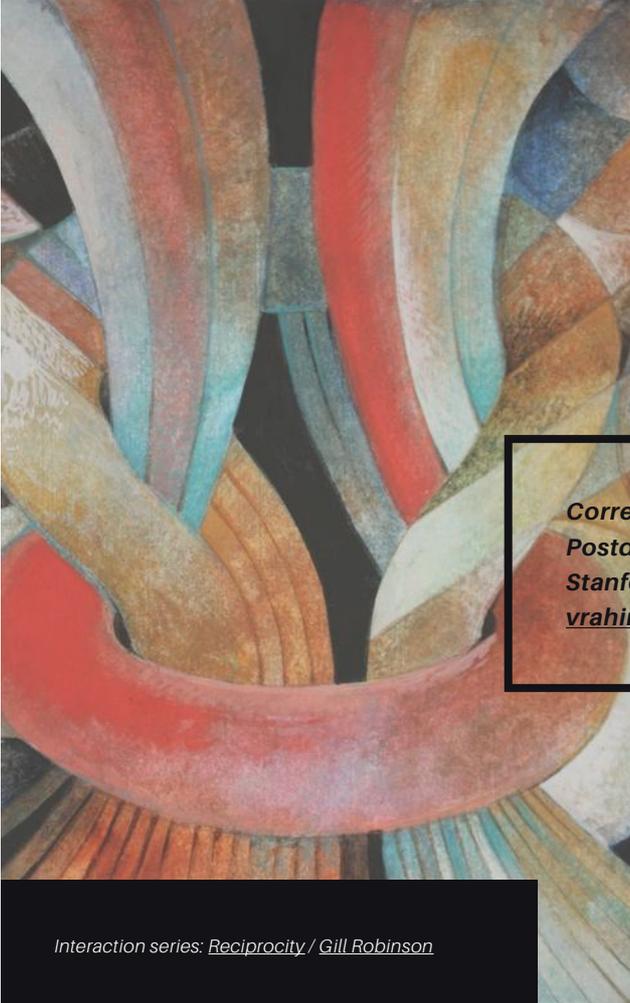


Ethics review mutual recognition and multinational research collaboration in pandemic response settings.

January / 2021



COVID-19 Clinical Research Coalition

Ethics Working Group

*Correspondence to Vasiliki Rahimzadeh, PhD
Postdoctoral Fellow, Stanford Center for Biomedical Ethics
Stanford University
vrahim@stanford.edu*

Interaction series: *Reciprocity* / Gill Robinson

Acknowledgements.

January / 2021

Funding for this report was provided by the WHO Global Health Ethics & Governance Unit. The report was prepared with assistance and support from the Co-Chairs of the Covid-19 Clinical Research Coalition Ethics working group, Jantina DeVries and Jennyfer Ambe, who also served as advanced readers. Thank you to the individual members of the Coalition working group; to numerous informants who provided valuable input on the ethical, legal and political implications of ethics review mutual recognition in their home countries; and most importantly, to all research ethics committee members worldwide who work tirelessly to uphold the highest standards of research protections for human participants before, during and beyond the Covid-19 pandemic.



Research ethics review mutual recognition and multinational research collaboration in pandemic settings.

Table of Contents.

January / 2021

Executive Summary	6
Highlights	7
List of Figures	9
List of Boxes	10
List of Terms	11
Introduction	15
Covid-19 Clinical Research Coalition project summary	17
Report goals	18
Consultant process	18
Evidence retrieval, generation and synthesis	18
Literature review	19
Consultative activities	19
Report limitations	22
Approach	23
Part I. Research ethics review and committee oversight	25
Regulatory history	26
Institutionalization of RECs	29
Research collaboration and centralized review modalities	31
Accelerated review via centralization during public health emergencies	35

Conceptual challenges to independent, local REC reviews	39
Part II. Ethics review mutual recognition: justifications, standards and models	44
Standards	46
International	46
WHO	46
GA4GH Ethics Review Recognition Policy	47
National	47
Canada	50
United States	51
Conceptual models	53
Federation	54
Delegation	54
Reciprocity	54
Sounding board model	56
Part III. Mini case reports	59
Case study 1—AVAREF	60
Case study 2—Philippines	65
Case study 3—PAHO, Brazil, Chile, Caribbean, Peru, Argentina, Columbia	68
Case study 4—Kazakhstan, Azerbaijan, Belarus, Armenia, Kyrgyzstan, Uzbekistan and Ukraine	76
Part IV. Opportunities and Challenges	79
Protecting the roles and authorities of local RECs	82
Regulatory organization of REC	83
Equity in North-South research collaborations	84
REC coordination and communication	86

Part V. Needs identified to augment trust and cooperation among international RECs	88
Summary of findings	89
Practical points	90
Future directions	92
Conclusions	93
References	96
Annexes	
Annex 1. Literature search strategy	102
Annex 2. General international guidance documents on (multisite) REC standards, responsibilities, procedures and operations	103
Annex 3. Summary of consultative activities	106
Annex 4. Covid-19 specific guidelines for accelerated reviews and special standard operating procedures for RECs during public health emergencies	109
Annex 5. Report Art.	114

Research ethics review mutual recognition and multinational research collaboration in pandemic settings.

January / 2021

Executive Summary.

This report presents findings from a project undertaken in collaboration with the Covid-19 Clinical Research Coalition. An environmental scan of the literature was conducted, which reviews the ethical, legal and policy implications of system of ethics review and approval for studies that span multiple sites and jurisdictions termed “ethics review mutual recognition.” The report additionally identifies barriers to, and opportunities for implementing ethics review during public health emergencies in low-and middle-income countries from the perspectives of Covid-19 Clinical Research Coalition members and their affiliates.

Highlights.

