Spring 5-12-2023

# Ethical Considerations of Clinical Research in Emergency Care Settings: A Review

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**Abstract**

Emergency and acute care settings are some of the most volatile and high intensity areas of any healthcare operation. Better understanding of systems and treatments in these spaces are critical to improving outcomes for the high risk patients that are treated there. Clinical research serves as a cornerstone of modern medical research, and is critical to the further improvement of clinical care in these settings. This thesis serves to explore the ethicality of such research given the constraints of emergency medicine settings. Not only does this thesis provide a strong foundation regarding the history and current practices of clinical research, but it also utilizes vivid examples from current literature to illustrate the ethical questions that are raised. While it is clear that there are solutions to some of these questions, it is also evident that there are larger challenges that still need to be addressed in order to better satisfy the ethicality of this research given its need. Ultimately, this thesis reviews a number of modern publications on this topic, giving a synopsis of current standards and issues, as well as potential solutions to the ethical dilemmas found in emergency care clinical research.

**Acknowledgements**

I would like to thank my thesis supervisor, Dr. Elizabeth Kline, of the Molecular and Cell Biology Department at the University of Connecticut for all of their advisement on this thesis. Without their initial guidance and help on revision, I would not have been able to write such a thesis. I would also like to thank my Honors advisor, Dr. Louise Lewis, of the Ecology and Evolutionary Biology Department at the University of Connecticut for their help in completing this and other portions of the Honors Scholar. Further, I would like to thank Dr. Sharon Smith as it was their course that gave me an opportunity to explore the idea that serves as the basis for this thesis. Additionally, I would like to thank all of the professors I have had the privilege of learning from at the University of Connecticut, without their tutelage this thesis would not have been possible. Finally, I would like to thank my parents as well as all other family and friends that have supported me through the past four years and this rigorous process.

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## Introduction

Clinical research is defined as the study of health and disease in people.[1] By observing and collecting data in a systematic manner, all aspects of a disease and its effects can be documented and better understood. We can further evaluate this disease by adding variables such as different treatments to see which is the best way to treat this disease. The core ideas of clinical research can be found as early as 500 BC where stories of kings ordering their subjects to eat particular diets for their better health led to the discovery of the importance of eating vegetables at that time.[2] The most recent concrete evidence of the advent of clinical research, however, begins in 1747 with a comparative experiment conducted by Dr. James Lind aboard a British vessel. Scurvy was a major health concern on these ships, and so Dr. Lind decided to create different groups with his findings concluding that the group eating oranges and lemons had the best recovery from scurvy.[2] Over the next two hundred years, clinical research exploded with the creation of better tools such as randomization (where the patients are randomly assigned to particular treatments), the placebo (when one of the treatment options was fake), and the double blind control (where neither patients nor providers knew their treatments). But, clinical research has also had severe growing pains. As the desire to conduct science grew, so did the scope and size of these experiments. And unfortunately, this led to a lack of safeguards when completing this testing. Some of the most heinous examples include the forced sterilization and radiation experiments that occurred in Nazi concentration camps, as well as the Tuskegee study in America lasting from the 1930s-1960s when African American men with and without syphilis were studied.[3] The study led to transmission of the disease to other participants and families, and even when Penicillin became standard treatment for the disease in the 1940s, the researchers continued to not provide this treatment.[3] Such examples led to the creation of the many international bodies and documents found today, designed to protect and safeguard patients in the clinical research setting. These include the Nuremberg Code of 1947, the 1964 Declaration of Helsinki, and the 1979 Belmont Report.[3]

There are multiple forms of clinical research now utilized. The main fields include: epidemiology, where disease patterns are studied; behavioral, where associations between human behavior and diseases are studied; clinical trials, where actual treatments and interventions are studied; and health systems, where the organization of healthcare is studied to better improve patient care.[1] In each of these fields there are many more subfields such as specific types of clinical trials that deal with studying prevention versus screening or quality of life, or types of epidemiological studies ranging from retrospective to observational.[4] Clinical research follows the same scientific process as any other experiment. Researchers first identify a question that might be related to a new drug, or about how to improve a hospital infection rate. They then utilize a variety of tools to study this question. They can compare and contrast groups of patients, they can follow one cohort of patients, or just look through previously collected data. Once they have analyzed the data behind the question, they can begin to draw conclusions on whether a new drug is effective and important to use in the future.[5] Clinical trials follow a four phase process where the first phase includes a small population of patients with a focus on dosage and

safety followed by a second phase with a larger patient population focused on side effects and effectiveness of the treatment itself.[6] The final two phases continue to increase the number of patients with the third phase focused on comparing the new treatment to existing options, and the fourth phase occurring after Food and Drug Administration approval as a mode of long term effects observation.[6] This general format for clinical trials is followed across the world with regulatory agencies of other countries acting similarly to the FDA. Aspects of clinical research work focused on systems can help improve hospital and practice efficiency in order to reduce operating costs that translate to savings for patients, and an ability to treat more patients.[7]

