

Clinical research ethics for critically ill patients: A pandemic proposal

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Pandemic H1N1 influenza is projected to be unprecedented in its scope, causing acute critical illness among thousands of young otherwise healthy adults, who will need advanced life support. Rigorous, relevant, timely, and ethical clinical and health services research is crucial to improve their care and outcomes. Studies designed and conducted during a pandemic should be held to the same high methodologic and implementation standards as during other times. However, unique challenges arise with the need to conduct investigations as efficiently as possible, focused on the optimal outcome for the individual patient, while balancing the need for maximal societal benefit. We believe that

clinical critical care research during a pandemic must be approached differently from research undertaken under nonemergent circumstances. We propose recommendations to clinical investigators and research ethics committees regarding clinical and health services research on pandemic-related critical illness. We also propose strategies such as expedited and centralized research ethics committee reviews and alternate consent models. (Crit Care Med 2010; 38[Suppl.]:e138–e142)

KEY WORDS: critical care; pandemic; H1N1 influenza; clinical trials; research ethics committee; informed consent

The H1N1 2009 pandemic poses unprecedented research challenges in critically ill patients. The severe acute respiratory syndrome outbreak of 2003 demonstrated how difficult it is to develop and implement studies of critical illness during ep-

idemics when clinical services are overwhelmed (1). Early reports of the recent influenza season in the southern hemisphere indicate that young, otherwise healthy adults are predisposed to H1N1-related critical illness, characterized by refractory, life-threatening respiratory failure. Given the 20% risk of death, the possibility for improved outcomes will not be realized without collaborative national and international investigations. Accordingly, as we approach influenza season in the northern hemisphere, many fundamental clinical and health services research questions remain unanswered, leaving clinicians caring for the most seriously ill patients without current, valid evidence. Investigations will need to be developed, implemented, and completed in a timely manner to maximize the chance of informing clinicians and public health policy. Essential investigations during the pandemic will be impossible without advanced planning and rapid implementation strategies.

Research is crucial to understanding existing and potential critical care services, and the consequences of excessive demands placed on them. The anticipation of increased need for intensive care resources during the H1N1 pandemic raises concerns that the capacity to deliver basic and advanced life support in the intensive care unit (ICU) will be ex-

ceeded. Although plans to expand critical care resources have been made in some countries (e.g., United Kingdom) (2), other jurisdictions are not as prepared. If local capacity is overwhelmed, then some critically ill patients may be subject to triage and denied ICU admission. Care for patients without H1N1 may also be curtailed as scheduled elective surgery is postponed. If and when triaging protocols are invoked, real-time analysis of patient outcomes will be ethically imperative. Accurate timely clinical research regarding epidemiology, diagnosis, and treatment will be crucial for critically ill patients presenting with potential H1N1 infection. Predictors of early respiratory deterioration will help to inform rational use of monitoring devices and critical care. The sensitivity and specificity of initial and sequential screening tests in the ICU setting are unknown. False-negative test results could prompt the premature lifting of isolation precautions and dangerously delay in treatment. False-positive test results could waste scarce drug supplies and increase demands on resources for isolation. Pharmacologic and technological therapies that favorably influence morbidity and mortality and decrease nosocomial transmission to other critically ill patients and health workers will require rapid identification and implementation.

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Barriers to research implementation in the ICU setting during the H1N1 pandemic in the northern hemisphere will be legion. These include the need to test for and treat H1N1 under emergency conditions, study an acute illness with its attendant high morbidity and mortality, and recruit patients within narrow time windows. The rapid onset and dissipation of the pandemic may preclude coordinated efforts, and research staff may be deployed to provide clinical care to a surge of critically ill patients. Some clinicians may be reluctant to enroll gravely ill patients into randomized trials, while resorting to unproven or potentially harmful treatments. Other clinicians may view the H1N1 pandemic as an incomparable opportunity, or a mandate, to answer urgent research questions that might otherwise never be answered. For instance, when several thousand patients with severe acute respiratory distress syndrome need mechanical ventilation within in a short time frame, readiness with a large, simple, international trial could evaluate the impact of systemic corticosteroids, antivirals, or high-frequency oscillatory ventilation.

Just as specialists in public health, family, emergency, pulmonary, and critical care medicine are planning the appropriate clinical response to the pandemic, investigators and institutions need to plan their research response. Herein, we propose recommendations to clinical researchers and research ethics boards (REBs) preparing for H1N1-related critical illness.

