Emergency care research ethics in low-income and middle-income countries

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ABSTRACT
A large proportion of the total global burden of disease is caused by emergency medical conditions. Emergency care research is essential to improving emergency medicine but this research can raise some distinctive ethical challenges, especially with regard to (1) standard of care and risk–benefit assessment; (2) blurring of the roles of clinician and researcher; (3) enrolment of populations with intersecting vulnerabilities; (4) fair participant selection; (5) quality of consent; and (6) community engagement. Despite the importance of research to improve emergency care in low-income and middle-income countries (LMICs) and the widely acknowledged ethical challenges, very little has been written on the ethics of emergency care research in LMICs. This paper examines the ethical and regulatory challenges to conducting emergency care research with human participants in LMICs. We outline key challenges, present potential solutions or frameworks for addressing these challenges, and identify gaps. Despite the ethical and regulatory challenges, conducting high-quality, ethical emergency care research in LMICs is possible and it is essential for global health.

INTRODUCTION
A large proportion of the total global burden of disease is caused by emergency medical conditions, including asthma, severe diarrhoea, maternal haemorrhage, myocardial infarction, sepsis, stroke, and trauma. The majority of this burden is in low- and middle-income countries (LMICs). Emergency care research—defined as research conducted on diseases, syndromes and systems of care for patients with acute, potentially life-threatening or disabling illness or injury—is essential to improving emergency medicine. However, emergency care research in LMICs has received low priority and is under-funded relative to disease burden. Consequently, there is a shortage of good quality data for improving emergency care and health systems.

Research conducted in any emergency care setting can raise ethical challenges. For example, potential participants may face high baseline levels of risk following an unexpected change in their health. Their capacity to give informed consent is often compromised, and the need for rapid decisions about treatment or research may put further pressure on obtaining fully informed and voluntary consent from patients or families. Such challenges can be intensified in LMICs due to higher patient volumes, overworked providers, weak hospital and health system infrastructure, lack of research infrastructure, over-crowded emergency departments, and more vulnerable patient populations.

Despite the research gaps and the widely acknowledged ethical challenges, very little has been written on the ethics of emergency care research in LMICs. A search of the PubMed/MEDLINE database on keywords related to ethics and clinical research in emergency or acute care settings identified just three articles, and snowball methods identified two more. Instead, the bioethics literature has predominantly addressed issues relevant to high-income countries (HICs), particularly the USA. LMIC emergency care researchers and the research ethics committees (RECs) that review their work lack specific guidance that is sensitive to the contexts in which they work.

This paper examines ethical and regulatory challenges to conducting emergency care research with human participants in LMICs. We outline key challenges, present proposed...
solutions to address these challenges, and identify gaps. We focus on the conditions under which research studies should be permitted; thus, we hope to inform the deliberations of national and local ethics committees. We do not address other important ethical questions, such as how to set priorities for research. Our main message is that despite the ethical and regulatory challenges, conducting high-quality, ethical emergency care research in LMICs is possible and it is essential for global health.

DISTINCTIVE FEATURES OF EMERGENCY CARE RESEARCH

All research with human participants must meet ethical criteria, including respect for participants, fair participant selection, an acceptable risk–benefit profile and sufficient social value. Research in LMICs sometimes raises further ethical challenges, such as regarding standards of care, ancillary care responsibilities, post-trial access, building local research capacity and responsiveness to local needs. These ethical considerations are important for emergency care research in LMICs just as for other human subjects research. We do not repeat here the important work that has been done elsewhere on these topics.

We focus instead on regulatory and ethical issues that result from distinctive features of the emergency care context with particular attention to how they arise in LMIC settings. This means that our primary focus is on issues that result from the fact that research is being conducted on an acute condition, where interventions occur within a limited time window, and the consequences for patients without effective intervention are expected to be severe.

