Principles Guiding Nonpandemic Critical Care Research During a Pandemic

Deborah J. Cook, MD, MSc, FRCPC
Division of Critical Care
Department of Medicine
Faculty of Health Sciences
McMaster University;
Department of Health Research Methods,
Evidence and Impact
Faculty of Health Sciences
McMaster University; and
Department of Critical Care
St. Joseph’s Healthcare Hamilton
Hamilton, ON, Canada

Michelle E. Kho, PT, PhD
Department of Physiotherapy
School of Rehabilitation Science
Faculty of Health Sciences
McMaster University; and
Physiotherapy Department
St. Joseph’s Healthcare Hamilton
Hamilton, ON, Canada

Eric H. Duan, MD, FRCPC
Division of Critical Care
Department of Medicine
Faculty of Health Sciences
McMaster University;
Department of Health Research Methods,
Evidence and Impact
Faculty of Health Sciences
McMaster University; and
Department of Critical Care
St. Joseph’s Healthcare Hamilton
Hamilton, ON, Canada

Waleed Alhazzani, MBBS, MSc, FRCPC
Division of Critical Care
Department of Medicine
Faculty of Health Sciences
McMaster University;
Department of Health Research Methods,
Evidence and Impact
Faculty of Health Sciences
McMaster University; and
Department of Critical Care
St. Joseph’s Healthcare Hamilton
Hamilton, ON, Canada

Alyson Takaoka, MSc
France J. Clarke, RRT
Nicole Zytaruk, RN

Meredith Vanstone, PhD
Department of Family Medicine
Faculty of Health Sciences
McMaster University
Hamilton, ON, Canada

Objectives: To describe the importance of critical care clinical research that is not pandemic-focused during pandemic times; outline principles to assist in the prioritization of nonpandemic research during pandemic times; and propose a guiding framework for decisions about whether, when and how to continue nonpandemic research while still honoring the moral and scientific imperative to launch research that is pandemic-focused.

Design/Data Sources: Using in-person, email, and videoconference exchanges, we convened an interprofessional clinical research group, conducted a literature review of empirical studies, ethics documents and expert commentaries (2010 to present), and viewed traditional and social media posts (March 2020 to May 2020). Stakeholder consultation involved scientific, ethics, clinical, and administrative leaders.

Setting: Clinical research in the ICU.

Patients: Patients with and without coronavirus disease 2019.

Interventions: None.

Measurements and Main Results: While clinical research should be prioritized to advantage patients with coronavirus disease 2019 in order to care for affected patients, it ideally would not unduly disadvantage patients without coronavirus disease 2019. Thus, timely, rigorous, relevant, and ethical clinical research is needed to improve the care and optimize outcomes for both patients with and without coronavirus disease 2019, acknowledging how many studies that are not exclusively focused on coronavirus disease 2019 remain relevant to patients with coronavirus disease.
The global coronavirus disease 2019 (COVID-19) pandemic is leading to an overwhelming number of patients with acute critical illness who need basic and advanced life support in the ICU. In preparation for the anticipated surge of patients with COVID-19, critical care leaders have grappled with—and now directly confront—challenging questions about which services should be prioritized, which should be reduced, and which should be halted to increase critical care capacity and maximize safety for all.

Although clinical research in the ICU is always important, it is a global priority during the COVID-19 pandemic (1, 2). The ability to appropriately prioritize pandemic-specific research requires quickly constituted or established research teams, a responsive funding system, rapid ethics and contract review, and the commitment of research and bedside staff. Observational studies and randomized trials are imperative to advance our knowledge of pathophysiology, immunology, diagnosis, prognosis, prevention, treatment, triage, and palliation. While hundreds of protocols are being newly developed to understand or mitigate COVID-19, others are ready-made such as the severe acute respiratory infection registry (e.g., Short Period Incidence Study of Severe Acute Respiratory Illness [SPRINT-SARI]) (3), or in place and readily adapted such as the community-acquired pneumonia management trial, augmented now with a pandemic treatment domain (e.g., Randomized Embedded Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia [REMAP-CAP]) (4).

During this pandemic, most institutions have released instructions to focus on pandemic-specific research. Some organizations have required the cessation of research not specifically related to COVID-19, in anticipation of the increase in clinical workload required to care for patients with life-threatening infection during the pandemic, the need to institute physical distancing for employees, and consideration of limited personal protective equipment (PPE).

