A risk–benefit framework for human research during the COVID-19 pandemic

Julie C. Lumeng[a,b,c], Tabbye M. Chavous[a,d,e], Anna S. Lok[f], Srijan Sen[a,g,h], Nicholas S. Wigginton[a,1], and Rebecca M. Cunningham[a,i,j,1]

The coronavirus disease 2019 (COVID-19) has had a profound impact on the academic research enterprise. Over the span of just a few weeks in March 2020, most large U.S. research institutions closed the majority of their laboratories, studios, and offices, suspended travel and fieldwork, and paused the majority of human research, resulting in the halt of more than 80% of all on-site research activity (1). After months of limited operations, laboratory- and field-based research in the basic and natural sciences were among the first activities to resume. These activities presented relatively low risk for transmission with implementation of proper control measures such as face coverings, health screens, and social distancing.

Performing human research during a global pandemic, however, raises new ethical and practical challenges on a scale never before seen. Across the clinical, social, and behavioral sciences, human research can require close contact between researchers and participants, over variable observational periods, and across a variety of locations (e.g., clinics, schools, prisons). Therefore, research with human participants has been slower to resume given the risks associated with potential direct and/or airborne transmission between and among researchers and participants. Indeed, early evidence suggests that research disciplines that rely on face-to-face human contact are among the disciplines that have seen the steepest drop in productivity during the pandemic (2), despite the fact that human research constitutes a significant fraction of the research enterprise.

Not all human research paused as stay-at-home orders were implemented across the United States. Work continued on projects that could be performed remotely, as did critical clinical work to help understand and develop solutions for the ongoing pandemic. Some COVID-19 therapeutic trials with potential immediate, life-saving benefit began with numerous safety precautions (3, 4). Many clinical trials with potential immediate life-saving benefit for a range of conditions continued through the pandemic,

Performing human research during a global pandemic raises new ethical and practical challenges on a scale never before seen. To safely and ethically restart more of the human research portfolio, institutions must develop guiding principles and an explicit plan for managing human research during the pandemic. Image credit: Carey Lumeng (University of Michigan, Ann Arbor, MI).

[a]Office of the Vice President for Research, University of Michigan, Ann Arbor, MI 48104; [b]Department of Pediatrics, University of Michigan, Ann Arbor, MI 48109; [c]Department of Nutritional Sciences, University of Michigan, Ann Arbor, MI 48109; [d]Department of Psychology, University of Michigan, Ann Arbor, MI 48109; [e]Department of Educational Studies, University of Michigan, Ann Arbor, MI 48109; [f]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109; [g]Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109; [h]Michigan Neuroscience Institute, University of Michigan, Ann Arbor, MI 48109; [i]Department of Emergency Medicine, University of Michigan, Ann Arbor, MI 48109; and [j]Department of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI 48109

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[1]To whom correspondence may be addressed. Email: stroh@med.umich.edu or nwigg@umich.edu.

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as did activities related to monitoring for safety after clinical trial participation. Electronic consent protocols and other regulatory flexibilities (5) allowed many studies to continue, as did the use of technological tools (e.g., video-conference interviews). However, these changes sometimes introduced inequities in study participation related to technology access, and they introduced the need for additional steps to validate data quality.

To safely and ethically restart more of the human research portfolio, which at large institutions like ours can include thousands of active research studies, institutions must develop guiding principles and an explicit plan for managing human research during the pandemic.

Most U.S. institutions had not yet restarted large portions of their human research activities as of late July 2020, more than 4 months after shutting down. Based on correspondence with research leaders at 21 major research universities across the United States, we estimate that 50–80% of clinical human research studies, and fewer than 25% of nonclinical human research studies, were active at that time. To safely and ethically restart more of the human research portfolio, which at large institutions like ours can include thousands of active research studies, institutions must develop guiding principles and an explicit plan for managing human research during the pandemic. Here, we describe an integrated approach that is applicable to a variety of institutions and public health conditions. This approach also applies broadly to human research across clinical, social, and behavioral sciences—disciplines that are often managed and overseen separately by different administrative units within institutions, but for which better coordination is required to reduce uncertainty during a pandemic.

