Do National and International Ethics Documents Accord With the Consent Substitute Model for Emergency Research?

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ABSTRACT

In 2010 Largent, Wendler, and Emanuel proposed the “consent substitute model” for emergency research with incapacitated participants. The model provides a means to enroll participants in emergency research without consent, if five conditions are met: 1) the research addresses the patients’ urgent medical needs, 2) the risk–benefit ratio is favorable, 3) there are no known conflicts with patients’ values or interests, 4) cumulative net risk is minimal, and 5) consent is given as soon as possible. We review national and international ethics laws, regulations, and guidelines to determine 1) whether they accord with the consent substitute model’s five conditions and 2) the level of congruence across these documents. We find that only one document meets all five conditions and that there is significant disparity among the documents, particularly between national and international ones. These differences may have stymied international collaboration in emergency research. We recommend that the two international documents used most, the International Council for Harmonization’s Guideline for Good Clinical Practice and the World Medical Association’s Declaration of Helsinki, are revised to include more specific provisions on emergency medical research.

In 2010 Largent et al.\textsuperscript{1} proposed the “consent substitute model” for emergency research with incapacitated participants. The model provides a means of resolving the “fundamental ethical dilemma” of whether to “prohibit valuable research because informed consent is not possible or enroll individuals in clinical trials without informed consent.” It consists of five conditions: 1) the experimental intervention must address patients’ urgent medical needs, 2) the risk–benefit ratio of the intervention must be at least as favorable as that of alternatives, 3) there must be no known conflict with the patients’ values or interests, 4) the cumulative net risk must be minimal, and 5) consent for ongoing research must be given as soon as possible.

Largent et al. pointed out that emergency research without initial consent was permissible under U.S., Canadian, and Australian regulations, but seemingly prohibited by European Union law. Moreover, they described the status of such research as “uncertain internationally.” These differences and uncertainties may have discouraged, if not prevented, multinational emergency research. The European Union Directive of 2001 on clinical trials is soon to be replaced. Thus a review of the legal and ethical status of emergency medical research is timely and necessary.
research is timely. We analyzed national and international ethics laws, regulations, and guidelines to determine 1) whether research conducted under their provisions would meet the five conditions of Largent et al.’s consent substitute model and 2) the level of harmony across these documents.

**NATIONAL AND INTERNATIONAL ETHICAL FRAMEWORKS ADDRESSING EMERGENCY CARE RESEARCH**

European Union Directive 2001/20/EC, on good clinical practice in clinical trials, applies in European Economic Area states (that is, the European Union member states plus Iceland, Norway, and Liechtenstein). It requires consent by a legal representative for research with incapacitated patients. This has impeded emergency research where surrogate consent is unavailable and/or infeasible, although some states have continued to allow such research. This has been possible because a directive contains goals to be achieved through national laws and is thus open to interpretation. The directive is soon to be replaced by Regulation 536/2014, which will be directly binding on states and contains provisions enabling emergency research without consent. (Note that while the United Kingdom is no longer a member of the European Union, the directive still applies. Whether or not the Regulation will apply in the United Kingdom will depend on the length of the U.K.’s transition period.) The Council of Europe’s Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (2005), also addresses research in clinical emergency situations. The protocol is binding on those states that have ratified it, but only 12 of 47 member states have done so.

The most comprehensive and well-known national regulations on emergency research are the exception from informed consent (EFIC) and waiver of informed consent (WIC) regulations introduced in the United States in 1996. These allow emergency research to proceed without consent if certain conditions are met. Many other states also have specific provisions on emergency medical research, albeit within general ethics legislation, regulations, or guidelines.

There are also some important international guidelines. The International Council for Harmonization (ICH) Guideline for Good Clinical Practice (2016) provides a unified standard for clinical trials in the European Union, Japan, the United States, Canada, and Switzerland. Many other states also use it (see Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/ace m.14179/full). The guideline was revised in 2016, but the provisions on emergency research are unchanged from the 1996 version. The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-Related Research Involving Humans, also revised in 2016, have extensive sections on emergency research with those unable to consent. The provisions on emergency research are similar to those in the previous 2002 version. Both the ICH Guideline and the CIOMS Guidelines, like other ethics documents, are aligned with the World Medical Association (WMA) Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (2013). Although this does not mention emergency research specifically, it does contain a section on research with unconscious persons that cannot be delayed to get surrogate informed consent.

