UNBLOCKING HUMAN CHALLENGE TRIALS FOR FASTER PROGRESS

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Summary

Human challenge trials (HCTs), in which volunteers are deliberately infected with pathogens to test potential treatments, provide in-human data earlier and at smaller scales than traditional trials. By doing so, HCTs can cut costs, reduce risks for drug companies, and speed the development of critically needed treatments. However, particularly in the US, HCTs are held back by burdensome manufacturing requirements, outdated quality assurance standards, and a lack of clarity on their utility for drug approval. Removing these barriers would speed access to critically needed treatments.

Challenge and Opportunity

Developing and commercializing a new drug is a long and arduous process that typically spans ten to 15 years and can cost pharmaceutical companies between $334 million and $4.46 billion per drug[1]. A major driver of both long timelines and costs is clinical trials – which usually take between five and seven years[2]. Particularly challenging are failures late in the development process, which renders all previous investment futile. For example, 39% of Phase III trials fail[3]. These late-stage failures not only represent an inefficient allocation of resources, but also carry profound implications for patient populations eagerly anticipating novel therapeutic interventions. The repercussions of such setbacks extend beyond economic considerations, encompassing the unfulfilled expectations and unmet medical needs of individuals awaiting innovative treatment options.

Human challenge trials, in which volunteers are deliberately infected with pathogens to test potential treatments, are uniquely suited to reducing late-stage failures for treatments targeting infectious diseases. Providing in-human data as early as possible in the clinical research process can reduce the risk of ineffective treatments advancing to late-stage phases, and allow companies and investors to focus resources on more promising products. HCTs do this by providing controlled in-human data without the need for large field trials. This can be particularly useful for smaller biotechnology companies, as well as potentially shortening the time companies need to analyze data and bring products to market.

A *Lancet* review[4] on HCTs for vaccine development specifically points to earlier down-selection (discarding ineffective vaccines) and knowledge of "correlates of protection" as important benefits of HCTs. For example, multiple ineffective vaccines against Shigella were discarded after disappointing results in HCTs. HCTs are also relatively safe. A review of all HCT trials from 1980-2023[5] found no deaths and 24 serious adverse events (SAEs) out of more than 15 thousand participants for whom data was available — and none of these SAEs meritied more than brief hospitalization.

Despite their utility and safety, in the United States, HCTs face a number of regulatory hurdles that make them more difficult to set up and diminish their commercial value. As well as making research using current models less attractive, this also increases the cost of developing new challenge models. Manufacturing the pathogen used to infect volunteers (the challenge agent) is currently difficult, expensive, and time-consuming, and presents an enormous hurdle for any team that wants to attempt a challenge study. In addition, how data from human challenge studies can actually be used in the regulatory approval process is currently unclear, meaning the commercial value of such studies is hard to predict. The regulatory environment in the US makes the process more burdensome than in Europe or the United Kingdom, where the majority of HCTs currently take place.

Plan of Action

Recommendation one: Extend Phase I Good Manufacturing Practice[6] (GMP) guidelines to include challenge agents.

Currently, the Food and Drug Administration (FDA) regulates challenge agents as investigational medicinal products (IMPs), which require a license to use in a study, and have to be manufactured in compliance with Good Manufacturing Practice (GMP) standards. By contrast, neither the European Medicines Agency (EMA) or the UK's Medicines and Healthcare products Regulatory Agency (MHRA) require GMP for agent production, nor require agents to be registered as IMPs (or equivalent).

GMP guidelines are designed to ensure drugs are manufactured to the highest standards of purity and quality. However, they add significant cost and complexity to the manufacture of such agents, requiring specially trained staff, dedicated facilities, and various checks during production. GMP guidelines are designed for drugs manufactured in large, repeatable

1 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820562#:~:text=Studies%20have%20estimated%20that%20the,%2C%20data%2C%20and%20modeling%20assumptions.

2 https://www.antidote.me/blog/how-long-do-clinical-trial-phases-take#:~:text=This%20process%20can%20take%20a,seven%20years%20of%20that%20time.

3 https://www.appliedclinicaltrialsonline.com/view/phase-iii-trial-failures-costly-preventable#

4 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00294-3/fulltext

5 https://academic.oup.com/cid/article/76/4/609/6758436

6 https://www.fda.gov/media/70975/download

batches (either for larger, later-stage trials or for sale on the open market) and are appropriate for those settings. The FDA has therefore developed specific guidelines for Phase I drugs, which are designed for smaller, one-off production scales.

These phase I guidelines would appear to be much more applicable to challenge agents, but, as challenge studies are invariably phase II studies, they cannot be used for the manufacture of challenge agents. Creating challenge-agent specific guidance based on this phase I framework could make agent manufacture swifter and less expensive for study teams, while aligning the FDA more closely with other regulatory agencies. Agent-specific guidance, along with the existing IND framework, would ensure that quality standards are maintained in the absence of GMP, while allowing much-needed flexibility in designing the manufacturing process and choosing suitable facilities and staff.