- Research ethics committees (RECs) institutionalized the review of responsible conduct of research involving humans and proliferated in response to abusive practices in the late 20th Century
- Advances in communication and computing dramatically improved the ability for researchers to collaborate but have not resulted in parallel improvements to REC review policy
- Growing empirical data show that an institution-by-institution approach to ethics review is redundant, costly, and inefficient when applied to multisite studies. A secondary concern emerges where research spans multiple jurisdictions, raising issues of regulatory parity and varied measures of equivalent protections.
- The pandemic has demonstrated that multisite/national reviews can be accelerated via centralization without comprising review quality or rigor when provided adequate human and material resources.
- Ethics review mutual recognition is a reciprocal system of institutional research ethics review and approval in which the decisions of a competent, qualified REC or institution are recognized by another RECs based on shared procedural standards.

Highlights continued.

- Procedure, not substantive ethics is the locus of reciprocity under ethics review mutual recognition. Reciprocal agreements pursuant to mutual recognition of REC procedures do not supplant authorization from local sites, nor do they sidestep community representation that local RECs embed in the review process.
- Successful implementation of ethics review mutual recognition is conditional on i) determining procedural equivalence and ii) establishing reciprocity among participating RECs
- Findings from the consultative activities affirm that centralizing elements of the ethics review workflow perturbs at least three embedded relationships in the research institution with implications for establishing reciprocity: between the reliant or centralized REC and the local i) REC, ii) researchers, and iii) communities.
- National legislation, guidelines and policies reflect the normative ethics principles codified in international conventions such as CIOMS, UNESCO Declaration on Bioethics and Human Rights, and broadly adhere to WHO Standard Guidelines on RECs. This suggests broad consensus on REC roles, responsibilities and structure upon which the condition of procedural equivalence could plausibly rest.
- Chief barriers to establishing reciprocity included lack of conceptual clarity on the protected roles of local RECs, the heterogeneity of regulatory environments within which RECs currently operate and perceived inequities in North-South research collaborations that mutual recognition could further inflame.
- All models of ethics review mutual recognition summarized in this report aims to balance the need for quality and expedience in multinational reviews based on shared REC standards while preserving local input required to ensure a given study can be conducted effectively at local sites.
- If pursued, the future scalability of mutual recognition would require at a minimum, equal representation from research systems with highly integrated as well as newly developing REC infrastructure in modeling approaches to establish reciprocity.

Research ethics review mutual recognition and multinational research collaboration in pandemic settings.

List of Figures.

January / 2021

Figure 1	<i>Consultative activities by type</i>	20
Figure 2	<i>Consultative activities by region</i>	21
Figure 3	<i>Timeline of international REC standards and guidance since 2000</i>	27
Figure 4	<i>Centralized models of multisite REC review</i>	30
Figure 5	<i>Simplified REC committee workflow and perturbations due to ethics review mutual recognition between centralized REC and local i) REC, ii) researchers, and iii) communities.</i>	42

Research ethics review mutual recognition and multinational research collaboration in pandemic settings.

List of Boxes.

January / 2021

Box 1	<i>Ethics review mutual recognition in pandemic response settings. A global Covid019 Research Coalition Project aims and deliverables</i>	17
Box 2	<i>GA4GH Ethics Review Recognition Policy Essential Elements</i>	48
Box 3	<i>GA4GH Ethics Review Recognition Policy Common Elements</i>	49
Box 4	<i>Regulatory channels for multinational ethics review in Canada and the United States</i>	50
Box 5	<i>Three models for building ethics review mutual recognition for data-intensive international research organized from most, to least integrative with local RECs</i>	54
Box 6	<i>AVAREF Tools for Processing Clinical Trial Applications by Ethics Committees and National Regulatory Authorities in Africa</i>	61
Box 7	<i>Three processes and corresponding tools AVAREF developed to facilitate quality review and responsible conduct of vaccine clinical trials</i>	62
Box 8	<i>Levels of REC accreditation overseen by the Philippine Health Research Ethics Board</i>	66
Box 9	<i>Harmonizable elements at the protocol and committee levels to support coordinated reviews for multinational studies based on feedback from informants</i>	81

Research ethics review mutual recognition and multinational research collaboration in pandemic settings.

List of Terms.

January / 2021

-
- Benefit** *A favourable consequence arising from a study, for example the demonstration that a vaccine is effective in a randomized controlled trial or the identification of a workplace hazard in an observational study.*
- Bioethics** *A field of ethical enquiry that examines ethical issues and dilemmas arising from health, health care, and research involving humans.*
- Compensation** *That which is given in recompense, as an equivalent rendered, or remuneration.*
- Confidentiality** *The obligation to keep information secret unless its disclosure has been appropriately authorized by the person concerned or, in extraordinary circumstances, by the appropriate authorities.*
- Conflict of Interest** *In the research context, scientists have a conflict of interest if they stand to achieve personal gain (money or the equivalent) by failing to discharge professional obligations, either to protect the welfare of participants or to uphold the integrity of the scientific process.*

Terms are excerpted from the World Health Organization. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*. 2011. https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=2CB78BE4794C241B287C824F200DA282?sequence=1 (accessed 12/16/2020).

Consent form	<i>An easily understandable written document that documents a potential participant's consent to be involved in research which describes the rights of an enrolled research participant. This form should communicate the following in a clear and respectful manner: research time-frame; title of research; researchers involved; purpose of research; description of research; potential harms and benefits; treatment alternatives; statement of confidentiality; information and data to be collected; how long the data will be kept, how it will be stored and who can access it; any conflicts of interest; a statement of the participant's right to withdraw from participation at any point; and declarative statement of understanding that the potential participant agrees to and signs. The consent form should be in a language that the potential participant understands. For potential participants with limited literacy, the verbal communication of the consent document details should be provided along with proper documentation of consent, if it be given.</i>
Ethical guidelines	<i>Guidance documents which assist with decisions relating to the responsibility to adhere to established and relevant standards of ethical principles and practice.</i>
Ethics review mutual recognition	<i>A conceptual system of multinational research ethics review and approval in which the decisions of a competent, qualified REC in the sponsoring country are recognized by RECs in a host country based on shared procedural standards.</i>
Expedited/accelerated review	<i>Review of proposed research by the REC chair or a designated voting member or group of voting members rather than by the entire REC.</i>
Multisite/institution review	<i>REC review of a research study conducted according to a single protocol but at more than one site or institution, and, therefore, carried out by more than one investigator.</i>
Multinational	<i>Of or relating to more than one country e.g. multinational review.</i>
Participant	<i>Individual involved in a research protocol. Also referred to as human subject.</i>
Personal data	<i>Data that relate to a living person and contain personally identifying information.</i>
Principal investigator (PI)	<i>The main researcher overseeing or conducting the research process.</i>

