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CHAPTER 8

HOW TO EXPEDITE EARLY-PHASE SARS-COV-2 VACCINE TRIALS IN PANDEMIC SETTING — A PRACTICAL PERSPECTIVE

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The COVID-19 pandemic is the biggest global health crisis of this century, straining health care capacity worldwide and bringing nations to a standstill with an unprecedented social and economic impact. A safe and effective vaccine is needed to help counter the COVID-19 pandemic. Vaccination development, however, is a complex and lengthy process and attrition rates are high.¹ It is not unusual for a new vaccine to take up to 10 to 15 years from antigen discovery to licensing. These timelines become problematic when acute outbreaks demand immediate interventions for novel infectious agents. This has been exemplified in outbreaks with severe-acute-respiratory syndrome (SARS) (2003), H1N1/09 influenza (2009), Middle East respiratory syndrome (MERS) (2012), ebola virus disease (2013), zika virus disease (2015). For H1N1/09 a vaccine was approved only after the outbreak reached its peak. A vaccine for ebola was approved six years after the major outbreak in West-Africa. No vaccines against zika and the coronaviruses causing SARS and MERS have been licensed to date. Several vaccine candidates are currently in development for COVID-19, either in the preclinical or early clinical phase. However, previous outbreaks show us that vaccine development typically does not keep up with the speed of a pandemic.

Several bottlenecks can be identified in the vaccine development process.² After preclinical studies and manufacturing processes, a rate-limiting step in vaccine development is the conduct of clinical trials. In addition, the majority of vaccine candidates fail in clinical development and never reach market authorization.¹ Only 77% of the vaccine candidates will successfully transition from phase I to phase II and only 58% will successfully transition from phase II to phase III.³ These early phase clinical trials (classical phases I and II) are essential to assess safety, tolerability and immunogenicity of the vaccine candidate, as well as preliminary information on its efficacy, before progressing further to large scale phase III trials. In the current COVID-19 pandemic it is more important than ever to identify and select the most promising vaccine candidates as early as possible and stop clinical development for failing candidates to avoid wasting valuable time and resources.

Here, we discuss several practical suggestions that could accelerate early phase vaccine trials in the COVID-19 pandemic.

1 COLLABORATION AND COMMITMENT OF ETHIC COMMITTEES AND REGULATORY AUTHORITIES TO REDUCE APPROVAL TIMELINES

Thorough and critical appraisal of a clinical trials submissions by medical ethics committees (MECs) and competent authorities (CAs) is essential to safeguard the health and wellbeing of participants in medical research. However, approval for a clinical trial can take up to several weeks or even months. These timelines are simply too long to allow rapid development of a pandemic vaccine. Fortunately, there are several options to expedite the clinical trial submission process.

Timelines for clinical trial approval can be substantially reduced if dedicated and mandated (sub)commissions are established to prioritize the review of COVID-19-related research files. Expert members can be identified beforehand to participate in these dedicated sub-commission and provide the necessary background knowledge to facilitate a high quality and effective review. Also, investigators and sponsors spent a tremendous amount of time drafting documents and assembling a trial application dossier that is submitted as a complete dossier to the MEC and CA. Time can be further reduced if applicant and reviewer work in parallel. For instance, the key documents (e.g. study protocol, investigator's brochure and investigator's medicinal product dossier) should be submitted immediately once available for initial assessment by the MEC. Other key documents, such as subject information leaflets, consent forms and recruitment materials can be prepared while awaiting the first assessments of the clinical trial application and should be submitted once finalized. The clinical trial submission process can be accelerated if applicant and evaluator are willing and able to work in tandem. Optimization of submission procedures will require good communication and flexibility of both investigators, MECs and authorities to minimize timelines in pandemic setting.

We had discussions with the Central Committee on Research Involving Human Subjects (ccmo) in the Netherlands to explore the possibilities for such an accelerated review procedure for COVID-19 vaccine research on a national level. Already early on in the COVID-19 pandemic the committee implemented a national *Fast Track* procedure for COVID-19 vaccine research to reduce approval timelines.⁴ Following this decision several accredited local MECs and competent authorities initiated similar fast track procedures pertaining to COVID-19 related research.

2 CLINICAL TRIALS APPLICATIONS FOR GENETICALLY MODIFIED VACCINE CANDIDATES

Progress in biomolecular insight of pathophysiology combined with innovation in biotechnology has led to an increase in genetically modified organisms (GMO) based vaccine platforms. These platforms are currently deployed to develop novel vaccines against SARS-CoV-2. GMO-containing vaccines candidates for SARS-CoV-2 mainly consist of viral vector-based vaccines and viruses that have been genetically modified to become attenuated.⁵ Performing vaccine trials with GMOs is inherently more complex due to additional legal requirements. Obtaining environmental permits for trials with GMO interventions can be difficult. In Europe, clinical trials involving a GMO must be compliant with the European GMO legislation; authorization needs to be obtained from national authorities besides the 'regular' approval of the competent authority and MEC.⁶ Legislation pertaining to the use and deliberate release of GMOs is not fully harmonized between countries. Therefore, regulation by national authorities can differ substantially between countries. In addition, regulatory bodies often work independently from each other. Obtaining the environmental permit for a clinical trial with a GMO-based vaccine can take up to several months, depending on the country-specific regulatory framework for the use of GMOs.⁷ These timelines impose a significant hurdle for rapid clinical development of a vaccine against SARS-CoV-2. However, temporary legal exceptions can be made to the application process when there is a clear and urgent need for human health develop a GMO for the purpose of a vaccine. In NL, an accelerated licensing procedure has been implemented for GMO-based vaccine candidates. Following discussions between researchers and regulators, an emergency regulation has been implemented in NL by use of a ministerial decree. In short, the emergency regulation means that permits can be issued immediately, even before the clinical trial approval. This emergency regulation allows to process permit application through the regular licensing procedure, but drastically shortens the decision period of the application from 120 days to maximum of 28 days.⁸

