Worldwide Clinical Trials

Including Patients and Healthy Volunteers in First-in-Human Clinical Trials:

The opportunities and limitations of “hybrid” clinical studies

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Phase 1 hybrid studies as described here are clinical trials that incorporate healthy volunteers as well as patients from the target indication in a single protocol. The insights gained from such hybrid studies can be extremely valuable, potentially delivering a deeper understanding of the safety, tolerability, and pharmacokinetics of a product, as well as a greater insights into the product's pharmacodynamic effects and therapeutic potential — all at a very early stage of clinical development.

Given an increased business and scientific interest in hybrid studies, this white paper provides an overview of key concepts and practical considerations regarding the merits, regulatory considerations, and operational challenges associated with hybrid studies.

Introduction

Traditionally, first-in-human (FIH) investigations, particularly those involving small molecules, rely exclusively on healthy volunteers (HVs).[1] They are designed to address questions about tolerance, safety, pharmacokinetics, and the biodisposition of an investigational product (IP). The early assessments of both pharmaceutical properties as well as drug activity derived from a study in cohorts of healthy subjects constitute a foundation on which future studies are built.

However, developers must consider multiple stakeholder perspectives at every stage of development, and early phase investigations can have an inordinate impact on future development strategies. Invariably developers must contemplate both scientific *and* business mandates — frequently needing to address both with constrained resources and pressure to truncate development timelines. Phase 1 studies that are "hybridized" to include both HVs *and* patients under the umbrella of a single investigation from the earliest possible date may produce scientific or clinical insights that studies involving HVs exclusively might not. Those could include

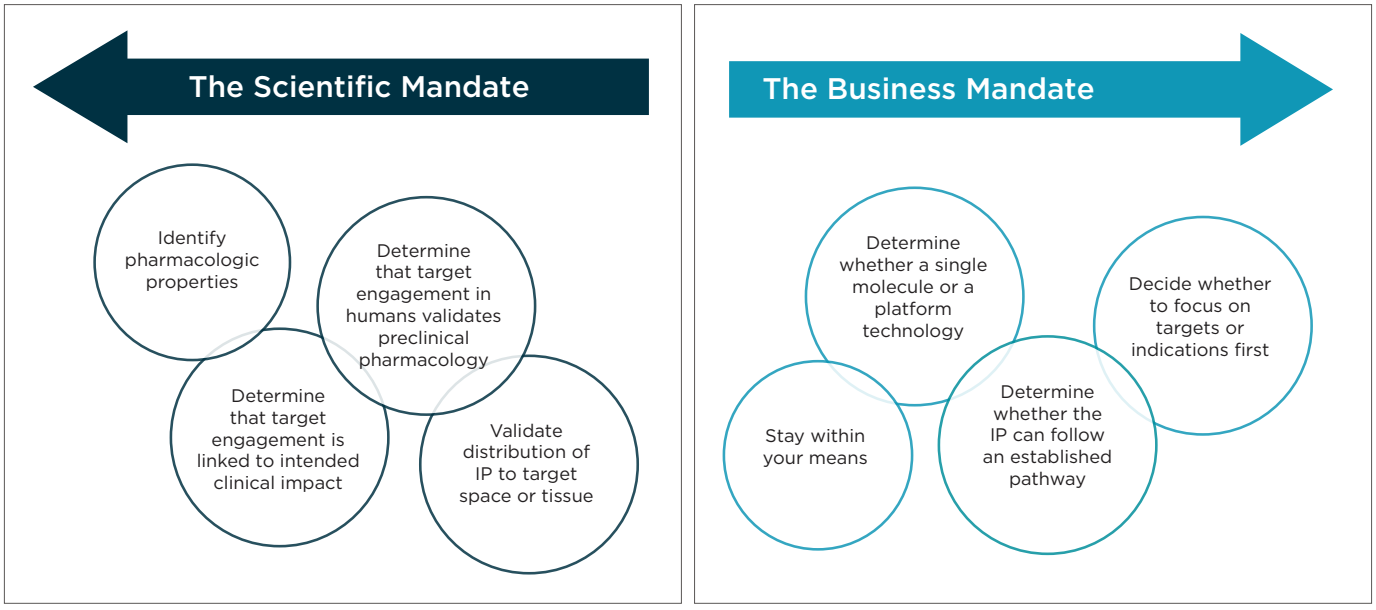


Figure 1: Developers must consider multiple stakeholder perspectives at every stage of development, which invariably involves trying to address scientific and business mandates concurrently

