

Benefits of a Single Versus Multicenter Approach in Early-Phase Patient Studies ^{HS}

A Case Study of Multiple Sclerosis Patients

This paper intends to show that the use of a single-center, early-phase trial setting with patients has benefits over the widely accepted multicenter approach.

Patient studies during early-phase clinical research are commonly associated with oncology trials. Due to the cytotoxic nature of the medicines under investigation in oncology trials, it is not common practice for these medicines to be tested in healthy volunteers; thus, oncology trials in patients in Phase I account for approximately 20% of all Phase I trials approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and ethics committees in the United Kingdom each year.¹ This widespread understanding that trials of these medicines are better suited to being conducted in patients has added weight to the argument that this practice could and should be adopted in other therapeutic areas.

The widely adopted rationale for the use of healthy volunteers in Phase I trials is explained in the Association of the British Pharmaceutical Industry (ABPI) guidelines for Phase I Clinical Trials,² which delineate them as easier to find than patients with specific conditions, free of other medicines, more likely to respond uniformly, and better at completing long and complex trials. The ABPI guidelines go on to suggest that some trials should involve only patients with the target disease due to safety and ethical reasons.

In recent years, there has been an increase in the number of combination studies during the early phases of a new medicine's development. Differing from combination therapy trials involving the use of two or more medicines,³ combination trials referred to in this article typically involve cohorts of healthy volunteers followed by one or two cohorts of patients with the target condition for which the medicine is intended.³ The rationale for the use of combination studies is that it increases the efficiency of the drug development process by allowing investigators to answer a series of questions about a new medicine with fewer trials at this stage of development, namely:

- *Safety*—Is the medicine tolerated in humans?
- *Pharmacokinetics*—How does the human body process the medicine?
- *Pharmacodynamics*—What effects does the medicine have on the body?
- *Efficacy*—Might the investigational medicinal product (IMP) work in patients?

Although the efficiencies of combination (healthy volunteer and patient) trials in a Phase I setting are clear, sponsors remain cautious about running larger early-phase patient trials in a Phase I setting due predominantly to apprehensions over the ability of single-center sites to recruit large patient panels, and over the tolerance of the target patient populations for the typical environment and intensity found in Phase I studies.

^{HS} Home Study article

LEARNING OBJECTIVE

After reading this article, participants should be able to identify what factors to consider when conducting early-phase patient trials and then discuss if these trials can and should be conducted in a single-center or multicenter approach.

DISCLOSURES

Keith Sean Berelowitz, BSc (Hons), MSc, Christian Wolf, MD, MPPM, and Jörg Täubel, MD, FFPM, disclose that they have no actual or potential conflict of interest in relation to this article.

This paper provides an example of the fact that the efficient recruitment and retention of a large patient panel in early-phase trial setting is possible, and can be achieved by single-center sites equipped to deal with varying volunteer needs via the approach taken by these centers' marketing and volunteer recruitment divisions. Indeed, this paper intends to show that the use of a single-center, early-phase trial setting with patients is not only possible, but has benefits over the widely accepted multicenter approach taken by many pharmaceutical sponsors in an attempt to mitigate the perceived risk associated with the conduct of a clinical trial in just one site.

Case Study Background

The study being used to demonstrate the efficient recruitment and retention of a large patient panel in a Phase I environment is "A Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Study in Subjects with Relapsing Forms of Multiple Sclerosis (RRMS) to Evaluate the Effects of Different 'IMP XXX-XXX' Doses on Biomarker Patterns as well as on Safety and Tolerability."³

The objectives of the study were to:

- assess the exposure-response relationship between the IMP and changes in biomarkers;
- identify putative biomarkers of disease activity and treatment response; and
- better understand the IMP's mode of action at a molecular level, through proteomic analysis of plasma and gene expression analysis of blood.

The IMP in development was a small molecule inhibitor of vascular cell adhesion molecule 1 (VCAM) binding to alpha-4 integrin (VLA-4), which was in development for the treatment of immune system disorders, including multiple sclerosis (MS).

The study enrolled patients with RRMS who were required to undergo an intensive four-week oral treatment phase involving two in-house stays within

a Phase I clinical trials unit. This unit in South London had MHRA Standard and Supplementary Phase I Accreditation, and was adapted for habitation by patients with RRMS. Patients were also required to be available for a two-month intensive study period including 10 visits, in addition to two late follow-up visits at three and 12 months.

The challenge of the study was to enroll 70 subjects with RRMS who met stringent study inclusion/exclusion criteria in a four-month period. The study had no therapeutic benefit for subjects enrolled, and the demographic of suitable patients with RRMS in the U.K. was identified at an early stage to be less than 10% of the total population of MS patients living in the U.K.

