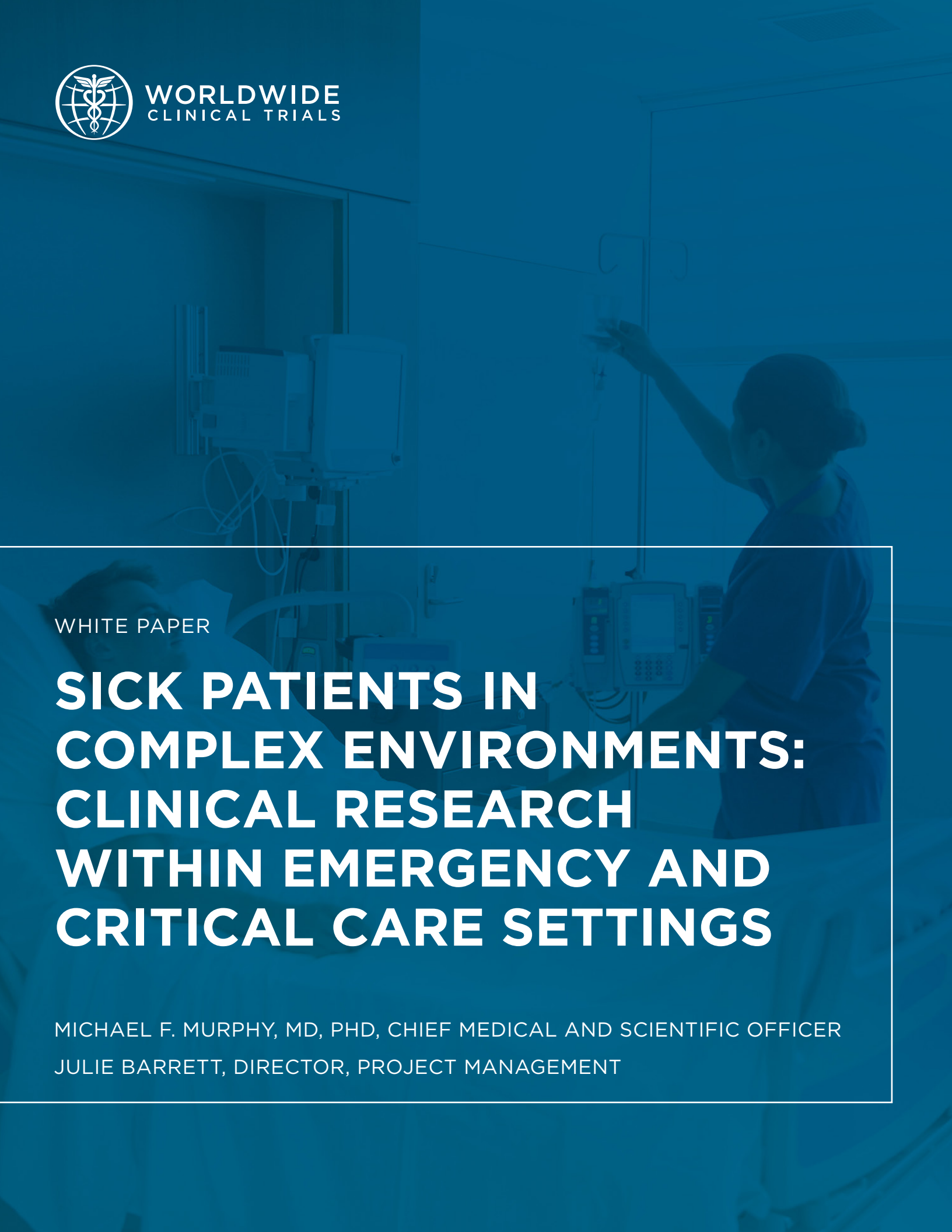

WORLDWIDE CLINICAL TRIALS

WHITE PAPER

SICK PATIENTS IN COMPLEX ENVIRONMENTS: CLINICAL RESEARCH WITHIN EMERGENCY AND CRITICAL CARE SETTINGS

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Emergencies are often characterized by the rapid onset or progression of an injury or pathophysiologic disturbance, and time is rarely on the side of the caregiver. Although an emergency department (ED) setting offers a unique environment in which to conduct observational or interventional research leading to more advanced diagnostic tools and novel therapeutic interventions, neither staffing nor the initial mandate for care are easily compatible with the constraints of a mandated protocol. Successful implementation of a research trial requires an understanding of operational differences in areas ranging from staffing, care delivery, patient pathway management, long-term follow-up procedures, and more. Considering in advance how to accommodate the needs of research and emergency care teams – each with different priorities and backgrounds – is the key to ensuring the success of both teams within this critical care environment.

