

# Principles Guiding Nonpandemic Critical Care Research During a Pandemic

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**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

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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 2019. Considerations to continue nonpandemic-focused research include the status of the pandemic, local jurisdictional guidance, capacity and safety of bedside and research personnel, disposition of patients already enrolled in nonpandemic studies, analyzing characteristics of each nonpandemic-focused study, research oversight, and final reporting requirements.

**Conclusions:** Deliberation about continuing nonpandemic research should use objective, transparent criteria considering several aspects of the research process such as bedside and research staff safety, infection control, the informed consent model, protocol complexity, data collection, and implementation integrity. Decisions to pause or pursue nonpandemic research should be proportionate, transparent, and revisited as the pandemic abates.

**Key Words:** clinical research; critical care research; healthcare worker; pandemic; priority

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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 multistudy management. 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 health-care 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 <sup>a</sup> (new)	Adaptive unblinded RCT	Acetyl salicylic acid/ rivaroxaban/interferon	Standard care	SDM/patient a priori, phone option
CATCO <sup>b,c</sup> SOLIDARITY (new)	Adaptive unblinded RCT	Lopinavir/ritonavir, interferon, remdesivir	Standard care	SDM/patient a priori or deferred, phone option
CONCOR-1 <sup>c</sup> (new)	Unblinded RCT	COVID-19 convalescent	Standard care	SDM/patient a priori, phone option
COVACTA <sup>a</sup> (new)	Double-blinded RCT	Tocilizumab	Placebo	SDM/patient a priori, phone option
COVI-PRONE <sup>d</sup> (new)	Unblinded RCT	Early awake proning	Standard care	SDM/patient a priori or deferred, phone option
LOVIT <sup>b,c,e</sup> (ongoing)	Blinded RCT	4 d of vitamin C	4 d of placebo	SDM/patient a priori or deferred, phone option
REMAP-CAP <sup>b,c,f</sup> (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 <sup>b,c</sup> (new)	Observational	Pandemic registry of patients hospitalized with confirmed COVID-19, including ICU patients		Waived
3 Wishes Project in the pandemic <sup>d</sup> (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 <sup>b,c</sup> (ongoing)	Unblinded RCT	7 d antibiotic therapy	14 d antibiotic therapy	SDM/patient a priori, phone option
CYCLE <sup>b,c</sup> (ongoing)	Unblinded RCT	In-bed cycling + usual physiotherapy	Usual physiotherapy	SDM/patient a priori, phone option
Dysphagia ICU <sup>d,g</sup> (ongoing)	Observational	Understanding risk factors for dysphagia post extubation		SDM/patient a priori, phone option
FAST <sup>b,c</sup> (ongoing)	Factorial unblinded RCT	Bid screening for weaning Once daily 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 <sup>b,c</sup> (ongoing)	Blinded RCT	Normal saline	Ringers lactate	SDM/patient a priori or deferred, phone option
FORECAST <sup>b,c</sup> (ongoing)	Observational	Understanding association of frailty with ICU outcomes		SDM/patient a priori, phone option
REVISE <sup>b,c</sup> (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, COVI-PRONE = COVID-19 Prone 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.

<sup>a</sup>Industry funding.

<sup>b</sup>Canadian Critical Care Trials Group studies.

<sup>c</sup>Peer-review funding.

<sup>d</sup>Local funding.

<sup>e</sup>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.

<sup>f</sup>Preplanned pandemic studies.

<sup>g</sup>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 reinstitute 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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## REFERENCES

1. Rome BN, Avorn J: Drug evaluation during the Covid-19 pandemic. *N Engl J Med* 2020; 382:2282–2284
2. Cook DJ, Marshall JC, Fowler RA: Critical illness in patients with COVID-19: Mounting an effective clinical and research response. *JAMA* 2020; 323:1559–1560
3. For the SPRINT-SARI investigators: Using research to prepare for outbreaks of severe acute respiratory infection. *BMJ Glob Health* 2019; 4:e001061
4. REMAP-CAP Trial: A Randomised, Embedded, Multi-Factorial, Adaptive Platform Trial for Community-Acquired Pneumonia. REMAPCAP Trial. Available at: <https://www.remapcap.org>. Accessed April 21, 2020
5. Cook D, Burns K, Finfer S, et al: Clinical research ethics for critically ill patients: A pandemic proposal. *Crit Care Med* 2010; 38:e138–e142