One of the most difficult spaces for clinical research, however, is in emergency care medicine. Given the pace of care and the high level of risk involved, it is often difficult to perform clinical trials and research in a safe manner. Before discussing the challenges involved in emergency care clinical research, however, it is important to have an understanding how exactly an "emergency/acute care" setting is defined. The American College of Emergency Physicians defines emergency medicine as the diagnosis and treatment of unforeseen illness or injury, with additional literature including the concept of a time sensitive nature as necessitated by the "acute" aspect of care.[8,9] It is critical that research occurs in these spaces, as improving outcomes of patients in life or death situations is vital. That can range from studying new heart attack medication, to improving the speed of antibiotic delivery, to studying how hospital environments can affect disease progression in such an emergency setting. Without research in this field, many thousands of people would be unnecessarily and unethically dying. Further, certain demographic groups are at higher risk of emergency visits.[10] As such, emergency settings might be the only way to conduct research and collect information on the health of particular groups and how to better serve and help them through the healthcare system.

Ultimately, the purpose of this paper is to serve as an introduction to clinical research, and more importantly, to describe the ethical challenges of this form of research in emergency care settings. It is to provide a basic understanding of the history of clinical research ethics, and then to provide specific questions and challenges that modern emergency research faces in countries around the world. It will also provide detailed analysis of how current ethical issues are resolved within clinical research, and provide future solutions for continuing to improve the ethicality of this research. This paper is meant to serve as a foundation and baseline for those interested in clinical research and ethics. It is addressed to students and hospital faculty to help them learn about the basics of ethics in clinical research, and what challenges are the most pressing. The objective of this paper is to provide the reader with enough information to be able to successfully consume further peer reviewed publications in this topic, and to think critically about these challenges and how they might be addressed or discussed in the future.

## Current Clinical Research Ethical Guidelines, Policies, and Procedures

This section will begin with a more detailed look at the three important previously mentioned documents concerning clinical research ethics. Globally recognized as the

foundations of modern clinical research ethics, the Nuremberg Code, Helsinki Declaration, and Belmont Report were all stepping stones to the modern understanding of ethics.

After the second world war, nearly 40 physicians were placed on trial in the Nuremberg tribunal for crimes against humanity as a result of the lethal and terrifying experiments they conducted.[11] The lessons gained from the Nuremberg Code that was published at the culmination of the trial were many, but most importantly, the Code focused on the voluntary nature of informed consent provided by a potential participant, and the right to withdraw at any point and for any reason from an experiment.[11] Aside from its voluntary nature, informed consent is also defined by three other characteristics: disclosure of risks and details, an understanding of the study, as well as a reasonable decision making ability.[12] Other important outcomes from this Code include an understanding that benefits must always outweigh the risks to justify any experimentation, that research results cannot be obtained in any other method such as animal or cell experiments, and that all unnecessary suffering be avoided.[11] Another tangential establishment of the Nuremberg tribunal was the World Medical Association which began by establishing a committee on medical ethics aimed at outlining an international biomedical ethics code, and it continues to be revised and referenced today. While the Nuremberg Code had emphasized the importance of informed and voluntary consent, the Helsinki Declaration authored by the WMA committee understood the existence of exceptions and extenuating circumstances in which such informed consent could not be obtained, for example, in emergency care settings.[11] In these cases, the WMA writes that research protocols including research participants who may not be able to consent must first have its procedures approved by an independent review board, with consent being obtained from a legal representative or the individual as soon as possible.[11]

This is not to say, however, that medical experimentation was ethically sound the years following the Nuremberg and Helsinki documents. As mentioned earlier, The US Public Health Service conducted a 40 year long experiment called the Tuskegee study. Beginning in 1932, the study followed African American men with syphilis and continued even after ethics documents were published and an extremely effective antibiotic treatment of the condition was widely available.[3] Another prominent example was the harvesting of cancer cells from an African American woman named Henrietta Lacks in 1951.[13] Still used today for research, these cells were taken without consent or due compensation. The total amount of revenue generated from HeLa cells is unknown considering its widespread use but the average cost for just 1 mL of these cells is on average $4000.[13] Willowbrook State Hospital in New York hosts another example of such unethical scientific experimentation. Children with mental disabilities at the hospital were intentionally injected with Hepatitis to be studied.[11] The study lasted nearly 14 years, and left hundreds of children with long term damage and liver harm.[11] Even today, the study of social determinants in clinical research is integral, and it cannot be understated the importance of those same social factors being manipulated for the unethical experiments that occurred in years prior. In the examples above, these patient groups were taken advantage of because of their

vulnerability in society, and it is imperative that we continue to provide legal protections for such vulnerable groups.