**COMPARISON OF ETHICAL FRAMEWORKS WITH THE CONSENT SUBSTITUTE MODEL**

We compared the five conditions of the consent substitute model with the emergency research provisions within international and national ethical frameworks, to determine whether it could be employed by researchers adhering to these frameworks. We chose this model because previous research has demonstrated the difficulties involved in seeking informed consent in emergency medical research. Largent et al. provide an alternative to unsatisfactory consent processes used in this context. Furthermore, their model continues to be cited regularly in the emergency research literature. The International Compilation of Human Research Standards (2020) was used as a starting point to identify states that have specific guidance on emergency medical research, but are not in the European Economic Area (plus the United Kingdom) or among the 12 ratifying states of the Council of Europe’s Additional Protocol. To ensure accuracy of interpretation, our analysis was limited to states providing documentation in English. Twenty-four states were found to have national laws, regulations, or ethical guidelines with substantive provisions on emergency medical research. Of these, 11 were discounted from the analysis, because their documents only use
wording from other, previously published texts (the ICH Guideline and the 2002 CIOMS Guidelines, for example). Ukraine and Mali were also excluded, because it is not clear that these states allow emergency research without consent or consultation with a surrogate, rendering them incompatible with the basic premise of the consent substitute model. Google Translate was used to give an indication of the content of documents in languages other than English, to determine the equivalent numbers for states with no English documents. We found 13 such states with substantive provisions on emergency research, of which seven appear to use only previously published texts. Further details of the document review process and links to all those examined can be found in Data Supplement S1. Our findings on the five international organizations and 11 states analyzed are summarized in Table 1.

### Responsiveness

The first condition in Largent et al.’s model includes two elements: “the experimental intervention must be responsive to patients’ urgent medical needs” and “an emergency research intervention without initial consent should be responsive to the urgent medical condition characterizing the class of patients that will be enrolled in the trial.” Canada’s Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (2018) mirrors the first element very closely: “research involving medical emergencies shall be conducted only if it addresses the emergency needs of the individuals involved.” Japan’s Ethical Guidelines for Medical and Health Research Involving Human Subjects (2017) similarly state that there must be “sufficient possibility of saving the life of the research subject in a life-threatening condition by implementing the said research.” Several other regulations contain provisions analogous to the responsiveness condition, often using the language of direct benefits. Australia’s National Statement on Ethical Conduct in Human Research (2018) addresses both elements, because emergency research without consent must be of potential benefit to the individual participant and likely to lead to better understanding of, or care of those with, the condition in question. Under the new EU Regulation (2014), emergency research without consent will need to relate directly to the medical condition that has rendered the participant unable to consent and be of potential direct and clinically relevant benefit to them. Ethiopia’s National Research Ethics Review

<table>
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<th>State or Organization</th>
<th>Responsiveness</th>
<th>Favorable Risk-Benefit Ratio</th>
<th>No Conflicting Preferences</th>
<th>Minimal Net Risks*</th>
<th>Consent as Soon as Possible</th>
<th>Number of Conditions Met</th>
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CIOMS = Council for International Organizations of Medical Sciences; ICH = International Council for Harmonization; WMA = World Medical Association.

*Those states and organizations that do not meet this condition state that risks must be minimized, minor, low, or reasonable, rather than minimal. In South Africa the research must be no more risky than alternatives, which is analogous to minimal risk. Only CIOMS addresses net risks.

†These documents contain only general statements on the risk-benefit ratio, rather than specifically in relation to emergency research.
Guideline (2014), Israel’s Guidelines for Clinical Trials in Human Subjects (2006), Singapore’s Biomedical Research Act (2015) and Health Products/Medicine (Clinical Trials) Regulations (2016), the Philippines’ National Ethical Guidelines for Health and Health-related Research (2017), and the United States’ EFIC and WIC Regulations (1996) also all state that the research must hold out the prospect of direct benefit to participants. The Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006) stipulate that emergency research without consent must be intended to be therapeutic, but also include the restriction that emergency care patients, due to their “extreme vulnerability,” should be “excluded from all but minimally invasive observational research.” The ICH Guideline (2016) concurs with the responsiveness condition by implication, because nontherapeutic research can only be conducted with the consent of the participant or their legally acceptable representative.

