CONSIDERATIONS FOR INFECTIOUS DISEASES CLINICAL TRIALS IN AT-RISK POPULATIONS

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INTRODUCTION

Clinical trials are notoriously complex, yet contemporary clinical trials in infectious diseases (ID) can be even more complex due to the at-risk patient populations often studied. ID clinical trials historically have tended to be larger, focused more on special populations, and involved more countries outside North America and Europe than non-ID trials.[1] With an aging population, increased use of potentially immunosuppressing therapies, increased prevalence of comorbid conditions (e.g., various cancers), and emerging/re-emerging infections that have spread into new geographies, novel ID therapeutics are now focused on these at-risk populations more than ever.

This report will look at the challenges of infectious diseases clinical trials in various at-risk populations. It will address specific risks that introduce unique complexities in ID trials, including population-inherent risks, geographic factors, and infections occurring in a time-dependent pattern. In addition, the report will discuss recruitment, retention, and resource considerations while assessing at-risk populations, along with the importance of an experienced clinical trial partner.[2]

RIGHT PATIENT

Age, history of cancer, organ transplant status, chronic kidney disease (CKD), diabetes, autoimmune diseases, HIV and medications[3] are just a few examples of population-inherent, specific risks that introduce unique complexities into ID clinical trials. Studies may be designed to only enroll such a specific at-risk population; enrich for a certain population that may be particularly vulnerable to the infection of interest; or enroll a general population, knowing that even with a broadly defined population, certain at-risk subgroups will introduce variability to the data and influence the endpoint.

A key consideration for sponsors is balancing the need to enroll a reasonably homogenous population that is aligned with the mechanism of action of the investigational product with the need to generalize those findings to a potentially broader population that will likely be included in more advanced clinical trials or that could use the product once approved. Orchestrating the need for active recruitment with quality data that will be broadly supportive can become quite complicated. The patients are quite ill, and their management will be dictated by the local standard of care. In order to successfully recruit patients and keep them in the trial, understanding what is feasible at the site level and changes to the current standard of care is paramount before finalizing the protocol.

Still, there will be inevitable and significant variability among the patients and the standard of care that they will be provided:

- Infections in the elderly may be due to the patient's waning T-cell immunity that predisposes them to reactivation of latent infections (e.g., TB); B-cell defects result in increased susceptibility and worse outcomes to *Streptococcus pneumoniae* and COVID-19 and a decreased response to various vaccines; more frequent interactions with medical facilities increase the risk in the elderly for multidrug-resistant organism (MDRO) infections — especially with longer hospital/ICU stays — *Clostridium difficile* infection, and iatrogenic infections; and mechanical problems (e.g., difficulty swallowing or walking) predisposes the elderly to respiratory and skin infections.

- Infections in hematopoietic cell transplant (HCT) and solid-organ transplant (SOT) recipients may originate from endogenous flora (e.g., invasive candidiasis), from the community (e.g., histoplasmosis, TB, disseminated strongyloidiasis), or from the hospital (e.g., aspergillosis, legionellosis and MDROs).

- The risk of genitourinary and pulmonary infections increases with a decline in kidney function. Compared with patients with an eGFR ≥90 mL/min/1.73 m2, eGFRs between 60 and 89, 45 and 59, and 15 and44 mL/min/1.73 were associated with 16%, 37% and 64% greater risks of all-cause infection-related hospitalization, respectively.[4] Careful attention should be paid to preventive measures, such as influenza and pneumococcal immunization.

- Patients with autoimmune disorders (e.g., lupus) or chronic lung disease (e.g., COPD) on immunosuppressants, such as chronic corticosteroid therapy, may be predisposed to common bacterial, fungal and viral infections or reactivation of latent infections (e.g., Strongyloides) and opportunistic infections (e.g., *Pneumocystis jirovecii*).

LOCATION IS A KEY FACTOR THAT MUST BE CONSIDERED WHEN CONDUCTING INFECTIOUS DISEASES CLINICAL TRIALS.