The objectives of this article are to: 1) describe the importance of critical care clinical research that is not pandemic-focused during pandemic times; 2) outline principles to assist in the prioritization of nonpandemic research during pandemic times; and 3) propose a framework for guiding decisions about whether, when, and how to continue nonpandemic research, while still honoring the moral and scientific imperative to launch research that is pandemic-focused.

The perspective of this article is single-site multidisciplinary. Although intended for those operationalizing research protocols in a single site, many of the principles and considerations can be adapted to single-site methods centers conducting multicenter studies.

MATERIALS AND METHODS
Using in-person, email, and videoconference exchanges, we convened an interprofessional clinical research group representing medicine, nursing, respiratory therapy, physiotherapy, epidemiology, and ethics. A literature review included empirical studies, ethics documents, and expert commentaries from 2010 to the present, augmented by traditional media and social media posts in March 2020 and April 2020. By telephone and email, we then consulted research institute leaders, senior university scholars, hospital administrators, ethics board chairs, investigators, research staff, clinical directors, and consultants in critical care and infectious diseases in our own hospital, as well as investigators in two other healthcare organizations. This process, and lessons learned from ICU research during the severe acute respiratory syndrome and H1N1 pandemics (5–8), informed our approach to balance interests of the public regarding the scope of research during a global health crisis.

RESULTS
General Principles
Clinical research during a pandemic should ideally maximize the benefit to individuals while also maximizing the benefit to society (9). A pandemic situation may require us to adopt a public health ethics approach, prioritizing community and population health over individuals (10). Applied to the question of what research to continue, this approach reminds us of the larger good that research can do to improve the health of critically ill patients with and without COVID-19. That is, while clinical research should be prioritized to advantage patients with COVID-19 in order to urgently care for affected patients—ideally, it would be done in a way that does not unduly disadvantage critically ill patients without COVID-19. Thus, timely, rigorous, relevant, and ethical clinical research is needed to improve the care and optimize outcomes for both patients with and without COVID-19 (5, 6, 9, 11–15). Such an approach also acknowledges that many previous and many ongoing critical care studies that are not exclusively focused on COVID-19 remain relevant to patients with COVID-19 (16).

We propose the concurrent conduct of research that is pandemic-focused and research that is not pandemic-focused, whenever safe, feasible, and locally approved. Suspension of some studies may be needed, with mechanisms to consider reinstatement at the earliest appropriate time. Continuation may be possible for other studies when certain conditions are met.
A transparent process outlining key considerations and objective criteria can help to achieve fairness in decision-making when allocating resources in crisis situations (17)—including research resources. Considerations determining these decisions should also influence approaches to starting new clinical research that is not pandemic-focused—not only while the pandemic unfolds but also as it dissipates.

Consider the Status of the Pandemic. COVID-19 has consumed and completely overtaken all available critical care resources, and in some situations, overwhelmed entire healthcare systems, rendering any research extremely challenging if not impossible (18, 19). The pandemic burden in each local context will dictate whether and what research is appropriate and realistic. Research should not be conducted if it will avert necessary clinical knowledge and skills, or require space, PPE, and other key resources that are required for an optimal clinical response to the outbreak (20).

Consider Jurisdictional Guidance. Jurisdictional guidance regarding research during the COVID-19 pandemic has been variable, as international monthly self-reported surveys indicate (21). Responses have ranged from institutional silence, to suggestions for investigator discretion on suitable studies to conduct, to mandates and associated funds to focus exclusively on pandemic-specific research, paired with directives to suspend all nonpandemic research. Just as during inter-pandemic periods when institutional sanctions influence academic operations, local jurisdictional guidance is the starting point for local deliberations about which research to conduct during the pandemic.

Consider the Capacity of Research Personnel. The capacity of research personnel is a key determinant of the conduct of both nonpandemic and pandemic-specific research. Clinically trained research staff with up-to-date professional credentials (e.g., nurses, respiratory therapists, physiotherapists, and physicians) may need to be deployed to the frontline to care for patients as the pandemic progresses. Research staff may also be affected by illness, precluding any research whatsoever. On the other hand, research opportunities for staff working on paused research, or in other areas closed during the pandemic (e.g., outpatient clinics, elective surgery), could fortify existing critical care research personnel.

Specialized personnel are often required for both pandemic-focused and nonpandemic-focused research. For example, if research pharmacy staff are reassigned to clinical pharmacy activities, pharmaceutical studies may become difficult to pursue. Studies requiring the procurement and processing of biological specimens may be impossible if protective measures are too resource intensive, or if laboratory research staff are overwhelmed with the demands of COVID-19 testing to meet the hospital’s basic clinical needs.

