

**COVID-19 Clinical Trial Oversight at a Major Academic Medical Center: Approach of
the Michigan Medicine COVID-19 Clinical Trial Committees**

Kayte Spector-Bagdady JD, MBE

Department of Obstetrics & Gynecology and the Center for Bioethics & Social Sciences in
Medicine, University of Michigan Medical School, Ann Arbor, MI, United States;

kaytesb@med.umich.edu

Peter D.R. Higgins MD, PhD, MSc (CRDSA)

Department of Internal Medicine, Division of Gastroenterology and Hepatology, University
of Michigan Medical School, Ann Arbor, MI, United States; phiggins@med.umich.edu

Anna S. Lok MD

Department of Internal Medicine, Division of Gastroenterology and Hepatology, University
of Michigan Medical School, Ann Arbor, MI, United States; aslok@med.umich.edu

Corresponding Author:

Anna Suk-Fong Lok, MD

Department of Internal Medicine, Division of Gastroenterology and Hepatology

University of Michigan Medical School

Taubman Center, 1500 E Medical Center Dr.

3912 Taubman Center, SPC 5362

Ann Arbor, MI 48109

Tel: 734-936-7511 Fax: 734-936-7392

aslok@med.umich.edu

Summary: Here we share the approach and instruments of the University of Michigan regarding how to determine which COVID-19 randomized clinical trials have the best chance of benefiting patients and how to recruit participants.

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Abstract: Clinicians – eager to offer the best care in the absence of guiding data – have provided patients with COVID-19 diverse clinical interventions. This usage has led to perceptions of efficacy of some interventions that, while receiving media coverage, lack robust evidence. Moving forward, randomized controlled clinical trials (RCTs) are necessary to ensure that clinicians can treat patients effectively during this outbreak and the next. To do so, academic medical centers must address two key research issues: (1) how to effectively and efficiently determine which trials have the best chance of benefiting current and future patients, and (2) how to establish a transparent and ethical process for subject recruitment while maintaining research integrity and without overburdening patients or staff. We share here the current methods used by the University of Michigan to address these issues.

Keywords: COVID-19, randomized clinical trial, research ethics, informed consent, ethics

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Introduction

The SARS-CoV-2 (COVID-19) pandemic has caused unprecedented disruption to both clinical care and research globally. While the causative virus has been isolated, the disease itself is poorly understood and no effective therapeutic has yet been established.¹ The mainstay of treatment remains supportive care. Consequently, clinicians – eager to offer the best care in the absence of guiding data – have provided patients with COVID-19 diverse clinical interventions under the auspices of innovative care, compassionate use, expanded access, and emergency use authorizations. This usage has led to perceptions of efficacy of some interventions that, while receiving media coverage, lack robust evidence. Moving forward, randomized controlled clinical trials (RCTs) are necessary to ensure that clinicians can treat patients effectively during this outbreak and the next.^{2,3} It is therefore critical to efficiently and ethically enroll enough participants into RCTs of diverse therapies to both establish an evidence-based standard of care and to cease interventions that are ineffective or harmful.

A global pandemic alters the typical processes for review and recruitment to clinical research to accelerate analysis and result distribution. Additionally, in the case of a novel pathogen, researchers must evaluate multiple interventions concurrently, which might also exacerbate competition between trials for research resources including prospective participants.

Large hospitals and academic medical centers must address two key research issues that occur along with the surge of both patients and RCTs: (1) how to effectively and efficiently determine which trials have the best chance of benefiting current and future patients, and (2) how to establish a transparent and ethical process for participant recruitment while maintaining research integrity and without overburdening patients or staff. Neither of these

requirements is unique to COVID-19 RCTs, but the complexities of both are exacerbated by its breadth and urgency.⁴

We share here the current methods used by the University of Michigan (Office of Research) and its health system, Michigan Medicine, to address these issues. To do so, we also adopted three overarching goals: (1) support the *rapid development of generalizable evidence*; (2) ensure *responsible stewardship* of scarce research resources; and (3) establish a *fair and transparent system* of protocol review and recruitment from the perspective of patients, clinicians, and researchers.

Assessment of which trials have the best chance of benefiting current and future patients

While researchers want to explore all potential interventions, and hospitals want to support as many trials as feasible, limited research and participant resources can slow enrollment and delay results. Hospitals need a formal process to efficiently evaluate proposed trials.⁵ We established the Michigan Medicine COVID-19 Clinical Trials Feasibility Review Committee, made up of neutral and diverse experts, to assess the safety and scientific plausibility of proposed interventions in order to best allocate participants into well-designed studies of promising agents. We designed a rigorous and transparent process modeled after the National Institutes of Health study sections to review the following domains: scientific plausibility, significance, research plan, practicality, investigator and study team, patient and institutional burden, and safety. (Table 1)^{6,7}

While these areas are common across trial assessment rubrics, concurrently running multiple RCTs at a single institution studying the same disease, the virulence of COVID-19, and exacerbation of health disparities, require additional considerations. As to the first issue, important questions include: Is the scientific plausibility of the proposed intervention sufficient to justify testing in very ill and vulnerable patients? Is the therapeutic mechanism

proposed distinct from an existing trial? If there is overlap in inclusion criteria, are there enough prospective participants to rapidly meet enrollment targets?