Recommendation two: Clarify how next-generation sequencing can be used in the manufacture of challenge agents

Before being used, challenge agents must be tested for other pathogens and biological contaminants. This time-consuming but important step is known as adventitious agent testing (AAT).

Currently, these tests are performed by culture (growing pathogens on a slide) or in vivo (eg, in live mice), where agents are detected by their ability to grow. These methods take up to a month, are relatively expensive, and can detect all types of contamination, known and unknown, with demonstrated low sensitivity[7].

Direct detection using nucleic acid sequencing could offer a quicker, simpler, and cheaper method of performing these tests. This involves testing the Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) of the challenge agent directly, instead of waiting for it (and possible contaminants) to grow. Next-generation sequencing (NGS) allows for many sequences to be evaluated in parallel, allowing an agent to be screened for the presence of all genetic sequences that indicate the presence of any contaminating microorganisms or viruses on a timeframe of days, rather than weeks.

Technically, various studies have shown success in using NGS to screen for AAs; a 2010 study[8] found that a commercially available rotavirus vaccine was persistently contaminated with a non-infective porcine virus. In 2014[9], NGS techniques were shown to identify a virus undetected by traditional methods in an insect cell line.

Work to introduce NGS into adventitious agent testing (AAT) is progressing. The FDA has already established a number of working groups, and is creating a number of panels of reference viruses[10] which can be used to validate next-generation techniques[11]. A 2014 study[12] showing NGS performed as well as standard in a test of doped cell lines, and a 2017 multi-center, multi-technique study[13] on such spiked samples showed acceptable efficacy throughout. The FDA has also created a database[14] which allows for the identification of AATs from genetic sequences.

However, work is still progressing relatively slowly, even as mounting evidence shows that NGS is suitable for AAT. It is currently unclear in which situations the use of NGS is acceptable, and what gaps in research currently exist, slowing down adoption. The FDA should provide more clarity on how NGS can be used for challenge agent AAT, or what steps are required before investigators can do so, which would lower the risks of agent production and their timelines.

Recommendation three: Develop formal guidelines setting out how challenge data can affect the regulatory approval process of investigational drugs

Despite their utility, the lack[15] of a clear regulatory framework for the use of HCTs in vaccine evaluation and licensure by the FDA hampers their broader application. The FDA's existing guidance on HCTs is limited (see pages[16] five to six) and does not provide sufficient clarity on the conditions under which these trials can be used to demonstrate efficacy. This uncertainty discourages developers from utilizing HCTs in scenarios where they could be particularly advantageous, such as a Zika or Hepatitis C vaccine.

7 https://www.sciencedirect.com/science/article/pii/S0264410×14001947?casa_token=Mtq_0opGxw0AAAAA:5cyH9AdDbfURTail587RZEz-5doL65j9mgK-B7yzkm5ik_itQwOitt3-yr9SS3x-lKofe85rwdo

8 https://journals.asm.org/doi/10.1128/jvi.02690-09

9 https://www.scopus.com/record/display.uri?eid=2-s2.0-84899650653&origin=inward

10 https://www.sciencedirect.com/science/article/pii/S1045105620300634

11 https://www.sciencedirect.com/science/article/abs/pii/S1045105620300245?fr=RR-2&ref=pdf_download&rr=8e30d2682d81c337

12 https://www.sciencedirect.com/science/article/abs/pii/S0264410×14013851?fr=RR-2&rr=8e310a94d8c372ab

13 https://journals.asm.org/doi/full/10.1128/msphere.00307-17

14 https://journals.asm.org/doi/full/10.1128/mspheredirect.00069-18

15 https://pubmed.ncbi.nlm.nih.gov/34480650/

16 https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--General-Principles-for-the-Development-of-Vaccines-to-Protect-Against-Global-Infectious-Diseases.pdf

Using an HCT for approval is not unprecedented: in 1998, the FDA licensed a cholera vaccine[17] based on the data from a human challenge study. However, this decision was based on the fact that cholera was too uncommon to perform a phase III study in the US, and that the vaccine was designed for travelers to cholera-endemic areas. Products tested in challenge studies in the UK have also been granted FDA Breakthrough and Fast Track status, but how human challenge studies may have played a role in this decision is also unclear. Publishing guidelines on how data from human challenge studies may be interpreted would improve the commercial case for performing such studies by reducing uncertainty for sponsors, and help create a more efficient pipeline for the overall testing of products for infectious diseases, stimulating research into this vital area.

Conclusion

HCTs can de-risk product development by providing earlier in-human data for pathogen vaccines and/or treatments. However, their application is limited, especially in the US, by burdensome regulation and their unclear value-add in the approval process. Aligning the FDA's GMP manufacturing guidelines with other regulators, modernizing contamination testing, and providing guidance on HCT's role in product approval is a promising path for stimulating innovation.

17 https://www.fda.gov/media/134489/download

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