Consider the Safety of Research Personnel. For any clinical research—be it pandemic-focused or not—strategies are needed to minimize or replace typical face-to-face research interactions (e.g., for informed consent, questionnaires), replacing these with other methods (e.g., telephone consent, videoconferencing). Provision for off-site work for clinical research staff may require new safeguards to ensure confidentiality of identified data on personal computers or home networks. Timely administrative approval to access hospital servers may be needed for remote electronic medical record access.

On-site work that is central to research conduct during the pandemic should involve only the minimum number of essential trained research staff who agree to carry out this work without coercion or concern for consequences regarding safety and job security. It is crucial that on-site research personnel receive safety and PPE training and that safety protocols and guidelines be reviewed during rapidly changing working conditions.

Consider Patients Already Enrolled in Nonpandemic-Focused Studies. If nonpandemic-focused research is restricted, investigators should identify the current status of patients already enrolled in these studies (e.g., receiving the study intervention, undergoing follow-up assessments) to determine whether any interventions must continue for patient safety. For example, some study interventions may be dangerous to terminate (e.g., a drug which could lead to withdrawal if stopped). Strategies should be developed to complete the treatment course and collect data on at least the primary outcome, if safe and feasible. If remaining assessments require in-person data collection (e.g., physical function performance-based measures), collecting the primary outcome(s) should be prioritized while determining if any data could be collected using alternate methods (e.g., questionnaires via secure video link or telephone). Patients or their substitute decision-makers should be notified about any relevant changes to the status of their study participation in light of the pandemic.

Consider Characteristics of Each Individual Nonpandemic-Focused Study. All stakeholders should consider how their institution and research program can best serve patients during the pandemic. All studies should be reviewed and a portfolio of studies selected based on the center’s capacity, case mix, and clinical and research expertise. Necessary adaptations of non-COVID research should be considered during this process such as considering the suitability of COVID-19 patients for enrollment (as long as this does not preclude enrollment in COVID-focused studies). Consider whether it is relevant to revise case report forms and databases to document COVID-19 status.

When reviewing and selecting studies to continue, consider leveraging preapproved studies that could specifically apply to those with COVID-19. For example, consider continuing ongoing studies relevant to conditions with high morbidity and mortality in the general ICU population, such as therapies for severe sepsis and septic shock (e.g., balanced vs unbalanced crystalloid [e.g., Fluids and Septic Shock (FISSH)] [22] or vitamin C [e.g., Lessening Organ Dysfunction with Vitamin C Trial (LOVIT)]) (23). The LOVIT trial obtained specific Health Canada and research ethics approval to enroll patients with COVID-19, acknowledging that viral infections can cause septic shock, and recognizing that vitamin C was prioritized by the WHO as a treatment for investigation in COVID-19 (24). Other ongoing trials may have particular pathophysiologic relevance during the pandemic (therapeutic heparin [e.g.,
### TABLE 1. Examples of Early Pandemic Phase Multistudy Management

| Study Name (Status When Pandemic Started) | Study Design | Interventions/Exposures | Consent Model |
|------------------------------------------|-------------|------------------------|---------------|
| COVID-19 focused                         |             |                        |               |
| ACT (new)                                | Adaptive unblinded RCT | Acetyl salicylic acid/rivaroxaban/interferon | Standard care | SDM/patient a priori, phone option |
| CATCO SOLIDARITY (new)                   | Adaptive unblinded RCT | Lopinavir/ritonavir, interferon, remdesivir | Standard care | SDM/patient a priori or deferred, phone option |
| CONCOR-1 (new)                           | Unblinded RCT | COVID-19 convalescent | Standard care | SDM/patient a priori, phone option |
| COVACTA (new)                            | Double-blinded RCT | Tocilizumab | Placebo | SDM/patient a priori, phone option |
| COVI-PRONE (new)                         | Unblinded RCT | Early awake proning | Standard care | SDM/patient a priori or deferred, phone option |
| LOVIT (ongoing)                          | Blinded RCT | 4 d of vitamin C | 4 d of placebo | SDM/patient a priori or deferred, phone option |
| REMAP-CAP (new)                          | Adaptive unblinded RCT | Domains for antibiotics; antiviral duration; corticosteroids; pandemic domain: lopinavir/ritonavir, hydroxychloroquine with relevant domains for randomization selected by clinical team | SDM/patient a priori or deferred, phone option |
| SPRINT-SARI (new)                        | Observational | Pandemic registry of patients hospitalized with confirmed COVID-19, including ICU patients | Waived |
| 3 Wishes Project in the pandemic (new)   | Observational | Humanizing the dying experience by honoring patients and comforting families | Verbal consent for patient care, a priori for family/clinician interview, phone option |
| Non-COVID-19 focused                     |             |                        |               |
| BALANCE (ongoing)                        | Unblinded RCT | 7 d antibiotic therapy | 14 d antibiotic therapy | SDM/patient a priori, phone option |
| CYCLE (ongoing)                          | Unblinded RCT | In-bed cycling + usual physiotherapy | Usual physiotherapy | SDM/patient a priori, phone option |
| Dysphagia ICU (ongoing)                  | Observational | Understanding risk factors for dysphagia post extubation | SDM/patient a priori, phone option |
| FAST (ongoing)                           | Factorial unblinded RCT | Bid screening for weaning | SBT with T-piece SBT with pressure support ventilation ± positive end-expiratory pressure | SDM/patient a priori or deferred, phone option |
| FISSH (ongoing)                          | Blinded RCT | Normal saline | Ringers lactate | SDM/patient a priori or deferred, phone option |
| FORECAST (ongoing)                       | Observational | Understanding association of frailty with ICU outcomes | SDM/patient a priori, phone option |
| REVISE (ongoing)                         | Blinded RCT | Placebo | Pantoprazole | SDM/patient a priori or deferred, phone option |