Tiered Prioritization

High-level guiding principles must inform decision-making across an institution for consistency and transparency. Our guiding principles for conducting human research during the current pandemic include the following: 1) The safety of research participants is paramount; 2) The risk of COVID-19 community spread, including spread to the researchers themselves, must be minimized; 3) Policies and practices must be designed and implemented in a way that attends to inequities explicitly and proactively.

These principles must be kept in mind when prioritizing research in specific tiers. Tiering studies achieves several goals. First, tiers allow an orderly and gradual ramp-up of human research activity. The gradual reintroduction of activity aligns with public health guidelines recommending phased reopening (e.g., ref. 6). Second, tiering studies allows research activity to expand or contract in an orderly fashion depending on current community transmission. Tiering allows stakeholders to clearly forecast impending contraction or expansion of the research enterprise dependent on trends in COVID-19 community transmission. Third, tiering provides a unified structure that prevents differential approval of some studies but not others or ad hoc decisions based on variable application of best public health principles.

We tiered studies based on weighing potential direct benefit to the individual study participant against the risk of COVID-19 community transmission introduced by the research activity. Whereas human research ethics typically focuses on weighing risks versus benefits of human research participation to the individual participant, the pandemic necessitates newly considering risks of COVID-19 transmission introduced to the community, including to the researchers themselves. For example, even in the context of receiving no potential direct benefit, a healthy participant may be enthusiastic about incurring a small risk of exposure to COVID-19 to participate in an in-person focus group study in a church. However, that focus group may generate an outbreak of COVID-19 in the community that closes businesses and prevents children from attending school.

There are also unique factors to consider with regard to evaluating benefit in the context of the pandemic. Specifically, studies of COVID-19 are highly prioritized given their implications for public health, even when potential direct benefit to the individual participant is modest. Further, for many participants, the calculus of risk has been changed by the pandemic. Although older adults may not be willing to accept the risk of contracting severe COVID-19 incurred by leaving their home to participate in an observational research study, they may be willing to incur such a risk for the opportunity to potentially derive benefit from participating in an investigational drug trial for their own life-threatening health condition that's been unresponsive to all previous treatments.

Risk versus Benefit

To address these needs at the University of Michigan, Ann Arbor, we implemented a framework to prioritize studies in tiers based on a combination of the incremental risk of COVID-19 community transmission introduced by the research activity with the potential direct benefit of the study to the individual participant (Table 1). Risk of transmission varies across studies based on the types of interactions occurring during the research encounter, including both the amount of close contact, the number of different contacts between individuals, and the use of personal protective equipment (PPE). The risk of having more severe COVID-19 varies across individual participants, with certain characteristics clearly associated with greater risk (7).

The tiers are designed to provide a structure by which, during more severe periods of the pandemic, studies that provide greatest potential direct benefit

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Table 1. Incremental risk of COVID-19 community transmission compared with benefit level and categorization of individual risk