Second, while we are used to assessing potential benefit to the participant and importance of the knowledge expected to result from research, the virulence and transmissibility of COVID-19 requires us to weigh these potential benefits against both the potential risk to the participant *as well as the study team*. For example: Does the study team have the experience and ability to recruit with infection prevention precautions? Can the procedures be remote? If there must be contact between the study team and participant, is there sufficient personal protective equipment available?

Finally, we must be cognizant of the fact that COVID-19 is overrepresented in minority patients.⁸ Ensuring equitable enrollment in, and access to, RCTs is critical. In addition, any future effective therapeutics must be available across the diverse communities from which our participants are derived.

Establishment of a process through which patients are recruited

The second important issue is how to transparently and ethically establish a process through which participants can be recruited. Under the foundational ethics principle of ‘respect for persons,’ we enable informed consent for each individual participant by discussing risks, benefits, and alternatives to enrollment. Nevertheless, offering patients a ‘choice’ between several different COVID-19 RCTs for which they might qualify raises three important considerations.

First, this presentation could mislead patients regarding the efficacy of experimental interventions. Giving patients a choice between experimental interventions, as we would for indicated clinical interventions, risks exacerbating the ‘therapeutic misconception’ that RCTs are alternatives with established clinical benefit. In the absence of established treatment,

RCTs offer a *potential* benefit, but even investigational utilization of off-label drugs with safety records can cause harm in patients with COVID-19.

Second, we are already challenged to ensure that prospective participants comprehend the complexities of a single research protocol. With COVID-19, usual communication is severely impaired by requirements for airborne isolation. To attempt to fully brief acutely ill patients on the protocols of multiple RCTs, particularly without the physical presence of supportive friends or family, is both impractical and often overwhelming.

Third, we must be aware of the politicization and media coverage regarding several interventions under study which might affect prospective participant choice of RCTs in ways that might skew results.

Therefore, in order to provide a balance between enabling participant autonomy as well as the timely production of generalizable results, we have adopted a process by which patients who meet inclusion criteria for multiple trials are prioritized to a ‘primary’ and a ‘secondary’ trial. If they choose not to enroll in the primary trial, but express interest in future research opportunities, the secondary team will approach them. If they choose not to enroll in the secondary trial, they will be offered no further trials at that stage of disease (but may be offered other trials in the future). (Table 2) The research teams discuss nuances of recruitment daily and also address any conflicts.

Conclusion

COVID-19 requires institutions to modify standard clinical trial practices in response to unprecedented circumstances. While we cannot reliably predict which interventions will be most effective in treating COVID-19, the design of and recruitment into well-designed and unbiased clinical trials is necessary to determine which proposed interventions are safe and efficacious.

Our approach addresses the current problem of multiple competing single-sponsor RCTs; however, we hope that it will eventually yield to platform, adaptive RCTs studying multiple therapies head to head – dropping the weakest, and adding new promising therapies – in a process that combines the rigor of RCTs with the efficiency of continuous quality improvement.⁹ Until that time, Michigan Medicine’s current approach seeks to balance the importance of autonomy and choice for our current patients, with robust and feasible clinical trial design, to offer evidence-based interventions for our current and future patients and our communities.

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Members of the Michigan Medicine COVID-19 Trials Prioritization Committee:

Keith D. Aaronson, MD, MS; Judy Birk, JD; Kevin S. Gregg, MD; Robert C. Hyzy, MD;
Daniel R. Kaul, MD; Adam S. Luring, MD, PhD; Anna S. Lok, MD; John C. Magee, MD;
Pauline K. Park, MD; Phillip Scott, MD; Kayte Spector-Bagdady, JD, MBe

Members of the Michigan Medicine COVID-19 Trials Feasibility Review Committee: Keith

D. Aaronson, MD, MS; Kevin R. Flaherty, MD; Peter D.R. Higgins MD, PhD,
MSc(CRDSA); Adam S. Luring, MD, PhD; Anna S. Lok, MD; William J. Meurer, MD, MS

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Conflicts of Interest

Kayte Spector-Bagdady JD, MBE – No conflict

Peter D.R. Higgins MD, PhD, MSc (CRDSA) – No conflict

Anna S. Lok MD – No conflict

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Table 1: Review Criteria for COVID-19 Clinical Trials

Domain	Questions to Ask	Score
<i>Scientific</i>	<ul style="list-style-type: none">• Is the proposed therapy specific to SARS-CoV-2?	
<i>Plausibility (10%)</i>	<ul style="list-style-type: none">• Is there evidence of efficacy <i>in vitro</i> and in multiple animal species?• Is there evidence of safety of this therapy in humans?	
<i>Significance (10%)</i>	<ul style="list-style-type: none">• If this study enrolled only 50% of target, would it still meaningfully contribute to generalizable knowledge?• Is there something novel or innovative (socioeconomically, scientifically) that would lead you to choose this trial over an otherwise meritorious (but less novel or innovative) one?	
<i>Research Plan</i> <i>(20%)¹</i>	<ul style="list-style-type: none">• Is there a reasonable rationale for the sample size?• Are study procedures clearly specified and well justified?• Is the therapeutic mechanism distinct from existing trials at Michigan Medicine?• Are endpoints reasonable and easily measured?• Are study procedures largely remote, with minimization of time points/study burden?	
<i>Pragmatic and</i> <i>Practicable (10%)</i>	<ul style="list-style-type: none">• Are there enough prospective participants, considering the current number of COVID patients in the hospital or available as outpatients?• How many other trials with similar inclusion and	

