Managing Human Challenge Trials: A Case Study

Volunteer Infection Studies (VIS) or Controlled Human Infection Models (CHIM) are an extremely effective way to gather pre-clinical evidence on efficacy, minimize potential risks, and maximize the outcomes when progressing a new drug or vaccine onto critical clinical studies. Their success relies on careful preparation by an experienced team that is capable of adequately managing the risks associated with the study.

In this bulletin, we will share firsthand management experience from a recently completed malaria human challenge trial conducted by the SGS Clinical Pharmacology Unit in Belgium. We will focus on the main operational challenges encountered by the study team during the preparation and the strategies implemented to overcome them.

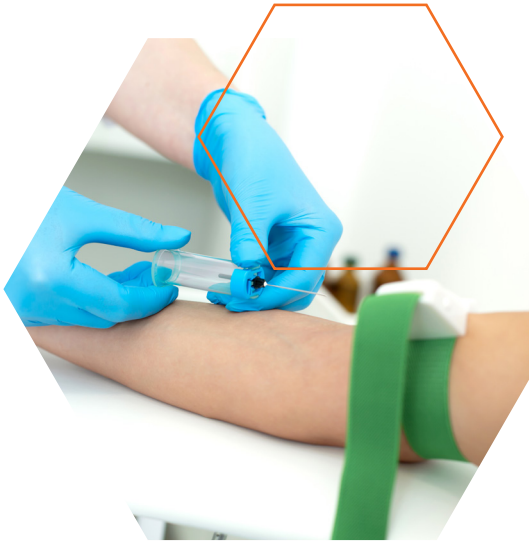
GETTING STARTED

A human challenge trial involves healthy volunteers being inoculated with a challenge agent. In other words, an infectious agent is introduced into a healthy volunteer. This is done either after the volunteer has received a vaccine or before the administration of an Investigational Medicinal Product (IMP). In our example, the challenge agent was Plasmodium falciparum, the most relevant causal agent of malaria.

Experience from previous human challenge trials concerning influenza has identified some of the key factors that can impact the preparation and conduct of a trial. However, since this was the first malaria human challenge trial to be conducted in Belgium and the disease is not prevalent in the country, several additional factors had to be considered, with specific topics requiring deliberation in advance of the study.

The key points can be categorized into four groups:

- Regulatory aspects
- Experts and experienced laboratories
- Study team selection and training
- Recruitment



REGULATORY ASPECTS

One of the main aspects to be considered in every human challenge trial is the regulatory requirements linked to using the specific challenge agent. The team must understand what special conditions need to be enforced to handle, prepare, and store the challenge agent in order to mitigate all biological risks. Depending on the biological risks associated with the agent, specific containment guidelines may need to be followed.

Likewise, it should be confirmed in advance whether specific licenses and safety measures are required. At all times, staff, volunteers, and the general population must be protected from the potential risks associated with the challenge agent.

An in-depth risk assessment should be undertaken involving all the main stakeholders to identify possible issues that could negatively impact the conduct of the study. For our malaria challenge study, active consultations were held with regulatory affairs, our infectious diseases expert, the site's pharmacy, alongside medical and operational teams. Another key step in the regulatory flowchart is organizing a Scientific Technical Advice (STA) meeting with Belgium's Health Authorities and the Belgian Biosafety Committee (required when biological agents are used in clinical trials).

Seeking advice from regulatory and safety experts at an early stage allowed their feedback to be incorporated into the study protocol. This then guides the operational team on the logistical aspects required to safely conduct the study at the site. For example, where and how to store the challenge agent and the specific safety measures need at the site.

EXPERTS AND EXPERIENCED LABORATORIES

Since this was the first time a malaria human challenge trial has been performed in Belgium and there was no previous experience to rely on, scientific experts were involved from an early stage in the setting up of the study. These included a malaria expert and professor of infectious diseases from the local university hospital and the SGS infectious diseases expert and trial investigator. They also provided training for members of the study team, plus support with protocol development and during communications with the health authorities.

A determining factor in the site selection process was the availability of qualified laboratories to perform the required safety assessments with short turnaround times. These can be very specific, depending on the human challenge trial. For the malaria human challenge trial, a laboratory had to be selected that could, on a daily basis, measure the number of malaria parasites in the blood (qPCR) and confirm the presence of parasites in blood by microscopy (thick blood smears).

When the required turnaround time for results is short (for instance when they are driving medical/safety decisions), or when they are needed at weekends or outside normal working hours, a detailed shipment plan for the delivery and receipt of samples, with clear and strict arrangements, needs to be made between the trial site and laboratory. In our case, a bike courier was hired to transport the samples between the site and laboratory to minimize travel times.

An additional step that can be implemented to improve data quality is the performance of a validation study. This will establish the sensibility and specificity of the laboratory and the methodology that will be used for reference and comparison during the validation.

Setting clear expectations on deliverables between the study team, site, and laboratory, prior to the commencement of the study, facilitates better communications. In turn, this will streamline the flow of samples and results as the study progresses.

STUDY TEAM SELECTION AND TRAINING

Teams conducting clinical studies need to be motivated, engaged, and they need to understand the relevant protocols. This is particularly true where there may be concerns over safety or a lack of understanding of the disease and its associated transmission risk. A proactive approach to disseminating information ensures all stakeholders are informed and are working in concordance.

Organizing training sessions for all staff members prior to the start of the trial will help to solve this problem. These should include details of the study protocol, the specific procedures that will be used (e.g. the malaria challenge trial had specific instructions for handling, preparation and inoculation of the challenge agent), as well as clear information about the risks associated with the trial and the measures being implemented to guarantee staff and study participant safety.

Conducting sensibilization/training sessions in this manner ensures the team is fully aware of the study model and the protocol's specificities. It has the additional benefit of being inclusive and clearly demonstrates that the safety and wellbeing of volunteers and staff is at the core of the study's design.

VOLUNTEER RECRUITMENT

When defining a recruitment strategy, it is important to consider factors such as the disease and the volunteer's familiarity with the study's procedures and safety measures. In addition, for the malaria human challenge trial, it was essential that the volunteers understood that the study was being conducted using a controlled method of challenge inoculation and that their safety was being monitored at all times. Similarly, it was important that they understood the restrictions and instructions associated with participation in the study.

To facilitate this, a short movie was prepared in which the investigator conveyed a clear and easy-to-understand message to the volunteers. Furthermore, a detailed but understandable informed consent form was prepared that contained information about the study model, the risks to volunteers, and the safety measures that were being implemented.

The recruitment plan should also include a strategy to tackle any difficulties encountered during the recruitment process. The team should reflect on the potential barriers to recruitment at each stage of the process and create a plan that incorporates actions to overcome them. It is important that good communication is maintained at all times and between all involved parties – recruitment team, investigator, project manager, etc.

CONCLUSION:

Successful human challenge trials begin with good coordination and communication. An experienced project manager will encourage and enforce this behavior from an early stage, well in advance of the study's commencement. Brainstorming sessions and open discussions between stakeholders will not only provide insights into possible hurdles during the study, they will also generate a motivated and highly prepared team that is capable of responding to any difficulty that may arise during the trial.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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