Institutional Review Boards

The need for research oversight by REBs is no less essential during a pandemic than

in less emergent circumstances. REB oversight ensures that the rights, safety, and well-being of vulnerable participants are protected. Today, REBs face increasing demands because of an increasing number of studies and volume of regulations (3). Redundancy in the approval process for multicenter studies and variation in REB responses to the same study (4, 5) prompt the credo of “do it once and do it well” (6).

H1N1 research will escalate REB workload, particularly for multicenter protocols, which are typically reviewed by each participating center. Experience in the winter months of Australia, New Zealand, and South America portends a sudden influx of patients with peak ICU occupancy occurring within approximately 6 wks, decreasing quickly thereafter. Thus, adherence to the usual timelines for investigators to prepare and submit proposals to REBs, for multicenter REB review, and for investigator responses to REB conditions would mean that the pandemic will have passed before any research can be initiated.

We believe that during a pandemic, expedited and preferably centralized full review will help to ensure patient safety while avoiding delays that could block investigations necessary to advance knowledge and improve outcomes. A centralized process starts with one authorized national, provincial, state, or regional in-depth REB review; after conditions are met, the (potentially revised) protocol, central REB documents, and approval letter are submitted to all participating local REBs. Local REBs then consider and typically endorse the “central approval” and more rapidly review the protocol to primarily provide

guidance to investigators on local adaptations and implications. When performed well, central REB review can expedite the process of research ethics oversight and obviate replication at each participating site. However, if central review merely duplicates full reviews, this could waste time or create confusion over differing opinions between central and local REBs. In Table 1, we present recommendations for REB approval processes for clinical research protocols during the H1N1 pandemic.

Informed Consent

Critically ill patients invariably lack decision-making capacity, rendering first-person consent for research participation a rare event. Therefore, *a priori* consent is usually sought from surrogates who are often under considerable emotional stress. However, *a priori* consent from surrogates is not possible for adult patients in some countries (7). Furthermore, relying exclusively on *a priori* surrogate informed consent could preclude clinical research during the pandemic, thereby slowing enrollment into studies, denying potential participants the opportunity to benefit from research participation, limiting the generalizability of study results, delaying the identification of treatments as effective, ineffective, or harmful, and potentially foregoing the acquisition of new knowledge on the pandemic (8).

There is a growing recognition that alternative consent models require consideration in the setting of critical illness (Table 2) (9). The Declaration of Helsinki allows research involving individuals from whom it is not possible to obtain consent if the condition that prevents obtaining informed consent is a key characteristic of the research population (10). Many national research councils have attempted to strike a balance between the need for clinical research and the challenge of involving patients in this process at times of serious threat. For example, the Canadian Tri-Council Policy (11) permits research to be conducted in emergencies “without the free and informed consent of the subject in the presence of a serious threat requiring immediate intervention, where no efficacious standard of care exists or research offers a real possibility of direct patient-benefit and the risk of harm is not greater than that of standard care or is clearly justified by the direct benefits to the subject.” The

Table 1. Recommendations for research ethics boards protocol review for clinical critical care research during the H1N1 pandemic

At the local level, and ideally at the regional or national level, REBs should develop a plan for managing clinical research during the H1N1 pandemic and share this with investigators, clinicians, and the community
During the H1N1 pandemic, REBs need to balance the ethical principle of autonomy and the individual right to information privacy with social justice and population ethics
For single-center H1N1 studies, protocols should receive emergency expedited REB review
For multicenter H1N1 studies, protocols should receive full REB review at the lead institution and emergency-expedited review at other participating centers
For multicenter H1N1 studies, if emergency-expedited REB review is not possible locally, REB approval from an institution within a similar jurisdiction should be considered; thereafter, the protocol should be rapidly reviewed for guidance on local adaptations and implications
For multicenter H1N1 studies, local REBs should consider endorsing a central REB review process (from a regional, provincial, state, or national REB, as available); thereafter, the protocol should be rapidly reviewed for guidance on local adaptations and implications

REB, research ethics board; H1N1, novel swine origin influenza virus (S-OIV) A/H1N1.