insights into differential effects on safety, tolerance, pharmacokinetic (PK), and pharmacodynamic (PD) endpoints. The literature is replete with examples of "hybrid" clinical development concepts. For example, the "hybrid design" concept discussed in Zhu *et al.* focuses on attempts to integrate real-world data into clinical research, not just endpoint data collected through routine healthcare visits and standardized procedures defined within a protocol.[2] The early phase *hybrid studies* frequently voiced in the peri-approval space are distinctively different, however. For the purposes of this paper, *hybrid trials* refer to the studies taking place during the earliest phases of clinical research in which highly granular and multidimensional assessments are obtained from both HVs *and* patients, frequently through specialized procedures and assessments.

While distinct benefits may accrue from hybrid trials over the course of a Phase 1 program, it is important to approach cautiously when considering the inclusion of patients in a Phase 1 study. There may be a limited number of patients who could be examined for a given hypothesis, for example, acknowledging that sample size and duration of exposure are key elements underpinning the detection of any pharmacodynamic effect. Involving patients may entail medical management issues that would not be encountered when working exclusively with healthy subjects. For example, many facilities suitable for Phase 1 trials are not designed to accommodate patients, their routines, or their support personnel. Then, there may be pragmatic issues: recruiting patients with a rare disease, particularly children, for a FIH trial may take a long time and involve considerable expense. Recruitment could end up delaying rather than accelerating the completion of the Phase 1 program. Suppose the key strategic questions about safety, tolerance, exposure, and biodisposition could be more expeditiously addressed in HVs. In that case, it may be more prudent to include patients in later trials after the basic pharmaceutical properties of the test agent have been defined.

This paper will offer insights and observations on the use of hybrid clinical trials to accelerate a clinical development program and identify the insights that can be gained when the right conditions exist to design and conduct a hybrid study.

The scientific, medical, and operational mandate for hybrid studies

Much has been written about the evolution of the Phase 1 study, particularly FIH investigations.[1] Today, its purpose is understood to focus on gathering the data required to prove to regulators and drug discovery subject matter experts that the basic attributes of a product whose potential is suggested in pre-

Hybrid trials and regulatory considerations

As per ICH E8(R1) guidance, Phase 1 studies may be conducted in HV subjects or in a selected population of patients who have the condition or the disease.[3] The choice of the appropriate study population would typically depend on the IP's properties and the program's objectives. For example, cytotoxic drugs or advanced therapy medicinal products (ATMPs) would typically be studied in patients. Special consideration should also be given if there is an endpoint of interest and an appropriate PD measure that can provide early estimates of activity and efficacy to guide the dosage and dose regimen in later studies.

Generally, the regulatory environment appears permissive when it comes to recruiting patients. It sometimes even mandates Phase 1 development in patients, depending on the IP's attributes. On the regulatory front, however, it is important for developers to consider which regulatory jurisdictions are applicable, given the study's planned geographical footprint.[4] Not all regulatory authorities are comfortable including patients in FIH studies, as these studies bear the highest risk in the clinical development pathway. Regulators may require developers to submit HV data for the agency's review before allowing the study to proceed in patients. This may affect timelines to proceed to Phase 2.

clinical studies can translate safely and tolerably into a human population. Studies designed to ascertain the safety, tolerance, exposure, and biodisposition of an IP would include single-ascending dose (SAD) studies and multiple-ascending dose (MAD) studies, using either rule-based or model-based designs, with or without special population studies. Additionally, studies involving HVs increasingly include specialized procedures and assessments designed to identify any pharmacological effects associated with the test agent (such as unique central nervous system [CNS] or cardiovascular adverse events) or effects related to IP distribution (peripheral versus central compartment distribution), as well as changes in clinical, electrophysiological, or fluid biomarkers. Genotyping, for example, has emerged as a particularly relevant option for metabolic pathways that have been identified preclinically in order to permit the inclusion or exclusion of patients who are extensive versus poor metabolizers. Fifteen years ago, all these studies would have been conducted in a measured and highly codified sequence. Today, many of them are conducted in parallel or blended into one investigation, with a bioanalytical component commonly incorporated into the overall service offering.[5] A suite of clinical pharmacology studies may be amenable to this approach, including FIH, SAD, and MAD studies, and multiple titrating dose (MTD), drug-drug interaction (DDI), food effect (FE), and metabolic pathway/mass balance (MP/MB) studies. Opportunities for both methodological rigor and scientific creativity exist across this entire spectrum.

