EU-wide network for COVID-19 vaccine trials and studies

Concept note – Draft v2.0 – 15 September 2020

Introduction

According to the World Health Organization (WHO), as of 9 September 2020, nine COVID-19 vaccine candidates have registered for Phase III trials.[1] Phase III trials aim at assessing vaccine efficacy and safety, to collect the necessary information to allow regulatory approvals for market authorisation. Four of these trials are led by companies in China, two in the US two in Europe, and one in Russia.

Following the experience of the COVID-19 treatment trials in the early stages of the crisis, strong European coordination of vaccine Phase III and Phase IV studies is needed to ensure the generation of robust evidence for vaccine safety, efficacy and effectiveness, and to avoid fragmentation of study initiatives or competition for trial participants. A functional model of coordination has been set up for the treatment trials, based on the REMAP-CAP[2] and the DisCoVeRy[3] trials, two large-scale trials that work towards an appropriate geographical spread throughout Europe; a common trial coordination board will ensure coherence and complementarity between these two platform trials.

The outline below provides a proposal for a similar coordinated initiative for the Phase III and Phase IV vaccine trials.

Scope of EU-wide network for COVID-19 vaccine trials

Vaccine trials bring together scientists and clinicians, as well as public health authorities and industry, with the main objective of assessing vaccine efficacy and safety for the purpose of rapid authorisation. Authorisation is the first step towards having vaccines available in countries, and the data from pre-approval studies will provide the basis for the initial recommendations from public health authorities. However, public health authorities require additional information to inform specific questions from a public health policy perspective, for instance for informing vaccination strategies and complementary measures. This requires evidence e.g. on immunogenicity in elderly, the influence of some co-morbidities on immunogenicity, the potential occurrence of vaccine-enhanced disease, etc., but also evidence on vaccination impact and effectiveness in the post-marketing phase, on vaccine coverage or the long-term safety profile.

Therefore, to ensure that the appropriate data are available to inform public health policy, a coordination on European level is proposed, focussing on three main aspects: (1) networking networks, (2) a continuously up-dated overview of planned and ongoing vaccine trials, and (3) public health needs:

1. Network of networks

Many European Member States have longstanding experience in vaccine trials; some are organised in networks with a central level coordination. Furthermore, the abovementioned two therapeutic trials build on a vast network of research sites in primary care and hospital settings throughout Europe that could serve the purpose of vaccine trials.

[1] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
[2] https://www.remapcap.org/
[3] https://www.clinicaltrialsregister.eu/ctr-search/search?query=+2020-000936-23

The most efficient approach will be to capitalise on this extensive experience and previous investments and to build on existing infrastructures, both for pre- and post-approval studies. For this purpose, an extensive mapping exercise is needed, to develop a comprehensive overview on existing vaccine trial sites and infrastructure in the Member States, and the extent to which these are organised as (national) networks with a central hub. Germany (German Centre for Infection Research (DZIF)) has agreed to initiate and centralise this mapping exercise; in addition, information will be asked through the Clinical Trials Facilitation Group (CTFG) and through the European Clinical Research Infrastructure Network (ECRIN).

The mapping can facilitate a common basis for the operational readiness of vaccine trial sites, which is of interest for the organisation of developer-led vaccine trials in Europe. Such an updated mapping of vaccine trials is likely to be of particular value to smaller developers that do not necessarily have experience in Phase III trials nor easy access to the necessary network. They might also be in need of further operational and financial support for the trial implementation.

2. Up to date overview of active and planned trials

Some trial sites in the EU are already participating to COVID-19 vaccine trials, others are actively planning to engage. An EU-wide network could contribute to a continuous update of the main features of ongoing and planned vaccine trials in the EU, e.g. key research questions that are addressed, participant inclusion criteria, etc. Such a continuous mapping, done in collaboration with Member State competent authorities and EMA, and including information from the EU clinical trials database (EudraCT), will help identifying the potential gaps in scientific questions that need to be investigated, in particular from a public health perspective. In addition, it might provide some insight in the reasons for and possible solutions to the (currently) limited involvement of Europe in Phase III trials.

3. Public health focus

Public health authorities are keen to receive timely data that will inform public health policy regarding COVID-19 vaccination strategies. Thus, information on the efficacy of a vaccine in certain populations groups, which is provided both from Phase III and Phase IV trials, will influence the prioritisation for the primary and subsequent booster vaccination. For instance, if a vaccine shows a much lower efficacy in the elderly than in younger people, the latter may be vaccinated first in order to protect the elderly from infection.