Table 2. Alternative consent models for research participation of critically ill patients

Alternative Consent Model	Description
Deferred patient consent	Enroll an eligible patient in a study in the absence of <i>a priori</i> patient consent because of lack of decision-making capacity, with the intention of procuring <i>post hoc</i> consent from the patient when decision-making capacity is regained
Deferred surrogate consent	Enroll an eligible patient in a study in the absence of <i>a priori</i> surrogate consent, with the intention of procuring <i>post hoc</i> consent from the surrogate once contact can be made
Authorized representative consent	Enroll an eligible patient in a study after two independent physicians (neither of whom are involved in the study's design or implementation) provide <i>a priori</i> consent on the patient's behalf
Objection to participation	Enroll an eligible patient in a study with <i>a priori</i> affirmative response to the question of whether the patient would "object to participating," as opposed to asking if the patient would "agree to participate"
Waived consent	Enroll an eligible patient in a study without consent because it is not required

Table 3. Food and Drug Administration guidelines for conducting research without informed consent

1. The research involves human subjects who cannot give informed consent because of their emerging life-threatening medical condition
2. The condition requires immediate intervention
3. Available treatments are unproven or unsatisfactory; further research is needed to determine the best therapy
4. Clinical equipoise exists between the treatments under study and standard treatment
5. The research might provide direct benefit to each subject
6. The research cannot move forward without the exception to informed consent because the subject cannot consent as a result of his/her medical condition; and intervention must start before consent from a legally authorized representative is feasible; and there is no reasonable way to identify likely research subjects prospectively
7. The study plan includes a defined therapeutic window
8. The principal investigator commits to try to contact, within the therapeutic window, the legally authorized representative and family members who might object to the study
9. The investigator has provided an informed consent procedure to use if and when feasible, information to provide to family members who might object to study participation, and procedures to inform, when appropriate, of the details of the study after the subject's inclusion and disclosure of the subject's inclusion in the event of the subject's death
10. The additional patient safeguards that exist are in effect beyond those additionally required
11. The applicable laws allow research with an exception from informed consent (state laws supersede federal research regulations)
12. The sponsor has received written permission from the Food and Drug Administration to proceed with the research

Adapted from Biros (12).

U.S. Food and Drug Administration similarly allows for exceptions to informed consent (Table 3) (12). Despite this directive, waived consent is unusual for studies of critically ill patients, and individuals other than family members seldom provide surrogate consent in this setting (13).

Conditions have been proposed under which informed consent could be waived; we believe these should be invoked during the pandemic. These include when all treatments offered in the trial do not involve more than minimal additional risk

in comparison with alternatives, and when treatments offered in the trial could be offered outside the trial without informed consent. Furthermore, genuine clinical equipoise needs to exist among the treatments offered, and patient preference for one treatment over any other needs to be unlikely. Finally, patients should be informed of the guidelines for waiver of informed consent so that they have the opportunity to seek additional information or care elsewhere (14).

Abuse of vulnerable persons under the auspices of research has been docu-

mented throughout history. Today, cultural shifts are occurring in the way that the public considers research participation. Biomedical knowledge obtained through clinical research is a public good available to benefit an individual, even if that individual does not contribute to it. The "public good argument" suggests that individuals at least consider research participation when approached unless they have a good reason not to, rather than the opposite, i.e., participate only if they have a good reason to do so (15).

Informed Consent for Observational Studies

Available evidence indicates that mandating traditional *a priori* first-person or surrogate informed consent sometimes may be contrary to the public good. We believe that this applies to research involving critically ill patients during the H1N1 pandemic regarding *a priori* informed consent for registries, audits, retrospective chart reviews, and prospective observational studies that do not influence patient care. For chart reviews (16), authorization bias can result in statistically significant differences in prognostic variables between participants and non-participants, threatening the validity and generalizability of study results (17).

Privacy legislation may lead to requests to obtain informed consent for enrollment in registries, which could also threaten the credibility of registry results. For example, mandatory *a priori* first-person consent for enrollment in the Canadian Stroke Registry initially resulted in inclusion of only 39% of eligible patients, which increased to 51% when a dedicated research nurse worked at each site. Mortality was significantly lower in enrolled vs. eligible patients (7% vs. 22%, $p < .001$), thereby creating a selection bias. Unsuccessful attempts to obtain *a priori* informed consent for the Canadian Stroke Registry led to temporary cessation of enrollment (18).

