Randomized, Controlled Trials
Marc S. Sabatine, MD, MPH

In medicine, a randomized, controlled trial (RCT) is a form of research designed to provide information regarding the potential benefits and risks of a treatment in individuals (Figure). Treatments typically are new drugs or medical devices, but could also include new diagnostic tests or therapeutic strategies (ie, an approach to treating a patient). RCTs are invaluable to the medical community to help improve the care of patients.

RCTs come in many shapes and sizes, from enrolling a few patients at 1 hospital to enrolling tens of thousands of patients at hundreds of hospitals or clinics across the world. Given the size and complexity of such RCTs, they are typically designed by a panel of experts (eg, physicians experienced in treating a certain disease) and sponsored by a governmental agency (eg, the National Institutes of Health) or a pharmaceutical or biotechnology company. A scientific protocol serves as an operating manual for how the trial is to be conducted, ensuring consistency across all sites. Common elements of the trial protocol that a study team is likely to discuss with a potential research subject are listed in the Table.

Key aspects of an RCT are best described in the answers to some of the questions most frequently asked by subjects:

Why Should I Participate in an RCT?
RCTs are considered the most effective means to evaluate the benefits and risks of treatments and are typically required by regulatory agencies (eg, the Food and Drug Administration) before a treatment can be approved for general use by physicians. Thus, they help advance medical care. Almost all of the new treatments patients receive are available to their physicians thanks to information gathered from individuals who had volunteered to participate in clinical trials of those treatments.

Why Can’t Everybody Get the New Drug or Device?
The “C” in RCT stands for “controlled,” which means assignment to the different arms of the trial (eg, experimental versus control) is done at random (like flipping a coin). Randomization is crucial to ensure a valid comparison. Randomization eliminates the differences that would exist if one simply analyzed individuals to whom their physician chose to give treatment A versus those to whom they chose to give treatment B. A comparison between these groups runs the risk of telling us less about differences in the treatments, and more about the differences in the people who are selected to or are willing to take those treatments.

Why Can’t I Know to Which Treatment Arm I Was Assigned?
RCTs are frequently double-blind, meaning that neither the subject nor the researcher knows to which treatment the

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Is the Research That Is Being Done Ethical?

Before starting an RCT, the protocol must be reviewed and approved by an independent institutional review board (IRB). Government regulations outline standards for the composition, operation, and responsibility of an IRB, which, broadly speaking, is responsible for protecting the rights, safety, and well-being of participants in research. The IRB reviews the protocol to see whether the objectives are valuable, the design is scientifically valid, and there is a favorable risk-benefit ratio.7 As part of this assessment, the IRB ensures that there is clinical equipoise, meaning that there is reasonable uncertainty with regard to whether the experimental treatment will be beneficial or not in the planned study population. A trial is conducted because it is hoped, on the basis of preliminary data gathered to date, that the experimental treatment will be better than the current standard of care. However, this is not known with certainty, and thus, there is the need to do a trial to gain the required knowledge. Before enrolling in a trial, an individual must give informed consent, a process in which the individual is informed of and understands the purpose, methods, potential benefits and risks, and possible alternatives to the research, and then voluntarily consents, or agrees to participate in the trial, which is usually documented by signing an IRB-approved informed consent form.

Once I Am in the Trial, Who Is Looking Out for My Safety?

There are multiple safety mechanisms in place. First, the local study team monitors each subject’s safety during the study visits. Second, the IRB periodically reviews the conduct of the trial and the safety of the subjects in the trial at that site. Third, the physician or group responsible for the overall trial management monitors the frequency of adverse events trialwide and considers whether a modification of