In light of these goals and the advances in trial conduct, it is reasonable to ask why *not* include carefully selected volunteers who are afflicted with the condition the IP is intended to address. These patients, particularly in the early stages of disease progression, are often eager to be included in early studies — as are their healthy family members who want to contribute to finding a treatment/cure. Understanding the PK and PD of the IP in a patient population can be informative, adding a different dimension to the data obtained in a healthy population. This is particularly true if PK/

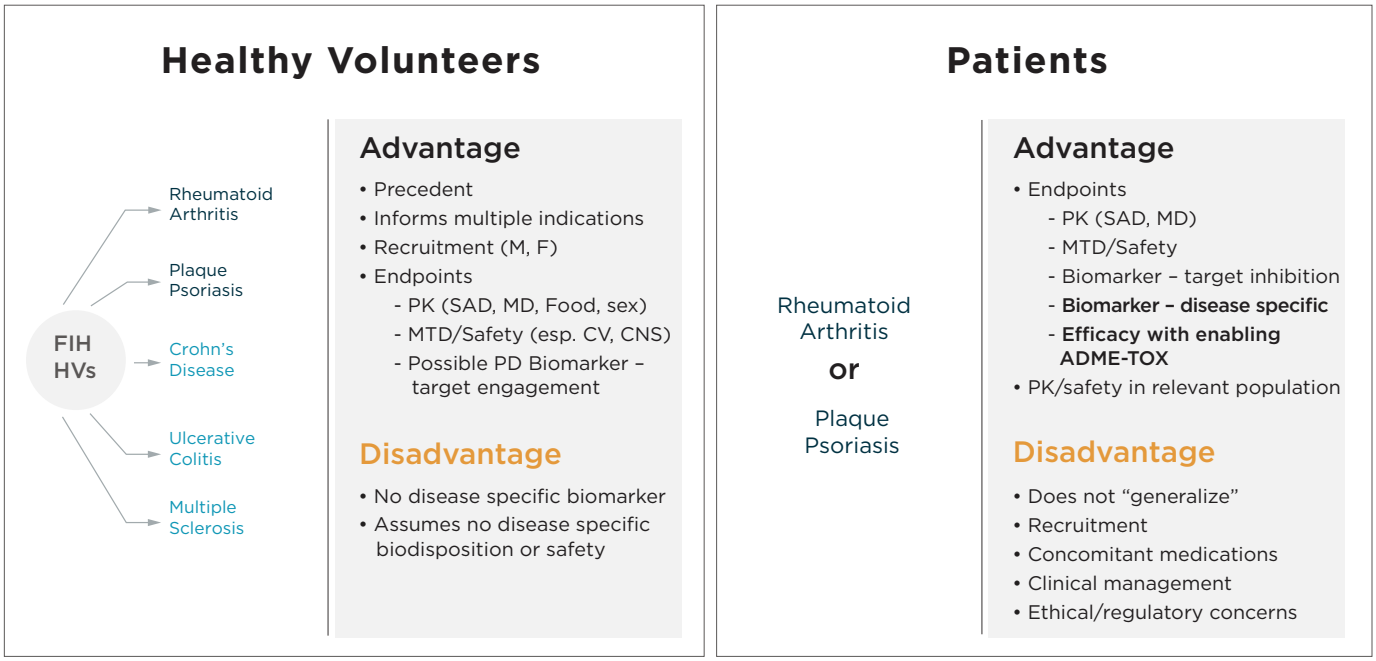


Figure 2: Multiple decisions must be made when considering whether to include patients in a Phase 1 trial. When adding patient cohorts to a phase 1 study, particularly rare disease patients, the impact on study conduct, completion, and database lock can be substantive, even with a small number of patients. For example, timelines may be extended by 6-8 months or more by what at first blush appears to be a modest modification of study design.

