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A site assessment tool for inpatient controlled human infection models for enteric disease pathogens

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Abstract

The use of the controlled human infection model to facilitate product development and to advance understanding of host-pathogen interactions is of increasing interest. While administering a virulent (or infective) organism to a susceptible host necessitates an ongoing evaluation of safety and ethical considerations, a central theme in conducting these studies in a safe and ethical manner that yields actionable data is their conduct in facilities well-suited to address their unique attributes. To that end, we have developed a framework for evaluating potential sites in which to conduct inpatient enteric controlled human infection model to ensure consistency and increase the likelihood of success.

Keywords

Controlled human infection models, enteric infection, diarrheal disease, vaccine

The establishment of critical clinical research capacities is essential to the successful conduct of clinical trials globally. Clinical trials require nuanced and specific attributes of the facilities in which they are to occur. In particular, controlled human infection model (CHIM) study designs necessitate specialized facilities to help ensure their safe and scientifically rigorous conduct. Although many nuances in these studies may be inherently associated with pathogen-specific factors, some of the most clinically demanding studies involve inpatient CHIM studies with an enteric pathogen. These CHIM studies require clinical facilities equipped with a sufficient number of beds and rooms to house study participants for more than a week, as well as 24-h nursing support and appropriate restroom facilities, and function best when co-located with research and/or clinical microbiology facilities, research pharmacy, and clinical assets that can manage ill subjects.

Given growing interest in the use of these models to support vaccine and therapeutic development,[1–6] an increasing number of sites have an expressed interest in conducting enteric CHIM studies; however, no standardized metric for assessing the capabilities of clinical sites is available to investigators or sponsors. In an attempt

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to address this gap, we have developed a checklist (see Supplemental Material) for the evaluation of potential clinical trial sites for inpatient enteric CHIM studies. This qualitative checklist covers the following range of domains: capacity, recruitment, clinical and laboratory experience, investigational product storage and preparation, personnel, facility description and volunteer well-being, research experience, infection control practices, waste management, ability to isolate volunteers, access to emergency care, regulatory considerations, and disaster preparedness. In addition, a study-specific addendum is included to enable assessments for a specific clinical trial.

We hope that this checklist will serve as a useful tool for investigators and sponsors in assessing the suitability of potential clinical sites to conduct enteric CHIM studies. As the specific requirements and objectives of enteric CHIMs are study-dependent and variable, the importance of each parameter should be weighed by sponsors and/or study partners depending on its relevance to the site, research questions, and the study design so that the sites being considered can be prioritized based on their full range of capabilities assessed in the survey. Below, we delineate several examples to assist in its use.

Studies utilizing controlled human infections include those for model development, preliminary assessments of vaccine efficacy for product down-selection and in some instances pivotal studies supporting licensure of final formulations, among others. Each of these CHIMs may prioritize different parameters. The primary objectives in model development studies are to characterize the clinical profile of disease through meticulous data collection and expert clinical care, describe microbiological and immunological outcomes, and establish standardized processes for future studies. As such, clinical trials focused on model development may prioritize a site with the capacity to conduct several iterations of smaller cohorts (Part A—Capacity), and a well-established and skilled microbiology laboratory (Part F—Microbiology Laboratory) and research pharmacy (Part G—Investigational Product Storage & Preparation). Some resources may be provided by an external contractor if not available or established at the site (i.e. a microbiologist/research pharmacist with extensive strain-specific experience in preparing the inoculum, or a contract research organization for safety and clinical data management). In addition, the sponsor/site may consider training by specific experts to build human resource skills for study site personnel.

Established CHIMs with extensive safety profiles may be used to assess the efficacy of a vaccine or other prophylactic or treatment. These are often larger studies requiring multiple cohorts and tend to be more logistically complex with increased regulatory scrutiny. Such larger studies may prioritize a site(s) with greater capacity (Part A—Capacity), existing recruitment capabilities and subject population (Part B—Recruitment), robust data management and quality control capabilities (Part J—Personnel), extra features pertaining to subject meals and recreation (Part I—Treatment and Well-Being of Subjects), and sufficient sample storage and sample transportation capacities (Part D—General Laboratory). The frequency, timing and batching of clinical, microbiological, and immunological samples may also be important; specimen storage prior to shipment or testing may be equally important.

CHIM studies are conducted in a variety of settings with an increasing interest in moving enteric CHIM to low- and middle-income countries. The CHIM location and the parties involved add additional parameters for consideration in prioritization. These may include regulatory considerations (Part L) or important regional—and cultural-specific factors (Parts B and I).

Strain- and protocol-specific considerations should also be weighed. If utilizing a lyophilized inoculum, a site with general microbiology expertise may be sufficient; however, studies using freshly harvested bacteria will likely require more specialized experience and/or training. Certain challenge strains are associated with a higher frequency, severity, and output of diarrhea, or result in more complex management of subjects requiring a lower ratio of beds to toilets and clinicians to subjects. In terms of bed-spacing, at a minimum, there should be sufficient distance to facilitate movement; however, separate rooms are typically not required. It should be noted that infectious disease epidemiology external to pathogen under study may necessitate less bed density. In terms of staffing and facilities, minimum parameters will be determined by the anticipated disease course and the number of subjects simultaneously needing medical attention. In an ideal setting, a single toilet would be available for each subject; however, often one for every three to four subjects is sufficient. While subjects are healthy, staffing can be geared to ensure adequate supervision and performance of study procedures. If subjects are expected to be quite ill or require more frequent sample collection, vital sign measurements or intravenous hydration, nursing and support staffing levels should be increased to ensure participant safety. Specific microbiological testing (e.g. quantitative culture and quantitative polymerase chain reaction) may also be required and a site experienced in those procedures may be a high priority.

We hope these scenarios and this survey will serve as a framework for the establishment of other site assessment tools for the evaluation of trial facilities across a diverse range of clinical research study designs. Such a framework can provide confidence to the investigator and sponsor in the ability to conduct such studies, assurances regarding subject safety, and an increased likelihood for consistency of data across research sites.

Declaration of conflicting interests

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Disclaimer

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Supplemental material

Supplemental material for this article is available online.

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