnostic codes, procedure codes, and national drug codes. An analyst can translate the words of inclu-

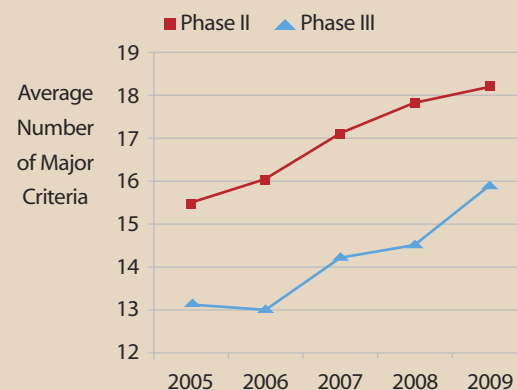
sion and exclusion criteria into these codes and then count the patients. Further sophistication is possible, such as using the sequence of events over time to classify patients by stage of disease.

In my company, the starting point is a data warehouse of de-identified claims. Next, we use SAS programming to create “flags,” which work like on and off switches. The first flags are diagnosis and age. When the flags are turned on, the computer program shows the patient count. From there, it is a process of subtraction. Each additional specification is a flag, and fewer and fewer patients qualify as the flags are turned on.

Figure 3 shows an example for schizophrenia, a serious mental disorder. Not many patients present themselves for treatment, making them hard to find for a clinical trial. We identified 8,310 patients using the nation's largest insurance claims database. Next, the client wanted only those patients with exacerbation, such as a hospital stay. Schizophrenics avoid intense treatment, and very few receive it. The exacerbation specification eliminated 90.7% of the eligible patients. Trial planning rested on the remaining 775 patients.

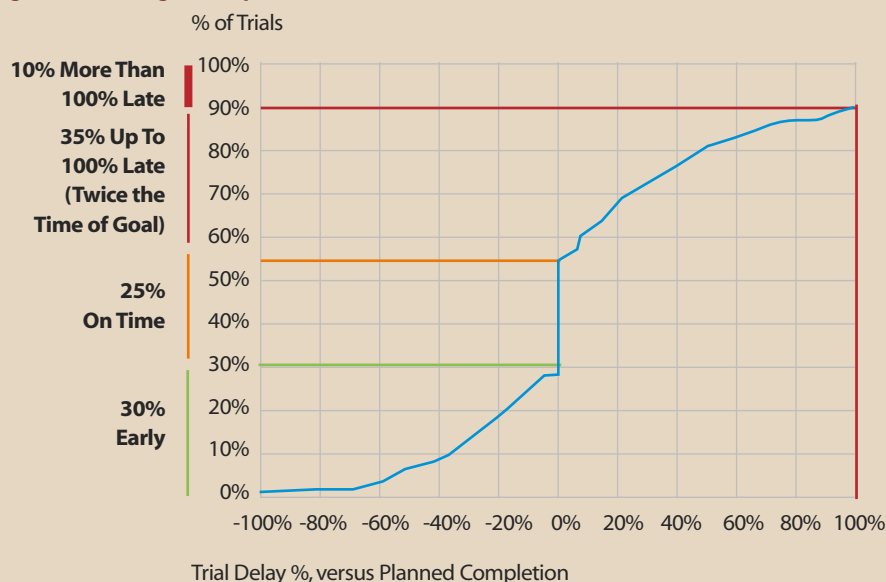
The flags allow for experimentation. The initial age range in the schizophrenia protocol was 18 to 55. By increasing the age to 65, there were 29% more patients. The number of treating physicians and treating investigators went up by a similar amount.

Figure 1. Major Inclusion & Exclusion Criteria



Source: Business Insights, 2010

Figure 2. Average Delays in Clinical Trials



Source: Business Insights, 2010

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Figure 3. Schizophrenia Patient Counts

Specification	Patient Count
Schizophrenia Patients Ages 18-65 (ICD9 Diagnosis Codes: 295.2, Catatonic; 295.3, Paranoid; and 295.9, Undifferentiated)	8,310
Net Number of Patients With Exacerbation (Required in past year: hospitalization, major increase in drug level, or major increase in insurance spending)	775
Patients Lost Due to Exacerbation Requirement	7,535 (90.7%)

Source: QualityMetric Insurance Claims, 2009

Finding the Investigators

To find investigators, the most powerful technique is to combine insurance claims with an investigator directory. My company has one of the largest databases of investigators — 136,056 physicians — in the United States. This is up 17% from last year, when the database was first profiled (see the June 2010 issue of PharmaVIEW). The tabulation counts an investigator as active if he or she has done at least one trial in the past five years. Although the number of new investigators has decreased, due to a weak economy, there are still more names coming into the database than going out.

The biggest investigator name source is the Bioresearch Monitoring Information System (BMIS), which has a public file from the FDA. To find secondary investigators not identified by the FDA, a sophisticated set of Web crawlers can be used to discover names on the Internet.

Using insurance claims, an analyst can create patient count by investigator and rank the resulting list by patient count. The list does not have patient identification, but investigator names are visible. For example, in the

schizophrenia project, we found 749 investigators treating schizophrenics with exacerbation.

When the number of matching patients per investigator is high, enrollment will be high. My previously published retrospective studies (see June 2009 PharmaVIEW) established statistically significant correlation between patient counts and enrollment rates, and the concept is intuitive. To find eligible patients, you should “fish where the fish are.”

Using metrics for trial planning was uncommon 10 years ago, but the industry is now embracing them for better efficiency and faster trials. The new norms in clinical trial information are constant innovation and growth. The companies that embrace information analytics will set new standards of excellence. PV

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