Patients were recruited to the trial via a targeted marketing approach involving neurology specialists, direct advertising to patients, and registered MS support groups and therapy centers.

Results

Over the period of recruitment, approximately 1,000 patients with varying forms of MS registered their interest in becoming involved in the study. Following registration of these patients and prequalification by the patient recruitment team, 367 patients moved through to a telephone screening with a physician in order to ensure that, based on a detailed medical history, subjects who underwent a full medi-

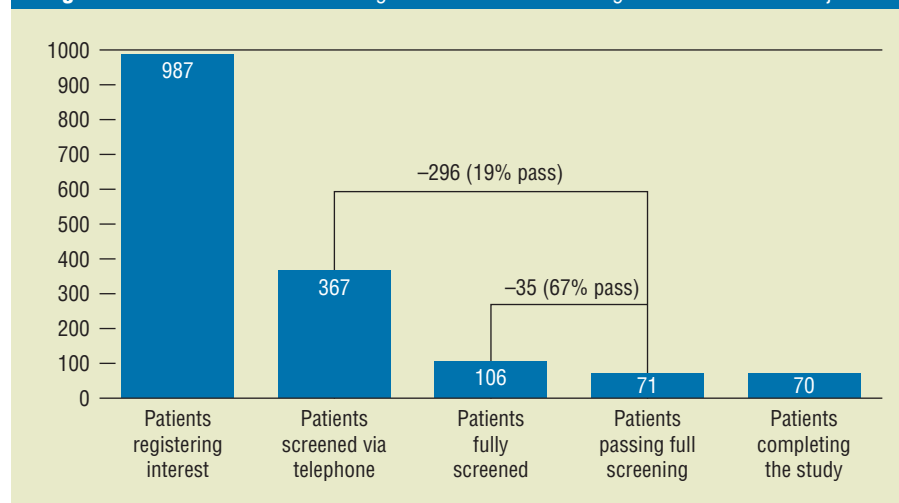
cal screening had a greater probability of being eligible for inclusion. The medical history telephone screening and subsequent consultation with the patients' general practitioners and neurologists led to 106 of the 367 patients being invited to undertake a full medical screening for this study.

Following an intensive two-visit medical screening within the Phase I unit, according to Phase I standards, a total of 71 patients with RRMS were enrolled into the study; of these, 70 completed the intensive study period of four weeks. One subject was withdrawn for medical reasons (pregnancy); otherwise all included subjects would have completed the intensive clinical investigations.

The clinical phase of this study began in August 2008 (first subject, first screening), and the final subject completed the last visit (of the intensive clinical phase) in March 2009. This demonstrates an efficient recruitment timeline, leading to the enrollment of an average of 11.8 patients with RRMS to this single-center study per month.

This efficient recruitment process was possible due to the existing setup of the Phase I unit, which was typical of many Phase I units with longstanding records of early-phase clinical trial conduct. Unlike numerous clinician-led research groups, typically located within teaching hospitals and commonly used in late-phase trials, Phase I units are trained and equipped to con-

Figure 1 Recruitment and Screening Selection Effort Involving Enrollment of 71 Subjects



duct studies including higher volumes of volunteers in shorter time frames. The successes of these units are very commonly associated with their ability to take on a study in its entirety and deliver volunteers and the resulting clinical data in relatively short time frames to a very high and standardized quality. It was this thought process that prompted the sponsor company to identify and place this study with a suitable Phase I unit, rather than run the study over multiple sites, as it did with another study of the same IMP.

Although the study met all of its objectives and showed the anticipated effects on biomarkers, unfortunately due to a lack of efficacy (resulting from data from numerous trials of the IMP), the development of this medicine has since been discontinued.⁴ However, the data provided relating to recruit-

ment and retention demonstrate that efficient and timely recruitment and retention of a large patient population into an early-phase clinical trial conducted in a typical Phase I environment is possible.

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A separate Phase II study of the same compound, "Placebo Controlled Study in Subjects with Relapsing Forms of MS to Evaluate the Safety, Tolerability, and Effects of 'IMP XXX-XXX,'"³ was conducted following a typical multicenter, multinational approach with the intention of enrolling 279 subjects. As of January 3, 2011, the study is described as "terminated" on www.clinicaltrials.gov, having enrolled 232 patients in a 26-month period at a rate of 8.9 patients enrolled per month.³ The study was conducted over 71 locations across North America and Europe, with an average of 0.12 patients enrolled per site per month. Although some sites will have performed above this average and the design and objectives

Discussion

of the study were different from those of the study conducted in the single-center study described in the results, one cannot escape the observation that the single-center study outperformed the multicenter, multinational study at a rate of almost 100 to 1 in the same patient demographic.