PD characteristics turn out to differ between patients and HVs, and all the more true if it can be ascertained that a limited sample size and brief duration of exposure would be sufficient for target engagement detection with patients having the index condition. When physiological differences between patients and HVs can be anticipated (as in the case of autonomic dysfunction in Parkinson's disease patients), then it is imperative to include a limited sample of patients in the FIH trial to evaluate the impact of those differences on PK and possibly metabolism.[6]

An illustrative example is available involving an immune-modulating agent, a small molecule, which in principle may be directed into several immune-mediated inflammatory diseases, ranging from multiple sclerosis to rheumatoid arthritis (see Figure 2). The advantages of conducting a study using HVs include precedent, the ability to inform multiple indications, ease of recruitment for both males and females, and the acquisition of information relating to pharmacokinetic endpoints from single and multiple dose regimens — all of which will ultimately prove to be informative. This therapeutic stratagem assumes no disease-specific biodisposition or safety observations and acknowledges that no disease-specific biomarkers may be ascertained.

However, the situation changes if the agent modulates a specific pathway or cell function across various conditions. Adding one or more patient cohorts can capture PD-, pathway- or function-, and disease-specific biomarkers (contingent upon sample size) and may offer insights on preliminary efficacy within the context of broader absorption, distribution, metabolism, excretion, and toxicity (ADME-TOX) insights. At the same time, potential disadvantages exist, including the inability to generalize findings into other potential indications where the compound presents a comparably strong rationale. There may also be difficulties in recruitment and clinical management of patients, the possibility that prohibited medications may affect patient eligibility, the use of concomitant medications may complicate the interpretation of findings, and ethical/regulatory concerns because the duration of exposure in a Phase 1 trial is unlikely to produce any enduring clinical benefit.

Since lack of efficacy is the most common reason for failure in Phase 2, the opportunity to examine a PD response and mechanism of action earlier in the development cycle is very attractive. Although some pharmacodynamic elements of target engagement may be assessed preliminarily in HVs (e.g., cognition, elements of electrophysiology), in most cases these endpoints, which will drive subsequent development decisions, can only be evaluated in patients. Thus, one of the most important questions to ask when considering a hybrid study is this: *Will the inclusion of patients at this stage accelerate or impede the timely execution of the overall program?*

Acknowledging an emerging trend

Interest in conducting early-phase clinical trials that integrate HV subjects with patient cohorts is abundant. A search on clinicaltrials.gov of early phase trials since the start of 2019 returned more than 550 studies.[7] An analysis of the first 75 listed studies suggests that about one-third of them are hybrids i.e., studies that accept both patients and HVs. This suggests that hybrid studies are becoming more widely embraced across various therapeutic areas, as summarized in Table 1.

The analysis further suggests that the general approach applied to hybrid study designs is very similar to that of FIH studies involving conventional HVs, including a SAD component followed by a MAD component, with the patient cohorts customarily enrolled following the enrollment of HVs. Other studies, looking at the effect of food on the extent and rate of absorption for an orally administered product, for example, or DDI studies, may be included. If multiple cohorts are involved at different levels of exposure, dose proportionality may be assessed, as may disease-related PD parameters for exploratory signals of efficacy (depending on the target indication and availability and accessibility of sufficiently sensitive predictive disease-related biomarkers).

