# Multiple-arm, adaptively randomized trials are advantageous for comparing COVID-19 interventions

Amalia S. Magaret1,2,6, Shevin T. Jacob3,8, M. Elizabeth Halloran2,6, Katherine A. Guthrie7, Craig A. Magaret6, Christine Johnston3,6, Noah R. Simon2, Anna Wald3,4,5,6

Departments of Pediatrics1, Biostatistics2, Medicine3, Laboratory Medicine4, and Epidemiology5, University of Washington, Seattle WA

Vaccine and Infectious Disease Division6, and Public Health Sciences Division7, Fred Hutchinson Cancer Research Center, Seattle, WA

Liverpool School of Tropical Medicine8, Liverpool, United Kingdom

We propose platform trials with outcome-adaptive randomization to efficiently select the most effective COVID-19 treatments. The global pandemic spread of SARS-CoV-2 infection is alarming in its geographic scope and in the number of associated deaths. There are currently no treatments proven to decrease mortality from COVID-19 further than what can be achieved through supportive care. Thus far, the choice of therapeutics has been limited to existing, repurposed medications. Because some of the medications are perceived to have low toxicity, many have been embraced without evidence. While remdesivir was recently found to shorten time to symptom resolution, evidence for survival benefit is inconclusive (1).

Well-designed, placebo-controlled trials have begun. On June 1st, 2020, at the US National Institutes of Health online trial database (clinicaltrials.gov), we found 308 phase 2 and phase 3 intervention studies aimed at COVID-19 that are open to enrollment; an additional 287 trials were posted but not yet recruiting (2). Those already recruiting are largely treatment trials testing known antiviral medications (remdesivir, favipiravir, oseltamivir); antimalarials (hydroxychloroquine); immunosuppressive drugs known to be effective in treatment of inflammatory or autoimmune disorders (e.g., sarilumab, tocilizumab, baricitinib); or antiretrovirals for treatment of HIV infection (lopinavir, ritonavir, darunavir, cobicistat).

Several large trials are already engaged in simultaneous testing of multiple treatment strategies in separate arms, with plans to discontinue any arm that is definitively inferior at planned interim analyses, a format known as a platform trial. For example, the DisCoVeRy trial in France is testing standard of care, remdesivir, lopinavir/ritonavir, and lopinavir/ritonavir/interferon ß-1a; the World Health Organization’s SOLIDARITY trial includes hydroxychloroquine in addition to those interventions listed above; the United Kingdom’s RECOVERY trial is simultaneously testing 5 treatments as well; and REMAP-CAP has amended its international treatment trial for community-acquired pneumonia (3-6). Other multi-arm trials are taking place in Belgium, Norway, Spain, and the US. In a very short time span, many trials have been initiated to test potentially beneficial interventions, some with adaptive design incorporated. While cost, availability, and regulatory issues may limit the appropriateness or feasibility of testing certain treatments in some settings, these large trials demonstrate the feasibility of testing multiple interventions simultaneously to facilitate direct comparison.

A further innovation in the design of the clinical trials would be a broader use of outcome-adaptive randomization, a specific adaptive design feature which potentially reduces the number of deaths or other adverse outcomes incurred during a trial. To favor arms with more advantageous outcomes, outcome-adaptive randomization updates the allocation proportions based on observed outcomes from cumulatively enrolled persons to date. For example, consider a study with a favorable or desirable binary outcome. After observing early arm-specific event rates during an interim analysis, outcome-adaptive randomization permits reallocating twice as many subsequent participants to an arm with a high event rate than to an arm with half that event rate. These later-enrolled participants stand to benefit from the experience gained earlier in the trial. This approach is suitable for COVID-19 disease outcomes which are known rapidly: patients either recover or die within a few weeks. As such, the follow-up period for antiviral studies using remdesivir ranges from 14 to 29 days (1, 3). While platform trials can drop ineffective arms at interim analyses, outcome-adaptive randomization further concentrates allocation among the better performing current arms. A simulation study conducted in 2016 showed that, relative to platform trials allowing early dropping of ineffective arms, a platform trial additionally incorporating outcome-adaptive randomization (or response-adaptive randomization) can lead to an 18% drop in the number of poor outcomes (7). The advantages of updating randomization allocation is thus also measured in adverse outcomes averted.

A few issues require consideration when adaptively randomizing. One issue is drift, which occurs when participants randomized at later stages of the trial have a different pre-treatment outcome risk relative to those enrolled earlier. Drift could potentially occur in this setting if: 1) the stage of illness at the time of presentation for medical care changes as diagnostics become more available; or 2) the virulence of the infection changes through viral mutation and/or repeated person-to-person transmissions. For example, if widespread diagnostic testing is made available, persons enrolling later may present at an earlier stage of infection. In this scenario, genuine treatment benefit leading to higher allocation in some arms may not be distinguishable from benefit due to earlier presentation. However, this problem can be mitigated through stratification on the stages of allocation, or through the use of previously developed re-randomization tests (8).

The second important issue to consider when updating randomization proportions during a trial is that early study results can be highly variable. When few participants are enrolled, some arms can appear to perform better than others based on chance alone. The problems of bias and inflated significance induced by decisions made early in a sequentially designed trial can be addressed by validated post-hoc corrections that account for potentially exaggerated treatment benefit estimates (9).

A third concern is the need for clinicians providing care to patients to remain agnostic regarding the relative potential benefit of the treatments they provide, even as randomization allocations change. Should care providers’ equipoise falter prior to the end of the study, they might be strongly tempted to ignore subsequent treatment assignments. Approaches that mitigate this concern include masking investigators (when possible) and separating the roles of clinicians who are providing treatment from those assessing outcomes (10).

In summary, an adaptively designed, multi-arm trial with outcome-adaptive randomization is especially appropriate for this large-scale SARS-CoV-2 outbreak. If interventions are tested separately over the next few months, then additional time will be required to perform direct comparison of the most effective treatments. A collaborative effort will help us to widely implement the most effective treatments as quickly as possible, and with potentially more persons receiving the most effective treatments. These recommendations complement those of the World Health Organization’s R&D Blueprint group who recently encouraged core protocols that are maintained until a definitive answer regarding efficacy is reached, perhaps spanning multiple infectious disease outbreaks (11).

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Full addresses of authors

Amalia Magaret

Department of Pediatrics, Box 359300

University of Washington

Seattle, WA 98195-9300

Shevin T. Jacob

Liverpool School of Tropical Medicine
Pembroke Place Liverpool
L3 5QA UK

M. Elizabeth Halloran

Fred Hutchinson Cancer Research Center

1100 Fairview Ave. N.
P.O. Box 19024
Seattle, WA 98109-1024

Katherine A. Guthrie

Fred Hutchinson Cancer Research Center

1100 Fairview Ave. N.
P.O. Box 19024
Seattle, WA 98109-1024

Craig A. Magaret

Fred Hutchinson Cancer Research Center

1100 Fairview Ave. N.
P.O. Box 19024
Seattle, WA 98109-1024

Christine Johnston

Harborview Medical Center

University of Washington

325 9th Ave, Box 359928

Seattle, WA 98104

Noah R. Simon

Department of Biostatistics, Box 357232

University of Washington

Seattle, WA 98195-7232

Anna Wald

Harborview Medical Center

University of Washington

325 9th Ave, Box 359928

Seattle, WA 98104