Privacy	<i>The state or condition of being alone, undisturbed, or free from public attention, as a matter of choice or right; seclusion; freedom from interference or intrusion; absence or avoidance of publicity or display; secrecy, concealment, discretion; protection from public knowledge or availability</i>
Quorum	<i>A quorum is the minimum number of members that must be present to constitute a valid meeting where decisions can be taken concerning submissions put forward for ethical review. A meeting is quorate when a quorum is present.</i>
Reimburse	<i>To repay (a sum of money which has been spent or lost).</i>
Researcher	<i>A person who engages in the methodical and systematic investigation of hypotheses with the goal of contributing to new knowledge.</i>
Research ethics committee (REC)	<i>Also known as ethical review board [ERB], ethical review committee [ERC], human research ethics committee [HREC], institutional review board [IRB]: Group of individuals who undertake the ethical review of research protocols involving humans, applying agreed ethical principles.</i>
Research involving human participants	<i>Any social science, biomedical, behavioural, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge in which human beings: (1) are exposed to manipulation, intervention, observation or other interaction with investigators, either directly or through alteration of their environment; or (2) become individually identifiable through investigators' collection, preparation or use of biological material or medical or other records.</i>
Research protocol	<i>A document that provides the background, rationale, and objective(s) of a social science, biomedical, behavioural, or epidemiological project and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.</i>
Revision	<i>Requirement by the research ethics committee to alter the protocol in some way prior to approval or additional review by the committee.</i>
Risk	<i>The probability that an event, favourable or adverse, will occur within a defined time interval. Although often contrasted to benefit (as in a "risk/benefit ratio"), the term "potential harm" is better for that context.</i>

Sponsor

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of research.

Voluntary

Performed or done of one's own free will, impulse, or choice; not constrained, prompted, or suggested by another; free of coercion, duress, or undue inducement. Used in the health and disability care and research contexts to refer to a consumer's or participant's decision to receive health or disability care or to participate (or continue to participate) in a research activity.

Vulnerable research population

Vulnerable persons are those who by nature of their situation are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, capacity, education, resources, strength, or other needed attributes to protect their own interests. Individuals whose willingness to volunteer in a research study may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate may also be considered vulnerable. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other potentially vulnerable persons may include patients with incurable diseases, people in nursing homes, unemployed or impoverished people, patients in emergency situations, ethnic minority groups, homeless people, nomads, refugees, minors, and those incapable of giving consent. This list may not be exhaustive as there may be circumstances in which other groups are considered vulnerable, women for example, in an orthodox patriarchal society.

January / 2021



*Reciprocity /
Angel Garcia*

Introduction

At the time of writing, an estimated 2 million people have died and 92 million more have been infected worldwide with Covid-19. National healthcare systems have been crippled, international borders restricted, and entire economies halted as a result. These grim realities rank the Covid-19 pandemic among the gravest public health crises ever experienced in human history. Not all populations, however, have suffered equally from its health-related, social and economic impacts [1]. Since first identifying the virus in the Wuhan province of China in late 2019, scientific research has been essential

in the generation of knowledge needed to manage and address the pandemic. For instance, epidemiological research has shown that gross inequalities in the social determinants of health heighten mortality rates and are directly linked to how effectively communities can exercise known strategies to mitigate the risk of Covid-19 transmission—such as social distancing, hand hygiene and use of personal protective equipment [2].

Pandemics intensify the need for timely, rigorous, and accessible scientific evidence that can guide

[1] One multi-country comparison demonstrated that the Covid-related mortality risk increased with age, with social and material deprivation and in the presence of long-term conditions such as obesity, diabetes and vascular and kidney diseases [Kontis V, Bennett JE, Rashid T, et al. Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. *Nat Med.* 2020;26(12):1919-1928. doi:10.1038/s41591-020-1112-0]. See also Bambra C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. *J Epidemiol Community Health.* 2020;74(11):964-968. doi:10.1136/jech-2020-214401.

[2] See for example the role of communication in addressing social determinants of health in pandemic responses in developing countries [Ataguba OA, Ataguba JE. Social determinants of health: the role of effective communication in the COVID-19 pandemic in developing countries. *Glob Health Action.* 2020;13(1). doi:10.1080/16549716.2020.1788263] as well as the specific effects of inequalities hindering effective hand hygiene campaigns in Sub-Saharan Africa [Okoi O, Bwawa T. How health inequality affect responses to the COVID-19 pandemic in Sub-Saharan Africa. *World Dev.* 2020;135:105067. doi:10.1016/j.worlddev.2020.105067].

public health responses and catalyze therapeutic discovery. Scientific collaboration accelerates this evidence generation. Siloed regulatory environments within which multisite/national studies are reviewed and approved, however, can delay important research, increase administrative burdens and apply inconsistent protections. Already the experiences of several research consortia in the Global Clinical COVID-19 Research Coalition indicate that multiple ethics reviews have delayed the start of research projects, and this is of pressing concern.

The COVID-19 Clinical Research Coalition (<https://covid19crc.org/>) seeks to promote global research collaboration on COVID-19, particularly in the context of low- and middle-income countries. Its Ethics WG has been working on various ethics issues in relation to COVID-19 and identified a need for additional analysis and guidance development as it relates to ensuring expedient and comprehensive ethics review of Covid-related research protocols where such research involves institutions across jurisdictions.

