As of April 27, 2020, the coronavirus disease 2019 (COVID-19) pandemic involved 2,916,338 reported cases and had claimed 205,923 lives. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading in almost every country, causing widespread health challenges and social instability. People most vulnerable to COVID-19 include those with underlying health conditions. Yet the pandemic is disrupting clinical trials addressing these same health conditions. There were more than 300,000 studies being conducted worldwide registered on clinicaltrials.gov. in March 2020. Hence, there is a necessity to continue some ongoing research studies safely, a critical need for novel research into the prevention and treatment of COVID-19, and we must try to anticipate the ethical and social implications of this global pandemic.

This commentary is directed at these two pressing ethical questions: How can clinical trials be conducted ethically in the midst of the current global pandemic? What social and ethical issues prompted by COVID-19 merit further research?

CLINICAL TRIALS
Impact and Measures to Mitigate Impact for Ongoing Clinical Trials
For clinical trials, the challenges are unprecedented and amplified by the sheer specificity of different study needs. Ongoing trials are at various stages in their natural history (ie, not actively recruiting, actively recruiting, or closed for recruitment). Each trial is also accountable to a variety of local, national, and international organizations including funders, regulatory bodies, and institutional review boards. Driven by the need to adapt to a dynamic environment, these stakeholders have been identifying and implementing measures to maintain research and minimize the risks of exposure to participants and researchers.

Resources permitting, one option is to continue trials that have the potential to have high impact (eg, a potentially life-saving medication) or moderate impact (eg, disease-modifying agents) on participants’ health (eg, Johns Hopkins, 2020). By contrast, studies that advance the science but do not offer participants a prospect of direct benefit should probably be paused, also to conserve resources and protect subjects from inadvertent exposure to those who are asymptomatic but infected with COVID-19. Other options include providing follow-up care and research tests at facilities closer to home or virtually using video conferencing technologies, and shipping study-related investigational products directly to participants when appropriate.

Some studies have been closed for enrollment, including those informed by prior research ethics debates on closing studies due to futility or lack of initial benefit. However, ceasing or slowing studies is not always the safest option for participants. Indeed, it is important to continue or appropriately transition studies that have the potential to directly benefit participants. Elements of studies, such as ancillary care or access to investigational drugs and/or devices, might be maintained even if other research protocol aspects are modified.
Honoring our commitment to foundational research ethics principles of respect for persons, beneficence, and justice is demanding, especially when such tenets could very well be in tension. Acknowledging the core function of human research protections, European clinical trials guidelines, and US Food and Drug Administration guidance emphasize that in cases where prioritizing participant safety and data validity conflict “subject safety always prevails.” Nevertheless, enacting the priority of protecting research participant safety amid the pandemic is not always clear-cut. For example, altering clinical trial follow-up plans may compromise participant safety and impact beneficence if key safety assessments are missed due to social distancing, shelter in place local regulations, and suspension of travel options.

A variety of guidelines have been released to inform research response. Recent US Food and Drug Administration guidance provides recommendations for ongoing studies, development of contingency plans as conditions change, and reporting of COVID-19 impact in study reports. Elsewhere, agencies are clarifying what constitutes a protocol deviation. For example, the National Cancer Institute has advised that for some clinical trials, providing care locally or remotely is not considered a protocol deviation. The National Institutes of Health also have guidance for participant safety and granting of extensions and administrative supplements.

The need for nuanced and iterative decisions for each clinical trial is also placing additional demands on already overstretched institutional review board resources and staff. Furthermore, pandemic-associated mortality and morbidity may impose additional impediments to post-pandemic follow-up activities by researchers, research ethics committees, and regulators, thus straining the tenuous research system even further. Proactive measures to mitigate such consequences are necessary.

Accelerating COVID-19 Clinical Trials to Improve Prevention and Treatment

Modern medicine depends on evidence-based therapies to guide treatment across all disease states. While the pandemic is rapidly evolving, there is no specific treatment available for patients diagnosed with COVID-19. Current clinical practice relies on supportive care such as mechanical ventilation to manage acute hypoxemic respiratory failure and treatment of secondary infections. There is a compelling need to provide an evidence base that informs improved standards of care, develops novel interventions, and guides management.

Randomized controlled trials (RCTs) are most ethically controversial when offering potential participants randomization into a placebo arm that could result in individual harm, especially serious physical harm including additional pain, suffering, or death as well as randomization into an active treatment arm where benefit of treatment is not established and unrecognized treatment-associated harm may exist. Ethical issues of clinical research are heightened when the condition (COVID-19 in this case) being investigated has an actual or perceived high mortality risk; activation of trials, including oversight processes, must and can be conducted rapidly without compromising human subjects research protections.

Despite informed consent practices, uncertainty during emergencies can exacerbate and create new possibilities for social, racial, and economic divisions; in research there is very real risk of undermining community trust.