Recent reports in the literature as well as results from industry-sponsored clinical trials indicate a marked increase in clinical studies associated with emergency departments (EDs). Historically, studies within the ED setting have concentrated on prognostic biomarkers and other diagnostic tools used in the evaluation and treatment of cardiometabolic disorders. This is not surprising given the need to determine rapid and effective methods of intervention and the emerging and critical role of biomarkers in that decision process. But the ED is a common portal for admission for all patients requiring acute care intervention. As such, the ED and its staff are a natural extension of a broader research capability, particularly in tertiary care settings. In addition to cardiovascular (CV) studies, ED studies have also focused on respiratory ailments, gastrointestinal disorders, and a wide range of infectious diseases, including the coronavirus disease (COVID-19).[1-11]

AS A PORTAL FOR ADMITTING ALL PATIENTS REQUIRING ACUTE CARE, THE ED AND ITS STAFF ARE A NATURAL EXTENSION OF A BROADER RESEARCH CAPABILITY.

A search on PubMed in May 2020 using the title keyword “emergency department” and the filter category “clinical trials” identified 1,264 results. A similar search on the website clinicaltrials.gov using the keywords “emergency department” produced 8,744 results, with most of these trials concentrated in North America and Europe.[12] As shown in Table 1, 6,301 of these trials are interventional, and 1,530 of the interventional trials are industry-funded.[13, 14]

The explosive interest in the role of the ED in research prompts a reconsideration of the elements of this complex setting that impact trial design, methods of clinical operations, and analysis.

UNIQUE OPPORTUNITIES

From the perspective of a contract research organization, the distinct value of an ED environment lies in the fact that it interacts with a diverse patient population presenting acute conditions that are frequently overlaid with medically important comorbidities requiring timely diagnosis and treatment. It is an environment where there is a mosaic of complexity that demands innovative trial design and even more innovative study operations. Mastery of trial operations is a hallmark of differentiated clinical research services.

These observations are true whether the patient is suffering from a CV event or pulmonary event associated with COVID-19. As an example, clinical studies conducted in EDs have established the role of natriuretic peptide levels in risk stratification, with regard to the need for hospital admission or direct ED discharge, and as powerful independent predictors of death in acute coronary syndrome.[15, 16] Other important contributions of research in emergency medicine can be found in the treatment of acute heart failure, as illustrated by a 2016 study showing that monitoring changes in systolic blood pressure assisted risk stratification of acute heart failure patients, particularly patients with intermediate emergency room systolic blood pressure measurements.[17] This study highlights the unique capacity of EDs to enroll patients in urgent medical need (hypertensive crisis), to perform rapid assessment and therapeutic intervention, and to evaluate and document efficacy parameters within 30 minutes.

DETERMINING TRIAL AND SITE COMPATIBILITY REQUIRES A DETAILED INQUIRY INTO TOPICS AS DIVERSE AS HOSPITAL POLICIES, ETHICAL CONSTRAINTS, AND THE INTERPLAY OF EXTERNAL EMERGENCY SERVICES AND INTERNAL SPECIALIST ACTIVITIES.

Regardless of the therapeutic focus or interventional technology, however, all studies initiated or completed within an ED require integrating the demands of GCP research with the exigencies of prompt and effective clinical care. Determining the compatibility of a specific type of trial with the specific capabilities of an ED site requires due diligence and a detailed inquiry about topics as diverse as hospital policy and ethical constraints and the interplay of out-of-hospital emergency services and in-hospital specialist activities. Essential skills include therapeutically unbiased approaches toward trial design, guidance regarding appropriate staffing structure and training, the ability to enable a platform for data acquisition and analysis that is compatible with routine electronic medical records (EMR), and the ability to create quality measures providing key performance indicators during study conduct.

IS THE ED A DESTINATION OR A GATEWAY?

In many institutions, emergency services serve as centers for delivering definitive medical care as well as gateways to a broader range of healthcare services. The patients within an ED are often unknown to care providers and only present within the ED itself for a brief period before being discharged or transitioned to another level of care. Thus, access to simple historical metrics regarding patient phenotype, therapeutic interventions used during the process of care, and eventual outcomes often are elusive and largely incomplete during trial planning stages.

