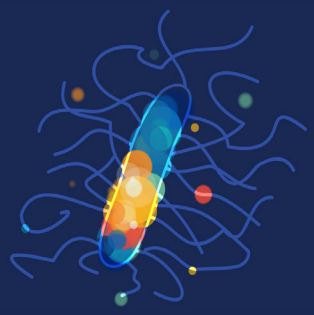

Article:

ADVANCING SEPSIS CLINICAL DEVELOPMENT: STRATEGIES TO OVERCOME HETEROGENEITY, PATIENT RECRUITMENT, AND DATA QUALITY CHALLENGES

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Sepsis remains a significant global health challenge, with an estimated 48.9 million cases and 11 million sepsis-related deaths worldwide, accounting for approximately 20% of all global deaths according to the World Health Organization.[1] Within the healthcare system, sepsis also remains a critical complication, affecting approximately 15 out of every 1,000 hospitalized patients.[1]

Defined as a dysregulated response to a known or suspected infection, sepsis can lead to dysfunction of multiple organ systems. As there is no uniform disease biology, two patients meeting identical sepsis criteria may have profoundly different underlying etiologies, immune responses, degrees of organ dysfunction, and treatment needs managed in a multi-disciplinary approach by clinicians in infectious diseases, pulmonary, nephrology, cardiology, etc. as well as specialized pharmacists, nurses, and laboratory specialists.

The evolution of sepsis from an infection to an excessively activated immune response to immunosuppression to disrupted organ systems is a complex cascade. Severe cases frequently progress to septic shock and organ damage, requiring intensive care unit (ICU) management. For those surviving sepsis, 50% of patients can develop a persistent post-sepsis syndrome of physical, psychological, and cognitive symptoms, some of which have even been linked to altered gene expression that can signify a long-lasting, dysregulated immune system.[2,3]

THE EVOLVING SEPSIS CLINICAL DEVELOPMENT LANDSCAPE

Due to the heterogeneous nature of sepsis and long list of drugs that have failed to move forward or meet endpoints, sepsis drug development is moving toward more focused interventions that will take into account specific etiologies and host immune responses.[4] There is now more of an effort in understanding the distinct sepsis endotypes through metabolomics, proteomics, and epigenetics. Biomarkers such as procalcitonin (bacterial vs nonbacterial), CRP (inflammation), lactate (tissue perfusion), and IL-6 (inflammatory state) are being incorporated to support clinical decisions. Recent advances in immunotherapy for sepsis have further reinforced the concept of sepsis being a complex syndrome with different biological drivers requiring precision treatment targeting specific sepsis endotypes rather than a “one size fits all” approach.

However, to really appreciate the impact of how precision medicine applies to drug development in sepsis, timely data about a patient’s endotype must be readily available to clinicians managing their patients with sepsis. Rapid diagnostic tools that support faster pathogen identification and characterize the initial host response are another cornerstone of effective sepsis management and appropriate anti-infective treatment and stewardship.

Artificial intelligence (AI) and machine learning are also emerging as important tools. By integrating clinical data, genomics, lab values, immunology parameters, and biomarkers, AI models may help identify sepsis earlier, predict patient trajectories, and support personalized therapies. These technologies hold significant potential for improving adaptive and data-rich clinical development in infectious diseases, where fragmented datasets and difficult trial recruitment have historically slowed innovation.

At the same time, evolving guidelines continue to shape sepsis management and trial design. The Surviving Sepsis Campaign guidelines focus on management across hospital, pre-hospital, and post-hospital settings, while incorporating antimicrobial stewardship principles such as responsible antimicrobial use, proper diagnostic strategies, and de-escalation of antimicrobial therapy.

Despite these advances, significant unmet needs remain in accelerating sepsis clinical development due to challenges in disease heterogeneity, patient recruitment, data quality and evaluability, and microbiology analysis. Addressing these barriers requires not only scientific innovation, but an experienced clinical, operational, and regulatory partner with tailored solutions for sepsis development. The following sections explore these challenges and strategies to advance sepsis research.