RCTs are often considered the ideal for grounding causal inference, although importantly, RCTs also exhibit epistemic limits for addressing population health. Adaptive and pragmatic clinical trial designs are often proffered as alternatives, but these designs also present challenging trade-offs between the type of knowledge produced and the prioritization of direct benefits provided to participants.
In all COVID-19 RCTs, participants in the control arm would receive supportive care and best-in-class medical therapy for any associated comorbidities. Developing a standard of supportive care for RCTs that spans sites around the world is both practically and ethically challenging. Pre-existing socioeconomic differences and health infrastructures within communities may drive local and regional differences in what is standard of care. Moreover, supportive care standards might also change over time, including in response to emerging data informing better care and to dynamic resource constraints as the COVID-19 pandemic unfolds.

Supportive care variability creates both scientific and ethical challenges. If standards of supportive care are not consistent across sites, study results might be confounded by extraneous variables. If standards of supportive care are unachievable in low-resource settings, study findings might not be generalizable to these contexts. During the 2014–2016 Ebola outbreak in West Africa, the national bioethics commission recommended allowing contextual variability of supportive care in clinical trials, such that research participants receive the “best supportive care sustainably available in the community in which the research is conducted.” Contextual differences in supportive care have occurred during the current COVID-19 pandemic; for example, integrative medicine practices are part of supportive care in China but perhaps not elsewhere. Meanwhile, the WHO is currently developing a “master protocol” to harmonize practices such as supportive therapy to direct coordinated multi-site adaptive COVID-19 RCTs.

Global Health Ethics Implications of COVID-19 Clinical Trials
As with other pandemics, COVID-19 has revealed the interdependence of a globalized world. We must bear shared responsibility for solutions as we collectively confront the problem. Clinically actionable data must diffuse rapidly, even when such knowledge does not meet the rigorous standards of clinical trials. Novel interventions to prevent and treat COVID-19 are needed all over the world. Likewise, there is a similar need for reciprocity. Affluent nations often have more capacity to conduct clinical trials. The knowledge clinical trials produce—and the innovations that result—must be informed by a commitment to justice in ensuring equitable access to resultant interventions.

A firm commitment to global equity might seem like an unreachable ideal in a crisis manifesting so differently across continents. Our current research and development pipelines are not designed to produce large quantities of vaccines, drugs, or devices at low cost to fill unmet public health needs. In vaccine researcher Peter Hotez’s recent US Congressional testimony, he contended that these systems failures are a main reason coronavirus research was not prioritized before the current pandemic. If we are not careful, these same factors will contribute to exacerbated global health disparities when responding to the current or a future coronavirus outbreak, even if an effective prevention and/or treatment are discovered.

SOCIAL AND BEHAVIORAL RESEARCH
ADDRESSING ETHICAL ISSUES RAISED BY THE PANDEMIC
The psychosocial impact of the current crisis also prompts several pressing questions. Could there be a mental health toll if social distancing occurs for extended periods? What additional support do health professionals need when scarcity of personal protective equipment creates high levels of anxiety for personal and familial safety? These are just a few of the social and ethical questions raised by the COVID-19 pandemic. Bioethics and social science research can be integral to improving current and future infectious disease research, policy, and practice. Because a full discussion of all these topics is beyond the scope of this commentary, we focus on the importance of research in moral distress as a starting point.

Moral distress is a concept that emerged from nursing ethics and has expanded to all...
health professions, encompassing instances in which a health professional believes he or she knows the morally right thing to do but is unable to do so. COVID-19 could create the type of uncertainty and constrained choices in which health professionals struggle to act according to familiar best practices. Previous public health and humanitarian emergencies have produced moral distress, providing us important evidence for anticipating these challenges should they arise in the weeks and months ahead.

Moral distress is a useful area for further bioethics and social science investigation because it can illuminate the underlying content and sources of the most pressing ethical concerns among health professionals. Sources of moral distress previously identified include institutional policies that have unintended consequences, and decisional hierarchies that can compromise a sense of professional integrity. However, moral distress can be difficult to disentangle from other forms of psychological anxiety and trauma induced by stress and crisis response. This distinction is crucial to ensuring health care professionals receive the mental health resources needed to sustain their efforts and personal wellbeing, given the link of moral distress to compassion fatigue and burnout. Exploring the distinct moral concerns at the core of moral distress is also important. Such research can be coupled with investigations into resilience, including the institutional structures and practices that most support frontline health care providers through these times of crisis.

**CONCLUSION**

Clinical research and social science research tend to embrace the long timeframe needed for cautious and deliberate knowledge production. However, prioritized research efforts now can be designed in ways that are sensitive to the exigencies of the moment. The global research community must act now to meet needs of patients and health care professionals both in the short term, and when this public health emergency subsides. The purpose of this commentary is to join the conversation to design research for health policy and practice grounded simultaneously in rigorous, ethical evidence, the highest standards of professionalism, and the experiences of health care professionals.

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**Abbreviations and Acronyms:** COVID-19 = coronavirus disease 2019; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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**Correspondence:** Address to Karen M. Meagher, PhD, Biomedical Ethics Research Program, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (Meagher.Karen@mayo.edu; Twitter: @karenthetical).

**ORCID**

Karen M. Meagher: https://orcid.org/0000-0002-1055-6091; Nathan W. Cummins: https://orcid.org/0000-0002-0703-1550; Adil E. Bharucha: https://orcid.org/0000-0002-7644-0390

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