Other regulations and guidelines appear to conflict with the responsiveness condition. The Council of Europe’s Additional Protocol (2005), New Zealand’s National Ethical Standards for Health and Disability Research and Quality Improvement (2019), and Switzerland’s Human Research Act (2011) allow emergency research that does not have the potential to be of direct benefit to participants, as long as it may ultimately confer benefit to them or people in the same category. The WMA Declaration of Helsinki (2013) says the same for research with those unable to give consent. The CIOMS Guidelines (2016) do not address responsiveness in the section specific to emergency care research, but do allow research with no potential benefit to incapacitated participants. All except Switzerland’s Act also specify that it must not be possible to do the research with participants capable of giving consent.

**Favorable Risk–Benefit Ratio**

The second condition in the consent substitute model is that “the risk–benefit ratio of the experimental intervention must, in light of the available evidence, be judged favorable and at least as favorable as the established standard of care and the control intervention, if any.” Most of the national and international documents examined contain general statements to the effect that the risks of a proposed research project must be outweighed, or justified, by its potential benefits (which may be societal). The Australian National Statement (2018) states this specifically for emergency medical research as well. As outlined in the previous section, several also require that emergency research without consent be of potential direct benefit to participants. Those of Singapore, the Philippines, and the United States further state that any available treatments must be unproven or unsatisfactory. In Japan, available treatments must be unlikely to be sufficiently therapeutic, while in Israel the proposed trial must offer a better chance of improving the medical condition of participants than alternative treatments and in South Africa the research must be no more risky than such treatments and potentially more beneficial than standard care. Under the new EU Regulation (2014), as well as being of potentially direct benefit to participants, emergency-based clinical trials must carry minimal risk and burden in comparison to standard treatments. In Canada, however, risks greater than those in standard efficacious care are permissible in emergency research without consent when outweighed by prospective direct benefits to participants. In Australia, benefits must justify any risks associated with not taking consent. New Zealand, Switzerland, and the Council of Europe allow emergency research without direct benefit to participants, but insist on minor or minimal risk. This is still technically an unfavorable risk–benefit ratio for participants. Where emergency research carries more than minimal risk in New Zealand, as well as being of prospective benefit to participants, it must be at least as favorable as alternative options. Under the CIOMS Guidelines (2016), for research with incapacitated participants where the requirement of permission from a legally authorized representative has been waived, risks to participants must be minimal, irrespective of whether the research carries the prospect of individual benefit.

**No Conflicting Preferences**

The third condition is that “there should be no compelling reason to think that the experimental intervention conflicts with patients’ values or interests.” It is found in most of the national and international documents reviewed, to varying degrees. The obligations of researchers to verify that the proposed intervention will not conflict with incapacitated patients’ probable preferences can be framed positively or negatively. In South Africa, under the Good Clinical Practice Guidelines (2006), “reasonable steps” must be taken to find out the “religious and cultural sensitivities” of potential participants, and under the Ethics in Health
Research: Principles, Processes and Structures Guidelines (2015), “the individual circumstances of the patient must be carefully considered to prevent inadvertent violation of personal or cultural values.”42 In the United States, study protocols should encourage investigators to examine information in a wallet or medical jewelry that might indicate a patient’s wishes with regard to participation, time permitting.43 In contrast, under the EU Regulation (2014) and the Council of Europe Additional Protocol (2005), as well as in Australia, Canada, and Israel, consent may be waived in emergency research provided that there is no known reason, such as previously expressed objections or a relevant prior directive, for thinking a patient may not wish to take part. Similarly, under Singapore’s Clinical Trials Regulations (2016), there must be no objection to enrollment by the participant, their legal representative, or a member of their family. Under Switzerland’s Ordinance on Clinical Trials (2013), any prior statement of wishes must be respected for emergency research with permanently incapacitated participants.44 Under its Human Research Act (2011), there must be no visibly expressed objection from participants in emergency research and their wishes must be ascertained as soon as possible, but this could be after the intervention has begun. New Zealand’s National Ethical Statement (2019) similarly encourages researchers to seek and respect verbal or physical refusal, where potential participants are capable of giving it. The participant’s values or prior wishes do not feature in the WMA Declaration of Helsinki (2013), the ICH Guideline (2016), Ethiopia’s National Guideline (2014), Japan’s Ethical Guidelines (2017), or the Philippines’ National Guidelines (2017).