REGULATIONS AND GUIDELINES

Most countries have regulations that govern research with human participants and processes for review by local RECs. In order to cover the distinctive features of emergency care research, regulations and guidelines need to include: (1) conditions for permitting a waiver of consent to research participation and (2) conditions for permitting surrogate consent to research participation and criteria to identify surrogates. In addition, the regulations must not have blanket exclusions; for example, if a country’s regulations prohibit all research with ‘vulnerable populations’, then it may be impossible to enrol patients with many conditions requiring emergency care.

We examined regulations for human subjects research in the ten LMICs with the highest disease burden caused by emergency medical conditions plus Egypt and South Africa (table 1). The relevant regulations vary widely between countries. A few high-burden LMICs have regulations that specifically refer to and permit emergency care research, including China, Ethiopia, Russia and South Africa. All the high-burden LMICs have provisions for surrogate consent, which appears to be typical globally. We are aware of a very small number of exceptions; for example, Chile’s regulations prohibit the participation in research of persons with mental or intellectual disability who cannot express their will. Of the high-burden LMICs, 10 allow a waiver of the informed consent requirement under specified conditions.

In general, there are stringent restrictions on the level of risk allowed for studies where informed consent is not obtained. Regulations specific to emergency care research in LMICs and in high-income jurisdictions, like the European Union and USA, permit this research only when it has the potential to directly benefit individual participants. Outside of regulations tailored to emergency care research, a waiver of consent is frequently permitted only for minimal risk research. Additional requirements also apply. For example, the South African guidelines pertaining to emergency medical research additionally require that ‘reasonable steps are being taken to ascertain the participant’s religious and cultural sensitivities’ and ‘the patient and the patient’s next of

| Table 1 Ethical regulations regarding emergency care research and consent |
|---------------------------------|-----------------|-----------------|-----------------|
| Country                        | Regulations    | Provision for surrogate consent | Provision for waiver of consent |
| Bangladesh                     | x               | ✓                | ✓               |
| Brazil                         | x               | ✓                | ✓               |
| China                          | ✓               | ✓                | ✓               |
| DR Congo                       | x               | ✓                | ✓               |
| Egypt                          | x               | ✓                | x               |
| Ethiopia                       | ✓               | ✓                | ✓               |
| India                          | x               | ✓                | ✓               |
| Indonesia                      | x               | ✓                | ✓               |
| Nigeria                        | x               | ✓                | ✓               |
| Pakistan                       | x               | ✓                | ✓               |
| Russia                         | ✓               | ✓                | ✓               |
| South Africa                   | ✓               | ✓                | ✓               |
kin or legal representatives will be informed as soon as is reasonably possible of the patient’s inclusion in the study and of the option to withdraw from the research project at any time.\textsuperscript{16} The Chinese regulations for emergency care research allow research without consent only if the treatment in the study has a prospect of helping the participant recover or relieve their pain, which may be quite restrictive.\textsuperscript{19}

The World Medical Association’s Declaration of Helsinki (Helsinki) and the Council for International Organizations of Medical Sciences’ International Ethical Guidelines for Health-related Research Involving Humans (CIOMS) both speak to emergency research.\textsuperscript{10,19} Helsinki states:

Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative. (Article 30)

CIOMS lists similar conditions, plus a requirement for community engagement:

If there is no opportunity to solicit informed consent of participants while fully capable of informed consent, plans to conduct emergency care research with incapacitated persons must be publicised within the community in which it will be carried out, where feasible. In the design and conduct of the research, the research ethics committee, the researchers and the sponsors must be responsive to the concerns of the community. (Guideline 16)

It is important to remain aware of potential mismatches between what is on paper and what occurs in practice. Regulatory requirements may be vague, in tension with other regulations, and open to interpretation. Other than one small survey that asked about the approvalability of a hypothetical study,\textsuperscript{15} we did not identify any literature that examined the practice of REC review of emergency care research in LMICs. Nevertheless, REC capacity in LMICs remains limited.\textsuperscript{22} RECs struggle with shortages of funding, staff, institutional support and training.\textsuperscript{22} Insofar as emergency care research is scientifically or ethically complex, these gaps in capacity are likely to impact its review.