Category	Finding	
Therapeutic area	Alzheimer's Disease Amyotrophic Lateral Sclerosis Asthma Atopic Dermatitis Cancer Pain Cancer Related Pain Chronic Kidney Disease COVID-19 Cystic Fibrosis, Pulmonary C3 Glomerulopathy Diabetes Hemophilia Hepatic Impairment of Moderate Child Pugh Category Hepatitis B, Chronic Hidradenitis Suppurativa IgA Nephropathy Major Depressive Disorder MELAS Syndrome	Methylmalonic Acidemia Mitochondrial Diseases Mitochondrial Myopathies Mitochondrial Respiratory Chain Deficiencies Multiple Sclerosis Nausea Post Chemotherapy Neoplasms Ocular Hypertension Open Angle Glaucoma Organic Acidemia Parkinson's Disease Paroxysmal Nocturnal Hemoglobinuria Propionic Acidemia Systemic Lupus Erythematosus Renal impairment Vomiting Wound Infection
Product type	Small molecules (18 of 25 products) Biologics (peptide, protein, RNAi, humanized antibody, monoclonal antibody)	
Study duration	3 – 169 days (mean 42, median 26)	
Number of healthy volunteers**	34 and 56	
Number of patients**	16 and 12	
Total number of participants	6 – 334 (mean 75, median 53)	
Typical outcomes	Safety and tolerability Pharmacokinetics profile Biomarkers Receptor occupancy Immunogenicity Preliminary efficacy	

* Worldwide wishes to thank Halle Bakir for her research contributions on this project.
** Specified in only two studies.

Table 1: Representative studies extracted from a larger data set to illustrate the diversity of therapeutic areas amenable to a hybrid approach*

Reducing "white space"

The arguments in favor of including patients in a Phase 1 trial actually extend far beyond addressing questions of safety, tolerance, and scientific interest. Importantly, business and operational considerations can amplify or dampen the enthusiasm for hybrid trials. Some developers speculate that the inclusion of patients under the umbrella of a single Phase 1 trial will reduce the amount of time and money expended during the overall Phase 1 program. By reducing the "white space" between different phases of clinical development, they can truncate overall development time and accelerate the development process.

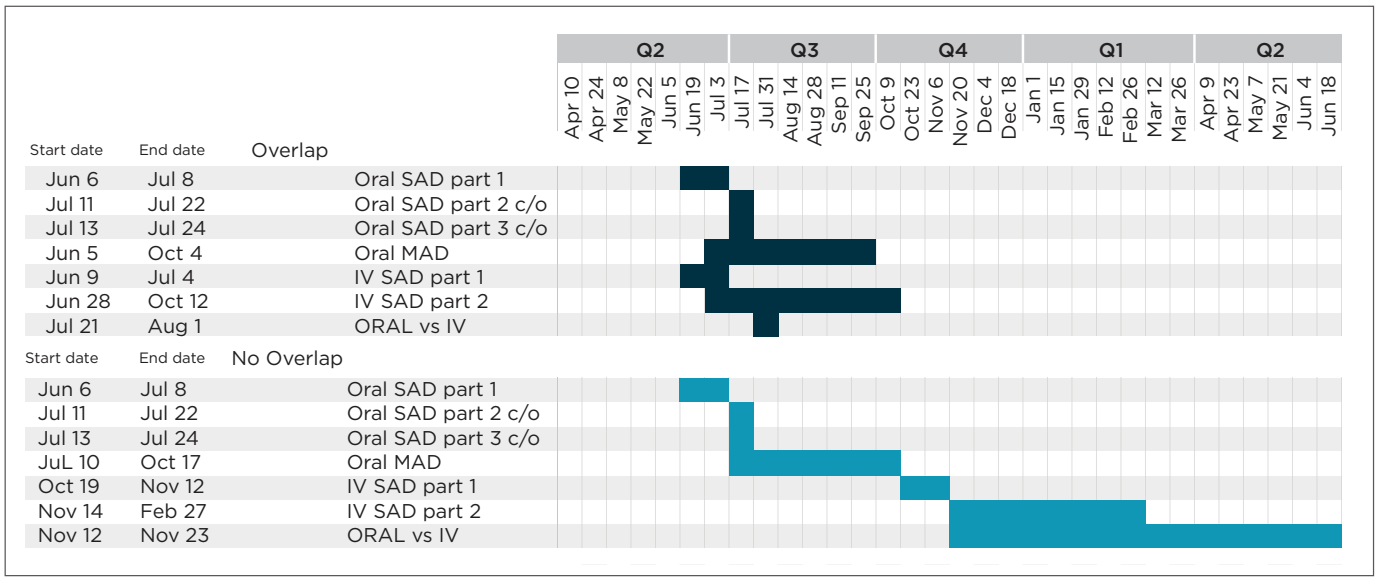
These calculations can be examined critically using simulations with key variables, such as the number of centers likely to participate in the hybrid program, the geographical location of those centers (when patient transportation is a part of the operational solution), and the anticipated accrual rate of patients given the required unique eligibility criteria.