"Sepsis is a highly complex, life-threatening syndrome that overwhelms standard interventions, underscoring the urgent need for novel therapeutics and coordinated expertise across many therapeutic areas to improve outcomes. At Medpace, we bring together multidisciplinary expertise, leveraging deep clinical experience with global trial capabilities to partner with Sponsors in accelerating the development of novel interventions within the sepsis space."

- Jen Heminger, MSN, APRN

STRATEGIC APPROACHES TO OVERCOME SEPSIS CHALLENGES

Heterogeneity and Study Design

Sepsis is a highly heterogeneous condition, with differences in genetic makeup, pathobiology, immune responses, and acquired host factors contributing to variable disease progression and treatment response.[5] This heterogeneity is a major reason why many prior therapies have often failed in clinical trials when patients were stratified only by clinical phenotypes and were informed by narrowly-designed or inappropriate preclinical models.[6] Clearly, sepsis is not a single disease entity, but a diverse syndrome initiated by numerous pathogens (sometimes concurrently), assorted sites of infections, and variable host responses. Patient responses are influenced by age, sex, comorbidities, environment, and genetic and epigenetic factors with different phenotypes and endotypes.

As therapeutic strategies are becoming increasingly targeted, this complexity becomes even more relevant. Many treatments are focused on specific pathways that may be upregulated in only certain sepsis endotypes. Consequently, a singular sepsis treatment that demonstrates efficacy in one endotype may show no benefit in another.

Results from the Phase 2a EMBRACE study highlight the growing recognition that sepsis is a heterogeneous syndrome with different biological drivers rather than a single disease. The concept explored a precision medicine approach in which patients with interferon-gamma-driven immune dysregulation demonstrated benefit from a targeted immunotherapy.

To mitigate some of these risks in trials of sepsis and improve the probability of success, clinical trials should be designed to ensure appropriate selection of patients and endpoints based on the mechanism of action of the drug and a clear focus on the specific sepsis endotype that the drug could potentially target. Streamlined protocols with carefully designed eligibility criteria are essential. Overly restrictive criteria may limit enrollment, whereas broad criteria may introduce excessive heterogeneity. If multiple endotypes are to be enrolled, stratification should account for physiological or immunological phenotypes and endotypes (e.g., baseline comorbidities, baseline endotoxin activity, macrophage activation state, etc.). However, stratification at enrollment still may not account for the dynamic clinical course of a patient with sepsis. Protocols may allow adaptive therapeutic strategies as the patient progresses, and statistical analysis plans should be innovative and allow for an interpretation of the outcomes beyond a traditional binary view.

Likewise, the efficacy endpoints should reflect the mechanism of action of the drug and the specific endotype(s) that are being enrolled. In addition to traditional, blunt mortality endpoints, sepsis trials are increasingly incorporating hierarchical composite endpoints such as length of stay in the ICU, number of antibiotics used, SOFA score, organ dysfunction scores, ventilator-free days, biomarkers, and other measures of recovery. Secondary efficacy endpoints evaluate inflammatory and immune biomarkers. Balancing scientific rigor with real-world applicability is essential to ensure that the study outcome can meaningfully inform future practice if the therapy is approved.

Finally, ongoing oversight is critical. Real-time evaluation of variations in adherence can signal a shift away from the study's intended direction. Early identification and mitigation of these issues protect endpoint integrity and maximize the likelihood of a successful trial outcome.

Patient Recruitment, Feasibility, and Collaboration

Patient recruitment presents unique challenges in sepsis clinical development. Sepsis is an acute, rapidly evolving syndrome characterized by rapid deterioration, organ dysfunction, and high mortality risk. As a result of this fast-paced environment, investigators and sites need to promptly recognize potential study candidates, react rapidly to confirm the pathogen, and initiate study treatment within a narrow window following ICU admission.

One of the primary recruitment barriers in sepsis trials is the non-linear manner through which patients enter the healthcare system. Eligible patients may present through the Emergency Department, ICU, or through a variety of other specialty wards. This fragmented patient journey complicates standardized processes and requires broad multidisciplinary coordination to ensure eligible patients are identified across all relevant environments. To support identification, sites may utilize local microbiology alerts, pharmacy triggers, and EMR alerts based on real time orders, ICD-10 codes, and Current Procedure Terminology Codes (CPT) codes (if available) such as intubation. Recruitment efforts may also be impacted by competing studies targeting overlapping patient populations. Partnerships with ICU research networks and critical care groups can further enhance recruitment efforts by expanding site engagement, increasing awareness, and supporting patient identification.