- ***Phase III***

The primary goal of phase III trials is to investigate efficacy and safety of the vaccine candidate in a large (in the order of 10,000 or more) sample of healthy volunteers in view of obtaining market authorisation. However, considering the epidemiology of COVID-19, there are particular concerns with immunogenicity in different age groups, and most importantly the elderly, as well as the potential influence of co-morbidities. Other public health aspects include e.g. the comparative immunogenicity, efficacy (and effectiveness) of the different candidate vaccines, the assessment of a combination of vaccine technologies, the occurrence of vaccine-enhanced disease, safety and efficacy in pregnant women and/ or children, etc. Importantly, the first wave of candidate vaccines that are available may not necessarily be the most efficacious, and trials will need to integrate these early findings.

Since the large industry-led Phase III trials do not necessarily cover such aspects of specific public health interest, Member States may be interested in taking the initiative of a number of specifically targeted trials each responding to different questions, and allowing for the most appropriate study design. E.g. France (Inserm) has developed a draft protocol synopsis for a trial on immunogenicity and safety in elderly.

In light of fluctuating disease incidence and increasing competition for potential trial participants, collaboration and coordination between Member States around such complementary trial protocols is paramount to yield sufficiently powered trials that can provide the evidence critically needed by public health authorities. As much as possible, an adaptive platform trial design should be applied to allow the necessary flexibility in the fast evolving environment of vaccine development. A common control group for the different trials could be established to increase efficiency and the comparability of data, and ideally, a single sponsor will step forward for each master protocol.

Such a coordinated approach can provide coherence and harmonisation in the data collected. Harmonised collection of and timely sharing of data across studies, through a common research data platform, will facilitate their partially or completely common analysis.

The availability of European funds in the range of 15-20 million EUR for such targeted trials would enable the geographic extension and support the operational preparedness and inclusion of vaccine trial sites where needed, as well as facilitate European level coordination of the different vaccine trials.

- ***Phase IV***

Phase IV studies are conducted after a vaccine candidate received market authorisation, when it is widely administered in the population, and aim for the longer term monitoring of vaccine effectiveness and safety, as well as vaccine coverage; they are likely to involve different stakeholders compared to the Phase III studies. Considering the number of COVID-19 vaccine candidates advancing in development, it is likely that several vaccines are brought to market in relatively short time spans. The post-marketing monitoring will require significant sample sizes (in the 100.000s) as well as different complementary study designs. Close coordination between public health and regulatory authorities, as well as with industry is essential.

Experience has illustrated the importance of solid Phase IV studies to identify rare and unexpected adverse events, e.g. in relation to the occurrence of narcolepsy following influenza vaccination in the 2009 pandemic.[4] The context of accelerated vaccine development requires extra caution, and monitoring should be for sufficiently long time. In times of vaccine hesitancy, it will be crucial to reach a broad consensus on the monitoring results, based on robust evidence and communicated in a transparent way, and the ensuing guidance in order to increase public trust and confidence.

Different initiatives already exist for the evaluation of influenza vaccine effectiveness, which can provide a solid basis for the COVID-19 vaccine studies. These include the I-MOVE network[5] and the

[4] Johansen K, Brasseur D, MacDonald N, et al. Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines? Biologicals. 2016; 44(4):276-280. doi:10.1016/j.biologicals.2016.04.007

[5] https://www.imoveflu.org/

IMI-funded DRIVE[6] project (which ends mid 2022); the recently selected project on pan-European COVID-19 cohorts, which is expected to receive H2020 funds, will also be of interest in this context. It is estimated that between 5 and 10 million EUR is needed to implement the post-authorisation monitoring for about 10 COVID-19 vaccines.

Global/international potential

The EU-wide network will liaise with the WHO-organised Solidarity trial for vaccines. ECRIN is in a postion to provide coordination of EU trial sites that participate in the Solidarity trial.

Coordination is also ensured with CEPI, as well as with the wider COVAX facility in the context of the Access to COVID-19 Tools (ACT) Accelerator.

Conclusion

An EU-wide network for COVID-19 vaccine trials will facilitate large-scale trials in Europe for large industry, SME and academic developers, and help to ensure that public health questions are answered in time for the deployment of authorised vaccines. In particular, it will enable a collaborative approach for targeted studies of direct public health interest, for Phase III trials as well as for post-marketing authorisation monitoring of vaccine safety and effectiveness. Finally, the network is an important investment to further build and strengthen EU capacity to do large-scale clinical trials, contributing to better preparedness for future epidemics or pandemics.

Exploratory meetings with representatives of some national institutions (the German DZIF, the French Inserm and the Dutch National Institute for Public Health and the Environment (RIVM)) demonstrated that a small number of Member States are ready to take some initiative for targeted public health studies.

The availability of European funds is needed to include a wider representation of trial and study sites, and thus to be better prepared for the unpredictable spread of the COVID-19 pandemic in Europe. The potential use and availability of European funds such as the Emergency Support Instrument (ESI) should be assessed, in particular regarding point 14 of the indicative list of measures, which refers to support for strengthened cooperation between EMA, industry and national regulators for symptomatic treatments and vaccines. In addition possible investments by Member States should be explored.

[6] https://www.imi.europa.eu/projects-results/project-factsheets/drive