Developers also strategize that the sooner they can include patients in a trial, the sooner they can gain insights that will be seminal when seeking support from a wider variety of interested parties — from patient advocacy groups to investors interested in funding promising IP. However, a reduction in the "white space" between successive studies can be accomplished — without the inclusion of patients — through other strategic planning techniques, as illustrated in Figure 3.

There are many factors that can affect the timeline of Phase 1 studies. Utilizing HVs certainly improves the timeline from a recruitment perspective and eliminates the confounding factors of the underlying disease and concomitant medication therapy. It is still critical in these early in human studies to design a very

deliberate, experienced, and thoughtful approach to ensure the safety of those individuals participating in these studies and to obtain the most meaningful data possible in order to determine whether to discontinue the compound or accelerate its progression — hopefully the latter! Important influencers of the timeline include, but are not limited to, the need for sentinel dosing in each cohort, the half-life of IP and how long PK, PD and safety assessments will be monitored before progressing to the next cohort, whether MAD cohorts can initiate prior to completion of all SAD cohorts, and others. Often, patient cohorts in the MAD portion of the study will be conducted in smaller sub-cohorts to accommodate the need for increased staff and for accommodating patient schedules.

It is also worth noting that the inclusion of one or more cohorts of patients within a study — even when elements of that study are run in parallel — may result in the request for more time to analyze the results,



Time savings (Clinical Conduct) = 134 days (4months + 11 days or 19 weeks)

Figure 3: SAD/MAD with IV versus ORAL FIH, including food effect and DDI sub-studies. By conducting studies in parallel, the timeline was reduced by 4 months and 16 days.

thus altering timelines and affecting overall program management. Moreover, the inclusion of patients in the earliest studies of a novel IP can limit the biostatistical inferences that may be plausible, given the limited sample size and relatively brief duration of exposure. The issue here is more logistical than analytical: if many studies — the single ascending and multi-dose studies, for example — are taking place concurrently, the logistical challenges arising from matters of timelines, information, data flows, analytics, and outcome reviews grow quite complex.[8,9] In fact, instead of *compressing* the duration of a study by capturing data from HVs and patients simultaneously, the inclusion of patients may, in fact, extend its duration as more complex data streams require more time to process.

Reducing the "white space" between studies *is* important and can accelerate a development program, but that goal in and of itself does not provide a sound justification for embracing a hybrid trial design without considering and carefully weighing all the advantages and potential limitations of the proposed approach. The complexity and the challenges that can arise when patients are included may, in fact, have an unfavorable effect on the overall program duration.

Identifying, screening, and facilitating patient access

Including patients and HVs in a Phase 1 program may pose challenges that were not anticipated in the initial concept proposal. A developer, who is unfamiliar with the complexities of hybrid trials, will encounter myriad issues — ranging from conceptual to logistical — when including even a small patient cohort, particularly if this cohort is appended to a healthy volunteer protocol.

For example, a Phase 1 study site that is well-suited to recruit, house, and medically manage HVs for the duration of a study may not be able to meet the needs of patients. Patients may require special medical devices, medications, assistance in basic activities of daily life, or other accommodations that will alter the usual ebb and flow of activities at a prototypical Phase 1 unit. This is a simple consequence of the eligibility criteria outlined within the protocol. Frequently, a partitioning of responsibilities results in one center being better suited for evaluating HVs and a different center (or centers) being more appropriately organized for managing patients. It is important to have strong project management oversight and frequent project communication when multiple sites are involved. This helps move timelines along and, more importantly, facilitates the exchange of medical and scientific knowledge.

Furthermore, the potential engagement of multiple sites raises a number of questions regarding:

- Skill sets present at each site
- Experience of each center in early phase clinical research, which in many respects involves clinical pharmacology rather than clinical care investigations
- Proximity of sites to appropriate drug compounding or manufacturing services (if that is a component of the investigation)
- Access to specialized medical services that may be required as a component of the clinical trial (such as anesthesiology services for cerebrospinal fluid acquisition, imaging, and others)
- Other services, such as bespoke dietary services

All these matters are undoubtedly simpler to address and manage if a study involves only one center; however, they become a managerial challenge when more than one center is required.