These caveats notwithstanding, we draw two key lessons from the regulations and guidelines. First, all countries whose regulations we examined permit research with individuals who cannot consent and most allow for a waiver of consent. While this is not the case for all countries and particularly not all LMICs, we believe this is true of most countries that have regulations for human subjects research and a functioning ethics review system. Many LMICs are also transitioning to include provisions for waiver of consent in their regulations. Consequently, a substantial amount of emergency care research could be approved by RECs in LMICs. Second, there is a lack of consistency across countries regarding emergency care research. Variation and vagueness—for example, regarding exactly what conditions must be met for a waiver of consent to be approved—is likely to impede important research within and across countries, as well as providing patchy protections for participants.

**The Ethics of Emergency Care Research**

Certain ethical concerns are particularly salient in the context of emergency care research in LMICs. These include: (1) risk–benefit assessment and standards of care for participants with elevated baseline risk; (2) blurring of the roles of clinician and researcher; (3) populations with intersecting vulnerabilities; (4) fair participant selection; (5) quality of consent and (6) community engagement.

It is worth mentioning two types of emergency care research that rarely give rise to these ethical issues—observational research and health systems research. Observational and health systems research that relates to emergency care will typically be no different ethically from other observational research or health systems research. For example, registry research that looks at patients admitted through emergency departments will generally be eligible for a waiver of informed consent for the use of de-identified data under the same conditions as other registry research. Health systems research may have its own challenges relating to informed consent.\textsuperscript{23} For example, cluster-randomised designs in which patients cannot opt out of the research remain hard to justify from the perspective of individual informed consent.\textsuperscript{24} But again, this is no different for emergency care systems research.

**Risk–benefit assessment and standards of care**

Participants in emergency care research often face elevated baseline risks as a result of an urgent condition. That is, without rapid, effective intervention they are likely to be seriously harmed. In LMICs, these baseline risks may be even greater, since patients may reach care later and have more underlying vulnerabilities, such as malnutrition or comorbidities.

Consequently, first, priority should be given to measures that may protect participants from the serious sequelae of their acute condition. In some non-emergency care research, it may be acceptable to delay intervention or not to intervene, since the immediate consequences would not be severe. In the emergency care settings with which we are concerned that is usually not the case.

Second, in some cases, there may be reasons not to provide the current globally best care to participants...
because of local resource and personnel constraints. Raising the standard of care for patients within a study might make it impossible to draw scientifically valid conclusions or might render the study results irrelevant to the local context. For example, the global standard of care for cardiogenic pulmonary oedema may include intravenous nitroglycerin and non-invasive positive pressure ventilation. However, both treatments are expensive and are not widely available in many LMICs. Researchers might want to conduct a study that investigates the best approach to acute pulmonary oedema in a low-resource setting using available medications and modalities.

Studies in which participants would not receive the globally best possible care require careful case-by-case analysis. Where the baseline risk of harm is great, at least the following conditions should be met: (1) the lower standard of care is scientifically necessary; (2) participants are not deprived of treatment that they would otherwise receive and (3) the research is intended to produce data of considerable value for the local population.

Policymakers and administrators should be included early on in study design so that the results of locally relevant research can be adopted and standards of care raised.

Third, though emergency care patients may face an elevated baseline risk of mortality or serious morbidity, risk-benefit assessments should focus on the incremental risks that the research adds. An observational study that simply requires a few additional blood draws would still be minimal risk, even if carried out with an acutely ill population.

How to assess the risk level in other research designs is debatable. Consider a comparative effectiveness study of oral amoxicillin versus co-trimoxazole for community-acquired pneumonia in otherwise healthy children, where there is uncertainty about which is superior. This might be considered minimal risk because clinicians are in equipoise about the best treatment. But if there is considerable uncertainty about one or other of the interventions and the condition is potentially fatal, it might be argued that the risk is not minimal despite the apparent equipoise.