Ethics review mutual recognition has been proposed as one approach to reduce procedural inefficiencies that

often confound multisite/national review. Mutual recognition refers to a system of extra-jurisdictional review and approval for multisite/national studies by which the decisions of one REC are accepted by another REC on the basis of shared procedural standards. Originally proposed to facilitate international research in the field of genetic/genomic sciences, ethics review mutual recognition has yet to be considered for application during public health emergencies or in low- and middle-income countries, specifically (See **Part II**). The current report seeks to map the barriers and opportunities for ethics review mutual recognition in the context of clinical COVID-19 research and future pandemics.

Covid-19 Clinical Research Coalition project summary

This report is the culminating deliverable of a project funded through Health Ethics & Governance Unit of the World Health Organization (WHO) in collaboration with the Ethics Working Group of the Covid 19 Clinical Research Coalition. The project aimed to support strengthening the research evidence base on systems of centralized ethics review and approval to better inform the development of international guidance for research organizations responding to the Covid-19 pandemic. This project sought to understand the obstacles to and opportunities for ethics review mutual recognition for multisite/national research taking place in the context of global pandemics and in low- and middle-income countries. The project addresses this important policy need by

January / 2021

Box 1 *Ethics review mutual recognition in pandemic response settings.*
A global Covid-19 Research Coalition Project aims and deliverables

- 1** ***Aim**–Describe the current state of ethics review mutual recognition, including a clear description of obstacles, cooperative agreements and approaches proposed in the empirical and policy literature.*
***Deliverable**–Peer reviewed publication of environmental scan and proposed applications of ethics review mutual recognition in pandemic settings.*
- 2** ***Aim**–Identify how institutions and Covid-19 researchers currently approach multiple ethics review and conduct a needs assessment among Coalition members.*
***Deliverable**–Provide a platform for Covid-19 researchers and ethics review boards to share experiences, lessons learned, and institutional approaches to reviewing multi-site protocols during the pandemic.*
- 3** ***Aim**– Develop priority areas, propose tools and practical strategies for taking ethics review equivalency forward in Covid-19 research for the Global Coalition and for sister organizations such as PHEPREN.*
***Deliverable**–Formal report describing a) the current state of the art of the academic debate in ethics review equivalency, including models and agreements; b) key roadblocks to and opportunities for ethics equivalency in Covid-19 ethics review and c) propose priority areas, tools and practical strategies to formalize ethics review equivalency.*

contributing three deliverables with corresponding specific aims provided in **Box 1**.

Preliminary discussions with members of the Covid-19 Clinical Research Coalition (herein referred to as the “Coalition”) generated considerable controversy around the conceptual definitions and proposals for ethics review mutual recognition. The associated project goals were modified accordingly to focus alternatively on nuancing the underlying social, cultural and policy roots of these concerns.

Report goals

This report is pursuant to modified Deliverable 3 (**Box 1**), and presents results from an environmental scan and consultative process, respectively, that

- i. Landscapes the current policy debate of ethics review mutual recognition identified in the empirical and grey literature and
- ii. Describes how Coalition members and affiliated institutions currently approach multisite/national ethics review, identifying key roadblocks to, and opportunities for mutual recognition to accelerate research related to pandemic management.

Consultant process

The Co-Chair of the Covid-19 Clinical Research Coalition Ethics Working group identified the consultant for the funded project based on the consultant’s expertise in ethics review mutual recognition and comparative REC policy. The consultant was subsequently approved by the Director of the Health Ethics & Governance Unit of the World Health Organization. The project was funded in November 2020; a completed report was requested by December 31, 2020 and was conducted independently with the following exceptions. The consultant received a consulting fee from as part of the approved project budget to conduct the background research on ethics review mutual recognition. The fee also supported the consultant in holding consultative meetings with Coalition members and their affiliates, as well as to present the project at academic conferences to inform the assessment of key challenges and opportunities of ethics review mutual recognition (**Aim/Deliverable 2**). Payment was not contingent on the conclusions found. The Ethics Working Group was presented with the opportunity to read and comment on the final report on January 27th, 2021. Editorial revisions were made to improve clarity, formatting and overall comprehension of the report based on feedback from this group and in preparation for final submission.

Evidence retrieval, generation and synthesis

Literature review

An environmental scan of the literature served as the primary mechanism for retrieving published evidence on ethics review mutual recognition. The consultant performed a systematic search in PubMed for conceptual and empirical articles relating to multisite ethics review within a single country, and experiences reviewing multinational studies. A detailed search strategy including MeSH terms is provided in **Annex 1**. Articles were screened for relevance and organized by region. In general, the articles retained for inclusion in this scan described the ethical, legal and policy implications of an extra-jurisdictional or multinational system of streamlining ethics review for international studies or detailed domestic approaches to multisite review via REC centralization.

Consultative activities

Current approaches to REC review of multisite/multinational studies related to Covid-19, REC experiences and lessons learned were collected through a series of consultative activities with members of the Coalition, their colleagues, and a snowball sample of researchers identified from the authors list of relevant peer reviewed publications related to ethics review mutual recognition. The activities included individual and group meetings held virtually, webinars and academic presentations. The consultant attended monthly Coalition meetings and reported on the progress of the project as well as openly invited Coalition members to meet on an individual basis. Coalition members referred the consultant to additional colleagues, experts or experienced policy actors in their respective countries.

Eleven, 1-hr consultative meetings were held from November 3 to December 15, 2020 with stakeholders who represented RECs in nine countries and four distinct geographic regions. Three informants corresponded with the consultant via email, sharing their perspectives in response to targeted questions centered on their pre-existing knowledge of the concept of mutual recognition, as well as whether and how it could be used to support multisite/multinational review based on existing REC structures in their country of origin. Findings from these individual meetings were supplemented by six webinar discussions and academic presentations that gathered ~50 stakeholders involved in ethics review or governance of Covid-19 research in their countries.