Emergency services serve as centers for delivering definitive medical care as well as gateways to a broader range of healthcare services. A clinical presentation commonly presents problems that require rapid diagnostic and therapeutic interventions, and the procedural demands associated with research can encumber clinical care if they are not designed to mesh cleanly with well-established ED procedures. These challenges can be exacerbated if ED physicians and attendant staff – whose priorities emphasize care and disposition of those patients coming in the door – have limited clinical research experience and if trial designers likewise have limited access to those ED personnel while developing the trial model.

PATIENT IDENTIFICATION AND RECRUITMENT

The emergency environment poses many barriers to patient recruitment, and this has always been considered an operational challenge.[18] The crowding typical of an emergency care facility and the urgency of the need to initiate treatment creates one such barrier. In non-ED trials involving myocardial ischemia, as an example, patients presenting with chest pain would undergo rapid assessment, including elements of an examination beyond routine clinical care, in a monitored setting to optimize the diagnosis of acute coronary syndrome and to verify all of the protocol's specific inclusion/exclusion criteria. But in an ED, the urgency of the moment usually demands the time-sensitive initiation of a treatment, which can preclude enrollment of potential research subjects within the window defined by protocol. To mitigate crowding-related enrollment problems in ED-based studies, processes should, if feasible, be implemented to enable emergency physicians to evaluate patient eligibility in a study-dedicated room (short observation unit) when all nurse-staffed stretchers are occupied.

HOW CAN RESEARCHERS MITIGATE CROWDING-RELATED ENROLLMENT PROBLEMS IN ED-BASED STUDIES? IS IT FEASIBLE FOR EMERGENCY PHYSICIANS TO EVALUATE PATIENT ELIGIBILITY IN A STUDY-DEDICATED ROOM WHEN ALL NURSE-STAFFED STRETCHERS ARE OCCUPIED?

The fluctuating dynamics of patient flow inherent in an ED create other barriers as well. The intensity and unpredictability of the workload in an ED can increase considerably if personnel are required to participate in clinical research. Unless a research study has been carefully designed to be consistent with the setting, protocol-mandated procedures potentially jeopardize the care the patient or other individuals within the ED who are competing for limited staff resources.

Other barriers arise from the arrival in the ED of patients with a wide variety of concomitant medication and concurrent illnesses, which can confound the severity of initial diagnosis yet are prognostically important to outcomes. Characteristically, such patients also present in a non-uniform pattern throughout a 24-hour period, which may warrant the placement of more study personnel in the ED than would normally be placed in non-emergency settings, where enrollment activities would largely take place within normal "office" hours.

TECHNOLOGY PLATFORMS

In addition to facility and staffing challenges, the technological infrastructure required for research can create challenges in an ED setting. Admission diagnosis and triage information must always be available to dedicated study staff, and this can be reached optimally through an electronic data entry system at the emergency site. Although electronic clinical charts are common in today's ED settings, they may not be designed with the data needs of the research team in mind and may provide insufficient granularity, constraining exploratory research. Additionally, chart compatibility across centers in a multicenter trial is not assured. This poses a potential disconnect that must be remedied without jeopardizing primary ED activities.

STANDARD ELECTRONIC CHARTS IN THE ED MAY NOT SUPPORT THE DATA NEEDS OF RESEARCHERS, AND CHART COMPATIBILITY ACROSS CENTERS IN A MULTICENTER TRIAL IS NOT ASSURED.

Although researchers need demographic and administrative information as well as the ability to collect audit and activity data as a matter of routine, they also need access to digital information generated by the ED's patient physiological monitoring systems. An appropriate data structure that facilitates transfer and analysis is a prerequisite. When these monitored physiological parameters are included in the clinical study database, any inconsistency must be addressed for study purpose. Despite this, or even because of it, data may be of poor quality. Lack of standards for data acquisition across different platforms in multicenter trials will simply accentuate the issue. Or, the significant clinical information that is frequently so informative may be embedded within unstructured natural text fields that require special data mining algorithms (or manual processes) to review. Additionally, data that may potentially be useful for study purposes may only be accessible for "secondary uses" within a clinical trial after navigating both legal and logistical barriers regarding access.[19-21]

INFORMED CONSENT AND PRIVACY CONSIDERATIONS

Two other important challenges associated with ED research involve informed consent and privacy considerations, which pose particular issues contingent upon a patient's clinical status and the setting in which the research will occur.