In 1974, the United States Congress finally chose to build a commission to create national guidelines for biomedical research yielding the Belmont Report, a document that has been central in modern discussion of the ethics of clinical research.[14] The Belmont Report not only firmly established the guidelines necessary to create Institutional Review Boards (IRB) as mentioned at Helsinki but also outlined three main principles regarding the ethicality of clinical research. Namely, it described the importance of respect for persons, distributive justice, and beneficence/nonmaleficence as its main principles.[14] The first principle addresses the core outcome of the Nuremberg Code, or the idea that an individual has autonomy, and must voluntarily and of their own volition consent to an experiment.[14] Considering this idea of participant autonomy, it is subsequently important that their consent is informed, as to minimize or prevent any issues regarding coercion or misinformation.[14] This idea of autonomy also leads to the concept of surrogate consent, when a legal representative can provide consent for a participant such as a child or for someone with mental disabilities.[14] The second principle speaks to another lesson from Nuremberg which is risk-benefit assessment and the idea that one must maximize benefits while minimizing risk.[14] Difficulties of this assessment can include the fact that some benefits may be for the entire society, while the corresponding risks are limited to only individuals. These assessments are often difficult in complex situations such as surrogate consent. When the patient is unable to consent and their family must do so, there is an ethical nuance which must be discussed with local communities to ensure that the risk benefit assessment is being appropriately conducted.[14] And finally, distributive justice ensures that those who receive the most benefits from research are the ones who are involved, participating, and sharing the risks to ensure that marginalized or institutionalized people do not bear the burden of research for other groups.[14] Ultimately, the Belmont Report led to the creation in 1991 of new FDA and Department of Health and Human Services responsibilities conducting oversight of clinical research and ensuring the use of IRB processes and ethical evaluations.[15] Today, all research involves the use of an IRB as a result of federalwide assurances, and it remains the most important aspect in confirming the ethicality of the research being performed.[15] Across the world, the use of IRB's or Research Ethics Committees are common and many operate very similarly to the system used in the United States. Unfortunately, there are still over 80 developing countries that have yet to implement a research ethics system utilizing systems such as the IRB or REC.[16]

This next section will delve into more details of the IRB and its associated components that function together to act as the regulatory bodies. The IRB can accept, reject, and require modifications of any research project taken on by an institution at which the board is anchored.[17] The board is usually composed of at least five members, with one not being associated with the institution, and one member not being of a science background. More than just requiring documents, the IRB works with research groups to continually modify and evolve protocols and procedures to ensure the utmost ethicality is present. IRB's are registered with the federal

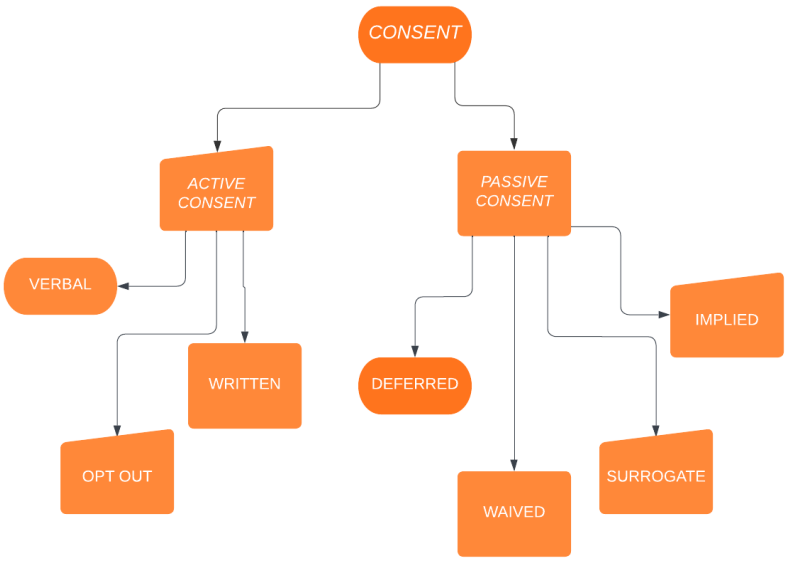
government through the FDA or HHS and work not only on research projects, but in such as site inspections, personnel review, and other aspects of common good practice.[17] Every IRB operates differently and can have its own specific policies, however, all of these organizations' fundamental goal is to protect the welfare of participants in federally funded human research projects. While there are guidance documents provided by the FDA and HHS, and a strong partnership built between these agencies and individual IRB's, there are no specific rules that an IRB must have to register. While there are regulatory components that an IRB must address, and a guiding checklist provided, each IRB can organize their responsibilities in different manners and then enter into a conversation with these agencies to register and be recognized.[17] Aside from assessing the research procedures and data collection methods, the IRB also questions the vulnerabilities of studied populations and the level of protections put in place and performs basic risk benefit analyses.[17] However, any experimentation involving human subjects, records, or tissues will require their approval, and while the scope is broad, the purpose of the IRB is ultimately to ensure the compliance of the researchers and institution with a high ethical standard.