ACT = Anti-Coronavirus Therapies to Prevent Progress of coronavirus disease 2019 (COVID-19), BALANCE = Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness, CATCO = Canadian Arm of the SOLIDARITY Trial, CONCOR-1 = CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness, COVACTA = Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia, COVIPRONE = COVID19 Proning Study, CYCLE = Trial of Early In-bed Cycling For Mechanically Ventilated Patients, FAST = The Frequency of Screening and Spontaneous Breathing Trial (SBT) Technique Trial, FISSH = Fluids and Septic Shock, FORECAST = Frailty, Outcomes, Recovery and Care Steps of Critically Ill Patients, HALO = Heparin Anticoagulation to improve Outcomes in septic shock, LOVIT = Lessening Organ Dysfunction with Vitamin C Trial, PPE = personal protective equipment, PT = physiotherapist, RCT = randomized clinical trial, REMAP-CAP = Randomized Embedded Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia, REVISE = Revisiting the Inhibition of Stress Erosions Study, RN = registered nurse, RT = respiratory therapist, SDM = substitute decision maker, SPRINT-SARI = Short Period Incidence Study of Severe Acute Respiratory Illness.

*Indicates industry funding.

*aCanadian Critical Care Trials Group studies.

*Peer-review funding.

*Local funding.

*LOVIT sought and obtained approval from Health Canada and Research Ethics Board for inclusion of patients with COVID-19 who met all other trial criteria, recognizing that viral infections can cause septic shock and that vitamin C was prioritized as a treatment for investigation in COVID-19.

*Preplanned pandemic studies.

*Studies are multicenter unless indicated.
| Bedside Staff Role(s) | Other Hospital Staff Role(s) | Infection Control Concerns | Proposed Course of Action |
|-----------------------|-------------------------------|---------------------------|--------------------------|
| RN open label drug administration | Research pharmacy dispense of study drug | No extra exposure PPE | Priority start |
| RN open label drug administration, nasopharyngeal swabs, blood sampling | Research pharmacy dispenses study drug | No extra exposure or PPE for bedside staff if timed with other clinical activities, but additional PPE to transport and process specimens | Priority start |
| RN blinded plasma administration | Blood bank dispense of plasma | No extra exposure or PPE | Priority start |
| RN blinded administration coordinated with routine care | Research pharmacy dispenses study drug | No extra exposure or PPE for bedside staff if timed with other clinical activities, but additional PPE to transport and process specimens | Priority start |
| Patients self-prone and un-prone with RN/RT assistance as needed | None | If patient assistance needed, additional exposure and PPE for bedside staff | Priority start |
| RN study drug administration and blood sampling day 1, 3, 7 | Research pharmacy prepares and dispenses study drug and placebo | No extra exposure but additional PPE to transport and process specimens | Continue |
| RN open label drug administration | Research pharmacy dispenses study drug | No extra exposure or PPE | Priority start |
| None | None | No extra exposure or PPE | Priority start |
| Assisting research team with wish elicitation and/or implementation | None | No extra exposure or PPE | Priority start |
| RN open label drug administration | None | No extra exposure or PPE | Continue |
| PT implementation of cycling or usual therapy | PT evaluations after ICU discharge on the ward | No extra exposure or PPE, but need to sterilize ergometer | Pause due to equipment sterilization and impending workload of PTs |
| Speech and Language Pathology video swallow examination | Radiology department assessment | Extra exposure and PPE for fluoroscopy assessment | Pause due to exposure risk |
| RT screens for weaning readiness and extubation | None | No extra exposure or PPE | Pause due to impending increased RT workload |
| RN study fluid administration | Research pharmacy prepares and dispenses study fluid and placebo | No extra exposure or PPE | Continue |
| None | None | No extra exposure or PPE | Pause due to resource human reallocation |
| RN study drug administration | Research pharmacy prepares and dispenses study drug and placebo | No extra exposure or PPE | Continue |
Heparin Anticoagulation to improve Outcomes in septic shock (HALO) [25], given the prothrombotic profile of patients with COVID-19. Such existing and similar new trials herald the potential of repurposing drugs approved for other indications for rigorous testing in the pandemic (26).