As an example, when a patient in the U.S. cannot meaningfully contribute to the informed consent process, the FDA provides an exception in emergency research settings. The patient must be in a life-threatening situation in which the acquisition of consent – either directly or through a family member or legal authorized representative (LAR) – is not feasible and access to the intervention at the heart of the research project may yield a direct benefit. If those conditions exist, and the clinical investigation could not otherwise be carried out in the absence of a waiver, then the FDA waives the need to obtain the patient's consent.[22]

However, a decision to include ED patients that cannot provide informed consent adds additional levels of complexity that must be accommodated. Trial designers and sponsors need to work closely with the institutional review board (IRB) to create and document procedures relating to the notification of family members or legally authorized representatives (LARs) of patients receiving a trial intervention without express permission, the need to document notification attempts as part of the trial record, and the need to provide information about the trial and the procedures involved to the family as quickly as possible. This is particularly important if the trial involves follow-up engagement with the participants after the initial intervention for the purposes of creating a more expansive data set. Trial sponsors and investigators must also consult with the communities in which the research will be conducted (including the communities surrounding each ED where research is taking place), and the plans for consulting with the communities must be reviewed and approved by the IRB before such consultation commences.[23, 24]

THE DECLARATION OF HELSINKI INCLUDES SPECIFIC PROVISIONS FOR THE WAIVER OF INFORMED CONSENT AND THE PROTECTION OF HUMAN SUBJECTS IN EMERGENCY RESEARCH.

ED-based studies with an international operational footprint involve an additional level of complexity because different countries have different policies on informed consent in emergency circumstances. Some

require consent of a relative or legal representative, for example, introducing considerable challenges in country and site selection independently of site capability in the index condition. In an attempt to resolve this dilemma and provide a framework for consistency, the Declaration of Helsinki includes specific provisions for the waiver of informed consent and the protection of human subjects in emergency research.[25]

THE ART OF FEASIBILITY

Traditional survey-based approaches to feasibility assessment may not effectively distinguish between EDs that are well-suited to supporting clinical research into an investigational medicinal product (IMP) and those that are not. As noted, the intensity and unpredictability of the workload in emergency medicine varies greatly by location and by shift, and this can complicate completion of a survey questionnaire addressing issues of patient management and clinical care. Indeed, a survey questionnaire often loses the "sense of the environment," which can be a key determinant in center selection.

A second difficulty arises from the level of detail that a contract research organization with a clear operational remit will require when evaluating the suitability of an ED setting. While a detailed questionnaire may yield incredibly valuable data from an operational planning perspective, the amount of time and energy required for busy ED personnel to gather the information and complete a complex questionnaire can be overwhelming. Given these difficulties, it is not surprising that the rate of return on feasibility surveys sent to ED and other critical care settings is approximately 1 in 10.

To streamline the process of identifying suitable ED sites, it is far more productive to engage directly with the medical director of an ED (or with an operational director of the ED with medical experience). A phone-based feasibility assessment methodology accomplishes that objective. It involves outreach to prospective EDs and explores the capacities and capabilities of an ED in four broad areas:

1. Site suitability
2. Pharmacy and lab logistics
3. Patient and treatment pathway mapping
4. Burden reduction

SITE SUITABILITY

The questions related to site suitability deal with proximity to research centers, patient populations, site team composure, and existing protocols and procedures into which the proposed research study will be placed. Representative questions under this umbrella include:

- Is there a designated research center associated with this facility? Ideally it will be in the ED itself, but it may be sufficient to know that the ED is affiliated with a research center that would be supportive and accessible.
- What population of patients with the condition in question has historically been encountered in the ED, and what is the potential for patient recruitment given current standards of care?
- What are the areas of expertise on the ED team, and what is the composition of the team in terms of physicians, physician assistants, nursing staff, and other technical services? Have they any experience in trial research and, perhaps more importantly, is there receptivity to the concept of a research project within a department that customarily focuses on brief, intensive, point-of-

care interventions followed by patient transfer and disengagement? It is also possible that this sentiment varies by shift, and maintaining this priority within the ED, given many different shifts and staff becomes an ancillary but critically supportive function.

- Are there studies already underway in the ED that involve the use of requisite resources (such as radiology, laboratory, or pharmacy services), and will accessibility to the services be unencumbered during the process of performing a GCP-compatible trial?

PHARMACY AND LAB LOGISTICS

The feasibility of conducting a trial in a particular ED setting is heavily influenced by pharmacy and laboratory capabilities.