In addition to the IRB, there are a number of other organizations that can help in maintaining the ethicality of the research. While they have various names, most of these organizations have offices that review topics such as compliance, biosafety, and conflict of interest. Furthermore, institutions can maintain Data Safety Monitoring Boards that are specifically designed with clinical research experts and statisticians to review all clinical trial and study data, and are independent of the institution, providing recommendations to continue or stop projects at any point in time.[15] Another alternative or supplemental safeguard is the Independent Safety Monitor, who again is a clinical research expert not associated with the study and institution, and can be brought in or contracted through a third party organization to serve as an independent monitor.[15] They review all project documentation, and ensure that the research lead and team are conducting their experiment as carefully as possible. Additionally, in certain circumstances, further initial review beyond the IRB can be required. For example, in cases where informed consent cannot be gathered, such as emergency scenarios, the Belmont Report and further doctrines have enshrined the ideas of community involvement. Given the potential risks and implications of community members utilizing this emergency location, it is incumbent upon the research institution to communicate the details regarding this study to the location population, gathering their input and feedback about this study as well.

Consent can be broken down into two major categories: active and passive. Active consent describes when a patient provides continuous and explicit consent towards the research either verbally or in writing. On the other hand, active consent can also include a system where participants are continually consenting till they explicitly choose to leave a study.[2] Meanwhile, passive consent is when a patient provides an indirect agreement to consent. This form is significantly weaker than an active process and includes implied, surrogate, deferred, and waived consent. Implied consent is where a patient provides consent through their participation, and thus their involvement implies consent.[3] As mentioned before, surrogate consent occurs when a legal

representative offers consent in the patient's stead, and deferred consent is obtaining consent after the research or intervention has occurred and deals with the inclusion of their data.[14] Waived consent is where consent procedures are not required as the circumstances of the study allow for such.[5] When research is minimally risky, or given situations such as an emergency where consent cannot be readily given, an IRB can waive the need for consent. In those situations, looking at alternative consent procedures in addition to a waiver such as surrogate or deferred can help bolster the rigor of the ethicality of the research.[7] The gold standard for clinical research, however, is active consent that is informed and voluntary where patients actively provide written and verbal consent for participation after having fully understood the risks and having made a thoughtful decision.

Shown below: Flowchart detailing consent types (Image 1)




**Ethical Questions Surrounding Emergency Clinical Research**

A strong background on the ethical foundations of clinical research has been provided, but it is also important that a sound understanding of general ethics questions relating to clinical research be communicated. Research is intended to improve patients outcomes and quality of life while also improving treatments and our ability to care. Tangentially, reduction in costs through better systems or prevention of illness is critical to the investigations of clinical research. And yet, even when research is performed in a robust and stringent manner, ethical questions can still arise as incidents of maleficence can even occur by mere carelessness.[18] One basic ethical

question that has troubled researchers is how to provide information to potential participants and patients that counters internal biases. For example, many patients might view a trial treatment as more effective regardless of the lack of data, they might believe that their participation can lead to more trained and attentive physicians, or they may believe that their lack of participation can negatively affect their care.[18] When language and culture barriers play a role in particular, this issue can be exacerbated, and so the next question is how to acquire this "informed" consent that is truly unbiased and properly made.[18] And while the focus thus far has been on the experimentation aspect of ethics, there are other portions of the scientific process and study design that have important ethical ramifications. For example, ensuring that all medical information is kept confidential, or that a research team or investigator is not biased by their desire to publish valuable information is an important ethical topic challenge to be addressed.[18] In a research career, it is easy to be pulled away from ethical standards by the need to publish constant and high value information for further grants and recognition. There have been cases of scientists even preventing the sharing and disclosure of adverse incidents in clinical trials, a very dangerous situation in which further people can be harmed during future research. Of course, ethical issues relating to plagiarism and fraud are always a concern in research and academic fields as well.[18] Ethical concerns have also been raised at the immense influx of private pharmaceutical money into research, and how funding needs can affect the results and priorities of the studies themselves creating unneeded pressure, and potentially biased results. Identifying conflicts of interest, thus, are key to performing good and ethical research as well.

One of the most profound and difficult ethical questions of clinical research is based upon the idea of informed consent. As previously mentioned, there are exceptions to this idea in the right circumstances, but that then presents the question of what conditions truly necessitate this waiver? This discussion can begin by looking at a publication from the Maastricht University Medical Centre in the Netherlands where researchers identified and followed the ethical components of a clinical intervention trial and analyzed it in the form of a case study.[19] When looking at this trial, a cardiac intervention called INCEPTION, it is clear the ethical issues that occur as a result of the level of risk, the inclusion of randomization, and the ability to consent. The INCEPTION trial utilized ECPR, otherwise known as extracorporeal cardiopulmonary resuscitation, to treat patients with refractory OHCA which is an Out Of Hospital Cardiac Arrest, or when a cardiac arrest outside of the hospital occurs and lasts longer than 15 minutes and is thus unmanageable.[19] Previous meta analysis showed that this technique, where a heart lung machine is rapidly implemented for those undergoing this type of arrest, could be beneficial but further data and experimentation was required to confirm this potential benefit.[19] The difficulty, however, is that this form of arrest has a very low survival rate, and while ECPR can potentially benefit a patient, it also has many risks such as severe complications, an inability to transport patients once a stable point has been reached, and an increased emotional burden on loved ones as they cling to hope that their loved one can be treated.[19] Furthermore, randomization can be difficult considering the results of this trial. For example, if ECPR is shown to be highly efficacious in treating refractory OCHA then patients must be crossed over to this treatment from

