ETHICAL GUIDELINES FOR HUMAN SUBJECTS RESEARCH IN LEAST DEVELOPED COUNTRIES: HOW DO THEY COMPARE TO THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES INTERNATIONAL ETHICAL GUIDELINES?

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Class of 2020

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Title Page (Following editorial guidelines for submission to Journal of Global Health)

Title:
Ethical Guidelines for Human Subjects Research in Least Developed Countries: How do they compare to the Council for International Organizations of Medical Sciences International Ethical Guidelines?

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Disclaimer:
Views expressed in this article are those of the authors and do not reflect the opinions of the institution or funders of this project.

Source of Support:
None

Word Count:
3,018

Number of Figures:
3

Conflict of Interest Declaration:
The authors do not have any conflicts of interest to report.

Abstract:
Background: The most vulnerable populations for human subjects research are those living in the most resource poor settings. As technology has progressed to support convenient long-distance travel, international communication, and data sharing via the internet, international research has become a more manageable task. While some dismiss the ethical guidelines for human subjects research as necessary only for the most barbaric researchers, history demonstrates the need for ethical guidelines as well as oversight of adherence to such guidelines.
Methods: Forty-eight countries designated as least developed countries (LDCs) were identified and selected for analysis. An internet search was utilized to identify research guidelines for LDCs available online or primary research studies conducted in such countries to determine to what extent authors noted ethical considerations. Council for the International Organizations of Medical Sciences (CIOMS) guidelines were distilled into keywords by the authors and compared to guidelines for LDCs. Frequencies and percentages of comparison to CIOMS guidelines were tabulated across the 48 LDCs.
Findings: Of the 48 LDCs identified, 22 did not have published research guidelines or mention of a Research Ethics Committee (REC). An additional 10 countries had documentation of some sort of REC, 3 countries had at least one ethical guideline in addition to a REC, and 13 countries had no mention of a REC but did have established ethical guidelines available online. Overall, the average number of guidelines per country was 5 with a SD of 4.11.
Conclusion: Over half of countries had online documentation of limited ethics oversight for research, indicating a clear lack of thoroughness in the available guidelines as compared to the international gold standard guidelines from CIOMS. The majority of primary research articles reviewed showed no mention of ethical considerations despite some of the articles using chart review or engaging in patient care interventions. Based on the findings of this study, authors recommend the adoption of existing ethical guidelines by countries still lacking individualized guidelines, as well as a movement toward journals requiring documentation of ethical approval or ethical considerations as a requirement prior to approving articles for publication.

Introduction:
Modern ethics guidelines for treatment of human subjects can be traced back to the Nuremberg trials, when 20 physicians were indicted on counts of crimes against humanity and war crimes ultimately leading to development of the Nuremberg Code.[1] While there were ethical treatment guidelines in place in Germany during Nazi control, these guidelines were largely ignored and failed to be included in laws of the Bundestag of postwar Germany. The 1931 ethics guidelines that were in place during WWII and the Nuremberg Trials seem to be the earliest ethics guidelines but were not well known or referenced during the Trials.[2] However, it is speculated that the Nuremberg Code was largely based on the 1931 ethics guidelines, although no reference to the 1931 guidelines was made by the Code's authors. Due to the timing of the Nuremberg Trials and subsequent presentation of the Nuremberg Code, the Nuremberg Code gained notoriety despite its lack of utility.[1]

While the 1947 Nuremberg Code has been shown to be deeply rooted in, if not plagiarized from, the 1931 ethics guidelines, the Declaration of Helsinki (DoH) is rooted in the Nuremberg Code.[1] The DoH was adopted in 1964 and has changed drastically in its over 50 years of existence to include changing technology and accepted practices. While the DoH serves as a code of ethics in its own right, it could be most influential in terms of its utility as the backbone for more detailed ethical guidelines.[3] One such set of guidelines is that offered by the Council for the International Organizations of Medical Sciences (CIOMS). Where the DoH is a concise outline of ethical standards, the CIOMS supplies detail and examples to serve as a true guiding force in ethical decision making, particularly when considering the global human subjects research community.