One may be able to explain away some of the vast differences in recruitment rates of the two studies described based on study design, patient commitment, and the inclusion/exclusion criteria; however, such factors cannot account fully for the chasm between them. The comparable data presented in this paper suggest very different recruitment strategies would have been employed in the two studies. Some of these differences

may be explained by regional variations in the sites involved, although the multicenter trial did include some U.K. sites. However, the predominant difference is most likely due to the attitude adopted by dedicated Phase I units with regard to the recruitment for, and conduct of, early-phase patient trials in a dedicated Phase I unit. The data presented in the case study suggest numerous benefits exist for sponsor companies that employ a single-center approach in preference to a multicenter one for the conduct of early-phase patient studies, including:

- The provision of staff and tools with dedicated function
- Scalability and reach
- Simplified communication channels
- Reduced variability regarding trial conduct and data collection
- Lower cost/greater value from investment of resources

Dedicated Functionality

The majority of commercial Phase I units will have a dedicated marketing and subject recruitment division in-house in order to recruit high volumes of healthy volunteers at minimal cost within short time frames for upcoming and ongoing clinical studies. These units will typically use a large, dedicated database to aid in the recruitment and retention of potential volunteers for a variety of studies, depending on the subject demographic required. The employees that staff these divisions are typically employed solely to recruit volunteers, and the tools at their disposal and their in-house status should therefore allow for immediate action to be taken if a change in strategy is required to scale up or down recruitment activities on short notice. This is essential to manage efficient subject enrollment and retention in a manner that provides the time and cost savings sponsors increasingly require of their third-party partners.

Unlike a commercial clinical trials unit, for which each aspect of a trial is most typically allocated to dedicated staff to perform each function from the preclinical recruitment phase through the clinic and postclinical data processing functions, noncommercial clinical trials units typically do not have this setup. Rather, they employ one or more individuals to cover many aspects of the trials, from subject identification, recruitment, and screening to clinical conduct, as well as postclinical functions. These individuals may have a dedicated research function, but more often than not are involved in the day-to-day clinical conduct associated with a hospital clinic.

Scalability and Reach

Commercial Phase I units are designed to ensure delivery of an "end product" within the shortest time possible with the use of resources appropriate to the requirements of a study. Successful commercial Phase I units will have several ongoing trials in different stages at any one time, and thus usually have the flexibility to reconfigure study teams quickly within the appropriate divisions

to increase activity where necessary. Normally, this flexibility comes in the form of increased outreach to the target population being recruited, as these units are not limited to using just one clinic's patient list, via increased marketing activity. If this outreach proves successful in terms of reaching potential volunteers, it will subsequently result in the need for increased screening activity, which often requires a bigger team to ensure adherence to the original study timelines.

Noncommercial trials units, which characteristically make up the bulk of sites in a multicenter approach, as stated previously usually have small teams to perform research activities. These teams are often limited in size by funding availability, and thus cannot easily scale up staff numbers without additional funding, meaning that the teams have to "make do" with the resources in place. Although these units make every effort to meet their targets,

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they cannot normally meet lofty objectives without additional funding or support for advertising efforts being made available by the sponsor company. In turn, this means the reach of these units within the patient community often extends only as far as their own departments' patients, thus providing little scope for recruitment of subjects outside the departments if they cannot find an adequate number of interested and/or suitable patients internally.

To limit the risk of not meeting their goals for recruitment at individual sites, sponsors invariably initiate more sites than may necessarily be required to complete the study were each site to deliver on the promises made. Sponsors also employ third-party patient recruitment companies to help noncommercial sites "source" patients. Use of such tactics will naturally add to the setup and ongoing cost of a study, and

may not provide a return on investment, even when every effort is made by noncommercial sites to perform as efficiently as possible.

Although the pharmaceutical industry may expect recruitment challenges when using noncommercial sites, and will attempt to limit this risk as described above, the attitude is very different when the decision is made to choose a commercial partner. When a commercial unit is commissioned to undertake a clinical study, sponsors quite rightly expect on-time and on-budget delivery of results. It is this expectation that drives the way in which commercial Phase I sites approach commercially funded clinical trials.

Simplified Communication

A single-center approach has the benefit of simplified communication channels—something that cannot be achieved when multiple sites and third-party suppliers are involved in the con-

duct of a trial. Usually when a single center is tasked with the conduct of a trial, the sponsor company will speak to only a handful of people to communicate instructions and receive relevant feedback. If time is of the essence for a clinical trial, as is frequently the case for early-phase studies, this is a major advantage, because actions can be taken and reported swiftly and consistently. This is not always possible using a multicenter approach.