the control or standard treatments in order to ethically conduct this trial.[19] That, however, reintroduces the bias that randomization is intended to prevent. One must consider whether high risk interventions require randomization given the possibility of a high level of crossover and subsequent confounded results. It's also important to determine whether such a study of a high risk intervention is subsequently even justifiable. Finally, the issue of consent is an incredible challenge for this INCEPTION trial considering the fact that most patients are not in a condition to give written and informed consent. As a result, this trial utilized two different forms: deferred and waived consent.[19] Deferred consent, in this case, was given either by the patient or by legal representative as soon as possible after the intervention, thus consenting to the use of the collected data.[19] In the instances of patient death, waived consent was instead utilized where once again legal representatives were asked to provide consent to crucial data if the following conditions were met: the patient during life did not object, the data can be used to improve population health, the patient received standard or new treatment with possible benefit.[19] Questions were once again presented however due to this waived process such as when the right time to ask for consent from a legal representative was given the emotional toll and whether they were even qualified to provide it. For example, at what level of relation would a family member no longer be able to consent, and what if there is a situation in which a patient no longer maintained contact with a close family member but they were still attempting to offer their consent after the patient's death. The INCEPTION trial presented these ethical issues surrounding consent, risk, and randomization; the three biggest ethical dilemmas of emergency care clinical research. Unfortunately, the publication while gleaning certain conclusions regarding equipoise and randomisation, did not provide any meaningful suggestions or recommendations. And while the INCEPTION trial highlighted the issues regarding informed consent and the importance of a rigorous approval process to ensure that the most applicable form of consent is utilized, another publication discusses how these stringent criteria for exceptions to informed consent can provide additional ethical questions about the nature of the research performed.

Another publication, "Ethics and Regulatory Barriers to Research in Emergency Settings," reviewed a study looking at the use of intramuscular sedatives in patients with acute agitation.[20] In this case, the IRB would not approve an informed consent waived control randomized effectiveness trial and instead approved a waiver of consent for a study where the hospital rotated four particular drug options for this intramuscular sedation.[20] In the original description of the study, the researchers were quoted describing the IRB choosing to prevent the original study because they did not believe that this population of patients could provide consent.[20] The other reasoning for the IRB decision is that agitation is not considered life threatening and so a waiver cannot be justified.[20] The authors assess that this change in protocol did not provide additional benefits to patients and made the actual study more complicated in terms of analysis.[20] And while it is imperative to always place patient safety first, such complications can build up and delay research results or prevent a holistic understanding of the medical issue. As a result, they questioned the need for creating changes that lead to suboptimal

science; an unfortunate reality in the extreme environments of emergency care, especially when no additional benefits or safety were provided to the patients. The authors further questioned the validity of the denial on the grounds of an inability to consent given the fact that patients who require sedation are most likely not able to consent regardless of the experimentation, and sedation is often administered to this population without consent.[20] And finally, the authors believed the reasoning that agitation was not life threatening and thus could not be justified for a waiver restricts the ability to conduct important research on low risk conditions that require such waivers due to their situation.[20] In truth, comparative drug trials in simple conditions, even though consent may not be technically attainable, should still be eligible for consideration in a waiver for informed consent. These ideas and difficulties are further described in a publication that documents a discussion that occurred during a workshop conducted by the NIH Department of Bioethics.[21]

Their discussion highlights the lack of legal language regarding research for conscious patients in emergency settings such as those with strokes.[21] These patients who are technically medically awake but are also severely neurologically impaired cannot provide informed consent and surrogate consent is unlikely as well due to the emergency nature of the condition and treatment. Current barriers for informed consent include this particular medical gray area, as well as the aforementioned emotional toll, timely nature, and complexity of much of the research being conducted.[21] It is clear, however, that regardless of barriers that consent should be strived to be obtained in some form or altered capacity, and data has shown that patients in previous trials and interventions prefer being involved in some manner.