The CIOMS Guidelines (2016) advocate a different approach. Where possible, emergency care researchers must try to identify potential participants in advance and ask them to agree to their future involvement in the research, perhaps through an advance directive. (When there is no advance directive, permission from a legally authorized representative must be sought, who must take account of any preferences or values expressed by the participant [although the requirement for surrogate permission can be waived if certain conditions are met].) The Canadian Policy Statement (2018) and New Zealand’s National Ethical Statement (2019) also include seeking consent from prospective participants before the emergency situation occurs as a suggested additional safeguard. Largent et al. are dismissive of advance consent for emergency research, deeming it infeasible, because the majority of emergency cases are unpredictable. Under the United States’ EFIC and WIC Regulations (1996) and Singapore’s Clinical Trials Regulations (2016), this infeasibility is a condition of approval for emergency research without consent: “There is no reasonable way to identify prospectively the individuals likely to become eligible for participation.” Largent et al. do, however, recommend community consultation, so that exclusion criteria reflect “predictable personal values” and potential participants are aware of any opt-out mechanisms. Canada’s Policy Statement (2018), Ethiopia’s National Guideline (2014), New Zealand’s National Ethical Standards (2019), the United States’ EFIC and WIC Regulations (1996), and the CIOMS Guidelines (2016) all specify that there should be community consultation and/or public disclosure of research prior to emergency research taking place.

**Minimal Net Risks**

Largent et al.’s fourth condition is that “nonbeneficial procedures included in the study cumulatively pose no greater than minimal risk.” Of the documents analyzed, only the CIOMS Guidelines (2016) draw a distinction between experimental interventions and secondary but necessary procedures. They state that in research with those incapable of consent, including in medical emergencies, each individual nonbeneficial intervention or procedure must carry no more than minimal risk, except where the social value is compelling, when a minor (fractional) increase in risk is permissible. Where the requirement to gain permission from a legally authorized representative has been waived, however, the study as a whole must pose only minimal risk to participants. Canada, Ethiopia, Israel, Japan, New Zealand, Switzerland, the WMA, the EU, and the Council of Europe require that risks in all research or clinical trials be minimized. In Australia, emergency research without consent must be low risk, meaning that discomfort is the only foreseeable risk. In the Philippines, Singapore, and the United States, risks to participants in emergency medical research without consent must be reasonable. This is to be assessed in function of what is known about the emergent condition (the Philippines), or the medical condition of potential participants and the risks and benefits of 1) any standard therapy and 2) the proposed intervention (Singapore and the United States). In all three, such research can only be conducted when it meets the inherently risky conditions that
participants are in a life-threatening situation and, as highlighted previously, there are no standard, proven, or satisfactory treatments available. In South Africa, risks must be no greater than those inherent to a patient’s condition or alternative treatments. The ICH Guideline (2016) states that the rights, safety, and well-being of participants in emergency research without consent must be protected but does not specify a minimum risk level, except for a general requirement that the potential benefits of trials justify the risks. As stated previously, where emergency research without consent that is of no direct benefit to participants is allowed, risks to participants must be minimal or minor. This is not analogous to the consent substitute model, however, as the first two conditions of the model require some direct benefit to participants.

Consent as Soon as Possible
The fifth condition is that “consent for ongoing emergency research interventions and additional interventions should be obtained as soon as possible,” from the participant or their surrogate. This is a condition of approval of emergency research without prior consent in most of the national and international ethics documents examined. Under the new European Union Regulation (2014), researchers must as soon as possible inform the participant or their legally designated representative (whoever is available sooner) of the trial and seek their consent to continued participation. If the surrogate is available first, the participant must be asked for consent once they regain capacity. The CIOMS Guidelines (2016) similarly require that a participant be informed of the research as soon as they gain capacity and their consent to remain in the study be obtained “as soon as reasonably possible.” In addition, the researcher and ethics committee should agree a maximum amount of time for inclusion of a participant in a study without their or their surrogate’s consent (where the requirement for the latter has not been waived) before the participant must be withdrawn, unless this would worsen their condition. The WMA, ICH, Israel, and Canada require informed consent to continue and/or for further interventions as soon as the participant or their representative becomes available. Japan’s Ethical Guidelines (2017) simply state that the investigator “shall promptly follow procedures to obtain written informed consent.”

