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Meeting report

Human challenge trials in vaccine development: Strasbourg, September 29 – October 1, 2014

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ABSTRACT

An international workshop to discuss the role of Human Challenge Trials (HCT) in vaccine development was held in Strasbourg, France from 29 September to 1 October 2015. In addition to scientific presentations, several panel discussions focused on key questions and proposed recommendations, including the acknowledgement that HCT have proven to be useful tools to explore vaccine targets, identify immune correlates of protection, and evaluate clinical efficacy, and when appropriate they should be continued and encouraged. In some cases, a HCT may be the only feasible way to move forward with development of an investigational product. HCT must be strongly scientifically justified, because the need for a given investigational objective must be always balanced against the risks a HCT may pose, understanding that an infectious organism will be given to the study participants. It should be noted that numerous HCT have been successfully performed, safely and ethically, to the benefit of vaccine development and public health. This workshop report highlights the scientific presentations, discussions by the panelists and attendees, and twenty recommendations that emerged as considerations for future development of international guidance on the role of HCT in vaccine development and licensure.

1. Introduction

Development of new vaccines for use in humans, as with other medicinal products, is an expensive and time-consuming process, estimated to take up to 20 years and $1 billion from original *in vitro* laboratory observations to clinical approval. This is the result of an established regulatory pathway to acquire data that demonstrates proof of concept (POC), safety and immunogenicity in animal models, and then the same in human volunteers, ideally culminating in proving efficacy against the targeted disease objective in the human at risk population. The prophylactic nature of vaccines, which may be administered to millions of people who may never be exposed to the pathogenic organism, means the fundamental issue of benefit/risk is more heavily weighted to safety, outweighing any potential efficacy against clinical disease.

The global healthcare community and pharmaceutical industry is seeking new strategies that will significantly improve the rate and potential of success in the development of new vaccines for currently unmet medical needs. These needs include not only well-publicized emerging global threats such as Ebola and potential pandemic influenza viruses, but also established pathogens such as malaria and dengue, and the less glamorous causes of the equally life-threatening diarrheal diseases, the second leading cause of death (after pneumonia) in children under five years of age [1]. With the current regulatory paradigm there is limited scope to encourage increased investment in the gamble that is novel vaccine development. After proof of concept and demonstration of safety in phase I trials, there is no guarantee that long and expensive phase II and III clinical trials will provide sufficient evidence of efficacy to achieve licensure of the final product. Accelerating this process requires development and acceptance of innovative new approaches that support direct measures of efficacy in the early phases, or indirect indicators such as human biomarkers of protection.

A workshop was organized by the IABS in Strasbourg, France, which brought together those involved in the different facets of vaccine development to examine the potential of human challenge trials (HCTs) to accelerate vaccine development. Carefully controlled infection studies to challenge and test vaccine candidates in human volunteers, with rigorous safeguards in place, can provide more relevant and accurate information on vaccine immunogenicity and potential clinical efficacy than animal models with unpredictable links to the human pathology. As with any innovation, HCTs will have to overcome many scientific, regulatory and ethical hurdles before they become generally acceptable in vaccine development,

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satisfying regulatory requirements to make them an acceptable tool to accelerate the overall process, or to make advances in scientific knowledge that will promote and protect public health.

This workshop was intended to summarize the current state-of-the art in HCTs with recent data and advances in this area, to be able discuss the outstanding issues primarily related to their regulatory acceptability in vaccine development and their role in defining immunological correlates of protection, and to tentatively provide some form of guidance about the design and conduct of HCTs. Speakers from different aspects of the vaccine-development industry were invited to present and then discuss how to achieve some degree of consensus on the basic requirements for HCTs to stimulate and advance this field of research.

To begin, **John Petricciani**, IABS President, established that the intent was to facilitate dialogue on critical issues in the development of biological products, to develop consensus on the key issues with an action plan for regulatory progress, and to work with other organizations with overlapping interests to improve the acceptance of HCTs in vaccine development. The goal was to reach concrete conclusions and recommendations on best practices, and draft guidance for the various stakeholders to accelerate vaccine development to meet currently medical needs.