Figure 1 organizes the details of these meetings, forums and presentations by activity type, while the geographic spread of activities are presented in **Figure 2**.

- Meeting
- Webinar
- Presentation/Q&A
- Email correspondence

January / 2021

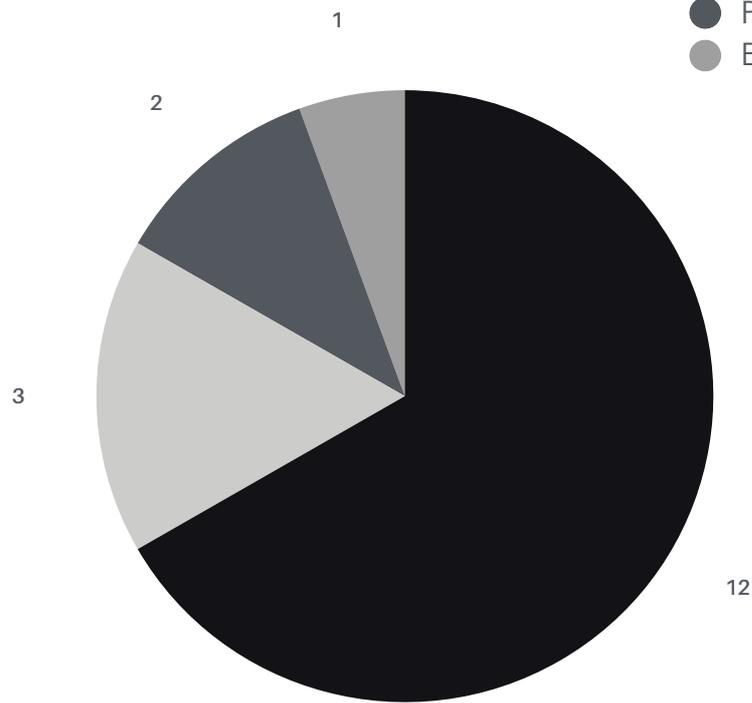


Figure 1.

Virtual meetings (individual and group), webinars, presentations and email correspondences

1hr consultative meetings held individually and in groups using a virtual platform were supplemented by attendance at regional forums and presentation at academic conferences related to multisite/national ethics review of Covid-19 studies.

Consultative activities by type

Consultative activities by region

Figure 2.

Virtual meetings (individual and group), webinars, presentations and email correspondences

Current approaches to REC review of multisite/multinational studies related to Covid-19, REC experiences and lessons learned were collected through a series of consultative activities with members of the Coalition, their colleagues, and a snowball sample of researchers identified from the authorship list of relevant peer reviewed publications related to ethics review mutual recognition.

January / 2021



Activities conducted from November 3rd to December 20th, 2020.

Report limitations

The conclusions drawn in this report should be considered in light of several limitations. First, the short timeframe allocated for the work precluded a geographically representative and participatory consultation process. Consultative activities were limited to the people, organizations and affiliates of the Covid-19 Clinical Research Coalition and WHO Health Ethics and Governance Unit. Second, the perspectives reported here stem from actors involved in various capacities in the institutional ecosystem of research ethics review, but certainly do not capture the breadth of REC experiences and lessons learned at all levels of these systems. Nor do the perspectives reflect the extent to which ethics review mutual recognition is being considered currently across jurisdictions, if at all. Importantly, the consultative activities focused engagement with REC actors namely from low- and middle income countries (LMICs). The extant conceptual and empirical literature on ethics review mutual recognition are primarily written by scholars based in North America and Western Europe and disproportionately reflect REC experiences in those regions. The literature was therefore used in place of direct consultation with REC actors there, and motivated a more focused attention on filling the evidence gap in LMICs through the consultative activities. The findings should therefore be interpreted with this lack of generalizability and underrepresentation in mind.

Third, the environmental scan, while comprehensive, does not provide an exhaustive review of the ethics literature discussing multisite/national REC review systems or processes of REC decision-making. One key reason for this is the varied terminology used in the literature as well as REC professional lexicon for referring to multisite systems of ethics review. Due to time constraints, only one database was searched systematically. Taken together, the single database approach and indexing were likely to have missed some publications relevant to ethics review mutual recognition. A detailed search strategy is included in **Annex 1**.

Fourth, the report does not present a comparative regulatory analysis of human research protections in every country surveyed. Where relevant regulations or policies are discussed, they reflect what was discussed during the consultative activities or the consultant's prior knowledge of the national regulations.

Finally, the report adopts the basic premise that minimizing barriers to otherwise ethical research optimizes the public's investment in that research and enhances the likelihood

of scientific benefit. Centralizing REC review and procedures in whole or in part is a permissible approach to minimizing the burdens associated with multisite/national reviews and, during public health emergencies, is widely recommended to accelerate the research process.

Approach

Part I briefly reviews the institutionalization of research ethics review committees and the evolution of early human research protections. It describes the contemporary roles, responsibilities, approaches and general regulatory organization of RECs as they accommodate for exponential growth in international research collaboration. Part II explores the implications of international research collaboration on the quality, effectiveness and efficiency of multisite/national reviews during public health emergencies and reviews the extant conceptual and empirical literature on REC centralization strategies. Part II also contends with arguments in the REC policy debate regarding whether and how centralization threatens the protection of community values, priorities and interests when local RECs authorize research to take place at their sites, rather than conduct additional full board review of the multisite/national protocol.