Data Quantity and Quality Variability

Even if the sites used in a multisite study approach consist of dedicated Phase I units and smaller consultant-led research sites, the variation in process that each site will have as a result of geographical and company/site ethos, coupled with the variation in accessibility of the target volunteer population, may not provide the control a sponsor

requires from an early-phase study. The control issues surrounding variation in data quantity (as a result of sites enrolling differing numbers of volunteers) and quality should be expected in multisite trials due to the differences in recruitment capabilities and regional practices in clinical trial conduct, which will naturally exist between sites. Although sponsors do their best to mitigate data variation through the use of standardized case report forms, study operation manuals, and equipment (where possible), there is an expectation that there will be variations in data quantity and quality between sites.

Although it is accepted that data variability between sites will be found and analysis algorithms exist to mitigate these variations, the data variability itself may be the driving force behind the large number of patients required for inclusion in order to demonstrate statistical significance. This variability should not exist when a single-center approach is employed, because single centers will most likely have the same team of staff working on a study from start to finish. A consistent team, coupled with the use of consistent equipment and trial conduct in a consistent environment, will reduce the variable factors that are expected in a multicenter approach, meaning that one may be able to conduct the study in a smaller target population while still achieving the necessary statistical significance if a single center is used.

The risk of a single center conducting the study in this case lies in the data quantity (number of volunteers enrolled); however, this can be reduced as noted earlier by flexing the marketing and recruitment arms of the single center, if and when required. In addition, if fewer subjects are required to demonstrate statistical significance, this should limit the quantity risk further, while also leading to cost and time efficiencies.

More for Your Money

Multisite studies are generally accepted to be more costly than using a single center, simply as a result of the cost of initiating, monitoring, and collating data from several sites as opposed to just one. A single-center approach

can also benefit a sponsor from a cost perspective through the potential for requiring fewer subjects to demonstrate statistical significance. Alternatively, a sponsor can take the cost savings made from using one site versus multiple sites to enroll more subjects in a trial in order to gather more data regarding the IMP.

Benefits of a Multicenter Approach

It goes without saying that there is a need for multisite studies during early-phase research; one cannot use a dedicated Phase I unit or adopt a Phase I approach for the conduct of all early-phase clinical trials involving patients. As such, it is widely accepted that numerous benefits exist for using a multisite approach for the

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conduct of early-phase clinical studies, including the ability to randomize a greater number of volunteers over a larger geographical area, thus taking into account “local” demographic factors (genetic, ethnic, environmental). In turn, this should provide a greater generalizability of the results, which is important when assessing how (and where) an IMP will be used if it were to become commercially available.

Although it is clear that benefits exist for both single-center and multicenter approaches in early-phase clinical studies, the case study data presented here should go some way to dispel the misconceptions relating to a single site’s ability to perform equally, if not better, than several sites in the conduct of early-phase clinical studies involving patient groups.

Summary

Although one cannot adopt a single-center approach in every situation, the

authors believe that it should be considered at the early planning stage of most, if not all, early-phase patient trials due to the benefits described in this article. There is a clear desire from the industry to move into patient trials as early as possible in an IMP’s development for numerous reasons, including time and cost efficiencies and the production of valuable patient data at an early stage of development. Evidence such as that described in this article shows what can be done. Sponsors and investigators are reminded, however, that “one size does not fit all,” and each Phase I study involving a patient population should be evaluated through a detailed feasibility study by the potential commercial Phase I and noncommercial units that may be involved in the study.

As with most clinical studies, the recruitment of enough suitable patient

volunteers in the time frame provided by sponsors is, more often than not, the critical factor in preventing delays to the development of a sponsor’s compound. As such, the merits of a single-center versus multicenter approach with regard to recruitment and patient retention must be evaluated with the same care and attention, if not more, as given to a site’s ability to conduct a study efficiently and produce high-quality data.

Factors that should be taken into account when deciding on which sites should be involved in a study, or if the study can be run in just one site, include:

- Company culture and structure
- Track record
- Safety record
- Approaches to recruitment
 - Advertising
 - Attraction
 - Retention
- Risk analysis relating not just to the compound, but also the viability of a site to deliver

These data will be invaluable for sponsors when determining how willing a center is to become involved, and should indicate how likely it is that the center will succeed. This feasibility study, and in particular the focus placed on the ability of sites to recruit and retain patients, will help to determine if the study can be conducted in a single-center environment, or if it needs to be conducted using a more conventional multicenter approach.

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