To further add context to this discussion, one can begin to introduce nuance with relation to patient populations that emergency medicine might specifically affect. For example, looking at low to medium income countries such as South Africa, issues relating to clinical research in emergency settings are further exacerbated in pediatric populations when compared to adult groups and especially in comparison to traditional Western healthcare settings.[22] Unlike in higher income nations, these LMI countries have a significant lack of pediatric resources, regulation, and clinical research in general.[22] Not only does this contribute to weaker pediatric care resources and an increased difficulty in understanding how to consent pediatric patients, but also a lack of pediatric clinical interventions and changes to help find better treatment options for specifically the children in LMI countries.[22] For example, the lack of research due to under prioritization and a desire to protect children has led to South African hospitals providing antiquated and even unlicensed medications as treatments.[22] The difficulties lie in the fact that many times adult data on treatments cannot be extrapolated and research with children is more complicated than adult studies because of the need to properly inform them of the research, a task made difficult by a child's emotional maturity and intelligence level. This leads to the funneling effect seen in South Africa where research in pediatrics is limited and an entire patient population is precluded from important discoveries that can improve treatment. Another example of an ethical question specific to pediatric clinical research is how to evaluate the risks in a fair tiered approach. While the US sees it as an absolute evaluation, in LMI countries the "average" risks as outlined in the

Belmont Report's Common Rule may be necessarily very different between children.[23] The literature suggests that instead of South African and other LMI countries evaluating risk in absolutes, it should be compared to the level of risk encountered in traditional clinical settings and the local environment of these children so that riskier locations can have more robust research to combat said risks.[22] One other interesting example cited had to do with the FEAST trial in South Africa where children were randomized to different fluid resuscitation strategies.[23] The current idea is that clinical equipoise is maintained such that the treatment intervention that is novel is as effective at least in comparison to the older treatment. In this case, the novel intervention while traditionally under studied and not viewed well for use in these cases well outperformed the typical treatment.[22] Thus, if this research had not occurred, a potentially life saving treatment could have been precluded because of equipoise, and thus a new system for evaluating a treatment's equipoise is required in these settings as well. Furthermore, the FEAST trial included a substudy on the consent process and found that only 18% of parents were able to fully recall the procedure to which they consented their child to given the mental strain of the condition, and it reinforces that in clinical research, identifying how to get consent even through surrogates can be difficult and is further exacerbated when asking parents of pediatric patients.[22] When looking at LMI countries, there are also sociocultural issues that are different from traditional Western cultures. Gender and social hierarchies make it so that women may not be able to consent for their children or in some instances parents might consent their children without fully understanding the procedures due to norms surrounding respect and answering in an affirmatory manner when faced with certain questions and people.[22] In another publication, researchers performed a review of 60 literature pieces relating to LMIC emergency clinical research and one of the important characteristics that they identified as ethically challenging was the evaluation of risk.[23] The idea of risk benefit assessments have been addressed earlier but this publication in particular makes a point of the need for a better literature and outline of how to conduct such assessments and institute protections for vulnerable groups especially in LMI settings considering the inclusion of additional risk factors not traditionally seen in Western societies and countries.[23] The authors believe that there is a significant lack of information on the specifics of how to perform best clinical research practices for LMI countries and cite the lack of information, for example, on when to choose a particular consent method and how to design the process around it.[23] Another challenge to ethical research in LMICs is requiring additional steps and methods in a place where resources are already taxed, emergency rooms are overcrowded, and ethics committees may be vacant or limited.[23] It is imperative that new solutions be introduced on how LMICs can not only conduct ethical emergency clinical research, but in a way that is efficient and counters difficulties with their sociocultural norms. It is clear that in LMI countries that need for greater foundations to support further clinical research is necessary, and it is evident that research in these settings requires additional attention and contains novel challenges.

Pivoting from these countries, however, to a different non Western setting; the ethics in emergency settings for clinical research can be evaluated in the kingdom of Saudi Arabia. This

particular article was utilized to demonstrate how Islamic law and societal aspects can be utilized to justify emergency clinical research, and more importantly, how these are grounded in the same ideas and principles as Western regulations.[24] For example, Islamic law has five foundational purposes with the protection of life being paramount and followed by the next three relevant laws which are the protection of reproductive ability, mental faculties, and the appropriate use of resources.[24] The authors write that even in Islamic law, when compared to Western documents on research ethics, it is clear that the protection of one's life while conducting this emergency clinical research is key and the most important aspect.[24] Furthermore, the principles of Islamic law dictate, for example, that the benefits must outweigh the risks and the principle of necessity prevents intervention of any kind without consent.[24] It is clear, thus, that multiple countries conduct emergency clinical research in some similar manners and with certain differences in terms of challenges to improve their systems of research. However, regardless of potential cultural differences, all clinical research aspects can be grounded in similar foundations between these countries.