Strategic feasibility is a critical component of successful patient recruitment in sepsis trials. Site selection should prioritize a consistent standard of care across sites. Study designs should be flexible enough to account for some variations among institutions while ensuring and monitoring that sites maintain the core pillars of sepsis care.[7] Medpace conducts comprehensive feasibility evaluations to assess site staffing, operational bandwidth, and capabilities. Successful sites often demonstrate:

- Multidisciplinary engagement with multiple sub-investigators across various departments (e.g., ICU, ED, labs, pharmacy, infection control, long-term or sub-acute rehabilitation centers)
- 24/7 infrastructure
- Comprehensive EHR/EMR alert pathways
- High-volume ICUs with engaged ICU champions or site leads
    - Integrated rapid response critical care workflow
    - Embedded research staff
    - Adherence and up to date with current sepsis guidelines (e.g., SCCM/ESICM Surviving Sepsis Campaign guidelines, NICE guidance, WHO guidelines)
- Successful integration with Sponsor and support systems (e.g., CRO and Clinical Coordinating Center (if applicable))
- Understanding of the drug's mechanism of action and the importance of careful selection of patients that are most likely to respond to it (as defined in the protocol)
- A commitment to both safety and efficacy outcomes (i.e., not only mortality which still may require following patients beyond the ICU but also composite endpoints such as length of stay in the ICU, number of antibiotics used, organ dysfunction scores, ventilator-free days, biomarkers and other measures of recovery)

Beyond selecting experienced sites, successful sepsis trials require Sponsors and CROs to implement targeted strategies that support patient identification, recruitment, and study execution. Key strategies include:

- Establishing site contracts to ensure adequate staffing for recruiting and managing complicated ICU patients
- A tiered site management approach, with tailored action plans for individual sites based on recruitment potential, including Sponsor-site calls, medical team calls, and discussions around recruitment challenges
- Supporting sites with training for non-traditional recruitment personnel (i.e., ED and ICU charge nurses, hospitalists) to enhance recruitment opportunities
- Encouraging high-performing sites to expand investigator and sub-investigator coverage across departments, which can optimize continuous patient identification and ensure appropriately trained personnel remain available
- Implementing study-specific patient identification and patient flow worksheets during SIVs and routinely reviewing to maintain alignment and ensure that all information is updated

Frequent and transparent communication between Sponsors, CRO teams, and sites can also streamline recruitment challenges. Effective communication strategies include:

- Weekly CRA touch bases with site staff to support timely enrollment
- Ongoing communication between medical monitoring teams and global site staff to discuss patient eligibility and clinical evaluation
- Presenting material at site sepsis committee meetings to train and keep study top of mind
- Targeted investigator meetings—both in-person and remote—to address recruitment barriers, data quality issues, and provide protocol clarifications
    - Support of local teams to allow investigators to ask questions in their local language
    - Monthly recruitment emails and regular teleconferences highlighting subject recruitment and retention tips, ideal patient profiles, recruitment status, recognition of top recruiters, and recruitment challenges

- Regional and country-level teleconferences focused on protocol retraining, lessons learned, and recruitment and retention tips
    - Case study focused reviews and discussions
    - Success stories shared by clinical champions (i.e., high enrolling sites sharing their strategies)
- Educational and Scientific rationale materials provided to support sites
    - Study specific materials designed to increase study visibility and optimize recruitment, including magnets, flyers, healthcare provider factsheets, healthcare provider patient pathway, pre-screening checklist, and patient brochures
    - LAR education to support clear and compassionate communication
    - Appreciation/recognition items for study coordinators, including holiday cards, handwritten notes, cups, pens, and water bottles

Data Quality and Evaluability

Ensuring data quality and evaluability in sepsis clinical trials presents significant hurdles due to the heterogenous nature of the syndrome and the complexity of managing critically ill patients. For instance, complications may arise from inconsistencies in APACHE II and SOFA score calculations, missing or incomplete data, delayed data entry, and variability in the interpretation of clinical findings across investigators and sites.