Blurring of roles

When researchers also provide clinical care, the line between clinician and researcher can easily become blurred for both patient–participants and clinician–researchers. In other clinical contexts, there may be time to clearly differentiate these roles. In busy LMIC emergency departments, where decisions about care and research participation must be made rapidly, this may not be practical or responsible.

Ideally, the person obtaining research consent should be different from the person with primary responsibility for the patient’s care. When that is not possible, additional safeguards should be instituted. For example, the consent process can be witnessed by an independent third party. For some protocols, it can help to have a third party clinician confirm ongoing consent for research participation after the point of time-sensitive interventions. Independent clinicians also play an important role in ensuring that patients are not enrolled in studies that are excessively risky for them, or inappropriately kept on protocols against their wishes or interests.

Intersecting vulnerabilities

It is widely agreed that ‘vulnerable’ research populations—such as children, refugees and institutionalised individuals—should be provided with additional protections. We accept a broad conception of vulnerable: ‘an identifiably increased likelihood of incurring additional or greater wrong’. Thus, someone might be vulnerable—within a specific context—because she is more easily exploited, at increased risk of harm, or lacks the ability to make her own decisions. Research participants in LMICs may be vulnerable by virtue of poverty, inadequate access to healthcare, lack of power (as when gender norms restrict female autonomy) or through local legal or regulatory barriers (as for Lesbian, Gay, Bisexual, Transgender/Transsexual and other sexual and gender minority community members in some countries). Participants in emergency care research are often vulnerable by virtue of having no or impaired decision-making capacity and by virtue of the risk posed by their acute condition.

The cause of someone needing emergency care can also be a source of vulnerability. This may apply, for example, to victims of violence, drug users who have overdosed or patients with stigmatised health conditions—such as schizophrenia. These sources of vulnerability intersect in emergency care research in LMICs.

Protections should be tailored to the ways in which the specific populations from which participants are drawn are at risk of being wronged. For example, some potential participants may be at increased risk if information about them is spread to third parties (eg, HIV-positive participants whose HIV status might be noted by family members). RECs may therefore need to pay special attention to how researchers plan to maintain privacy and confidentiality, which can be challenging in busy, crowded emergency departments in LMICs. Researchers and RECs should also be mindful of legal frameworks that are invoked in special circumstances or for specific vulnerable populations, such as regarding criminal suspects, which would override standard confidentiality protections and make it harder to protect participants.

Fair participant selection

Emergency care research is sometimes seen in LMICs as if it were motivated by the desire to take advantage of potential research subjects that suddenly find themselves in an emergency care setting and thus as intrinsically abusive. But the fact that a population is vulnerable does not entail that research with that population should be avoided. Exclusion sometimes deprives participants of potential benefits, for example, where a trial provides potentially life-saving interventions or free clinical care.
that would not be available in the public healthcare system. Further, if vulnerable populations are excluded, the data gathered in clinical trials loses generalisability. For example, consider a trial of an experimental treatment for traumatic brain injury. If patients who lack the capacity to consent are excluded, this will bias recruitment against the most severe trauma cases and may give a misleading impression of how effective the treatment is. Moreover, the populations that are excluded because they are vulnerable are likely to be those for whom we most need research. Protections for potential research participants should be balanced against the value of knowledge to be gained for the populations from which those participants are drawn: truly ‘protecting’ this population—as a group—is about infusing future care with better evidence.

**Quality of consent**

Informed consent allows competent individuals to protect their interests and respect their right to make their own decisions. The context of emergency care research often poses challenges to the quality of informed consent. This is a consequence of: (1) the conditions that lead to a need for emergency care, which frequently impair patient decision-making capacity; (2) the need for rapid treatment and research decisions to be made, which may reduce the amount of information that can be conveyed, put pressure on decision-making and make it harder to identify appropriate surrogate decision-makers; and (3) the fact that the need for emergency care results from unexpected events, so potential participants are likely to have limited understanding of their health situation.