All of these challenges have been identified and addressed by professionals working on this issue. As mentioned before, the information and opinions of the public play a large role in the development of research studies, and how effectively they occur. Both of the following articles address what insights can be gained from understanding public perception of emergency clinical research. The first article in particular searched multiple databases for public opinion on research without consent in the US and Europe. Pulling from 12 particular papers, they found the participants in the UK were willing to engage in research without consent through a deferred approach, and that the level of agreement to research without consent was inversely influenced by the level of risk and complexity of the study.[25] Analysis of documentation regarding community consultation for consent waived projects found that many participants appreciated an opt out mechanism for study involvement.[25] This investigation also revealed potential issues with community consultation as polling showed that only around 49% would even attend a meeting, and that would significantly weaken the purpose of community involvement.[25] Meanwhile, only around 50% of US participants were even willing to agree with research without consent.[25] The second article completed a similar systematic review of literature to identify keywords and associated attitudes, eventually concluding that many stakeholders in emergency clinical trials believe that deferred consent is the best way to proceed when informed consent is not possible and risk is held to a minimum threshold.[26] This gives insight into how clinical research, especially in the emergency setting, can be altered in the future to improve practices, while also ensuring that a wide range of research projects are still possible given the inclusion of as many protections as possible. And it leads this review into its next section which revolves around potential solutions to some of the challenges listed and how they would be implemented.

## Improving Emergency Setting Clinical Research

To begin, a brief recap of some of the challenges will be provided. While there are large international frameworks established by different governments and global organizations for the

last 50 years, the nuances of emergency care clinical research are still poorly defined and understood. A majority of the literature presented and surveyed spoke of this lack of information and the need to begin publishing more robust and accurate accounts of emergency clinical research, especially in LMI countries where research is under supported. A better explanation of consent processes, design details, and overall structure of emergency clinical research will allow smaller countries, hospitals, and teams to more efficiently and effectively produce valuable clinical research for their communities. Some of the more pressing challenges revolve around further questions. How does one determine the best consent model for a study? How can vulnerable patient groups be included in studies in LMI countries? How can researchers study patient populations who may not be able to consent but are characterized by a low risk condition?

Beginning with the aforementioned publication on regulatory barriers, one improvement to the current clinical research system can include reviewing and altering the current IRB policies on waiver of consent.[20] The authors cite how patients in a clinical trial with a non-life threatening condition but who are not of the mental capability to provide informed consent due to a condition such as agitation or anxiety are left unstudied.[20] In the described intramuscular sedatives study, the investigation of which treatment was most effective for such a low risk condition was prevented due to the IRB and FDA's strict regulations that waived consent only occurs in life threatening situations.[20] Changing this policy to one in which serious non life threatening conditions where consent is not possible (such as acute anxiety) can be included can help alleviate this gray zone. Along with this alteration, the traditional framework's desire to ensure that the existing therapy is ineffective must be changed as it prevents comparative effectiveness studies in these consent-waived, low-risk conditions.[20] Further, regulatory organizations such as the FDA as well as local IRBs must ensure that a more context driven discussion with researchers takes place such that even when a waiver of consent is utilized, other forms of consent such as assent or opt out can still be included to ensure that pieces of the consent process are involved.[20]

The publication, "Ethical Considerations in Accident and Emergency Research," further describes this need for a more granular, nuanced, and multi layered consent process.[18] Not only do they suggest the inclusion of a spectrum of consent options, as discussed earlier, available for studies that include waived consent or where consent is more difficult, they emphasize the importance of researchers providing information to participants in a more sensitive manner.[18] Their suggestions include utilizing an information sheet that either patients or surrogates providing consent can utilize in their decision making process.[18] They also suggest ensuring that communities can have access to the information sheet ahead of time in a public place like an online site.[18] The sheet should be manageable and visually appealing. The need for accurate and understandable information goes further than a mere sheet, however, and the authors also believe that details are necessary for this process. The sheet and online site should be translated into languages that are found in the community, and should include details on how the research process has evolved into this particular trial or intervention.[18] And of course, all of this is in

addition to the actual verbal and written consent process that can potentially happen if a patient is capable of consenting, or with a surrogate. In conditions where neither is possible due to time or emotional and mental strain, the spectrum of consent can be utilized such as prospective inclusion of data through a deferred model or even an opt out strategy employed as soon as a community is consulted for a waived consent study.[18]

This publication along with the discussion of the INCEPTION trial mentioned earlier strongly suggests a stronger community consultation model.[18,19] It is clear from the public attitude data listed earlier that a majority of community members would like to be involved in the decision making process, but also that many of them are not involved in community consultation and have a lack of understanding of the research process itself, an issue that compounds the implicit difficulties of emergency research.[20,21] As such, the authors of those public data articles emphasized the importance of better community consultations where citizens are included at a higher rate as a result of earlier promotion and more loud and widespread dissemination of the research being conducted.[20, 21] For example, it was suggested that questionnaires be sent to all community members in an effort to make sure that the entire community consulted, even beyond the meeting, to ensure their input is utilized in the design of the study.[20,21] The INCEPTION trial also take an in depth approach to the risks of performing research and interventions on high risk conditions.[19] In particular, the article describes how utilizing ratios of randomization can help balance the risk between control treatments and a newer treatment.[19] Thus, the ratio can be adjusted depending on the preponderance of evidence collected as the study progresses. This further allows for a more established criterion of crossovers, which is when patients are moved from control to trial because of the need for a more robust treatment where evidence shows their particular condition can improve through the trial treatment.[19]