- Where is the pharmacy in relation to the ED itself, and what are the logistics of accessing both approved and investigational study medications? The investigational medicinal product (IMP) is likely to be stored in the pharmacy so it is important to anticipate the transfer time from the pharmacy once a request for the IMP is delivered. Similarly, it is important to understand how activity related to the research medication is tracked and monitored for compliance assessments.
- What are the storage options within the ED for the IMP itself? If the IMP requires refrigeration, for example, trial designers need to know that options exist in (or near) the ED, contingent upon storage specifications provided by a sponsor. What kinds of security controls are in place to limit access to authorized personnel?
- What are the logistics of delivering samples and test kits from the ED to the lab? The lab kits themselves may be stored at a research center that is physically distant from the emergency department, so it is important to understand how the lab kits will travel to the ED and then how the samples and kit materials will be returned to the laboratory for assessment.
- What are the likely challenges associated with carrying out appropriate IMP dosing and administration instructions? If this is a first-in-humans trial measuring PK at specific times after dose administration, for example, it is important to understand how venipuncture (or CSF) collection can take place within the ED while maintaining sample integrity for those analytes that are sensitive to the vagaries of sample acquisition processing and storage. Similarly, if an IMP dosage is weight-dependent, then trial designers will need to determine how and where the proper dosage can be measured out for the patient.

While there are few right answers to these kinds of questions, a study trialist specializing in pre-empting and remediating obstacles to study conduct is critical to the success of an ED-based trial. These discussions are intended to capture as much site-specific information as possible. Ultimately, there will be some commonalities across all ED sites; there will also be differences between EDs that require levels of customization from site to site.

THERE WILL BE COMMONALITIES ACROSS ALL ED SITES, BUT THERE WILL ALSO BE DIFFERENCES REQUIRING CUSTOMIZATIONS FROM SITE TO SITE.

PATIENT AND TREATMENT PATHWAY MAPPING

The pathway mapping questions explore site processes during a trial.

- What is the treatment pathway for patients arriving in the ED with this condition? Some patients may be discharged; others may be admitted to the hospital – and in the hospital to different levels of care. Researchers and trial designers need to understand transitions after arrival and treatment in the ED, particularly the customary disposition for follow-up.
- Do procedures exist to ensure that all care providers can distinguish patients that are part of a study? This question persists from the time of initial screening onward and does not terminate until the patient is ultimately discharged. Some EDs use special sticky notes on a chart, for example, which personnel throughout the ED or hospital complex understand to indicate that the patient is participating in a study. This can ensure that there are no interventions occurring outside of protocol and that staff trained for that particular study are accessible for consultation for the duration of hospitalization.
- What are the site's communication pathways for internal and external stakeholders? Trial designers need to know that the study coordinator (SC) will be able to communicate with ED and ward staff – whether that's to coordinate the transportation of lab samples, to follow up on adverse events, or to seek clarification on a specific data entry. Having a research-dedicated SC available on-site can facilitate these issues and eliminate the need to ask ED nursing teams to complete required study tasks.
- Who will be responsible for electronic data collection (EDC) as the patient traverses the different pathways within the institution (and beyond)?
- Can roles and responsibilities be clarified and consistently applied? These dynamics are important to understand in order to determine how to engage with the existing team without creating an impediment to routine clinical care.

HOW CAN RESEARCH AND ED TEAMS INTERACT TO MINIMIZE THE BURDEN THAT A RESEARCH STUDY MIGHT HAVE UPON ED PROCESSES?

REDUCING THE BURDEN

Finally, a detailed set of questions can be advanced to clarify how research teams can interact with the ED teams in ways that minimize the potential burden that a research study might have upon ED processes. This initiative begins in protocol design and extends through various phases of operations. It highlights the axiom that there is no dissociation between trial design and study operations in a properly conceived program.

- What is the emergency consent procedure review, and what are the processes for ensuring mental capacity to provide an informed consent? Documentation requirements must be accommodated if a decision to include a patient in a trial is taken in the absence of formal consent obtained directly from the patient.
- What is the process for contacting next of kin to obtain details for appropriate follow-up?
- How are shifts in staffing orchestrated, and what are the handover processes? The importance of the interface between highly competent

functional groups is more critical than the competency within each group, as the incoming group's ability to operate competently could be undermined or hampered by a poorly coordinated transition in clinical care. Shift changes in the emergency room, the wards, the ICU, and step-down units are common points at which the protocol-mandated care and data acquisition can falter if not well understood and considered in advance.

