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The Platform Trial An Efficient Strategy for Evaluating Multiple Treatments

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VIEWPOINT

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An Efficient Strategy for Evaluating Multiple Treatments

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The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient populations, with the capability to add new treatments in the future and eliminate investigational treatments lacking efficacy. The term "platform trial" is sometimes used to describe trials designed with these goals in mind, signifying the intent to build an experimental platform that will exist after the evaluation of any particular treatment.[4] Currently, platform trials are enrolling patients or are under development in oncology, infectious diseases, neurology, and intensive care.

Platform trials are an extension of adaptive trial design. An adaptive trial allows prespecified changes in key trial characteristics during the conduct of the trial in response to information accumulating during the trial; however, most adaptive trials focus on evaluating a single treatment in a single population. Examples of adaptive trials include traditional group-sequential trials, as well as trials incorporating reestimation of sample size or using variable randomization proportions (response-adaptive randomization).[5] A platform trial is a type of adaptive trial designed to evaluate multiple treatments efficiently.

The Problem: Evaluating Multiple Treatments Efficiently

Although conventional 2-group clinical trials are simple, using such trials is inefficient when evaluating a series of therapies sequentially, both because a separate control population is required for each comparison and because data on different treatments may not be truly comparable. Use of such trials also may fail to detect real benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial.

During a platform trial, accumulating outcome data can be used to adjust the randomization probabilities to preferentially assign better-performing treatment regimens to future patients. This approach, response-adaptive randomization, improves the outcomes of study participants treated within the trial, increases the available information on treatment effects and adverse effects for the most effective treatments, and shortens the evaluation time for the best therapies.[5]

The heterogeneity of the patient population (eg, based on biomarkers, tumor genetics, illness severity, disease risk factors, or age) is considered explicitly in many platform trials, with the goal of finding the best treatment for patient subgroups defined by these characteristics. These confounding factors often have substantial effects on outcome—effects that may be larger than the likely benefit of the treatments being investigated. In a platform trial, all patients in the trial, even patients assigned treatments no longer under investigation, help in understanding and adjusting for the effects of confounding and secular trends.

Platform trials use decision rules (eg, based on the likelihood of a treatment benefit or of success in a future confirmatory trial[6]) to determine when a given treatment regimen has demonstrated sufficient efficacy to "graduate" from the trial and proceed to the next stage in development or to be used clinically. Bayesian probabilities can also be used to determine when a treatment should be eliminated from the trial, or from subgroups of patients, because it is no longer sufficiently

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

promising. Once a treatment is discontinued, it may be replaced by a new treatment. An example demonstrating how a platform trial may progress over time is shown in the eFigure in the Supplement.

Because a platform trial constitutes a long-term resource that can be used to evaluate multiple treatments, sources of financial support may combine federal, foundation, and for-profit entities. Substantial resources can be saved by the use of the same trial infrastructure to evaluate multiple therapies. This approach also allows participants access to treatments from different companies, with treatment allocation guided by experience within the trial, rather than having their options limited by the choice of trial.

Example Platform Trials

The I-SPY 2 clinical trial is a phase 2 platform trial of neoadjuvant therapy in women with breast cancer.[7] Subgroups of women are defined by 3 genetic markers to define 8 separate genetic subgroups, organized into 10 "signatures" that represent clinically meaningful groupings. Patients are adaptively randomized within their genetic subgroup. Treatments showing efficacy in 1 or more signature groups of women, based on the probability of success in the confirmatory phase 3 trial, are "graduated" from the trial for evaluation in separate confirmatory trials.

In late 2013, the Innovative Medicines Initiative of the European Union announced a call for proposals, supported by more than €50 million, to build a Bayesian platform trial for the prevention of Alzheimer disease.[8] The long-term trial will evaluate multiple treatments, from multiple sponsors, for persons at high risk for Alzheimer disease. Study participants will be characterized by their risk categories, with randomization proportions and estimated treatment effects being dependent on patients' risk category.

Platform trials are also being developed by PREPARE (Platform for European Preparedness Against Re-emerging Epidemics), a network funded by the European Commission, including the development of a randomized, response-adaptive, platform trial evaluating multiple treatments in the treatment of hospitalized patients with severe acute respiratory tract infection requiring intensive care. Interventions will be compared with standard care using a Bayesian approach, and the trial is intended to enroll 2000 to 4000 patients from more than 100 intensive care units across Europe.

There is increasing interest in implementing a platform trial for the treatment of Ebola virus infection, motivated by both the need to rapidly evaluate multiple potential treatments and the ethical imperative to achieve the best possible outcomes in trial participants.

Conclusions

Currently, researchers generally design trials to investigate 1 drug at a time, in homogeneous patient populations. Platform trials have the potential to accelerate efforts to identify effective treatments, especially combination treatments and treatments tailored to particular subgroups of patients, for challenging diseases. Realizing the potential of this approach will require continued teamwork and innovation in statistical methodology, clinical trial logistics and coordination, and a willingness to prioritize the goal of finding effective treatment over the evaluation of any single individual therapy.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Berry reported that he is part owner of Berry Consultants LLC, a statistical consulting firm that specializes in the design, implementation, and oversight of adaptive clinical trials, including platform trials. Dr Connor reported that he is an employee of Berry Consultants LLC. Dr Lewis reported serving as a consultant to Berry Consultants LLC (and that he and his institution are compensated for that work) and receiving grant support from the National Institute of Neurological Disorders and Stroke for teaching a course on clinical trial design.

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