The process of reviewing each study should consider protocol complexity. Some protocols may be simple, require no additional time of bedside staff or research staff, and consume no PPE, thereby maximizing the benefits produced through the allocation of scarce resources to research (9). Two such examples would be the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) trial, comparing 1 versus 2 weeks of antibiotics for bacteremia (27) and the Revisiting the Inhibition of Stress Erosions Study (REVISE) trial comparing acid suppression versus placebo for stress ulcer prophylaxis (28). The former trial requires no extra hospital resources; the latter requires additional research pharmacy time to prepare study drugs. More complex nonpandemic-focused trials may need to be paused. For example, the Trial of Early In-bed Cycling For Mechanically Ventilated Patients (CYCLE) trial of in-bed cycling requires bedside staff time and PPE that physiotherapists would use in usual care (29), but also transferring an ergometer into the patient’s room and cleaning it thereafter, followed by outcome assessments on the wards (30).

Consent requirements are an important consideration. Waived consent for low-risk observational studies and registries may be suitable, as is often the case during nonpandemic times. Studies with approved alternate consent methods such as witnessed verbal telephone consent, deferred consent, two-physician consent, delayed or waived wet ink signature confirmation, or email e-signature confirmation may be easier to continue. These approaches allow timely study enrollment and concurrently honor the ethical principle of autonomy in the research process while respecting physical distancing.

Reviewing the portfolio of research conducted in a single center should also consider opportunities or contraindications to coenrollment, which is the practice of enrolling patients in multiple studies either concurrently or sequentially. Some studies will be more viable for coenrollment than others. Where possible, coenrollment in COVID and non-COVID trials should be considered. Nonpandemic-focused studies evaluating commonly available interventions (rather than new biological agents) often allow coenrollment according to scientific, logistic, and ethical guidelines (31). Whatever their focus, trials designed to reduce mortality invariably allow coenrollment into studies aimed at humanizing end-of-life care, which is particularly important given restricted bedside family presence and communication barriers due to PPE during the pandemic. For example, the 3 Wishes Project (32), involving eliciting and fulfilling wishes for dying patients from families remotely, patients when able, and their clinicians, would not interfere with interventions being tested in other trials. Existing, adapted, or newly crafted coenrollment policies will also influence which nonpandemic studies to continue. When coenrollment is not possible, generally, pandemic-focused research should be prioritized. However, case-by-case decisions could consider patient-specific risk-benefit assessments, study-specific logistics, and the values of the patient or substitute decision-maker if feasible.

Review the relevance and resource requirements for each study. Every study involves opportunity costs including human time and financial resources. A run-in phase or important pilot work for unfunded pandemic research may be needed before securing future funding. Continuing nonpandemic-focused studies may confer financial stability to research teams and maintain accountability to granting agencies while awaiting funding decisions for COVID-19 investigations.

To illustrate how these principles may be applied in Table 1, we present an application of this framework to the consideration of studies in our center that were ongoing when the pandemic began or considered for start-up in response to the pandemic.

Consider Research Oversight. Pandemic mitigation efforts could interfere with all aspects of a successful clinical trial, including informed consent, accrual, intervention delivery, and safety monitoring and outcome assessment (16). Studies conducted during pandemic periods—whether pandemic-focused or not—should be held to the highest possible standards of implementation fidelity considering the extenuating circumstances. Therefore, when deciding to continue nonpandemic-focused research, centers should examine each study to ascertain whether research integrity can be maintained throughout the pandemic period.