- How are new staffing solutions accommodated? The manner in which new staff are introduced to the required procedures and concepts relating to the trial is critical, as are the procedures for updating new shift personnel about which patients are participating in a trial. A thorough understanding of how researchers will be interacting with both the patients and their care providers is of seminal importance.
- How can requisite trial materials be made available yet minimally intrusive within the ED? At some sites, for example, a simple rolling cart that could be moved to the patient's bedside upon admission to the ED might be ideal. The cart could contain everything from a checklist of procedures to the sticky notes for a chart, lab kits and more.

This depth of questioning – and different trials will prompt additional questions, of course – helps quickly identify sites where the right combination of patient population, physician and staff interest, and site features come together.

A TIME OF OPPORTUNITY

An untapped opportunity for clinical research in the ED exists at both site and country levels. Fundamental structural and staffing limitations must be addressed to ensure that there is compatibility between the interest and capabilities of centers and that the demands of GCP pharmaceutical research can be met. Considering the significant increase over the past years in investment in emergency research by the pharmaceutical industry, many organizations are already accommodating these requirements.

AT BOTH THE SITE AND COUNTRY LEVELS, THERE EXISTS AN UNTAPPED OPPORTUNITY FOR CLINICAL RESEARCH IN THE ED.

Facilitating the involvement of EDs in industry-sponsored clinical research should include coordination across ED research centers invested in this effort. Emergency medicine networks – such as the Strategies to Innovate Emergency Care Clinical Trial Network (SIREN) and the Pediatric Emergency Care Applied Research Network (PECARN) – are well established in the US. In the cardiovascular field, the Emergency Medicine Cardiac Research and Education Group (EMCREG), which is centrally coordinated through the Department of Emergency Medicine of University of Cincinnati, provides insights to the organization and procedures that must be implemented. International research networks range from the Pan Asian Resuscitation Outcome Registry (PAROS) and the Pediatric Emergency Research Networks (PEDN) to the Swedish Society for Emergency Medicine (SWESEM), the Danish Society for Emergency Medicine (DASEM), and the Global Research on Acute Conditions Team (GREAT), all of which represent comparable attempts to produce a coherent system for conducting clinical trials in emergency settings.

ED department research networks would benefit from additional formal clinical research training tailored for ED personnel – from methods of experimental design to the unique operational solutions required in emergency care settings. Such training would further relationships with the medical community for patients' referral and for patient aftercare and ensure a critical mass of eligible subjects at each participating center. This pre-emptive approach to trial conduct would justify the investment in resources. A proactive engagement of the pharmaceutical industry must also emphasize the importance of an industry mandate for predictable execution, pre-empting concerns regarding ED engagement in which "science and medicine are assumed, but data throughput is not."

SCIENCE AND MEDICINE ARE ASSUMED, BUT DATA THROUGHPUT IS NOT.

A TIME OF OPPORTUNITY

EDs can and should play an important research role in the development of new diagnostic and treatment strategies. These complex settings see patients from diverse populations presenting for acute care across a range of conditions. Recognized challenges for researchers include the need to modify customary study designs, research processes, staffing levels, information management, and, the occasional physical setting. However, for companies in the pharmaceutical industry to deliver effective solutions requires a proactive engagement with emergency settings. By building on the models of research success arising from individual centers and consortia, the opportunities for developing new research capabilities within this unique setting will expand.

Because of the urgency and the complexity inherent in ED settings, conducting research into the diagnosis and treatment of illnesses presenting in an ED turn operational acumen into an art. Researchers must understand the dynamics and complexities of hospital clinical trials, from presentation in the ED and through all the various transitions that could occur within the broader hospital setting (e.g., ED to ICU, ICU to step-down unit, step-down unit to ward, or to outpatient). Design and operational staff must be able to work flexibly with a dynamically shifting hospital staff. And researchers must expect the unexpected. Researchers intent on conducting a successful project within an ED or critical care setting must master different skills and methods and operationalize – first and foremost – an understanding of how to reconcile the strategic demands of the study with the real-time demands of urgent clinical care.

RESEARCHERS WORKING IN AN ED MUST MASTER DIFFERENT SKILLS AND METHODS TO RECONCILE THE STRATEGIC DEMANDS OF THE STUDY WITH THE REAL-TIME DEMANDS OF URGENT CLINICAL CARE.

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