While ethical guidelines are widely available in the developed world and developed governmental organizations enforce adherence to ethical guidelines in this setting, the engagement of LDC governments and researchers in adherence to ethical guidelines is unclear. Additionally, it has been shown that recent registered global clinical trials often fail to report ethical considerations in protocols, and research conducted in low income countries often measure clinical outcomes rather than surrogate outcomes as are measured in developed countries.[8] Furthermore, journals' instructions to authors for publication often lack guidance for ethical issues in biomedical research, even in developed countries.[7]

CIOMS

The CIOMS ethical guidelines arose from a collaboration between the World Health Organization (WHO) and United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 1949, with work on ethical guidelines taking place in 1970.[4] The CIOMS ethical guidelines were developed specifically for developing countries as a way of applying the ethical considerations set forth in the DoH. The CIOMS guidelines have been updated multiple times in response to advancing technology, epidemics such as the AIDS outbreak, as well as changing research practices. Most recently, in 2016 the CIOMS merged their epidemiological guidelines with biomedical research guidelines as well as expanded their ethical guidelines to include all health-related research rather than only biomedical research. The most recent version of the CIOMS ethical guidelines has 25 guidelines, each with considerable commentary regarding how to apply the guideline in practice.[4]

Ethical Treatment of Human Subjects

Among the many accounts of abuse of research subjects, perhaps the most widely known includes the unethical treatment of subjects during Nazi Germany. What is less understood is that the atrocities for which Third Reich physicians were tried during the Nuremberg Trials had been taking place in the United States prior to and following the Second World War.[5] Compulsory sterilization laws were in place in some US states through 1985, coerced experimentation on US prisoners continued through the 1970s, and Hitler's anti-Semitic Nuremberg Laws that limited the rights of Jewish people closely resembled the US segregation laws that persisted through the 1960s.[5]

Perhaps the most compelling example of unethical research in the US is the Tuskegee Syphilis Study, a study sponsored by the US Public Health Service which enrolled 600 black American men, 399 with syphilis and 201 without. The aim of the study was to study the natural course of syphilis in the human body. At the time of the study's onset, there was no identified treatment for syphilis. However, participants in the study were not informed of the purpose of the study or their disease diagnosis, and yet were compensated for participation. Even when Penicillin became the treatment of choice for syphilis in 1945, participants of the Tuskegee Syphilis Study were not informed of their disease nor treated for it. Shockingly, this study continued for 40 years; it existed through the Nuremberg Trials and establishment of the Nuremberg Code as well as the Declaration of Helsinki and even past the time of the Civil Rights Movement despite being in clear violation of these ethical codes. The study was finally exposed by a journalist and promptly halted.[6]

While the research garnered via studies such as The Tuskegee Syphilis Study have value, the model used does raise ethical concerns, particularly that as medication was introduced to the general population, it was not offered to the participants. Additionally, the participants didn't have a complete

understanding of the study for which they were enrolling at the time of enrolling, and it could be argued that compensation was disproportionate to burden of the study leading to incentive to participate.

While some dismiss the Nuremberg Code and similar ethical guidelines as necessary only for the most barbaric researchers or practitioners, history demonstrates the need for ethical guidelines as well as oversight of adherence to such guidelines.

Least Developed Countries

While individuals in the Western World have certainly been targeted as vulnerable research subjects on whom to experiment, the most vulnerable populations are the most resource poor and marginalized. As technology has progressed to support convenient long-distance travel, international communication, and data sharing via the internet, international research has become a more manageable task. Individuals in LDCs as defined by the United Nations Statistics Division are at risk for exploitation. With limited access to medical care, education, and basic needs such as food, clean drinking water, and sanitation, these populations may be easily coerced by researchers' compensation including access to medical care, and may not fully understand the research in which they are engaging due to lack of medical knowledge and education.

Methods:

Subjects

Using the United Nations Statistics Division[2], forty-eight countries designated as "least developed countries" were identified and selected for analysis. This subset was chosen as these countries are the most resource poor settings and represent the populations most vulnerable to exploitation.