COVID-19 Community Transmission Risk Feature of Study	Incremental Risk of COVID-19 Community Transmission Category			
	High	**Medium**	**Low**	**None**
-Contact distance -Contact duration -Participant wearing PPE	Contact distance is less than 6 feet ***AND*** contact duration is more than 15 minutes ***AND*** participant cannot wear PPE	Contact distance is less than 6 feet ***AND*** contact duration is less than 15 minutes (regardless of whether participant can or cannot wear PPE) ***OR*** Contact distance is more than 6 feet ***AND*** contact duration is more than 15 minutes (regardless of whether participant can or cannot wear PPE) ***OR*** Contact distance is less than 6 feet ***AND*** contact duration is more than 15 minutes ***AND*** participant is wearing PPE ***OR*** Contact distance is more than 6 feet ***AND*** contact duration is less than 15 minutes ***AND*** participant cannot wear PPE	Contact distance is more than 6 feet ***AND*** contact duration is less than 15 minutes ***AND*** participant is wearing PPE	No face-to-face interaction
# contacts between individuals per day	>10	3-10	1-2	0
Participant characteristics	-Age greater than 65 years ***OR*** -Immunocompromised ***OR*** -Self-identify as higher risk of severe COVID-19 ***OR*** -Known positive COVID-19 test result in past 14 days or new symptoms on COVID-19 health screen			
Benefit Level				
1. Potential immediate benefit to the individual participant that is life-saving, including stabilization of a high risk psychological condition	Tier 0	Tier 0	Tier 0	Tier 0
2. Potential benefit to the individual participant for a condition with no current other intervention options	Tier 1	Tier 1	Tier 1	Tier 0
3. Potential benefit to the individual participant for a condition with existing intervention options	Tier 2	Tier 2	Tier 1	Tier 0
4. No benefit to the individual participant	Tier 3	Tier 2	Tier 1	Tier 0

Activation tier is identified based on combining the feature of the study that provides the highest benefit to the individual participant in any study arm with the feature of the study that is in the highest risk category. If all face-to-face interaction with study participants occurs concurrent with a clinical encounter with no research staff, the study is classified as Tier 0, regardless of the risk or benefit category. Studies taking place outdoors will be given special consideration with regard to risk assessment. Number of contacts includes staff–participant contacts and participant–participant contacts (for group behavior studies).

to individual participants and have low risk of community transmission are prioritized over studies providing little to no potential direct benefit to individual participants and have a high risk for community transmission. In addition to pausing studies that provide ratios of risk versus potential benefit not deemed appropriate, it is important to ensure that studies that provide very substantial potential direct benefits to participants (e.g., a potentially life-saving or life-extending treatment to an individual with terminal cancer) continue during periods when the rate of COVID-19 transmission in the community is low enough such that the potential direct benefit to the participant outweighs the potential risk to the community.

Applying the framework requires several key elements. Leadership must monitor both the rapidly evolving scientific understanding of COVID-19 and local and regional infection rates on a daily basis. Up-to-date knowledge is essential to inform timely changes to research policy and study implementation that align with current public health conditions. Researchers are required to complete a new online training module regarding mitigating risk of COVID-19 transmission in the context of human research. Researchers submit an application detailing the study, the potential direct benefit to participants, and the risks of community transmission introduced by the study activities. Researchers also detail in the application the measures to be used to mitigate risk, and they sign an attestation of compliance with university protocols and other campus-wide and regional guidance on safe practices to mitigate COVID-19 transmission. Examples of policies include mandatory health screens for researchers, participants, and individuals accompanying participants (e.g., parents, spouses, or legally authorized representatives) before participating in a research encounter.

Careful record keeping of all close interactions that occurred during the research encounter are also required to aid in contact tracing if necessary. Two review committees—with overlapping membership divided by clinical and nonclinical settings—assess benefit and risk levels to assign the appropriate priority tier for studies requesting to begin interactions with human participants. These committees operate separately but in partnership with institutional review boards (IRBs).

Expectations should be clear that PIs must not compel trainees to participate in face-to-face research during high community transmission stages, and some trainees (e.g., undergraduate students) may be disallowed from participating entirely. Researchers and staff who are at elevated risk should also shift to work on other projects until public health conditions significantly improve.

Finally, policies and practices to establish a new normal for human research must be designed and implemented in a way that addresses inequities explicitly and proactively. First and foremost, it is critical

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to consider inequities experienced by study participants. COVID-19 has had disproportionate effects on racial/ethnic minority and lower income communities owing to a variety of social and structural factors (7). Researchers engaging human participants must include ethical considerations for conducting research in the context of potential direct benefits and costs to participants during this unprecedented time, especially when members of certain communities are particularly likely to experience life disruptions and stressors related to ill family and community members (e.g., ref. 8).

