THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

The ABCs (or more accurately, the 123s) of clinical trials: the path to approved vaccines*

Introduction

As immunologists, we embrace the opportunity to decipher and discuss with our scientific colleagues the complexities of our models, favorite cell types, molecules, and signaling pathways. In light of the COVID-19 pandemic, however, we have a new opportunity and responsibility: we are often the first people to whom a family member or friend may ask questions, particularly about the development of a safe, effective vaccine. To assist you in explaining the fundamental principles (the ABCs) of phases (the 123s) of clinical trials for an approved vaccine, we clarify below the review process and highlight important features of vaccine trials. We encourage all immunologists to be advocates for well-controlled clinical trials and to offer family, friends, and other members of the public substantive information about the process by which vaccine candidates are tested and approved.

Drug and vaccine development overview

There are many steps involved in the drug and vaccine development process, and each has a different set of key questions that must be addressed:

- ***Preclinical studies***
  - *Target validation*: Let's say you have an idea for a new therapy. This could be blocking or activating a T cell kinase, for example. To confirm it is a reasonable target, you need to identify all cell types, tissues, and species that express it. Knowing what tissues express the target helps you understand potential off- and on-target consequences, whereas different species provide preclinical data on the target (safety, pharmacology). Ideally, there will be a predictive animal model that helps you understand how it could work in a human disease setting. For vaccines, the goal is to stimulate the immune system; therefore, it is important to identify which cell types are likely to be most relevant and plan experiments accordingly.
  - *Compound generation*: Targets are not equally druggable, meaning it might be very difficult to produce a biologic (e.g., antibody), small molecule, or other modality to modify function. Knowing the tissues where the target is expressed is particularly important when testing compounds, as you must assess off-target effects. There will be many compounds generated and experiments conducted to identify that one candidate with the best profile (least toxicity, best efficacy) to move into the clinic. With vaccines, candidates will attempt to leverage the most immunogenic portion of a pathogen to stimulate a robust response.
- ***Clinical studies***
  - *Phase 1*: No matter how efficacious a compound or vaccine may be, safety must be evaluated. This is the focus of the first phase of clinical trials. If the potential therapy has too many safety concerns, it will not be allowed to move forward. This is where most drug candidates end their journey, because no matter how

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promising a therapeutic or vaccine looks in a mouse model or *in vitro* study, safety is fundamental.

- *Phase 2/3*: Once a candidate is confirmed to have an acceptable safety profile, it will be important to understand how effective it is – specifically, to understand how it compares to standard-of-care and which patient subpopulations are likely to experience the greatest benefit. It is also critical to evaluate the candidate with participants who appropriately represent all who are likely to be treated. When determining the number of participants for a clinical trial, Phase 2 studies are smaller in comparison to Phase 3 and evaluate whether the compound has the expected biological effect. This is typically confirmed through biomarkers for disease, target engagement, pharmacodynamics, and pharmacokinetics which are assessed from blood draws and biopsies. Phase 2 studies also identify the best dose for a compound. Phase 3 studies evaluate the applicability of Phase 2 results in an established dose (or doses) across a larger and more representative group of participants.

Pathway to approval for vaccines

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public by ensuring the safety and efficacy of drugs and other biological products for use in humans. The approval process is slightly different for vaccines compared to biologics and other modalities. With vaccines, studies are shorter (e.g., a few months) but are more challenging because effectiveness must be confirmed in humans who have vastly different immunological responses. Because we are exposed to different pathogens throughout our lifetime, and are genetically heterogeneous, no two immune systems will be the same. Given this wide range in immune responses and the fact that vaccines are intended for the entire populace, rather than only those with a given disease, vaccine trials must include even more participants than standard clinical trials. This could be on the order of 100 participants for Phase 1 clinical trials and tens of thousands for Phase 3 studies. Please note that timelines from start to finish of a trial are determined by factors such as disease prevalence and participant enrollment (e.g., a 3-month study can take up to two years if transmission and recruitment is slow). Because of the urgency of the COVID-19 pandemic, we have seen recruitment times accelerate significantly, even in light of multiple vaccine trials.

Once safety and efficacy are confirmed, there are still more issues that must be addressed prior to approval. These include evaluating how the compound is manufactured, ensuring that it will be manufactured consistently (same purity and potency with each batch), and confirming that there is a plan to have a sufficient supply of vaccine to offer to all who want it. When these concerns are addressed and key questions are answered, the FDA then moves to decide on approval. For more information on drug development in general, please refer to the FDA website (www.fda.gov), and for additional details on vaccines, click here.

Conclusion

Clinical trials share the same rigor as studies of fundamental biological processes. There are different key questions, to be sure. AAI hopes that this overview will enable our members to speak cogently on this matter. At this critical time, when lives and livelihoods are being lost, and when many Americans are uncertain about the safety of vaccines, it is essential that we communicate clearly the reliability of the clinical trials and vaccine approval process.

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