¹ Encourage following the SPIRIT statement, using the SEPTRE tool⁶ and CONSORT clinical trials reporting tool⁷

Domain	Questions to Ask	Score
	<p>exclusion criteria are currently active?</p> <ul style="list-style-type: none"> • Are there competing trials with a similar approach or mechanism? What is their target N? How fast are they enrolling (enrolled patients per week)? • Is the timeline realistic (N patients per week x Y weeks)? • Is there sufficient funding for this study, and is the budget realistic? • Is there sufficient drug for this study, and has it been procured? • Is there sufficient person-power in the study team/does the PI have enough time to commit to this study? • Is an IND required? If yes, how far along is the IND application? What is the anticipated IND completion date? 	
<p><i>Investigator and Study Team/ Resources (10%)</i></p>	<ul style="list-style-type: none"> • Does the PI or Co-I have experience with infectious diseases and/or critical care? • Does the PI or Co-I have experience with multiple clinical trials over multiple years? <hr/> <ul style="list-style-type: none"> • Does the PI or Co-I have experience with consenting/treating hospitalized/ICU patients with difficulty breathing? Consenting/phone consent? • Is the PI or Co-I willing and able to spend adequate time (e.g., 60-120 min) on each consent? 	

Domain	Questions to Ask	Score
<i>Patient and</i>	<ul style="list-style-type: none"> • What is the level of burden on the patient and family? 	
<i>Institutional Burden</i> (10%)	<ul style="list-style-type: none"> • What is the level of burden on the clinical care team/ICU team? • What is the burden on study coordinators and PI team? Do they have enough resources to do this study, given their other clinical and research responsibilities? • What is the level of burden on support systems needed (e.g., laboratories and study coordinators)? 	
<i>Safety (10%)</i>	<ul style="list-style-type: none"> • Is there adequate protection for patients? Is there an opportunity for truly informed consent? • Will any potential future benefit from discoveries be available in an equitable fashion and, in particular, to the community from which the patient comes? • Does the potential benefit to the patient and the importance of the knowledge expected to result justify the risks to the participant? <hr/> <ul style="list-style-type: none"> • Does the potential benefit to the patient and the importance of the knowledge expected to result justify the risks to the clinical care team? • Does the potential benefit to the patient and the importance of the knowledge expected to result justify the risks to the study team? • Does the potential benefit to the patient and the 	

Domain	Questions to Ask	Score
	<p>importance of the knowledge expected to result justify the risks to the community (e.g., risk of increased spread of COVID-19)?</p> <ul style="list-style-type: none"> • Is there any way to modify the protocol to reduce the risk of harm to the patient, to the clinical care team, to the study team, or to the community? 	
<i>Overall Impact and Priority Score (20%)</i>	<ul style="list-style-type: none"> • Given all the information and scores above, score this proposal (1-9) on its likely overall impact on COVID-19 at Michigan Medicine and in the world. 	
<p>Seven Domains Scored on a 1-9 NIH scale. 1= Exceptional, 9= Poor</p>		

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Table 2: Allocation and Recruitment Procedure for COVID-19 Clinical Trials

Point in time	Focus
<i>When a patient tests positive for COVID-19</i>	Assess patient with respect to all current clinical trial inclusion/ exclusion criteria
<i>If a patient meets multiple trial entry criteria</i>	Each patient meeting the criteria for multiple trials will be allocated to a 'primary' and a 'secondary' trial, based on a best fit determination
<i>Morning of recruitment</i>	The clinical and research teams will communicate each morning regarding which patients have been allocated to which trials and what their primary and secondary options are
<i>Recruitment to "primary" trial</i>	<p>The primary trial team will present the patient with the option to either receive standard of care <i>or</i> enroll in the primary trial to which they have been allocated</p> <p>The trial team will disclose that there are other trials going on at MM, the details of which are available on our public website, but this is the one that MM believes is both a potentially appropriate fit for this patient, and also the one that we can offer at this time</p> <p>At this point the patient may agree to enroll in the primary trial or request standard clinical care</p>
<i>If patient <u>declines</u> to enroll in the primary trial</i>	<p>The primary research team will ask the patient if he or she might be interested in other trial opportunities in the future:</p> <ul style="list-style-type: none">• If the patient <u>declines</u>, MM will not offer them any more COVID-19 clinical trial opportunities• If the patient says <u>yes</u>, the secondary trial study team will

be notified that they may recruit the patient when
appropriate

If the patient also declines enrollment in the secondary trial The patient will be offered no further trials at this stage of disease, but may become qualified for other trials in the future trial

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