Travel to and from sites in the aforementioned operational solution may also become a confounding factor. Generally, it is relatively straightforward to recruit HVs from a population residing near the study site. Recruiting appropriately screened patients, however, from the same geographical area may not be feasible. The distance to a study center and the management of patients during transport to the center thus become an additional element for consideration in study operations. As decentralized trials have evolved, a variety of innovative approaches have been implemented to overcome the challenges of including patients and multiple centers in Phase 1 studies.

Some assessments typically performed on-site for HVs could be conducted at home for patients. This approach could reduce patient burden by lessening the time a patient would have to reside on-site. Some assessments may be accomplished via remote monitoring or artificial intelligence (AI)-based technologies. Others may require engaging a home nursing vendor with access to patients' homes before their travel to the site, though this option may either be precluded in some regulatory jurisdictions or may add a significant cost to the study. In any of these scenarios, it is critical to factor training into the program to ensure that assessments are conducted and completed properly.

Data management is another factor to consider. Trial managers must create a mechanism by which these remote technologies or home health aides can easily, quickly, securely, and consistently upload the results of the home health assessments. A recent comprehensive review completed by Worldwide illustrates the opportunities and complexities associated with the logistics of managing a cohort of patients, particularly those within the orphan disease space.[10]

Even after incorporating home-based health assessments to limit the time a patient spends at the center, patients may still need to be accompanied to a trial site by a family member or a healthcare companion. This raises questions to be preemptively addressed about the viability of housing for family members or support companions on-site with the study participants versus in a nearby hotel or some other accommodations. Covering expenses for companions' food and local transportation adds further logistical complexity (and cost) to these considerations.

Patient medical management considerations

The presence of patients with acute or chronic illnesses in the study center can also directly impact the studies themselves. While a HV may have the flexibility and interest to participate in a clinic-based dose-ranging study that might last several days or weeks, a patient — or patient and attending companion — may not be able to commit to a prolonged on-site stay. Screeners can select

HVs who have not recently taken any other medications, thus obviating concerns about PK or PD drug-drug interactions mandated by the pharmacological properties of the test agents. However, patients may be taking other medications (at least up to the commencement of the study) that have not been preemptively considered in the trial design.

While discontinuing the medication may, in principle, be an option for some patients, discontinuation may also have a deleterious effect on the health and well-being of the participant. Gathering the data necessary to show safety and tolerance may take days and weeks as maximally tolerated dose (MTD) levels are identified. It simply may not be feasible to ask patients to participate if doing so will require them to forego other treatments that may be critical to their health, safety, or quality of life — particularly when the IP will have only speculative beneficial effects. After all, in a Phase 1 trial employing a truncated study design, generally limited in duration by the available IND enabling toxicology, it is not expected that a patient will experience benefits from the new IP. Nor can such benefits be suggested as a part of the consenting process. Moreover, in the absence of enabling nonclinical chronic toxicology data for most indications (oncology excepted), continued access to the IP, generally, cannot be guaranteed outside of the confines of the protocol.

But with complexity, there is often great value

The challenges above should not discourage a sponsor from considering hybrid studies; rather, they are enumerated to ensure that a sponsor is clear-eyed about the balance between the benefits and the possible limitations. Not all Phase 1 studies warrant a hybrid approach, even though frequently there appears to be a compelling conceptual rationale for their creation. The anticipated time and cost savings may not materialize, and the major conclusions derived from a hybrid study may not differ substantially from those acquired in a HV program.