Evidence: Informed Consent for Randomized Trials

Providing there has been peer scientific and REB review, many examples of alternate consent models exist for randomized trials of emergent or urgent conditions or treatments that permit clinical research on incapacitated patients. For example, a randomized trial of urgent albumin resuscitation was re-

Table 4. Recommendations for informed consent for clinical critical care research during the H1N1 pandemic

Registries, audits, retrospective chart reviews, and prospective observational studies regarding H1N1-related critical illness that do not influence patient care should use a waiver of consent

Randomized trials of treatments for H1N1 critical illness that are in widespread use (e.g., dose or duration of antivirals or use of corticosteroids) should use deferred consent or waived consent

Randomized trials of treatment with an established safety record but that are unproven for H1N1 (e.g., serum immune globulin) should consider deferred or waived consent

Randomized trials of new H1N1 treatments without an established safety record that are unproven for H1N1 (e.g., ECMO) base the consent model on level of risk

For patients with no existing surrogates or unavailable surrogates, alternate consent models should be considered, such as deferred consent (deferred from the patient, deferred from the surrogate), two-physician consent, a request for an “objection to participate,” or waived consent

Verbal consent should be considered for surrogates who are illiterate; consent through translators should be considered for surrogates speaking different languages or dialects

Telephone consent should be considered for surrogates who are prohibited from coming to or unable to come to the hospital during a pandemic

Consent models should be predicated on the anticipated level of benefit and risk incurred by study participation

Hybrid consent models (e.g., different consent models for the same study) that acknowledge whether surrogates exist or are unavailable) should be encouraged, adapted to local norms and circumstances

A taxonomy of REB-approved H1N1-related studies into which patients may be enrolled without *a priori* written informed consent should be developed locally; public notification (by community consultation, print, audiovisual, or Web media) should publicize enrollment as the default, akin to the assumption of consent for organ donation in some jurisdictions, with opportunities for the surrogates to opt out

Co-enrollment of patients in both H1N1-related treatment and observational studies and other unrelated studies should be allowed, adapted to local norms and circumstances

ECMO, extracorporeal membrane oxygenation; REB, research ethics board.

cently performed with deferred consent (19). For a randomized trial of emergency corticosteroids for head injury, different consent models were used (deferred, waived or *a priori* surrogate consent) in different jurisdictions (20). Within a randomized trial of intensive insulin therapy in which early implementation was considered important to rigorously evaluate the treatment effect, deferred consent was used in some centers in Australia and New Zealand, whereas *a priori* surrogate consent was used in Canada (21). When the consent model in a trial of corticosteroids for severe sepsis was changed from *a priori* surrogate consent to waived consent if no relative was located when inclusion criteria were met, enrollment increased from four to ten patients each month (22). In Table 4, we present recommendations for informed consent for clinical studies on critically ill patients during the H1N1 pandemic.

DISCUSSION

The H1N1 influenza pandemic is projected to precipitate the need for increased critical care resources for many patients worldwide; between 10% and 25% of these patients may die. We believe that the global research community has

an ethical obligation not only to document the pandemic and understand its epidemiology but also to conduct high-quality diagnostic, therapeutic, and health services research that maximizes the chance of improving outcomes. The ethical framework for pandemic research, similar to pandemic treatment, should hinge not only on the individual but also on the entire population of those actually or potentially afflicted.

CONCLUSION

We believe that clinical critical care research during the H1N1 pandemic must be approached differently from research conducted under nonemergent circumstances. Investigators need to prepare methodologically sound protocols carefully and quickly, thoughtfully suggesting appropriate approaches to informed consent. REBs will need to provide research oversight but avoid delaying the approval of sound protocols, unnecessarily duplicating the oversight process, or requiring *a priori* consent for all study designs. The H1N1 pandemic offers an unparalleled opportunity to use reduce redundancy, develop common REB review processes, and facilitate research on critically ill patients.

Acknowledging the different cultures and contexts into which healthcare systems are embedded, there are lessons to be learned from studying the effect of differing approaches to consent in various jurisdictions. Deferred or waived consent models will result in research questions being answered more quickly, thereby producing results more easily generalized than would otherwise be the case. Such approaches may hasten the acquisition of new knowledge, allow effective treatments for use during the pandemic, and liberate scarce resources for other patients. Increasing societal appreciation that research participation is recognized as a societal good is particularly germane under these circumstances. Failure to improve outcomes through rigorous efficient investigations during the pandemic is as ethically irresponsible as failing to provide care itself. We call on those whose responsibilities and actions influence the conduct of critical care research to take the steps necessary to make such research a reality.

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