Where possible, patients who cannot give their own consent should be represented by surrogate decision-makers (legally authorised representatives). A surrogate may be designated by the patient while capable or, failing that, may be a next-of-kin surrogate or a non-research clinician, according to the local regulatory regime or facility policy. Surrogates are expected to make decisions consistent with the values and preferences of the patient, where known, and otherwise based on the patient’s interests.

In emergency care research, when an enrolment decision must be made quickly for a potential participant who lacks consent capacity, it may not be possible to identify a suitable surrogate in time. In such cases, it may be appropriate to waive the informed consent requirement. Such waivers for emergency research are controversial, at least for interventional studies (scientifically necessary waivers are much less controversial in registry or surveillance research). RECs may consider approving such waivers only if: (1) a waiver is scientifically necessary, such that the research could not otherwise be carried out; (2) the net risk to participants is minimal or the research is judged to be potentially in participants’ interests; and (3) consent is obtained as soon as possible from the participants or surrogates. As discussed above, some regulations and guidelines also require additional protections, such as community engagement.

One condition on waiving informed consent is that consent to continued research participation should be obtained as soon as possible. Note that consent obtained after research participation has begun is only ever *prospective* consent to remain in research (and to have one’s data included). Consent to interventions that have already been given is not possible. In this regard, the use of terms such as ‘deferred’, ‘retrospective’ and delayed consent can be unhelpful and inappropriate euphemisms.

Even when a patient is conscious or a surrogate is available, obtaining fully informed, voluntary consent in the emergency setting may be hard. Patients may be disoriented and in pain; they may have cognitive or communication impairments and decisions may need to be made rapidly. In many LMIC settings, health literacy and knowledge of research may be very limited. These are not reasons to abandon informed consent, but researchers and RECs should carefully consider the context in which enrolment decisions will occur. Even if a full consent process is not possible, the opportunity to refuse participation (dissent) can be offered. For example, someone who is cognitively impaired as a result of a stroke may still be able to express clear preferences about how she does or does not want to be treated. Even if not every aspect of the study can be fully explained, a simplified process can be used and continuing consent to study enrolment obtained at intervals. Even if consent to the overall study cannot be obtained at enrolment, consent to the procedures and use of data that are not imminent can be delayed. In sum, challenges to an ideal consent process do not make the case for no consent process.

The Fluid Expansion as Supportive Therapy study provides an example of how a consent process can be appropriately modified. This randomised controlled trial examined the practice of fluid resuscitation in the treatment of children with shock and life-threatening infections in sub-Saharan Africa. It was imperative that the trial included children who were severely ill, to ensure the findings could be generalised to the appropriate patient population. But children in this situation are often accompanied by parents or guardians in distress who may struggle to understand the information they are given. The study sought written prior informed consent whenever possible, but modified the consent process if a potential participant (1) was preterminal, (2) needed immediate resuscitation or had other life-threatening complications like seizures, hypoglycaemia or hypoxia, and (3) the parent or guardian was unavailable or unable to receive or understand information. In such cases, brief information about the study was given and verbal parental or guardian assent was sought before enrolment. Afterwards, parents and guardians were approached for full, written informed consent. In the event of a child participant’s death, parents or guardians were not approached afterwards for the full, written informed consent.
In the LMIC emergency care setting, it is also particularly important to be aware of the power dynamics between clinicians and patients or their surrogates. The recommendations of clinicians may carry undue weight by virtue of their perceived expertise and authority. This influence is likely to be at its greatest when time is short and patients and families are extremely vulnerable and looking for guidance.

In many LMICs, families play a more active role in healthcare than they typically do in HICs. Family members may need to provide some of the care, buy medical supplies and provide food for inpatients. Moreover, cultural expectations may be such that people other than the patient are expected to make decisions on his or her behalf. Family members or clinicians might even prefer to keep important information, such as a diagnosis, from the patient. In other cases, the person who arrives with the patient may not have, or may not feel they have, the authority to make decisions about research participation. For example, Molyneux et al describe a paediatric emergency fluids trial where mothers were usually the parent bringing their child to the hospital. Some mothers were reluctant to give consent without the permission of the child’s father. How researchers should deal with these complicated culturally specific considerations has received little rigorous analysis from ethicists.