Nevertheless, there also may be studies that can *only* succeed if patients are included from the earliest phases. Studies involving advanced therapeutic medicinal products (ATMPs) — including cell, tissue, and gene-based therapies — may need to involve patients because the intended target of the therapy may be absent in healthy individuals, and the benefit/risk evaluation is not favorable. Similarly, the test product safety, tolerance, or exposure data may not accurately translate from HVs to patients, nor may inferences that might be made regarding the product's biological properties. For example, cytotoxic anticancer agents that may prove toxic to HVs may actually be tolerable and therapeutic in a patient cohort.[1] Moreover, it has also been shown in studies of IP targeting CNS disorders (for example, changes due to autonomic dysfunction in Parkinson's disease[6] and, possibly, amyotrophic lateral sclerosis[11] amongst other indications) that patients may tolerate and respond to doses of a novel IP at very different dosage levels than HVs, a reality that undermines the assumption that safety and tolerance levels identified in HVs can always be extrapolated to apply to patients.[1]

In these circumstances, although the rationale for a hybrid trial may be compelling, pragmatically separating and disaggregating HVs and patients may be a prudent path to discovering PK/PD and dose tolerance variations. Alternatively, a hybrid approach may offer neither business nor operational advantages that a sponsor has initially envisioned; however, it may be critical to elucidating crucial medical and scientific insights. It may also be strategic insofar as it encourages the involvement of patient support groups. Rare disease support organizations, in particular, closely monitor research activities.

Building the bridge carefully

As sponsors across therapeutic areas attempt to understand at the earliest possible date whether their IP has pharmacological properties of clinical importance in its target indication, the question of whether to conduct an early phase clinical program that includes HVs as well as patient population arises frequently. The motives behind this interest are usually multivariate, involving business mandates, scientific questions, the potential for program acceleration, and other factors. Interest in this early phase stratagem is exemplified by the many studies currently under review across therapeutic areas that acknowledge the potential utility of such an approach.

Despite this understandable interest in detecting an early signal of potential efficacy, a hybrid approach should be carefully evaluated in terms of the advantages and risks, with an informed appreciation of the limited inferences that might be obtained at the expense of operational encumbrances. The number of participants and the duration of exposure in a Phase 1 study limit the number of hypotheses that may be addressed effectively. Usually, safety, tolerability, and PK can be reliably extrapolated from HV studies, with notable exceptions as outlined above, depending on the therapeutic area of interest and the nature of the IP. While patient data may provide additional insights into PD- and disease-related biomarkers, this is contingent upon various study constraints — principally related to sample size, duration of exposure, and assumptions regarding the dose-response relationship as it may exist against a therapeutic target. Most frequently, the sensitivity of functional and clinician-reported outcomes tends to be limited due to the number of participants enrolled and the overall duration of exposure permitted by the enabling nonclinical data. These challenges can be exacerbated in multicenter trials.

Ultimately, for a hybrid strategy to be operationally successful, it must be formulated and evaluated early in the drug development process, with careful consideration paid to the potential endpoints, the mechanisms by which study progress and patient safety will be monitored, and the alignment of therapeutic area, IP, and study design to applicable regulatory expectations. The aforementioned considerations, therefore, lend credence to an axiom frequently voiced in clinical research, "build the bridge carefully in order to cross it quickly."

Considerations influencing a decision to go hybrid

Single- vs. Multi-dose Administration. As a general rule, there is no theoretical prospect of benefit to the patient in a single dose trial, nor can it be reasonably anticipated in brief multiple dose cohorts. Efficacy insights based upon clinical data will likely be limited.

Pharmaceutical Properties of the Test Agent. Small molecules might be conveniently administered to both HVs and patients within the framework of one study, but ATMPs and some biologics would be precluded from administration in studies with only HVs.

Patient Vulnerability. Patient participation frequently requires the washout of preceding medications, which could create vulnerabilities for the patients. If no washout is required, the presence of concomitant medications may lead to drug-drug interactions that may be incompletely described at the time of clinical trial application (CTA, in the European Union) or investigational new drug (IND, in the United States) application.

Rate of Recruitment. If the rate of patient recruitment is slow, as it may be if a unique phenotype/genotype has been identified, this may extend the duration of the Phase 1 program and delay the completion of the full clinical study report resulting in the deferral of the next phase of clinical study.

Operational Complexities. Relying on multiple centers to accommodate the inclusion of patients in a study that could otherwise be conducted with HVs can add operational complexities that range from contractual obligations to ethics committee approvals.

Clinical Assessment Profile. The patients' underlying condition may affect the clinical assessment profile across elements as diverse as safety, tolerance, and exposure. This entanglement could complicate the assessment of product- and disease-related attributes in a drug development program.

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