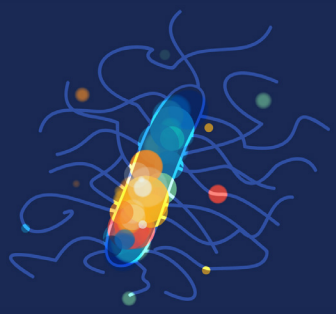
Case Study:

ADVANCING SEPSIS CLINICAL RESEARCH: INSIGHTS FROM A GLOBAL ICU STUDY



BACKGROUND

Study required identification of a bacterial pathogen and allowed enrollment of patients with sepsis due to bacteremia, hospital and ventilator-associated pneumonia, complicated intrabdominal infections, wound infections, and urinary tract infections in 2 parts

200 PATIENTS

100 SITES

17 COUNTRIES

Trial regions: Europe - North America - Asia Pacific - Latin America

CHALLENGES & SOLUTIONS

PATIENT RECRUITMENT

Challenges:

- Patient recruitment was inherently complex due to multiple, non-linear entry points within hospital systems with eligible patients presenting through various ICUs or being managed in other departments.
  - Potential patients were identified through local microbiology alerts (positive blood cultures and Gram stain results) or by the pharmacy triggers (prescription of anti-infectives, vasopressors, and/or sedatives)
  - Sites had to react rapidly to confirm the pathogen and to initiate study treatment ≤ 48 hours from ICU admission
  - Prompt recognition of potential study candidates
- Key-opinion leaders and large academic centers had studies competing for study team's time and attention.
- The study was actively recruited during the height of the global COVID-19 pandemic and was not the highest priority of the sites during that time.
- An enrollment pause following the completion of the first part of the study to allow for complete data analysis initially raised concerns regarding potential safety signals and led to frustration among highly motivated investigators.

Solutions:

- Medpace conducted detailed feasibility to evaluate site staffing bandwidth (e.g., number of coordinators dedicated to the study, how many studies coordinators are typically assigned, etc.).
- Site contracts were structured to ensure an adequate number of staff were assigned to the study with sufficient availability necessary to recognize, recruit, and manage complicated, ICU patients.
    - Special attention was given for timely recognition of potential candidates — prior to septic cascade becomes inevitably irreversible and fatal — avoiding moribund patients.
- Tiered sites by recruitment potential and worked closely with Sponsor to implement individual action items per site (e.g., Sponsor-site calls, Medical Team calls, etc.) to discuss the individual recruitment challenges.
    - Prioritized sites with multiple sub-Is across departments (including emergency departments).
    - Encouraged top tier sites to expand investigator and sub-investigator coverage across departments to optimize continuous patient identification and ensure appropriately trained personnel were available even if the PI was rotated out of the ICU.
- Implemented a study-specific patient identification worksheet that was initially completed during the SIV and routinely reviewed to ensure all information was updated (completion of Site-Specific Recruitment Plan with each site).
- Medpace Medical Monitoring Team communicated directly with global site staff (via phone and/or email) to discuss patient eligibility and clinical evaluation within the randomization window.
    - CRAs and Study Coordinators promptly engaged appropriate site personnel to ensure enrollment within the tight timeframe.
- CRAs maintained weekly touch bases with site staff via phone calls and emails during COVID-19 pandemic to ensure sites received adequate support (e.g., establishing remote monitoring, providing additional ancillary supplies, etc.).
    - This preserved site engagement with most sites, maintaining the ability to recruit during the pandemic.
    - Sites unable to recruit were primarily hindered by personnel and/or bed shortages, but quickly resumed active recruitment once shortages improved.
- Sponsor and Medpace team provided frequent, transparent communication with sites during enrollment pause and provided transparent communication regarding safety data.
- Medical Team led multiple targeted meetings with investigators (F2F or remote) to address recruitment barriers, data quality issues, and providing protocol clarifications. Meetings were supported by the local teams (CRAs) which enabled investigators to ask questions in their local language.
- Routine recruitment information provided to sites via Monthly Recruitment Eblast which included subject recruitment and retention tips, case studies, ideal patient profiles, recruitment status, recognition of top recruiter, and recruitment challenges.
- Provided study specific materials to help increase study visibility (i.e., magnets, flyers, HCP Factsheets, HCP Patient Pathway) and optimize recruitment (Pre-screening checklist, Patient Brochure, Patient Journey to support the consenting process).
- Provided appreciation items for study coordinators (holiday cards, handwritten notes, cups, pens or water bottles).
- Regional and country teleconferences for protocol retraining, sharing of lessons learned and subject recruitment and retention tips
- Booster visits performed by CRAs and Sponsor