1.1. Keynote: historical perspective on human microbial challenge models

Professor Myron M. Levine (Centre for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA) opened the workshop with a keynote talk on the historical perspective of and changing ethical attitudes towards human microbial challenge studies over time. Studies involving the deliberate exposure of humans to known or putative disease-causing material have been documented since 1722, when smallpox variolation was introduced into England. As the whole population at that time was at risk of smallpox infection, with a 30% fatality rate, experimental variolation was generally seen as ethically acceptable. To illustrate unethical research he cited later cases of hospital patients being deliberately exposed to gonorrhea to test a vaccine in 1930, experimentation on condemned prisoners and institutionalized orphan children, which continued with live viral vaccines against polio and measles in prisoners and children in custodial institutions in the USA through to the early 1970's, and the deliberate administration of enterpathogenic *Escherichia coli* to a two month-old infant with multiple congenital defects in 1950 [2]. Reflecting on these unacceptable examples, Prof. Levine warned us not to judge the practices of the past by the standards of today, but rather to appreciate how far we have come in conducting safe and ethical HCT.

To illustrate acceptable practice Prof. Levine presented the work at the Center for Vaccine Development (CVD) of the University of Maryland, which has been performing challenge studies in human volunteers since 1976, including data that has resulted in licensure of the CVD 103-HgR live cholera vaccine [3]. CVD has performed challenge studies with bacterial (cholera, *Shigella*, ETEC, EPEC, DAEC, EAggEC, typhoid, *Campylobacter jejuni*, gonorrhea, *Helicobacter pylori*, *Streptococcus pneumoniae*), viral (influenza, RSV, norovirus, rhinovirus, rotavirus, dengue) and parasitic (malaria, *Giardia*, *Cryptosporidium*) microorganisms. The center is careful to ensure the ethical acceptability of all studies, ensuring trial participants fully understand the risks, rationale, procedures and benefits of the study by having them take and pass a written multiple choice examination on the nature of the study prior to being enrolled.

Overriding practical issue is the ethical principle of *primum non nocere* (first, do no harm). Clinicians must take into consideration current public opinion and the perception of the dangers of human challenge studies, and balance these with advancing scientific knowledge for the potential benefit of future vaccine recipients and the public in general, decisions that cannot be left solely in the hands of ethical committees. As well as cautioning against financial conflict of interests, Prof. Levine suggested that two of the CVD ethical questions that should guide decisions about challenge studies are “Would I participate in this study?” and “Would I be comfortable with my family member participating in the study?” before concluding by referring to one of the darkest periods of recent history to emphasize the most important ethical aspect of HCTs. The trials of the Nazi SS doctors at Nuremberg who performed HCTs of typhus and vaccination on concentration camp prisoners. These lead to the writing of the Nuremberg Code of 10 bioethical points, including the concepts of informed consent and that the subjects should come to no long-term harm, and the primordial first point in this code: The voluntary consent of the human subject is absolutely essential.

1.2. Role of challenge trials in the decision making process of vaccine development: industry perspective

For the industry perspective **Dr. Taryn Rogalski-Salter** represented the IFPMA (International Federation of Pharmaceutical Manufacturers & Associations), which believes that improvements in global health must be based on four pillars: sustainable health policies, access to innovation, a science-based regulatory framework and ethical practices. In this respect HCTs may be useful in vaccine development pre-licensure to establish a POC and to aid in the go/no-go decision-making processes that vaccine companies must undergo throughout the development process, although there is no guarantee that the HCT will ensure that the correct decision is made. Data can vary from being partly supportive of licensure—providing another facet of the effectiveness—along with classical demonstrations of immune responses and theoretical measures of successful immune responses, to ultimately providing pivotal protective efficacy data and possibly immunological correlates of protection. Foremost consideration must be to the protection of the volunteers for whom the risks must be fully and clearly defined, as well as being mitigated to the fullest possible extent. IFPMA believes that best practices must be established for volunteer selection, with strict procedures during recruitment that ensure that all risks are identified, clearly communicated and understood. Volunteer protection must include insurance and indemnification against any unexpected consequences of the trial, which itself must be conducted by staff thoroughly trained in the procedures to be used, and the procedures to follow in the event of unexpected medical consequences. Protection of volunteers also extends to maintenance of confidentiality, which may be an issue in an era where there is a public demand for access to patient-level data. Planning, preparation and documentation of HCTs must be up to the same standards as those expected for Clinical Trial Applications/Investigational New Drug applications. This includes complete protocols with clear definitions of the clinical material, well-defined end-points using fully characterized challenge material prepared to GMP standards including purity and stability characterization. Study conduct must be according to prevailing GCP standards including data collection and analysis, definition of clear end-points with a proven dossier of established analytical techniques. All of these aspects require the creation of guidance documents on all considerations of HCTs, particularly the ethical aspects, the regulatory background, assistance on trial design and harmonization to ensure that the maximum benefits are achieved from each human volunteer.