6. Tansey CM, Herridge MS, Heslegrave RJ, et al: A framework for research ethics review during public emergencies. *CMAJ* 2010; 182:1533–1537
7. Kho ME, McDonald E, Zytaruk N, et al: Costs of clinical research preparation for the H1N1 pandemic in Canada: A single center, multi-site analysis. *Am J Respir Crit Care Med* 2011; 183:A2387
8. Burns KE, Rizvi L, Tan W, et al: Participation of ICUs in critical care pandemic research: A province wide, cross-sectional survey. *Crit Care Med* 2013; 41:1009–1016
9. Emanuel EJ, Persad G, Upshur R, et al: Fair allocation of scarce medical resources in the time of Covid-19. *N Engl J Med* 2020; 382:2049–2055
10. Peckham S, Hann A: Public Health Ethics and Practice. Bristol, United Kingdom, The Policy Press, 2020
11. Gobat NH, Gal M, Francis NA, et al: Key stakeholder perceptions about consent to participate in acute illness research: A rapid, systematic review to inform epi/pandemic research preparedness. *Trials* 2015; 16:591
12. Lurie N, Manolio T, Patterson AP, et al: Research as a part of public health emergency response. *N Engl J Med* 2013; 368:1251–1255
13. Busta ER, Mancher M, Cuff PA, et al; National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Board on Global Health; Committee on Clinical Trials During the 2014-2015 Ebola Outbreak: Conducting Clinical Research During an Epidemic. Integrating Clinical Research into Epidemic Response: The Ebola Experience. Washington, DC, National Academies Press (US), 2017. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK441674/>. Accessed April 19, 2020
14. Ortiz JR, Rudd KE, Clark DV, et al: Clinical research during a public health emergency: A systematic review of severe pandemic influenza management. *Crit Care Med* 2013; 41:1345–1352
15. Webb SA, Nichol AD: Bending the pandemic curve: Improving decision-making with clinical research. *Crit Care Med* 2018; 46:442–446
16. McDermott MM, Newman AB: Preserving clinical trial integrity during the coronavirus pandemic. *JAMA* 2020; 323:2135–2136
17. Rawls J: A Theory of Justice: Original Edition. Cambridge, MA, Harvard University Press, 2009, p 624
18. Grasselli G, Zangrillo A, Zanella A, et al: Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323:1574–1581
19. Richardson S, Hirsch JS, Narasimhan M, et al: Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020; 323:2052–2059
20. WHO Working Group on Ethics & COVID-19: Ethical Standards for Research During Public Health Emergencies: Distilling Existing Guidance to Support COVID-19 R&D. WHO International. 2020. Available at: <https://apps.who.int/iris/bitstream/handle/10665/331507/WHO-RFH-20.1-eng.pdf>. Accessed April 19, 2020
21. Duffett M, Strong G, Lee JH, et al: Impact of COVID-19 on Critical Care Research. PICU Trials. Available at: <https://picutrials.github.io/covid-survey/>. Accessed April 6, 2020
22. Rochwerg B: NCT03677102 Fluids in Septic Shock (FISSH). ClinicalTrials.gov. 2018. Available at: <https://clinicaltrials.gov/ct2/show/NCT03677102>. Accessed April 19, 2020
23. Lamontagne F, Adhikari N: NCT03680274 Lessening Organ Dysfunction With Vitamin C (LOVIT). ClinicalTrials.gov. 2018. Available at: <https://clinicaltrials.gov/ct2/show/NCT03680274>. Accessed April 19, 2020
24. World Health Organization: A Coordinated Global Research Roadmap. World Health Organization, 2019:16. Available at: [www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1](http://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1). Accessed April 19, 2020
25. Zarychanski R: NCT03378466 Heparin Anticoagulation in Septic Shock (HALO). ClinicalTrials.gov. 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT03378466>. Accessed April 19, 2020
26. Kaplan LJ, Bleck TP, Buchman TG, et al: Pandemic-related submissions: The challenge of discerning signal amidst noise. *Crit Care Med* 2020; 48:1099–1102
27. Daneman N, Fowler R: NCT03005145 Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE). ClinicalTrials.gov. 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT03005145>. Accessed April 19, 2020
28. Cook DJ: NCT03374800 Re-Evaluating the Inhibition of Stress Erosions Trial (REVISE). ClinicalTrials.gov. 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT03374800>. Accessed April 19, 2020
29. Thomas P, Baldwin C, Bissett B, et al: Physiotherapy management for COVID-19 in the acute hospital setting: Clinical practice recommendations. *J Physiother* 2020; 66:73–82
30. Kho ME: NCT03471247 CYCLE: A Randomized Clinical Trial of Early In-Bed Cycling for Mechanically Ventilated Patients. ClinicalTrials.gov. 2018. Available at: <https://clinicaltrials.gov/ct2/show/NCT03471247>. Accessed April 19, 2020
31. Cook DJ, Blythe D, Rischbieth A, et al: Enrollment of intensive care unit patients into clinical studies: A trinational survey of researchers' experiences, beliefs, and practices. *Crit Care Med* 2008; 36:2100–2105
32. Vanstone M, Neville TH, Clarke FJ, et al: Compassionate end-of-life care: Mixed-methods multisite evaluation of the 3 wishes project. *Ann Intern Med* 2020; 172:1–11
33. Chong S-A, Capps BJ, Subramaniam M, et al: Clinical research in times of pandemics. *Public Health Ethics* 2010; 3:35–38
34. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. 2020:16. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>. Accessed April 19, 2020