STUDY BLINDING

Challenges:

- Due to operational challenges in blinding the comparator, the study was open label at the site level, except for the site's blinded assessor. The regulatory authorities had requested that the study data should be collected and handled as if it were a blinded study.
    - The site level blinded assessor, the Sponsor, and the Sponsor's designees involved in medical and safety monitoring, data management, operations, and other aspects of the study (e.g., interpretation of the results) remained blinded to treatment assignment.
    - Given the complexity of treatment regimens, the Principal Investigators, treating clinicians, Clinical Research Associates (CRAs), and other site personnel (study coordinators, nursing, and pharmacy staff) were unblinded.
    - Patients remained blinded to their treatment assignment throughout the course of the study.

Solutions:

- Developed a Study Blinding Plan that clearly defined how unique blinding requirements would be operationalized across clinical systems (CTMS, EDC, IRT etc.) at sites and the Medpace and Sponsor project teams. All internal and external stakeholders (internal: Clinical Trial Management, Monitoring, Data Management, Biostats, Safety, QA; external: Sponsor, central labs, PK lab) worked closely together to develop innovative processes and procedures to preserve data integrity.
- Developed a detailed Site-Specific Blinding Plan prior to site activation clearly defining roles and responsibilities of site personnel understood and allowed/disallowed communication pathways.
- Ongoing, study specific training provided for Medpace personnel, particularly CRAs, during monthly monitoring plan meetings and on an ad-hoc basis to ensure blinded and unblinded communication pathways were followed.
- Site personnel trained at the Investigator Meetings, Site Initiation Visits, Remote Monitoring Visits, centrally via newsletter/email blasts, and during calls with Medical Monitoring Team.
- Predefined procedures for managing accidental unblinding including response strategies tailored to the scope and personnel involved in the unblinding, allowing for rapid mitigation and minimal study impact.
- Unblinded Medpace Medical Monitor added to the study team to facilitate real time discussion between the study team and site personnel including review of protocol-related, subject specific medical questions that involved treatment information, while maintaining the blind for all other team members.

CREATINE CLEARANCE CALCULATIONS

Challenge:

- The IP required dose adjustment based on renal function. Thus, daily assessment of creatine clearance was necessary and required consistent CrCl calculation across all sites.

Solutions:

- Regular reminders to collect daily serum creatinine at the local laboratory provided during routine CRA outreach and via email blasts and study newsletter.
- Sites provided with validated calculators for Ideal bodyweight and CrCl using the Cockroft Gault formula. The provided validated calculator allowed the investigator to calculate the CrCl in one step, without the need to decide which body weight was to be used for the calculation (ideal body weight, adjusted body weight, or actual body weight), ensuring the correct calculation of the renal function, minimizing the possibility of overdose.
- Actual study drug doses were automatically calculated in one step by IRT using validated calculators with notifications to pharmacist regarding the dose.

SUPPLY LOGISTICS

Challenge:

- Procuring essential medical supplies (e.g., saline bags, infusion lines, etc.) and equipment (e.g., infusion pumps, rapid test kits, etc.) across multiple countries with differing standards of care amidst global shortages and heightened demand during the COVID-19 pandemic.