The United States has failed to control COVID-19 the way that other countries have, and there continue to be uncertainties around vaccine efficacy and deployment. As a result, the research community needs to brace for the possibility that over the next several months or years, we may be in a cycle of ramping research up and down multiple times as a function of community transmission status.

For example, converting in-person, face-to-face research study protocols to remote interactions may exacerbate inequities by removing access to studies that may provide potential direct benefit from communities that lack access to appropriate technologies and reliable internet access. On the other hand, providing remote access to research studies with potential direct benefit to the participant could potentially alleviate disparities related to transportation or access to healthcare facilities. Further, providing opportunities to participate in research studies remotely may also alleviate disparities in community transmission (i.e., communities at greatest risk for COVID-19 may still be able to participate in research studies that provide potential direct benefit while also reducing the chance for increased community transmission). Researchers, academic institutions, and funders will need to examine and remediate disparities that were exacerbated by the pandemic by appropriately directing resources to re-engage communities that may have been left behind or excluded as a result.

In deciding which studies with human participants should be permitted to continue versus those paused during the pandemic, weighing the potential benefits and risks to study participants and their families and communities is indisputably and consistently paramount. However, in the aftermath of COVID-19, the academic and research community will also need to reckon with and repair the disparities that the pandemic has caused to the research workforce. COVID-19 has resulted in unique researcher productivity challenges for women, racial/ethnic minorities, and certain disciplines including human research (2). The challenges of K–12 schooling shifting online disproportionately affects women, given that they tend to take on more childcare and other domestic caregiving responsibilities (9). Additionally, African American and Black researchers have likely been more affected by disruptions to human research as a result of COVID-19 because they are significantly more likely to propose work that involves human subjects—particularly in areas that fall under NIH's Division of AIDS, Behavioral, and Population Sciences (10).

Although the identity of the researcher does not and should not impact whether a particular study is permitted to continue during the pandemic, articulating and implementing clear policies for evaluating and approving research projects will provide promotion and tenure committees discrete data regarding which researchers were directly impacted by these policies so that they can take these issues into account accordingly. Maintaining a diverse research workforce is essential to the research community's ability to address the diverse range of issues impacting all individuals in our society. Allocation of resources is a critical lever for reducing disparities. Institutions and funding agencies must carefully consider policies regarding resource allocation to repair the disparities in damage caused to the research enterprise as a result of COVID-19.

Aligning with the Broader Community

Plans and protocols related to research during COVID-19 must be developed and implemented with careful attention to activity in the broader community. In the absence of strong national guidance or mandates, this means alignment with regional or statewide efforts to mitigate community transmission. Even with appropriate control measures in place, the incremental risk of COVID-19 transmission associated with a particular study (Table 1) is directly influenced by the rates of COVID-19 in the community. We have therefore aligned our research activities with State of Michigan "Safe Start" guidance for community transmission (*SI Appendix*, Table S1). Similar efforts at institutions in other states or regions will allow researchers and participants to plan ahead for what the next phases will require or how to prepare for situations when public health conditions require strengthened mitigation efforts. Such an approach also allows for consistency and transparency across types of research activities, which is crucial when designing for informed decision making at an institutional level.

The United States has failed to control COVID-19 the way that other countries have, and there continue to be uncertainties around vaccine efficacy and deployment. As a result, the research community needs to brace for the possibility that over the next several months or years, we may be in a cycle of ramping research up and down multiple times as a function of community transmission status. A principled framework informed by public health guidance provides a structure for operationalizing this reality—particularly for human research, which has a myriad of challenges associated with performing face-to-face research

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during a global pandemic. Certainly, the tension of benefit-to-risk will continue for all research, but especially for human research that provides benefits to participants. Over the long term, such frameworks will not only help inform necessary public health mitigation strategies on campuses of research institutions but also help reduce additional transmission in surrounding communities.

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