RIGHT PLACE

Location is a key factor that must be considered when conducting ID clinical trials, and a thorough understanding of the spatial patterns of the disease is a basic tenet. Just as the protocol should clearly define the population, feasibility must be up-to-date to incorporate the latest epidemiological data—understanding that technically savvy, large databases may be quite useful for endemic diseases but may not accurately reflect site-specific, local trends that can change rapidly during outbreaks (e.g., *Acinetobacter baumanii* local outbreaks, Ebola, COVID-19, monkeypox, etc.).[5,6]

Outbreaks can be widespread or very local, appearing in specific locations and then swiftly moving on, sometimes only to recur at a previous location. It can be challenging to plan a clinical trial for an ongoing outbreak that is rapidly evolving. Clearly, this is occurring during the COVID-19 pandemic, but as many antibacterial ID trials are looking at highly resistant organisms, considering this rapidly changing environment is as important in other non-COVID-19 ID indications.

For example, if we look at studies enrolling patients with antimicrobial-resistant organisms during COVID-19, there were interesting differences between sites that could maintain stringent infection-control policies versus sites where the pandemic left them with depleted resources — not only in terms of insufficient personal protective equipment (PPE) but also in terms of limited personnel. It is essentially a tale of haves and have-nots. It's fairly intuitive, but data support the fact that in environments where personnel and PPE were insufficient during the pandemic, hygienic conditions deteriorated, and rates of antimicrobial resistance increased.

A study by Tiri and a team in Italy during a COVID-19 surge found that the incidence of CRE acquisition in the ICU went from 6.7% to 50% over that period. The authors cited that a lack of PPE and a lack of experienced health care professionals were associated with an increased risk of spreading carbapenem-resistant *K. pneumonia* in ICUs. They also mentioned that the high intensity of care and even the positioning of intubated COVID-19 patients in a prone position required additional inexperienced health care workers (HCWs) and extended contact as part of the risk factors that drove the numbers higher. This high demand for care in the ICUs caused an immediate need for HCWs with no ICU experience and created a suboptimal nurse-to-patient ratio.

A study in the U.S. showed that carbapenem-resistant Acinetobacter cases also increased in specific regions and sites where COVID-19 surged. In that study, the authors also attributed this increase to corresponding shortages in personnel, PPE, and medical equipment that resulted in temporary changes to existing infection-control measures, such as efforts to conserve PPE and other equipment and pausing routine audits of infection-control compliance.

DURING THE COVID-19 PANDEMIC, INFECTION CONTROL AND PREVENTION MEASURES HAVE BEEN USED ON A GREATER SCALE IN AREAS WHERE RESOURCES WERE NOT LIMITED. WHEN THEY WERE FULLY IMPLEMENTED, THEY WORKED WELL.

Other studies looking at clonal spread of pathogens associated with VABP, including ESKAPE pathogens, demonstrated that the emergence of bacterial infections secondary to COVID-19 could be closely related to poor clinical practices by health personnel and inadequately cleaned medical equipment.

On the other hand, infection control and prevention measures have been used on a greater scale in areas where resources were not limited. When they were fully implemented, they worked well. Increased use of face masks, gloves, gowns, alcohol for hand hygiene, and restricted visitation policies significantly increased in many regions in 2020 compared with prior years. A study from Taiwan from sites where there was no real shortage of medical resources found that the overall incidence of hospital-acquired infections did not differ during the pandemic from the pre-pandemic baseline period. In fact, nosocomial UTIs significantly decreased, and the incidence of MDROs was lower in 2020 than the pre-pandemic baseline. The study especially noted that carbapenem-resistant *A. baumanii* and VRE were significantly lower during the first year of the pandemic than the pre-pandemic baseline. MRSA and carbapenem-resistant *P. aeruginosa* tended to decline. No change in carbapenem usage compared with the pre-pandemic baseline, and glycopeptide usage increased.[7-17]

RIGHT TIME

Various types of infections tend to occur in a time-dependent pattern. For example, in patients with transplants, various types of infections correspond with the timing and the nature of the patient's level of immunosuppression. In bone marrow transplant recipients, infections within one month of transplantation (pre-engraftment) occur as a result of neutropenia and disruption of mucosal surfaces; infections that occur in the second or third months are largely due to deficiencies in cell-mediated immunity and are more frequent in the setting of graft versus host disease.