In the manuscript that summarized the discussion findings from an NIH Bioethics meeting, a few points were chosen as immediate and necessary improvements to emergency clinical research.[21] For one, going beyond the idea of a spectrum of consent, the involved attendees determined that a staged consent process with each step including a consent process that fits the situation as aptly as possible would be a stronger approach to issues with consent in emergency settings.[21] Along with this staged process, the authors recommended that new emergency clinical research design include shortened and briefer consent procedures, where information can be provided in a multitude of manners, but the most important information is given in a briefer summary to make consent more available given the emergency time constraints.[21] In the vein of improving consent processes time, the researchers discussing pediatric emergency clinical research in South Africa suggested including consent procedures before admission.[22] Not only does this improve the timeline of the research, but it helps improve the issue of how to discuss research and consent while also being a patient's primary provider. Often, it can be difficult and ethnically ambiguous to have a physician or doctors act as both caretaker and clinical investigator.[22] This article suggests that in addition to a pre admission consent process, the inclusion of separate and even third party investigation teams dedicated to informing the community and obtaining consent can help reduce burdens of such research.[22] In

combination with this increase in brevity and separation of roles, changing the regulations surrounding waived consent to have a broader approach to the idea of minimal risk as discussed previously can be helpful. However, as with any improvement or change there are certain drawbacks such as the amount of resources available to do this in LMI countries, or even possibly eroding people's trust and overcomplicating research design with some of the earlier suggestions.[22] This article further mentions the importance of understanding risk and its relationship and analysis as more than just a balance but rather a tiered system.[22] A system where risks can increase with ability to consent and protections, and that risks are judged not just absolutely but within the context of daily life and average treatments. For example, non therapeutic versus therapeutic interventions should be specifically distinguished and delineated in research documentation and design so that there is an acknowledged understanding of relative risk in either situation but also opening the door to wider and greater research in less riskier situations even in difficult settings such as emergencies.[22] While emergency medicine clinical research is critical and has led to improvements in the conditions of many through trials and a better understanding of the most effective treatments, it is true that there is still much work to do in terms of ensuring its ethicality in the future. The idea of ethical research has only been existent for the last 100 years, and it's incumbent upon the scientists, researchers, and medical professionals of the future to continue the work towards better and safer emergency clinical research. Listed above are some of the most pressing ethical issues and potential remedies for them in this field. Topics covered have included difficulties with consent due to the emergency nature of this research where factors such as time and emotional burden can significantly impact our ability to collect informed and valid consent. Furthermore, the concepts of relative risk and its effect on the ability to design sound clinical research studies has been discussed. It's clear that evaluating risk and ensuring protections for vulnerable groups is important, but it is also evident that new regulations are necessary to ensure the continued study of conditions currently caught in the gray area of the law. And finally, the need for more information, thought, and analysis on not just ethical topics but actual practice of emergency clinical research is necessary. A part of this involves improving the regulations that currently restrict the ability to perform the most sound research possible. While founded in impenetrable ideals that protect human life, it is also clear that there are issues presented by the board regulations that currently exist, and that there is a significant and real need to harmonize regulations between countries and their institutions while also developing newer codes that have intentional work dedicated to addressing some of these topics.

## Conclusion

This literature review began with an introduction that overviewed the history of clinical research, and the origination of regulations surrounding it based upon various ethical principles. Today, there stands a strong community of bioethicists who have made it their mission to ensure the continuation of safe and ethical research. Having been witness to horrific missteps in research in years past, hundreds of international organizations have worked towards establishing guidelines

for best practices, urging countries to pass legislation that ensures the implementation of these ethical ideas. The importance of a continued focus on ethics cannot be understated as newer technology is introduced such as AI. There remains many topics related to clinical research that require further development, not just in practice but in ethical theory as well. Clinical research in emergency settings has traditionally been difficult not just to conduct but to also understand and theorize about. The mere intensity of the setting contributes to much of the ethical dilemmas of research. As a part of this discussion, the current regulatory practices for clinical research were detailed with institutions such as the IRB and explanations of various consent types being included. Also discussed in this review was the similarities and differences between clinical research and its relevant structures from different countries. It was clear that countries such as the Netherlands and the US had very similar systems in place while LMI countries such as South Africa were still progressing in their evolution of ethical clinical research. Given their own difficulties with resources and sociocultural issues, it is necessary that further research on ethics is conducted in these LMI settings. On the other hand, it was also demonstrated how a country such as Saudi Arabia, even given its vastly different legal and cultural origination, can still have clinical research principles and ethics grounded in the same ideas as Western societies. All in all, this review has attempted to demonstrate some of the ethical issues present in emergency clinical research, and how certain alterations to current research design and regulations can help improve not just the ethicality but the production of truly meaningful results in the future.

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