Community engagement
In the absence of an ideal individual or surrogate consent, other protections may be necessary. Prior REC review and independent monitoring are two common additional procedural protections. In emergency care research and for research in LMICs more generally, involving community members in research design and implementation and in the dissemination of results helps protect and respect potential participants and others, as well as improve the relevance of the research and its acceptance by the community. For example, a successful community-based emergency first aid responder (EFAR) system was developed in Manenberg township in the Western Cape of South Africa through multiple stages of community engagement. Prior to the start of the project, a survey was conducted to determine the feelings of the community regarding emergencies and local emergency response. Pre-training and post-training surveys were administered to participants trained as EFARs. Community members also provided input to develop the implementation strategy, which went through rounds of modification to achieve consensus. Ultimately, the community-based system was low cost and able to deliver prehospital emergency care and transport for patients.

Sometimes, community engagement activities also provide an opportunity for potential participants to opt out. If the details of a facility-level study are well publicised then patients or their families could opt out by going to a facility that was not taking part. Whether this is possible will depend on the research study and the context of receiving care—not everyone has a choice about where they get treatment.

Though community engagement is frequently valuable, a few cautionary points are in order. First, it is not always obvious what constitutes the community or who can speak for the community. For example, a substantial proportion of people in LMICs live in cities that are diverse and multicultural. Communities defined in cultural terms may be inappropriate for studies in these cities. Second, community engagement should not be conflated with ‘community consent’. Even if community leaders must give permission for researchers to enter a community, individual consent—where possible—is still required. Third, community engagement can be a laborious process and may not always be needed. In emergency care research, the greater the incremental risk of study participation, and the harder it is to obtain individual informed consent, the greater the efforts that should be put into community engagement.

CONCLUSIONS
An enormous amount of valuable emergency care research can be ethically and legally carried out in LMICs. Gaps remain regarding: (1) guidelines and regulations; (2) ethical analysis; and (3) best practices.

There are no internationally accepted guidelines for the ethical review of emergency care research. More detailed guidance would help researchers and RECs struggling with unfamiliar study designs and vulnerable populations. Such guidance can serve an educational function regarding the science, show how to apply the principles of research ethics and reassure reviewers that appropriately designed emergency care research can be conducted ethically. Variation in regulations and health systems means that country-specific guidelines may also be helpful. These could build on lessons learnt—good and bad—from not only US and European regulatory experiences but also within LMICs. They could provide clarity on exactly what emergency care research is legally permitted and under what conditions. As a first step, an international conference could bring together policymakers and researchers to set an agenda for harmonising emergency care research ethics practice.

There are outstanding challenges relating to risk–benefit analysis for studies in LMIC contexts where access to clinical care is limited. Strategies are needed for addressing participant vulnerabilities that are tailored to their particular situation and do not simply involve exclusion. Outstanding challenges regarding consent include the justification of exceptions from consent requirements, the identification of appropriate surrogates, the involvement of patients in decision-making when an ideal consent process is impossible and the protection of patient autonomy in contexts where clinicians need to be responsive to expectations about the role of the family.

Very little literature from LMICs addresses the ethics of emergency care research. More work—especially...
defining and describing best practices—would provide models for researchers facing similar contexts. The shortage of published information also means that we do not know exactly what researchers and RECs lack. A needs assessment of clinical researchers working in emergency care settings and the RECs that oversee them could identify the specific ethical and regulatory issues they face. Similarly, more data on public and patient perspectives on emergency care research in LMICs would help to inform research design. For example, further research could examine country-specific and community-specific views on research without prior consent or with modified consent processes.

Emergency care research can be ethically challenging, particularly when it involves enrolling critically ill patients under time-sensitive conditions. But the very severity of emergency medical conditions is reason to encourage their study. Conducting high-quality, ethical emergency care research in LMICs is both possible and important.

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