Search Methods

An exhaustive and multi-level internet search was utilized to identify research guidelines available online, as shown in Figure 1. Scanned PDF documents were text extracted using optical character recognition (OCR) software available for free download online. For non-English text, Google Translate was utilized via copy and paste to translate material into English.

Figure 1: Guideline search methods

In the cases of countries for which no ethical guidelines could be identified through the multi-level internet search, a PubMed search was conducted to identify studies conducted in such countries. The primary literature from these countries was analyzed for mention of ethical clearance to determine to what extent researchers considered ethics and sought ethical approval from a governing body.

Statistical Analysis
CIOMS guidelines were distilled into keywords by the authors. Ethical guidelines from LDCs, once identified and translated, were individually analyzed by the authors for key words and presence or absence of a related guideline was noted in an excel file. Frequencies and percentages of CIOMS guidelines were tabulated across 48 countries.

Results:
Of the 48 LDCs identified, 17 did not have any research guidelines available online or any mention of a Research Ethics Committee. An additional 15 countries had documentation of some sort of Research Ethics Committee and in some cases, submission guidelines for that ethics committee but no

specific ethical guidelines. Three countries had at least one ethical guideline in addition to a Research Ethics Committee, and thirteen countries had no mention of Research Ethics Committees but did have established ethical guidelines available online. In total, 16 countries had guidelines that were analyzed in comparison to the CIOMS guidelines.

Of the ethical guidelines analyzed, the most frequently mentioned guideline was informed consent. No countries had guidelines related to cluster randomized trials or use of data obtained online and digital tools. Overall, the average number of guidelines per country was 5 or 25% with a SD of 4.11. Results by guideline are shown in Figure 2.