Part III introduces the concept of a system of multisite/national system of ethics review and approval called ethics review mutual recognition based on the legal theory of equivalency. It synthesizes the ethical and epistemic justifications for such a system, as well as reviews proposed models and regulatory frameworks for its implementation. Part IV reports on the perceived opportunities, barriers and regulatory implications of ethics review mutual recognition analyzed from a series of consultative activities with regional REC actors across select resource-limited regions. Summaries from four mini case studies are provided, and offer lenses through which to better understand existing approaches, strategies and procedures that RECs have adopted to meet the demands for multisite/national reviews for Covid-19 related research during the pandemic.

Key mediating factors influencing whether, and how to pursue ethics review mutual recognition differed extensively by region. Findings from the consultative activities and environmental scan suggest that more research and engagement with actors at the committee- and policy levels is needed before proceeding with targeted guidelines on how to operationalize ethics review mutual recognition.

The report concludes that one of the requisite conditions for ethics review mutual

recognition, *establishing reciprocity* among participating RECs and their governing authorities poses an intractable barrier to moving forward with a supranational system of collaborative REC review at the present time. The reasons identified include a) lack of conceptual clarity on the protected roles of local RECs, the b) heterogeneity of regulatory environments within which RECs currently operate and c) perceived inequities in North-South research collaborations. Neither the urgency for, nor the increased volume in multinational research collaboration in response to the Covid-19 pandemic significantly lowered this barrier according to informants engaged for this report.

Finally, in lieu of formal policy recommendations, Part V offers practical points to consider in augmenting trust, transparency and equity among RECs implicated in multinational studies.

January / 2021

Part I.

RESEARCH ETHICS REVIEW & COMMITTEE OVERSIGHT



Ensuring the rights and welfare of humans participating in research is grounded in moral philosophical traditions and forms the bedrock of modern research protections. These protections are codified in international conventions, regulated by national laws and outlined in professional clinical and research guidelines around the world. Although all stakeholders in the research process “have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted” [5], an institutional responsibility for ethics oversight rests primarily with research ethics committees (RECs). RECs—also commonly referred to as institutional review boards, research ethics boards, or ethics committees—can be national, regional or institutionally-affiliated. They are primarily charged with

- Reviewing the scientific validity of the research proposed in relation to the scientific question(s) asked
- Assessing the social value of the proposed research
- Evaluating anticipated risks and benefits to human participants
- Conducting routine follow up and continuing reviews of ongoing studies

Regulatory history

The principles guiding REC oversight emerged in response to a troubling history of scientific experimentation wrought with human rights abuses. Early principles of research ethics were articulated in the Nuremberg Code in 1947, and later expanded in the 1964 World Medical Association Declaration of Helsinki. Among these early principles included mandatory informed consent to participate in research and special protections for vulnerable populations. While research ethics committees operated in hospitals and research institutions as early as 1966, they were not institutionally formalized until the early 1970s when written into the second revision of the Declaration of Helsinki and made a regulatory requirement for research involving humans first in the UK, US and Canada, among others. The Declaration, and subsequent national regulations authorized the creation of institutionalized ethics review upon which future RECs would be loosely modeled (**Figure 3**). Since then, numerous consensus reports have been produced to guide the international community on how RECs should be structured, staffed, governed and operated. **Annex 2** provides a list of these guidance documents and from which the standards for procedural equivalence in REC review this report evaluates are derived.

[5] Council for International Organizations of Medical Sciences (CIOMS). *International guidelines for health-related research involving humans*. 2016; Page 1.