In a review[18] of patients' status post-hematopoietic cell transplant (HCT), a multicenter, prospective study demonstrated the epidemiology and timing of infection in four important U.S. HCT centers. In the study, 444 HCT recipients showed the following results after 30 months:

- There was a high rate of bacteremia, occurring in 231 (52%) cases and occurring early post-transplant (median day 48). Gram-negative bacteremia infections were less frequent than Gram-positive, but Gram-negative bacteremia was associated with higher mortality within seven days (45% vs. 13%, P=0.02).
- *Clostridium difficile* infection was reported in 148 patients (33%), with a median time of onset of 27 days post-HCT, representing a continued risk in this population during the first months after transplant with a high recurrence rate.
- Invasive fungal infections were reported in 48 (11%) patients, with a median time to development of 142 days. Ten to 15 years ago, most of these infections were identified before the engraftment. Now, there is a shift in the timing, and most of these cases occur later.
- Approximately 35% of the patients experienced an episode of cytomegalovirus (CMV) infection, but only 4% developed disease organ involvement. This very low rate of tissue-invasive disease is directly related to the implementation of effective antiviral strategies in this population.

In the solid-organ post-transplant course, infections during the first month after transplant are typically due to a preexisting infection (from the donor or recipient, such as antimicrobial-resistant bacterial infections, graft-associated viral and parasitic infections, and fungal and mycobacterial infections) or an infection related to the transplant or hospitalization (e.g., *Clostridium difficile* infection and antimicrobial-resistant bacterial infections). Infections are often associated with immunosuppressive therapy from one to six months after the transplant. Here, opportunistic infections become a concern, including *Pneumocystis jirovecii*, CMV, endemic fungal infections, BK virus and respiratory viruses that may be active in the community (e.g., influenza, RSV, SARS-CoV-2, etc.). For the remainder of the first year, infections present in the community (bacterial or viral) become the chief concern, and CMV may appear as a late infection in patients who had previously been on prophylaxis.

These timetables are useful because infections that are unusual or occur outside the expected time frame may serve as sentinels for emerging opportunistic infections. Research priorities in this area include developing therapies that will enhance successful transplants without increasing the risk for opportunistic infections, strategies to reduce the risk of drug-resistant opportunistic infections, and a greater understanding of the role of cytokines in the relationship between graft versus host disease and opportunistic infections.

> **STUDIES IN AT-RISK PATIENTS DEMAND SPECIAL CONSIDERATION AND PRESENT UNIQUE CHALLENGES THAT THE STUDY TEAM NEEDS TO ANTICIPATE.**
>
> - **Carrie Sheil**, Executive Director, Clinical Trial Management, Medpace

RESOURCES, RECRUITMENT AND RETENTION

Carrie Sheil, Executive Director, Clinical Trial Management, Medpace, noted, "While there are numerous studies enrolling subjects for any number of infectious diseases, such as viral and bacterial pneumonia, urinary tract infections, and bloodstream infections that affect a broad range of populations, many studies now are exclusively enrolling at-risk patients with serious infections. Whether it is an at-risk patient who is immunocompromised with an invasive viral infection at a specific time after a solid-organ transplant, a patient receiving treatments for cancer or autoimmune diseases with a serious fungal infection, or a pediatric patient or elderly patient who is particularly at risk for a hospital-acquired infection, studies in at-risk patients demand special consideration and present unique challenges that the study team needs to anticipate."

While assessing at-risk populations, resources, recruitment and retention must be considered. They are not disparate entities; they are overlapping and intertwined, each affecting the other.

> **CLINICAL TRIAL SITES ARE OFTEN RESOURCE-CONSTRAINED WHICH AFFECTS THE RECRUITMENT OF THESE AT-RISK POPULATIONS.**
>
> - **Slobodan Ilic**, MD, Senior Medical Director, Medpace

The COVID-19 pandemic offers an example of why running a clinical trial in at-risk, special populations can be important. "During the peak of the COVID-19 pandemic, we were recruiting patients in COVID and non-COVID studies who were immunocompromised," Sheil said. "Due to the inherent risks that immunocompromised patients may face if infected with SARS-CoV-2, it only accentuates the critical need to ensure safety while maintaining the integrity of the data."