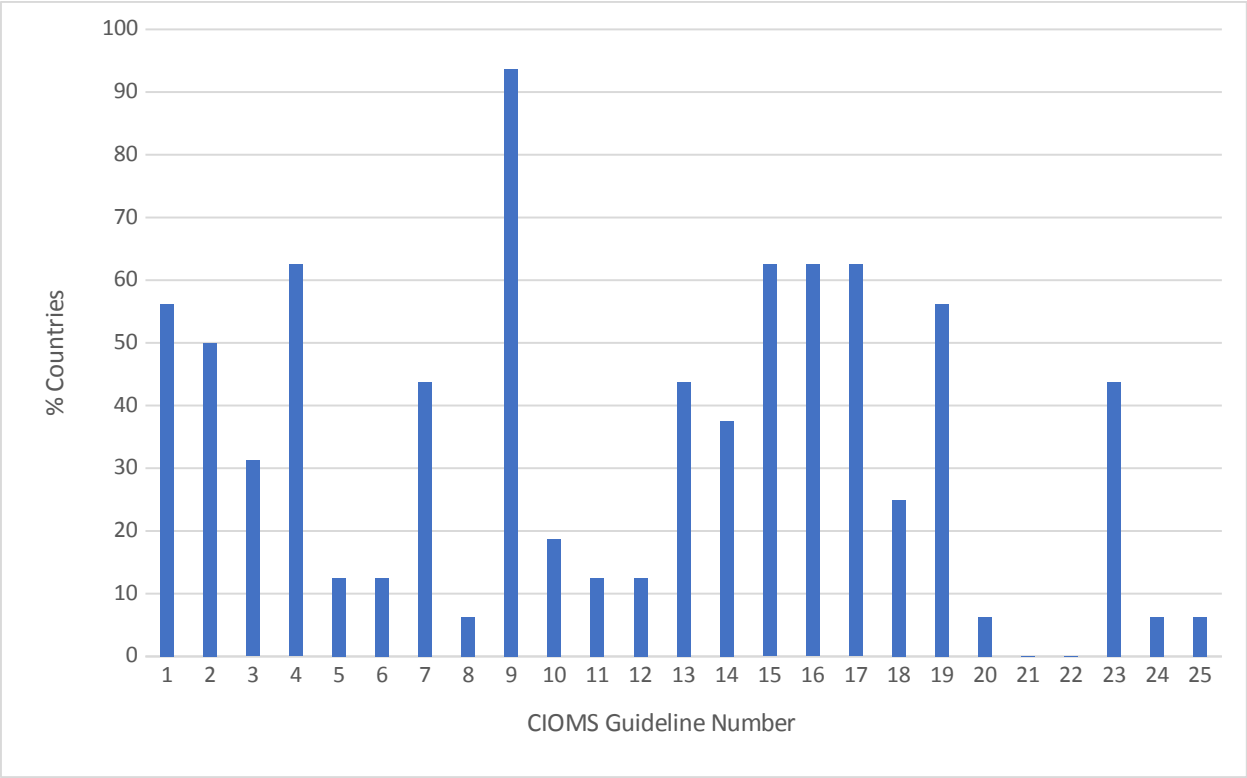

Figure 2: Breakdown of percentage of LDCs meeting each of the CIOMS guidelines as identified by keywords, demonstrating the focus of guidelines on informed consent and lack of focus on digital data

Guideline Number	Guideline Key Words	Number of countries including guideline (%)
1	Scientific value, social value, respect for rights	9 (56)
2	community responsiveness, sustainability, cultural competence	8 (50)
3	Equitable distribution of beneft/equitable distribution of burden	5 (31)
4	Minimized risk/ balanced risk in relation to	10 (62)

	value of knowledge gained	
5	Control group (effective intervention vs placebo)	2 (12)
6	Provision of health needs (during and after research)	2 (12)
7	Community engagement (in process, dissemination of results)	7 (44)
8	Capacity-building for research and ethics	1 (6)
9	Informed consent	15 (94)
10	Waiver of informed consent, modification of informed consent	3 (19)
11	Use of biological materials, storage of biological materials	2 (12)
12	Use of data, storage of data	2 (12)
13	Reimbursement, compensation, research participation	7 (44)
14	Treatment, reimbursement, research related harms	6 (38)
15	Protection of vulnerable populations/individuals	10 (62)
16	Adults not capable of giving informed consent	10 (62)
17	Research involving children and adolescents	10 (62)
18	Women as research participants	4 (25)
19	Pregnant and breastfeeding women	9 (56)
20	Research in disasters and disease outbreaks	1 (6)
21	Cluster randomized trial	0 (0)
22	Use of data obtained online and digital tools	0 (0)
23	Requirements for establishing ethics committee	7 (44)
24	Public accountability for research	1 (6)
25	Conflicts of Interest	1 (6)

Table 1: List of CIOMS Guideline key words corresponding with Figure 2

In the case of countries with no internet searchable ethics committees or guidelines, of the fourteen countries where primary research articles were found, the majority of articles did not mention ethical consideration as shown in Table 2 and Figure 3. Those that did most often cited an ethics review committee or IRB associated with either the country or the sponsoring institution, often an academic institution in the Western world conducting research in the LDC. In many cases, the research conducted included deidentified information from a database and therefore was not deemed to require ethical approval. In yet other articles, subjects included patients and chart review, yet no ethical considerations were addressed in the article.

	Article 1	**Article 2**	**Article 3**	**Article 4**	**Article 5**
Chad	None[8]	None[8]	None[8]	None[8]	None[8]

Comoros	None[13]	None[13]	None[13]	None[13]	None[13]
Djibouti	REC[18]	REC[18]	REC[18]	REC[18]	REC[18]
Eritrea	REC[23]	REC[23]	REC[23]	REC[23]	REC[23]
Madagascar	Deidentified data[28]	Deidentified data[28]	Deidentified data[28]	Deidentified data[28]	Deidentified data[28]
Mauritania	REC[33]	REC[33]	REC[33]	REC[33]	REC[33]
Sao Tome	Deidentified data[38]	Deidentified data[38]	Deidentified data[38]	Deidentified data[38]	Deidentified data[38]
Soloman Islands	REC[43]	REC[43]	REC[43]	REC[43]	REC[43]
Somalia	Institutional IRB[48]	Institutional IRB[48]	Institutional IRB[48]	Institutional IRB[48]	Institutional IRB[48]
South Sudan	External REC[53]	External REC[53]	External REC[53]	External REC[53]	External REC[53]
Tuvalu	External REC plus specific considerations[58]	External REC plus specific considerations[58]	External REC plus specific considerations[58]	External REC plus specific considerations[58]	External REC plus specific considerations[58]
Tanzania	REC[63]	REC[63]	REC[63]	REC[63]	REC[63]
Venuatu	Deidentified data[68]	Deidentified data[68]	Deidentified data[68]	Deidentified data[68]	Deidentified data[68]
Yemen	None[73]	None[73]	None[73]	None[73]	None[73]