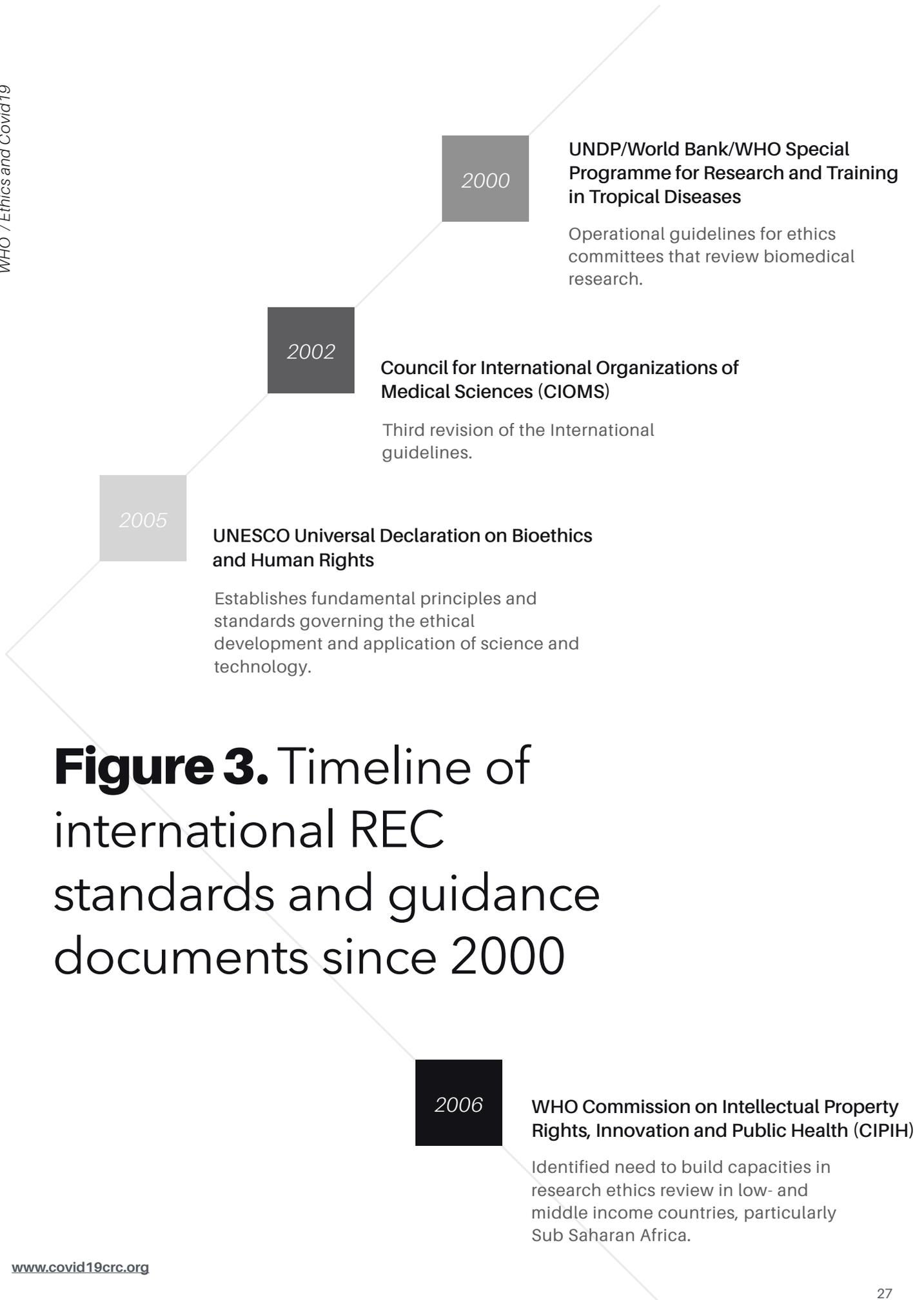


Figure 3. Timeline of international REC standards and guidance documents since 2000

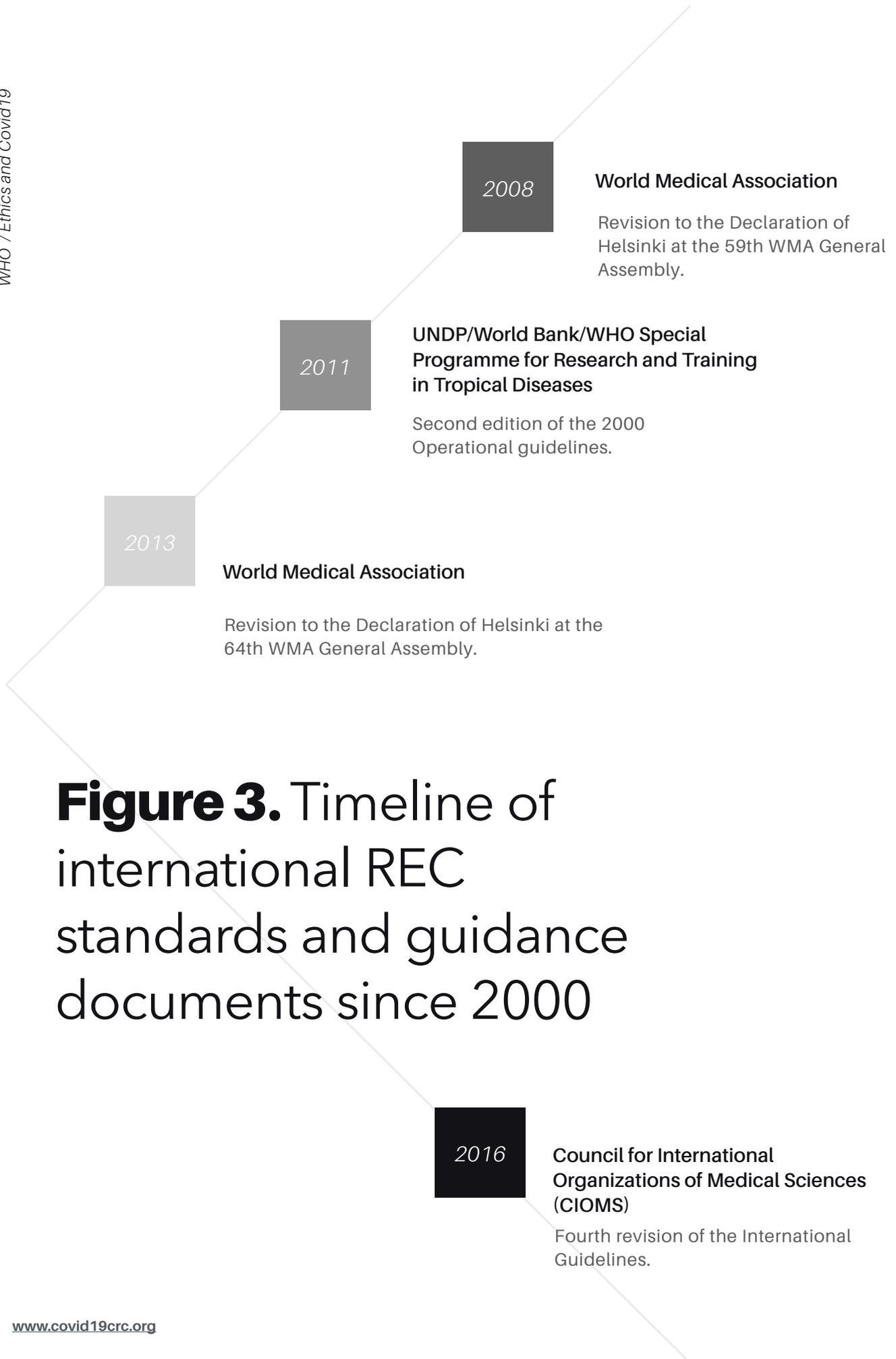


Figure 3. Timeline of international REC standards and guidance documents since 2000

RECs today are commonly comprised of core members with professional expertise in fields such as ethics, medicine, law and science. A REC may also consult with non-member experts on an ad hoc basis when it does not have the requisite expertise to review a study's design, when the research involves a particularly vulnerable population, or when the study has significant sociocultural implications, among other reasons. Importantly, many RECs—both local and regional—are required to include community representatives among their memberships. Community members review protocols through the lenses of prospective participants and help to represent the values and interests of the local population.