Existing research protocol implementation may need to be adapted. Modifications may relate to informed consent (e.g., alternate informed consent methods). Enabling and evaluating protocol adherence may need to be done remotely rather than on-site and may need to be retrospective rather than real-time. To keep safety assessments as current as possible, research staff phone calls or automatic e-alerts within the electronic medical record should be considered.

Centers may consider prioritizing data collection and entry for trials addressing the efficacy, safety, and futility of pandemic-specific interventions to hasten the analysis and dissemination of their results. Some data collection of nonpandemic-focused studies may need to be delayed. For centers with paper-based patient charts, data collection may need to be adapted, such as batching data collection, scanning daily flow sheets to the research office, or postponing noncritical data until medical records are uploaded into the hospital electronic charting system. Some data may be foregone if ascertainment requires real-time on-site assessment which is precluded by physical distancing.

Pandemic-specific standard operating procedures should be enacted to track any modifications to the protocol implementation for each study in your center. Document decisions in consultation with investigators, steering committees, sponsors, and other local stakeholders. Any changes should be approved by the relevant local institutional authorities and reported to ethics boards per local guidance.

Reconsider Decisions Regularly. As the pandemic continues and institutional impacts evolve or resolve, revisit research decisions regularly with a variety of stakeholders including...
representation from clinical staff, hospital and university leadership, ethics and regulatory authorities, funders, research staff, and investigators. This stakeholder consultation should respond rapidly as the pandemic evolves, to receive feedback about progress and problems, and remediate as necessary. This group will be important when considering how to reinitiate research as the burden of the pandemic abates. When paused research is reinstated, seek broad input and start first with familiar and less complex studies, so as not to unduly burden individuals affected.

Contingency plans should be developed for prompt cessation of recruitment in each study and follow-up of patients on protocol in case the pandemic surge overwhelms research capacity for any study. This plan should include alternate research management and local study oversight should staff or investigators become ill.

Consider Final Reporting Requirements. After the pandemic subsides, investigators should consider whether any changes or pauses to research during the pandemic have affected the internal validity or external validity of each study in your center. Periods of paused enrollment should be reported to the Methods center for each study.

Methods centers for single or multicenter studies should report temporary adaptations to their trial, if any (16). Consider whether changes are warranted to the statistical analysis plan, including characterizing patients with COVID-19, approaches to missing data, or post hoc subgroup analyses if sensible and sample size permits.

Limitations

We did not address other relevant issues such as how discontinuing nonpandemic-focused research during pandemic times may have cascading consequences beyond delaying study results. Sequelae may include lost staff time, contract modification, or staff unemployment. If ongoing studies are completely terminated, efforts to-date including patient contributions and research funds may be wasted. Decisions to halt the generation of medical knowledge should be made with awareness of opportunity costs in the short- and long-term for individuals and society (16, 33, 34).

This report did not benefit from the input of patients or the public, nor agencies funding ongoing studies. We did not undertake formal document analysis of hospital, university, or government policies. During the H1N1 pandemic in Canada, only 7% of critical care research coordinators reported deferring ongoing or planned non-H1N1 studies to facilitate H1N1 studies (8). Although we did not seek information on the influence of the COVID-19 pandemic on clinical research in other jurisdictions, an international survey is underway (21).

CONCLUSIONS

Clinical research will play a vital role in understanding the influence of COVID-19 on critical illness, informing patient care around the world. While research is key in the response to public health emergencies, it must never impede clinical response efforts.

Several lines of reasoning are needed to balance the interplay between COVID-19 specific studies and other studies, without jeopardizing the care of patients or the safety of staff. During the pandemic, research should not focus exclusively on the potential health needs of some individuals while neglecting the health needs of others. Clinical research is essential to improving the process and outcomes of care both for patients with and without COVID-19. The benefits and burdens of research should be equally distributed where possible or allocated according to objective and transparent decision-making processes.

We propose that decisions to pause or pursue nonpandemic research during pandemic times be made following careful deliberation based on objective criteria. Considerations include aspects of the research process for each study such as roles of bedside and research staff, the informed consent model, intervention complexity, protocol integrity, data collection, and infection control concerns such as use of scarce PPE. This framework considers capacity evaluation, safety assessments, and local approval. Plans to continue nonpandemic research should be proportionate, transparent, informed by key stakeholders, and revisited as the pandemic abates.

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For information regarding this article, E-mail: debcook@mcmaster.ca

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