The GMO application process can be further expedited if the applicant consults the competent authorities and advisory bodies in an early stage and the review board has previous experience with the vaccine platform. In the Netherlands, the authorities can be consulted to provide a

pre-advice (before the formal clinical trial application) to help streamline the application process. Pro-active and transparent communication between applicant, sponsors and regulators are essential to complete the mandatory GMO applications in an expedited manner.

3 ALLOW INVESTIGATORS TO START PREPARING FOR TRIALS BEFORE THE FORMAL CLINICAL TRIAL APPROVAL

Another possibility to expedite the start-up phase is to allow investigators to start recruitment and screening of potential participants before formal approval of the clinical trial. Recruitment and screening of participants are time consuming activities in early phase clinical trials. Significant time can be saved if potential participants can be identified, counseled and general health status assessed before the formal clinical trial approval. This can be achieved by a conditional approval of the clinical trial submission or by submitting a separate research protocol that solely aims to identify eligible participants for COVID-19 vaccine trials. This will allow the investigator to maintain an ongoing pool of (pre)screened healthy participants that are ready to be enrolled in vaccine trials. It is imperative that participants are again counseled and consented for the final, approved, study protocol prior to enrollment in the clinical trial. However, the majority of recruitment and screening activities will than already be completed and will allow for a rapid start of the clinical trial.

4 CENTRALIZATION OF FACILITIES TO PERFORM IMMUNOGENICITY ASSAYS FOR COVID-19 VACCINES

Another rate-limiting step in clinical trial start-up is the validation of immunogenicity assays. The relevant immune assays in vaccine trials will typically depend on the mechanism of action of the vaccine candidate and possible known correlates of protection. Unfortunately, for SARS-CoV-2 such correlate of protection have not yet been identified. However, most current COVID-19 vaccine trials use some form of virus neutralizing assay to assess immunogenicity. For biosafety reasons, such assays which involve propagation of SARS-CoV-2 should be performed at biosafety level grade 3 facilities. Centralized availability of facilities where such assays have been standardized, validated and implemented would accelerate initiation of trials and enhance comparability of trial results.

5 CONSIDERATIONS WHEN DESIGNING EARLY PHASE CLINICAL TRIALS FOR COVID-19 VACCINES

Vaccines are a heterogeneous group of medicinal products. A myriad of vaccine technologies are currently deployed to develop a prophylactic vaccine against SARS-CoV-2.⁵ Route of administration, dosing regimens and study endpoints are all dependent of the type of vaccine technology used. Consequently, clinical trials need to be tailored to the vaccine candidate. There are guidelines for clinical evaluation of vaccines, however, these are not developed for outbreak situations where accelerated development is key. The European Medicines Agency (EMA) is providing guidance and early support for COVID-19 treatments and vaccine development.⁹ The United States Food & Drug Administration (FDA) has created a similar emergency program (Coronavirus Treatment Acceleration Program).¹⁰ Input from regulators is needed to facilitate effective data collection for safety, immunogenicity and efficacy, needed for regulatory approval. Seeking early regulatory advice to improve early clinical trial design may pay off in the long run of vaccine development.

Another practical approach to expedite early phase clinical trials is to use combined phase I and II study protocols. Several developers have already registered phase I/II protocols for COVID-19 vaccine candidates (NCT04324606, NCT04352608, EudraCT 2020-001038-36). Combining classical phase I and II studies in a single trial protocol with clear go/no-go criteria enable researchers to rapidly move forward to pivotal trials if safety and efficacy endpoints appear favorable. Performing combined phase I/II research protocols requires greater monetary investment. Smaller biotech companies may need to acquire funding or engage in partnerships with larger biopharmaceutical companies to perform these kinds of study protocols. It is imperative that these combined phase I/II trials should incorporate sufficient safeguards such as independent data safety monitoring board reviews (DSMB) to identify safety signals at an early stage and prevent unnecessary exposure of participants. Nonetheless, a well-designed combined phase I/II clinical trial may save valuable time in early clinical development as this reduces the administrative burden and review processes by combining research protocols for each classical drug development phase.

In conclusion, the conventional vaccine development paradigm is not equipped to allow rapid vaccine development in view of pandemic crisis such as COVID-19.¹¹ This perspective gives some practical suggestions and examples that could help investigators, developers and authorities to accelerate early clinical vaccine development for COVID-19. Precious time can be saved during the initiation phase of early clinical trials, through fast track application pathways, by allowing investigators and authorities to work in parallel rather than a sequential order and by identifying, validating and centralizing immunogenicity assays as soon as possible. Early discussions with authorities and regulators about study design may also facilitate guided and rapid drug development. Vaccine development in a pandemic setting requires flexibility of both investigators, developers and authorities. In these trying times we need to find practical solutions and make joint efforts to expedite vaccine development for COVID-19.

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SUPPLEMENTARY FIGURES AND TABLES

All mentioned supplementary figures and tables in this chapter can be found on the corresponding website by scanning this QR code.