Solutions:

- Close collaboration with Medpace logistics team to establish efficient process for supply provision prior to site activation.
- Medpace contracted with vendors to organize procurement, storage, and distribution of ancillary supplies and equipment. Local purchase prioritized when possible, but if not feasible, thorough planning and monitoring ensured import/export and local depot requirements were met and that sufficient supplies were available at the time of site activation and throughout study conduct.
- Medpace assessed equipment availability (e.g., refrigerated centrifuges) during the site selection and arranged for rental equipment on behalf of the Sponsor, leveraging prior experience with medical equipment vendors.

DATA QUALITY/INTEGRITY AND EVALUABILITY

Challenges:

- Enormous number of concomitant medications and adverse events related to expected fluctuations of parameters in the ICU (e.g., oxygenation, blood pressure, etc.)
- APACHE II and SOFA score inconsistencies
- Missing data and delayed data entry

Solutions:

Data Quality/Integrity

- Recommended to capture only clinically relevant concomitant medications to avoid reporting routine medications (e.g., standard ICU order sets, IV fluids, tube feeding, sedations, bowel care medications etc.) and reducing unnecessary site burden without compromising safety or efficacy analyses.
- Suggested to avoid reporting adverse events that represent expected and typical fluctuations of parameters in ICU patients (e.g., fluctuations in oxygenation and/or blood pressure soon after an invasive procedure has been performed, preventing inflation of noninformative adverse event data.
- Provided standardized guideline for consistent APACHE II and SOFA scoring, addressing common clinical scenarios not explicitly covered in under the current versions of the scores.
- Clear guidance provided on handling of missing data, especially important for score parameters and patient death.

Evaluability

- Reconciliation reviews were completed by the Data Management Team, the Data Integrity Unit, Medical Team, and central lab, with additional reviews included near the end of the study.
- Biostatistics led a dry run to generate programmed reports that were in alignment with the Statistical Analysis Plan to proactively identify potential issues.
- Regular meetings between the Sponsor and Medpace to individually review the outcome of each subject and discuss discrepancies.
- Medical Team regularly attended meetings with investigators, especially at the sites where patients' evaluability for the primary endpoint analysis dropped below expected threshold.
    - These proactive interventions resulted in prompt recognition of site challenges with measurable improvements in primary evaluability across sites.

QUALITY OF MICROBIOLOGY ANALYSIS

Challenges:

- A consistent high standard and timely respiratory sample processing and analysis had to be established across all sites and local microbiology laboratories to produce evaluable microbiological data for outcomes.
- The study protocol required sample processing which was not always consistent with standard of care at the local microbiology lab.

Solutions:

- Engaged the Data Integrity Unit (DIU) team of microbiology experts during feasibility to ensure only sites capable of meeting protocol specific requirements (e.g., cultures, additional testing, etc.) were selected.
- DIU team collaborated with the Medical Team, CTMs, and CRAs to provide site microbiology lab support and trainings that were adapted in real time to meet study needs.
- Performed ongoing, real-time review of microbiology data to monitor study populations and identify trends and issues in data quality.
- DIU served as liaison between sites, Sponsor, and central microbiology laboratory.
- Medpace Medical and DIU teams closely monitored local microbiology and central microbiology data to ensure that a sufficient number of patients were enrolled that met criteria for the mMITT population (120 patients, mMITT= Microbiologically Modified Intent-to-Treat).
- Full implementation of mitigation strategies to improve microbiology recovery rate were not implemented initially (due to concerns from the Sponsor that doing so could negatively affect enrollment). Once sites were retrained on optimal sample collection and processing techniques and site-specific strategies were implemented, overall evaluable population improved by 20%.

RESULTS

Enrollment was completed within the projected timeframe, despite anticipated and unanticipated challenges (e.g. COVID-19 pandemic).

Primary and secondary endpoints were met, and were reviewed favorably by the regulatory agencies.

Close cooperation with DIU and central microbiology ensured that the goal of 120 evaluable patients in the mMITT population was met without over-recruiting.

There were no major findings at site inspections.

The unique blinding process, which was accepted by the FDA, can serve as a template and example for trials with a similar blinding set-up or requirement.

Due to networking from existing sites and ongoing site engagement from Medpace, new sites and Investigators requested to take part in the study.