New approaches to clinical trials and development

New approaches to conducting clinical trials on vaccines have the potential to reduce both the cost and time it takes to establish whether vaccines are safe and effective.

Without innovation in clinical practice, we may not see the successful development of vaccines to prevent future epidemics, or to tackle some of the world's biggest infectious disease threats.

Why now?

Clinical trials for vaccines currently follow a well-defined path. Whilst phase 1 and 2 trials can be conducted relatively quickly, for phase 3, thousands of participants can be required over a period of several years.

With vaccines for diseases with low or unpredictable transmission, or where incidence is spread over a large area, it can be very difficult or simply unfeasible to conduct traditional phase 3 trials. For instance, Nipah could take over 500 years.[1]

What are the potential solutions?

There are a range of innovative trial methods which could make testing vaccines more effective and efficient. These need to be enabled through ensuring regulatory acceptability of the data they generate and work to improve incentives for their use.

- **Using correlates of protection**

  Correlates of protection are measurable responses in the body that indicate a person is protected (immune) from infection or disease. These could act as "predictors of efficacy" with the potential to reduce some of the challenges of late phase clinical trials. Identifying these markers requires careful research into what immune response is adequate to protect against disease. Once established, vaccines could then be tested against whether they produce the right immune marker as part of late-stage clinical trials. This could potentially reduce the size required for trials if the data related to correlates is accepted by regulators. Whilst correlates are technically challenging to identify and validate, they offer significant potential benefits in advancing vaccine science.

- **Innovative trial models**

  Human infection studies – These are trials in which healthy adult volunteers are deliberately exposed to infectious diseases under carefully controlled conditions. The results can help researchers understand more about the body's immune system, to see how it responds to a disease and to test the effectiveness of potential new vaccines or treatments or even compare the performance of existing vaccines.

  Adaptive designs for trials – Adaptive trial designs allow for prospective and pre-approved modifications to one or more aspects of the design based on data from the trial[2]. There are many different types of adaptive design, e.g. seamless trial designs (common in Covid-19 vaccine) and designs that allow changes to volunteer allocations.

[1] CEPI, WHO, the U.S. NIAID and the Duke-NUS Medical School (Duke-NUS). (2019). Nipah Virus International Conference 2019. Retrieved from: https://cepi.net/wp-content/uploads/2020/06/2019-Nipah-Conference-Proceedings.pdf

[2] Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). (2019). Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry. Food and Drug Administration, U.S. Department of Health and Human Services. https://www.fda.gov/media/78495/download

Bayesian designs – These trials enable reduced sample sizes without undermining statistical robustness by employing Bayesian, rather than frequentist, statistics – i.e. a framework in which prior information (from previous trials, scientific research, or expert opinion) can be combined with information accrued during a trial.[3,4,5]

Master protocols and platform trials – A master protocol offers a unifying study concept which allows for evaluation of a single intervention against different diseases/disease types or multiple interventions against the same disease.[6] This includes 'Platform Trials' (e.g. the highly successful RECOVERY trial), in which patients with a single disease are randomly assigned to a group of different therapies on the basis of a decision algorithm.[7]

Research will need to continue to establish which of these new methods and approaches are most effective in enabling vaccine development, and how they can support each other. Not all approaches will be applicable to all vaccines, but the potential to use new methods flexibly could help see vaccine candidates progress through clinical trials more effectively. Estimates suggest recognised correlates could cut 5.5 years and $255 million from development, while innovative trial modes could cut 2 years and $155 million.

What needs to happen?

- **Data generated through innovative clinical models and methods needs to be acceptable to regulators.**
  Incremental changes have been made to regulatory science and practice to accommodate clinical advances, but at present these are not keeping pace with scientific innovation. Considering vaccines for which traditional phase 3 trials are unlikely to be possible is an important starting point for discussion between regulators and developers on the larger shifts required to enable future vaccine development.

- **Global research practice needs to change to prioritise data gathering and research to enable correlates to be identified, and to enable new methods of trials to be conducted.**
  Whilst regulatory acceptance of new clinical methods and models is key, this won't occur without researchers putting forward these new ways of conducting trials and shifting clinical norms. For example, gathering data relevant to research on correlates could be made a standard part of early-stage trials.

- **Key actors in the vaccine development space need to work together to ensure that incentive structures support new clinical methods, for example through better information sharing.**
  Pooling of knowledge and data across pathogens can help speed the understanding of immune responses and support the identification of correlates of protection. As individual developers operate in a competitive environment sharing this information is not easy to facilitate. Research prizes or other incentive mechanisms could be explored to facilitate discoveries that benefit the whole field of vaccine development.

[3] Jansen, J. O., Pallmann, P., MacLennan, G., & Campbell, M. K. (2017). Bayesian clinical trial designs. Journal of Trauma and Acute Care Surgery, 83(4), 736–741. https://doi.org/10.1097/ta.0000000000001638
[4] Giovagnoli A. (2021). The Bayesian Design of Adaptive Clinical Trials. International journal of environmental research and public health, 18(2), 530. https://doi.org/10.3390/ijerph18020530
[5] Quanticate. (n.d.). Bayesian Adaptive Designs | Bayesian Statistical Methods. Retrieved October 6, 2021, from https://www.quanticate.com/bayesian-adaptive-designs
[6] Bogin, V. (2020). Master protocols: New directions in drug discovery. Contemporary Clinical Trials Communications, 18, 100568. https://doi.org/10.1016/j.conctc.2020.100568
[7] Normand, S. L. T. (2021). The RECOVERY Platform. New England Journal of Medicine, 384(8), 757–758. https://doi.org/10.1056/nejme2025674