During the height of the COVID-19 pandemic, resource issues were an obvious factor limiting clinical trials. In fact, if a study could be paused without harming patients, many clinical trials were halted for significant lengths of time in 2020 because hospitals and clinics were shifting most of their resources to COVID-19 treatment as well as to minimize the risk of patients spreading the disease.

Slobodan Ilic, MD, Senior Medical Director, Medpace, emphasized resource issues, noting that "clinical trial sites are often resource-constrained which, in turn, affects the recruitment of these at-risk populations. The sites don't have enough staff capacity to support the efforts needed to recruit patients and to ensure that they properly follow the trial protocols, do the legwork, and identify and assess the patients."

There is often tension between clinical care and clinical trials due to resource limitations. In most cases, busy clinical staff have plenty to deal with just taking care of patients without the additional challenge of clinical trial activities. "To liaise between the two groups is challenging, even if, in the example of COVID-19, there was a huge catchment of patients to tap into," Ilic said. "Successfully navigating between high level clinical care and clinical trials is still very difficult for many sites due to logistical constraints."

Both recruitment and retention present different challenges to ID studies, depending on the exact indication, the nature of the at-risk population, and the clinical care setting. Patients in an ICU may be relatively easy to recruit for a clinical trial, depending on why they are in the ICU. Ilic said, "For an ICU patient, retention is not challenging until they are discharged, but making sure that the patient is able to return to the clinic for follow-up visits for a long-term protocol, which can go on for years, can be extremely difficult. With certain studies extending beyond their ICU stay, you may see a significant loss to follow-up that can affect your data and even risk the primary endpoint."

Sheil cited skin infections, common in intravenous-drug users, as an example of why recruitment can be achievable, yet retention can be difficult. Recruitment and compliance are relatively straightforward when the patients are in the hospital and under consistent care. Once discharged and the patients are feeling better, long-term follow-up in such a patient in a study can be challenging. It is important to ensure that expectations are reviewed during the consent process. In addition, mitigating barriers by decentralizing and reducing patient burden with support such as flexible follow-up visit options and transportation are keys to retention success.

FOLLOWING THE PATIENT

Resources, recruitment and retention present a challenge not only when patients are discharged but also when patients are moved from site to site, even within the same institution.

Brian Murphy, MD, MPH, FIDSA, Senior Vice President, Medical Department, Medpace, noted, "Clinical trials are complex in general, but infectious diseases trials in at-risk populations are even more so. At-risk populations — such as CKD patients, elderly or pediatric patients, cancer patients, transplant recipients, or pregnant women — are seen in multiple areas within and outside a hospital and may transition throughout that facility. How one handles the movement of a patient from one setting to another challenges the site's resources to ensure that proper patients are recruited and retained. Where do you recruit them, how do you retain them, and who are the teams that do that?"

These may vary from indication to indication, trial setting to trial setting, and the nature of the at-risk population, whether it's a special, at-risk patient or if there are geographical or temporal limitations with the disease under study.

Underscoring the importance of the patient's journey through various hospital units, outpatient rehabilitation centers, and the patient's home, the study team needs to safeguard that there is an acceptable degree of standardization of supportive care and consistent implementation of the protocol. As the level of supportive care may vary somewhat by region or institution and is managed by multiple providers at the clinical trial site, an overly prescriptive protocol that is not aligned with those practices will likely not succeed.

"Part of the solution," Murphy said, "is a dedicated research champion to coordinate all those pieces and follow the patient's journey. Working closely to follow the patient through the health care system is critical. Otherwise, the study will have issues throughout the entire trial, from identifying the right investigators to the quality of the data obtained."

With many precision medicine therapeutic studies now looking for very specific patients, study teams must be aware that outcomes vary significantly among subgroups of patients with different genetic or demographic profiles. Modern studies are often designed to ensure that the study follows the appropriate patient; interim analyses can confirm an adequate sample size and can evaluate the therapeutic's effect on novel biomarkers that may be an eventual surrogate for a clinical outcome, and adaptive clinical study designs can be progressively enriched to select for a subpopulation that proves to be most drug-sensitive for the initially targeted disease and can even introduce an alternative indication if the data support.

