Varieties of Standard-of-Care Treatment Randomized Trials
Ethical Implications

Scott Y. H. Kim, MD, PhD
Clinical Center, Department of Bioethics, National Institutes of Health, Bethesda, Maryland.

Franklin G. Miller, PhD
Clinical Center, Department of Bioethics, National Institutes of Health, Bethesda, Maryland.

Comparative effectiveness research has received considerable attention in recent years and has been accompanied by controversy, especially in response to the 2013 Office for Human Research Protections (OHRP) investigation of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)—a randomized trial of 2 contrasting oxygen saturation settings in mechanical ventilation of premature infants within the established standard of care.1 The OHRP convened a public meeting in August 2013 on “Matters Related to Protection of Human Subjects and Research Considering Standard of Care Interventions” and recently issued draft guidance on “Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care.”2 This guidance has been sharply criticized.

The phrase “research evaluating standards of care” suggests that standard-of-care treatment randomized clinical trials (RCTs) comprise a class of studies with ethically relevant characteristics (ie, testing of standard-of-care interventions) that have specific implications for determining what constitutes risk of research and what risks should be conveyed to participants. Although this assumption seems to be shared by commentators on both sides of the debate, it is problematic. This is because various positions regarding the ethics of standard-of-care treatment RCTs tend to rely on selected specific examples of such RCTs. It is not possible to determine whether such positions are generalizable or whether they reflect the specific risk-benefit and informed consent issues posed by the particular examples used. For instance, varying the time that an antianxiety drug is administered, such as 9 AM or 3 PM, is quite different from varying the amount of oxygen support administered to a newborn in a neonatal intensive care unit.

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Some studies involve challenges (of different types) to obtaining traditional written informed consent (studies 2, 6, and perhaps 1); others do not. Most of the studies compare 2 standard-of-care treatments, but one study (study 6) involves only one standard-of-care intervention group and another addresses an area without a clear standard practice (study 7). In some studies, the only research element is the randomization (with an electronic health record as the source of data; study 1). In other studies, other research-specific procedures and data collection are likely. In some studies, the degree of interest in whether costs can be reduced without impairing efficacy or safety is extremely high (studies 2, 5), whereas in others perhaps less so.

Determining the ethical importance of each of these differences among standard-of-care treatment RCTs would require detailed analyses. However, the need for such example-specific ethical analysis should be clear. The fact that a study is comparing 2 widely

Published online January 15, 2015

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they received no additional compensation. Helpful comments on an earlier draft, for which Wertheimer, PhD, and Robert Danner, MD, NIH, and Department of Bioethics, NIH, additional research funding for this article and was not policy of the NIH, Department of Health and Human Services, or US government. There was no Conflict of Interest Disclosures: The views expressed in this article are none were reported.

**Table. Potential Types of Randomized Clinical Trials Testing Standard-of-Care Treatments**

<table>
<thead>
<tr>
<th>Example Study Type</th>
<th>Clinical Context</th>
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<tbody>
<tr>
<td>1</td>
<td>Comparative evaluation of 2 Food and Drug Administration (FDA)-approved drugs for hypertension. Limited data suggest that drug A might be better, but drug B is much more widely used. They have a similar mechanism of action; in clinical practice instructions to patients are identical. The primary outcome is blood pressure readings for 1 year. Cardiovascular events are monitored but are not the focus. The only research element of this pragmatic trial is randomization.</td>
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<td>2</td>
<td>Comparative evaluation of 2 FDA-approved anticoagulants in emergency treatment of ST-segment–elevation myocardial infarction. Drug A is more expensive than an old drug B but theoretically better. Limited time and the clinical state of patients are obstacles to obtaining traditional informed consent. The primary outcome is a composite of serious clinical outcomes (including death) and a safety outcome of bleeding incidence, powered based on data.</td>
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<td>3</td>
<td>Comparison of 2 surgical procedures for cancer. One procedure is much more invasive and disfiguring, with greater potential adverse effects but thought by many surgeons to be more effective. The primary outcome is cancer-free survival and overall survival, powered based on existing evidence.</td>
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<tr>
<td>4</td>
<td>Comparison of an FDA-approved agent for macular degeneration with a biologically similar agent approved for cancer. Both are used by ophthalmologists, but drug A is much more expensive than drug B. Primary outcomes are improvement in visual acuity and safety.</td>
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<tr>
<td>6</td>
<td>Comparison of a standard-of-care treatment (widely used but without proven efficacy) with supportive treatment only. Endotracheal suctioning prior to resuscitation of nonvigorous neonates with meconium-stained amniotic fluid is currently recommended, but there are concerns about its efficacy and its burdens (delayed resuscitation, complications of suctioning). Primary outcome includes need for oxygen and ventilatory support.</td>
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<td>7</td>
<td>Comparison of morning vs evening dosing of FDA-approved antihypertensive drugs. Most people take their medications in the morning. A recent randomized clinical trial (n = 2 156) showed robust effect of reducing major cardiovascular events and the American Diabetes Association recommends taking at least 1 blood pressure medication at night, although some might suggest that a definitive US study is necessary. More than 5000 participants will be randomized, and primary outcome will be major cardiovascular events, including death.</td>
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**References**


