EDITORIAL

The RECOVERY Platform

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In a platform trial, patients with a single disease are randomly assigned to a group of different therapies on the basis of a decision algorithm to determine whether any therapy has benefit.[1] The principle underpinning such trials allows for the execution of efficient, less expensive designs by enrolling populations quickly and collecting minimal data to answer more than one question. These are sensible principles and, when successful, result in trials that provide clear answers to several questions in a timely and efficient way.

In using this approach, investigators designed the RECOVERY trial involving hospitalized patients with coronavirus disease 2019 (Covid-19) in the United Kingdom to assess the efficacy of different treatments using a single end point: mortality within 28 days after randomization; preliminary results are now reported in the *Journal*.[2] A total of 11,303 patients were randomly assigned to one of four treatment groups (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, or azithromycin) or to usual care. Patients could undergo further randomization to receive either no additional treatment or convalescent plasma, and those with progressive Covid-19 could be randomly assigned to receive no additional treatment or tocilizumab.

What lessons do we take from the outcomes of the 6425 patients who were assigned to receive dexamethasone or usual care in the RECOVERY trial? First, broad populations of patients with Covid-19, along with multiple hospitals and trial coordinators, can be rapidly deployed in a trial. No doubt the swift enrollment in the RECOVERY trial was due to the nature of the pandemic, but the rapidity of trial design, logistics, coordination, and execution are the work of the investigators. Second, minimal data collection with the use of a single online follow-up form as well as routine health care data and national registry data can provide meaningful outcomes. A well-established public health care system probably played a large role in the data availability. Third, dexamethasone showed promise for reducing short-term mortality relative to usual care. Fourth, the benefits of dexamethasone may be restricted to the sickest of Covid-19 patients, those who had been placed on mechanical ventilation at the time of randomization.

Are the findings from the RECOVERY trial clinically directive? In the total sample, the age-adjusted rate ratio of mortality for dexamethasone relative to usual care was 0.83 (95% confidence interval [CI], 0.75 to 0.93; P<0.001), with an absolute mortality benefit for dexamethasone of 2.8 percentage points. However, the adjusted rate ratio of mortality benefit among patients who were receiving mechanical ventilation was 0.64 (95% CI, 0.51 to 0.81), an absolute mortality reduction of 12.1 percentage points. Although there were no standardized criteria regarding who received mechanical ventilation, this finding is probably robust and may be helpful in guiding clinical care.

The platform design for RECOVERY has some limitations. Decisions that were made on removing or adding therapies are difficult in the best of circumstances and even more so in the context of the Covid-19 pandemic. Prespecification of rules for making these decisions is fundamental in platform trials, but this was not the case in RECOVERY. The possibility of chance should not be discounted, since the more analyses that are undertaken, the more likely an appar-

ent benefit is due to chance. A data monitoring committee viewed unblinded results from five interim analyses overall and in several important subgroups. The platform used the same control group as a comparator for each of the four remaining drugs and convalescent plasma that were randomly assigned. If by chance patients in the control group had particularly poor outcomes, several treatments may have appeared to be better than they would if each treatment had independent controls. The investigators elected not to randomize patients within hospitals owing to a concern about blinding. Randomization with the use of permuted blocks within hospitals would have offered protection to maintain the blind. Hospital practice tendencies, such as the choice of patients for mechanical ventilation, may have influenced the effect of dexamethasone and the other randomized therapies.

Fidelity to the scientific method is a major safeguard and a key determinant of the validity of the results of an investigation. In the era of Covid-19, the need for answers has generated enormous pressures across the research enterprise, from designing and conducting studies to reporting and vetting the results. Kudos to the RECOVERY investigators and trial participants for the rapid enrollment in the trial during a pandemic that has transformed lives worldwide. The results represent an important step in the fight against one aspect of the disease and undoubtedly will have an effect on practice. However, the methodologic caveats raised here are important to other investigators who are developing and revising treatment protocols in hospitals and to the broader research community struggling to produce reliable results in an efficient way, even in the face of a pandemic.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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2. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.

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