Working early and regularly with regulators and experienced partners can be crucial to success while working on an infectious disease clinical trial where there's more time to plan than, for example, for an Ebola outbreak or even COVID-19.

> **IT CAN BE CHALLENGING TO GET CERTAIN SITES ON BOARD FOR A CLINICAL TRIAL IF THE PROTOCOL'S REGULATORY-DEFINED ELIGIBILITY CRITERIA OR OBJECTIVES ARE NOT COMPLETELY ALIGNED WITH THE SITE'S WAY OF MANAGING THEIR PATIENT.**
>
> - **Brian Murphy**, MD, MPH, FIDSA, Senior Vice President, Medical Department, Medpace

For example, Sheil noted, "sometimes objectives and endpoints, especially primary endpoints that regulatory agencies expect to see, are not 100% in line with regular clinical practice and outcomes that would be satisfactory for investigators. In other words, sometimes investigators want to see something else as a primary endpoint."

Murphy added that regulatory considerations and recommendations might differ from academic practice. "It can be challenging to get certain sites on board for a clinical trial if the protocol's regulatory-defined eligibility criteria or objectives are not completely aligned with the site's way of managing their patient."

However, in some cases the site's knowledge and experience with regulatory requirements and good clinical trial design may not be extensive and may place the study at risk if the site assumes they understand the protocol based on how they practice.

In addition, regulatory requirements may not necessarily align with what a sponsor considers to be an important factor in the study. Murphy said, "Sometimes sponsors think that their drug's mechanism of action lends itself to an obvious surrogate endpoints (eg., microbiological burden or viral load) or that they have some impact on a biomarker that is one step removed from a clinical endpoint or has not adequately been correlated to a clinically meaningful endpoint as defined by the a regulatory agency."

For example, for some time in hepatitis C clinical trials, viral load wasn't viewed as the primary endpoint by regulatory agencies, but HCV viral load is now accepted. This is common with clinical trials using the Food and Drug Administration's accelerated approval pathway.[19] Often, the trial is designed around a surrogate endpoint. Additionally, some clinical trials for Alzheimer's disease are designed to prove reduced beta-amyloid levels rather than improvement in memory and cognition. If approved under an accelerated approval pathway, the sponsor company must conduct a post-approval clinical study to verify clinical benefit.

The decision whether to design a study using a surrogate endpoint or a clinical endpoint affects the power of the study, Murphy noted. "It likely changes the number of patients that need to come into the study to achieve that clinical endpoint, sometimes making these studies bigger than sponsors think they need to be because their endpoint has shifted from a surrogate to a clinical endpoint. Clearly, this can lead to frustrations for the sponsor and delays if the sponsor is not prepared for such a change."

In short, clinical trials in at-risk populations for infectious diseases present numerous unique challenges in terms of study design, resources, recruitment and retention. Working with an experienced partner to develop and implement a good clinical trial design with appropriate resources can save time, money, and frustration.

Ilic said, "If you don't have early engagement and an agreement for your development plan, then you will waste time, money and effort. And you won't be aligned with regulators. There are many details within a typical development pathway, but early engagement and getting buy-in with regulatory agencies is key for sponsors to keep in mind in their development plans."

THE ARGUMENT FOR AN EXPERIENCED CLINICAL TRIAL PARTNER

Clinical studies in at-risk populations present several problems, even outside the context of epidemics and pandemics. As Louise Sigfrid, et al., wrote in BMC Medicine,[20] "Clinical research takes time to plan, conduct and disseminate, a luxury that is rarely available during an outbreak. Ethical and regulatory frameworks designed for non-acute epidemics are not necessarily fit for the purpose of acute epidemic research. Conducting research under emergency conditions requires agility, intense activity, flexibility and adaptability to context."

Infectious disease trials require thoughtful design and implementation to address differential risks, exposures, and individual susceptibility. Infectious disease clinical trials in at-risk populations present additional unique challenges regarding resources, recruitment and retention and require a strategic and proactive plan to succeed.

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