To overcome these challenges, providing standardized guidance for consistent APACHE II and SOFA scoring is essential. However, many common clinical scenarios encountered in the ICU are not explicitly covered in the current versions of the scores. Study specific guidance should be developed to address these potential situations and promote standardized interpretation and application across sites. This should include clear instructions for handling missing data, which is especially important for score parameters impacted by patient death, early discharge, or incomplete assessments. Of equal importance is comprehensive investigator and site staff training to further minimize variability. Training should extend beyond score definitions to include practical applications though case-based examples that reflect common ICU scenarios. Ongoing reinforcement through targeted protocol retraining, E-blasts/newsletters, and centralized medical review help ensure consistent application of scoring criteria throughout the study.

Medpace implements cross-functional strategies to support data quality and consistency, including:

- Reconciliation reviews conducted across the data management team, Data Integrity Unit, medical team, and central lab
- Biostatistical dry runs to generate programmed reports that are in alignment with the Statistical Analysis Plan to proactively identify potential issues
- Regular meetings to review the outcome of each subject and discuss discrepancies
- Proactive meetings to promptly recognize site challenges with measurable improvements in primary evaluability across sites

Concomitant medications and adverse events related to expected fluctuations of parameters in the ICU (e.g., oxygenation, blood pressure, etc.) also create unique challenges, so it is important to minimize overcollection of non-informative ICU data. Capturing only clinically relevant concomitant medications can avoid reporting routine medications and reduce site burden without compromising safety or efficacy analyses. Avoiding reporting adverse events that represent expected and typical fluctuations of parameters in ICU patients can prevent inflation of inconsequential adverse event data.

Quality of Microbiology Analysis

Variability in local microbiology lab capabilities and standard-of-care processing workflows can significantly impact endpoint evaluability, pathogen confirmation, and interpretation of microbiologic outcomes. There is a need for consistent, high standard, and timely sample processing and analysis across all sites and local microbiology labs to produce evaluable microbiological data for outcomes. Additionally, the study protocol may require sample processing which is not always consistent with standard of care at the local microbiology lab, causing more complications.

The Medpace Data Integrity Unit (DIU) is a team comprised of highly trained microbiology specialists that provide ongoing evaluation and oversight of the microbiology aspects of infectious diseases studies. The team assists during site selection and ensures only sites capable of meeting protocol specific requirements are selected. The DIU team closely monitors local microbiology and central microbiology data with the medical team to optimize identification of a potential pathogen in a timely manner. Through collaboration with the Medpace medical team, CTMs, and CRAs, the DIU provides site microbiology lab support and training to meet study needs. The proactive approach in monitoring on an ongoing basis is essential to quickly identify trends or issues in the study while providing mitigations early on before they negatively impact the study's data quality.

CONCLUSION

Sepsis remains an urgent and complex challenge in healthcare, underscoring the need to accelerate clinical development of safe and effective therapies to improve the lives of those impacted by sepsis. Advancing sepsis clinical development will require a focus on targeting host response in sepsis treatment. At the same time, the development of faster, yet affordable diagnostics for pathogen identification is essential. As the landscape evolves, there is an increased importance in understanding the combination of pathogen and host metagenomics. Emerging technology and AI also hold significant promise to enhance sepsis trials.

> **"For years, Medpace has actively participated in sepsis research, contributing to advances in scientific implementation, improved diagnostics, earlier and more reliable predictions, novel targets, more effective therapeutics, better preclinical models, and new technologies—all leading to innovative approaches that are improving clinical research and patient outcomes."**
>
> *- Slobodan Ilic, MD*

Given the complexity and urgency of sepsis clinical development, selecting the right CRO partner is essential. A CRO with deep expertise brings valuable operational and scientific lessons learned from prior studies, allowing teams to proactively identify potential challenges and implement efficient mitigation strategies.

At Medpace our experienced medical leadership, specialized cross-functional teams, integrated laboratories, and extensive site and investigator relationships produce a truly seamless drug development process that can accelerate your path to approval.

Contact our sepsis experts to learn how Medpace can help support your next study.

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