Table 2: Ethics statements in primary research articles in countries without available guidelines or ethics committee statements.

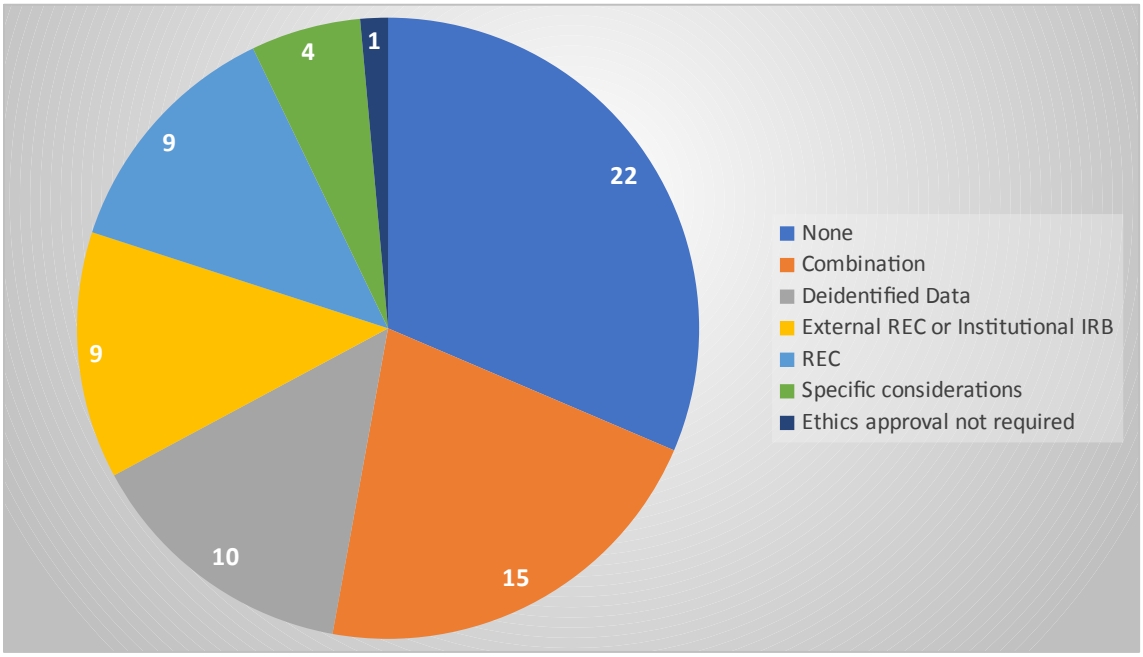

Figure 3: Breakdown of number of primary research articles mention of ethical considerations

Discussion:

Over half of LDCs analyzed in this study had online documentation of limited ethics oversight for research, indicating a clear lack of thoroughness in the

available guidelines as compared to the international gold standard guidelines from CIOMS. The majority of primary research articles reviewed showed no mention of ethical considerations despite some of the articles using chart review or engaging in patient care interventions

The authors of this study set out to investigate to what extent research guidelines for ethical treatment of human subjects exist in LDCs, and how existing guidelines compare to the CIOMS International Ethical Guidelines for Health-related Research Involving Humans. This was a daunting task, considering the lack of infrastructure and competing priorities in countries that are categorized amongst the most resource poor of the globe, and who are often in civil unrest. Nevertheless, a surprising number of countries had guidelines or REC information available online. The existence of online databases including Health Research Web and the International Compilation of Human Research Standards through the U.S. Department of Health and Human Services serve as testaments to the value placed on ethical treatment of humans throughout the world, as well as the importance of human subjects research on a global scale.