In New Zealand, only the participant can give consent for their continued participation, once they regain capacity, unless they have a welfare guardian or someone with power of attorney who can legally make a “substituted decision.” While participants remain incapacitated, researchers should try to consult “a person interested in the welfare of the participant,” to see whether continued participation would be consistent with the participant’s wishes. Similarly, in the Philippines and South Africa, a surrogate must be informed of the research and can withdraw the participant, but consent to continue is the prerogative of the participant only, once they have regained consciousness. The Council of Europe also draws a distinction between consent by the participant and authorization by their representative. The CIOMS Guidelines (2016) use both “consent” and “permission” to describe agreement by a legally authorized representative or surrogate. Singapore’s Clinical Trials Regulations (2016) outline a cascade system: if the participant cannot consent and their legal representative is unavailable, a family member must be sought and, if found, must not object to their relative continuing to participate. The legal representative’s consent must still be obtained once available and also the participant’s once they gain capacity, with each stage nullifying the previous one where there is disagreement. In emergency-based clinical trials in Switzerland, post hoc consent is to be sought from participants only, unless they are permanently incapacitated, in which case the consent of a representative should be obtained as soon as possible.

A few of the national guidelines do not specify that consent to continue must be sought in emergency research that has proceeded without prior consent. The Australian National Statement (2018) and the Ethiopian Guideline (2014) do not include any procedures for informing or consenting participants and/or their surrogates, once emergency research without consent has begun. In the United States, the participant’s legal representative (or a family member if the legal representative is unavailable) must be informed as soon as possible about the research and given the opportunity to discontinue participation, as must the participant if they regain capacity, but consent to continue is not required once a participant is enrolled. Largent et al. state that once participants gain capacity, they should be asked for prospective consent for their data to be used in publications. Only a few of the ethics documents analyzed specify this. The European Union Regulation (2014) states that if the participant or their legally designated representative does not give consent to their continued involvement in a trial, they
should be informed of their right to object to the use of data obtained. Researchers in New Zealand must seek consent for the use of data already collected once a participant regains capacity. In Switzerland, if a participant refuses to give post hoc consent, both their biological material and data collected may no longer be used. Finally, the CIOMS Guidelines (2016) recommend that the participant or surrogate be given the opportunity to object to the use of data collected without consent or permission.

**SUMMARY**

Only South Africa’s guidelines meet all five conditions of Largent et al.’s consent substitute model. Several of the documents reviewed allow emergency research without consent to be of no direct benefit to the participant, which contradicts the responsiveness condition and also implies a potentially unfavorable risk–benefit ratio. The majority require that the participant has no known conflicting preferences and that consent to continue should be obtained as soon as possible, with only Ethiopia excluding both of these conditions. Only the CIOMS Guidelines (2016) differentiate between experimental and procedural interventions with regard to risk, with most documents simply specifying that risks must be minimized, low, or reasonable in the context of the emergent condition. Those that allow emergency research with no direct benefits (only potential future benefits and/or benefits to those in the same category) impose a lower risk threshold for this type of research. Under Switzerland’s Human Research Act (2011), for instance, such research must entail only minimal risks to participants, while risks must only be minimized in directly beneficial emergency research. This may be a distinction that could be built into the consent substitute model.

There was little parity across the documents, with very few having the same configurations of consent substitute model conditions met. Of particular note is the lack of concordance between national and international guidelines and regulations, with only Canada, Israel, and Singapore meeting the same conditions as the European Union; only New Zealand and Switzerland matching the Council of Europe; and only Japan and the Philippines matching the ICH Guideline (2016), despite this being intended to provide a uniform standard for clinical trials in the European Union, the United States, Canada, and Switzerland. More research is needed to determine whether these regulatory differences and gaps have stymied international collaboration in emergency research.

As stated, several states not analyzed have based their emergency research provisions on preexisting texts. The majority of these have used the ICH Good Clinical Practice Guideline (2016); many more states require compliance with the Guideline as a whole (see Data Supplement S1). We thus recommend that the section on emergency research in the new version of the Guideline currently being developed be expanded in line with the consent substitute model, to 1) consider the maximum level of acceptable risk to participants in emergency research without consent, 2) include guidance on ways to ascertain and respect the preferences and values of these participants, and 3) address specifically (rather than by implication only) whether they can be enrolled in nontherapeutic research. Finally, as the Declaration of Helsinki is a foundational document for many laws, regulations, and guidelines on research ethics, both international and national, a section on emergency medical research would be a useful addition when it is next updated.

**References**

https://ec.europa.eu/health/sites/health/files/eudrak


Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14179/full

Data Supplement S1. Regional and National Documents Reviewed.