Table. Common Elements of a Clinical Trial Protocol

<table>
<thead>
<tr>
<th>Element</th>
<th>Description and Purpose</th>
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<tbody>
<tr>
<td>Clinical trial phase</td>
<td>Phase I trials are small initial studies to determine the pharmacological actions of drugs in humans and the side effects associated with varying doses. Phase II trials evaluate if the treatment has a benefit in patients with the disease under study and determine in greater detail the common short-term side effects and risks. Phase III trials are large studies intended to define the overall benefit-risk relationship of the treatment and provide an adequate body of information for review and potential approval by the FDA of the treatment for use by physicians in clinical practice. Phase IV studies are done after the treatment has been approved by the FDA to provide additional information about risks, benefits, and optimal use.</td>
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<td>Objectives</td>
<td>The goals of the research, including the outcomes that will be used to judge the efficacy and safety of the experimental treatment.</td>
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<td>Eligibility</td>
<td>Criteria for what types of individuals are and are not allowed to participate. The goal is to enroll individuals who are likely to benefit from the treatment and avoid individuals who are likely to be harmed.</td>
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<td>Intervention</td>
<td>How the new treatment (ie, the experimental arm) is to be given (in some studies, there can be more than one experimental arm) and what should be used as a comparator (ie, the control arm). A control can be either an existing drug or device (so-called active-controlled) or a placebo (so-called placebo-controlled). In active-controlled trials, the experimental and control drugs may be physically dissimilar, so a double-dummy design is used. Subjects are given both treatment A (the experimental drug and indistinguishable placebo) and treatment B (the control drug and indistinguishable placebo). Subjects take both treatments, with one of them being active and the other being placebo (ie, active A and placebo B or placebo A and active B).</td>
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<td>Study assessments and procedures</td>
<td>How subjects will be monitored during the course of the study. Typically this is accomplished by in-person clinic visits during which subjects are asked about their health status. During visits certain procedures may need to be performed that can range from relatively simple assessments (eg, obtaining an electrocardiogram and blood work) to invasive procedures (eg, cardiac catheterization).</td>
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<td>Sample size</td>
<td>The number of subjects the trial needs to enroll.</td>
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<td>Duration of follow-up</td>
<td>How long subjects are to stay in the study. The duration depends on the goals of the study and can range from days to years.</td>
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the protocol is warranted. Fourth, there is often an independent Data Safety and Monitoring Committee that reviews the safety of subjects over the course of the trial and is empowered to recommend modification of the protocol or termination of the trial if the Committee deems that subjects are being exposed to excessive risk not balanced by benefit.

Why Should I Continue to Take the Study Drug While in the Trial?

When an RCT ends, subjects are typically analyzed according to the treatment arm to which they were originally assigned at the start of the trial (so-called intention-to-treat analysis), regardless of how long or even whether they had taken the study drug. Logically, subjects who stop taking the study drug prematurely, while the trial is ongoing, can no longer provide useful information regarding the benefit of safety of the experimental drug in the trial. Thus, for the scientific integrity of the trial, it is important to have subjects stay on the study drug as long as is safely possible. If a subject experiences an adverse event that is possibly related to the study drug (ie, a side effect), a temporary interruption may be a reasonable first step, with a planned restart of the study drug once it is safe to do so.

If I Have Stopped the Study Drug Prematurely, Why Should I Continue to Participate in Follow-up Visits or Phone Calls?

At the end of an RCT, an accounting of the health status of all subjects is needed to ensure a scientifically rigorous analysis of the new treatment. Subjects who do not come back for follow-up or do not agree that the study team can contact them or their physicians to check on their health status create a serious problem in understanding the results of the trial. This uncertainty then undermines the contribution of all the subjects who did regularly follow up.

Summary

RCTs are the gold standard in the assessment of treatments in medicine. The data we gather from them serve as the foundation for the practice of evidence-based medicine by physicians. The medical community is indebted to those individuals who volunteer to participate in RCTs and follow through to the end, because they are helping to advance medical science and potentially improve the care of future generations of patients.

Disclosures

Dr Sabatine is the Chairman of the TIMI Study Group, an Academic Research Organization based at Brigham and Women’s Hospital that conducts cardiovascular clinical trials. These trials are funded by grants to Brigham and Women’s Hospital from both industry and the National Institutes of Health.

References


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