While over half of countries had online documentation of ethics oversight for research, our study identified a clear lack of thoroughness in the available guidelines as compared to the international gold standard guidelines from CIOMS. Whereas CIOMS guidelines encompass 25 individual guidelines, the average number of guidelines documented in the LDCs analyzed was only 5. Additionally, 2 of the CIOMS guidelines were never mentioned in any of the LDCs analyzed. The guidelines not mentioned included “cluster randomized trials” and “use of data obtained online and digital tools”. This could reflect the lack of technology and infrastructure found in LDCs, or perhaps prioritization of more immediately relevant guidelines for each particular country.

One interesting facet of many guidelines, while not an aim of this study nor analyzed as part of our data, was the inclusion of guidelines not related to CIOMS guidelines. While not tabulated, one guideline that came up often included punishment, fines, and prison sentences for individuals in violation of the other ethical guidelines. In the Western world, the legal system imposes such consequences for individuals in violation of human rights and health care protections. As such, it was interesting to see departments of health in LDCs imposing consequences within their research guidelines rather than separately through the legal system. This would be an interesting future project to pursue in conjunction with a review of what legal system is in place for enforcement of ethical guidelines in LDCs.

While analysis of Research Ethics Committee rules, regulations, and formation was not an aim of this study, authors did pour over REC documents in an effort to identify any available research guidelines. An

encouraging finding in this process is that many RECs had specific provisions to include community members from the LDC on their RECs to ensure cultural appropriateness of research and buy in from the community.

For the countries that did not have available documentation of research guidelines or RECs within the country, the majority of primary research articles showed no mention of ethical considerations despite some of the articles using chart review or engaging in patient care interventions. This finding provides the most compelling support for the need to develop and enforce ethical review for human subjects research as it provides evidence that even in the 21st century, without guidelines in place, researchers will ignore ethical considerations in their work.

The most alarming findings came from Yemen. In this case, PubMed results were cluttered by letters to the editor and opinion pieces regarding the civil unrest and healthcare crisis in Yemen. Simultaneously, there were articles published that included patient chart review and patient care that had no ethics statement. Subjects included children as well as adults, and these articles included photographs of patients, deidentified by placing black boxes over subjects' eyes. Readers are unable to determine the ethical considerations by the authors of such articles because no statement on ethics exists in the published articles. The case of Yemen was the most striking example of the dire need for ethical oversight for research in vulnerable, war torn countries whose inhabitants lack access to basic healthcare, making them prime candidates for health research but also at significant risk for exploitation.

Expecting governments of countries with little infrastructure, wealth, and education to establish their own research ethics committees and ethics guidelines may seem impractical. However, establishing research guidelines is as simple as adopting the Declaration of Helsinki or the CIOMS guidelines and enforcing them through existing governmental auspices. Alternatively, rather than putting the onus of ethical review on each country, it would make sense for journals to require ethical statements. Even in the case where ethical approval is not required, it would be simple to include a statement in each article submitted noting that ethical approval was not required and the reason for this, or alternatively what ethical considerations were in place for the published research.

Limitations of this study include the use of internet search for location of ethical guidelines from countries that may not have ready access to the internet. Contact with local departments of health for each country would have likely enhanced the yield of guidelines and REC information acquired. Additionally, translation of guidelines using online computerized translation service is imperfect, and access to an interpreter for each language would have allowed contextual nuances in the guidelines to be illuminated. Finally,

use of text mining software rather than human interpretation comparing countries' guidelines to CIOMS would likely result in reduction of human bias in results.

In conclusion, there is a lack of ethical oversight for human subjects research in the world's most vulnerable and resource poor countries. When not required to seek ethical approval and note ethical considerations, researchers overwhelming neglect research ethics in their work. Possible solutions to this global problem include use of established research ethics guidelines in leu of country specific guidelines in countries without guidelines in place, and/or a movement toward journals requiring ethical approval and/or ethics statements in each article prior to the article being accepted for publication.

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