Institutionalization of RECs

To date, most high-, middle- and low-income countries have established administrative bodies that oversee the ethics of research involving humans. Yet, the regulatory and institutional environments within which these bodies operate vary considerably around the world. RECs can be governed by national or regional authorities. **Figure 4** illustrates four typical models of REC centralization. First, RECs governed on a national level may operate under a ministerial mandate e.g. health, research, education or equivalent [6] and comply with national regulations that outlines REC roles, responsibilities, authorities and accountabilities. Alternatively, a single national REC can serve as the official reviewing authority for all research in the country [7]. RECs can also operate as a functionally independent, but integrated arm of the national health system [8]. RECs organized regionally may comply with national guidelines for human research protections but receive funding from or are mandated by a regional authority [9] (**Figure 4**).

Except where one national committee grants all ethics approvals, RECs localized to universities, academic medical centers, hospitals and other research institutions participate in the review process. Regional or centralized committees rely on local committees to assess context-contingent aspects of a proposed study. These assessments are both pragmatic and normative. A local REC is best positioned to comment on whether their site can accommodate equipment needs to carry out

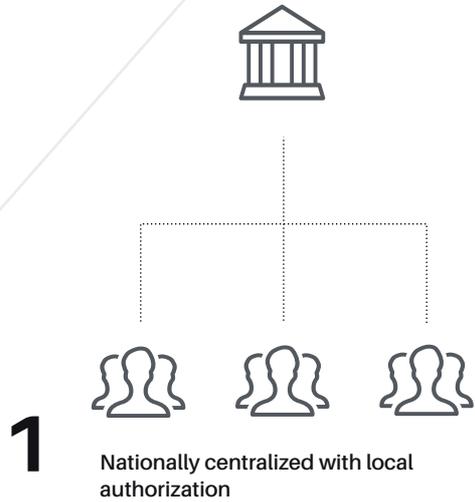
[6] Examples of countries with RECs that operate under ministerial mandates and comply with research protections regulated nationally include Nigeria, South Africa, Philippines, India and the United States.

[7] This nationalized model is reflected in small Melanesian and Polynesian island nations.

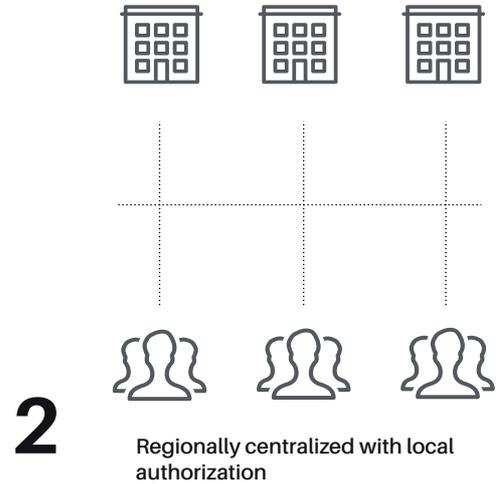
[8] The [Research Ethics Service](#) typifies this interlinked system which operates as a core function of the Health Research Authority in the United Kingdom.

Figure 4.

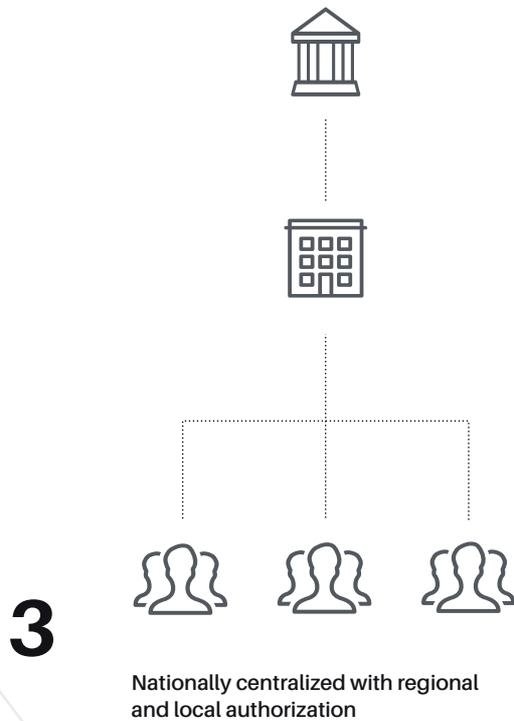
Centralized models of multisite review



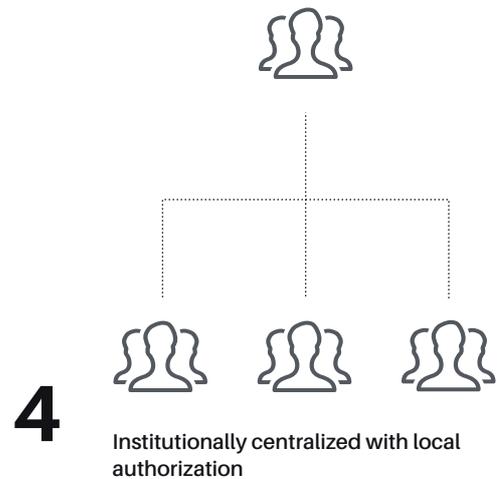
RECs based in hospitals, universities & academic medical centers coordinate with a centralized REC organized at the national level
Examples: Caribbean, India.



RECs based in hospitals, universities & academic medical centers coordinate with a centralized REC organized at the regional level
Examples: UK, Australia, EU Clinical Trials Regulation.



RECs based in hospitals, universities and academic medical centers coordinate with centralized RECs organized at both regional and national levels.
Examples: Chile, Brazil, Nigeria, Philippines.



RECs based in hospitals, universities and academic medical centers coordinate with a single REC of record named in the multisite study.
Examples: United States, Canada.

protocol interventions; provide adequate human and material resources; and recruitment is appropriate and feasible. There is also broad support in the literature that local RECs play a vital role in representing community values in decisions about what research should be permitted and how it should be carried out to ensure a fair distribution of benefits and burdens among local populations [10]. Prospective participants learn about relevant benefits and risks primarily during the informed consent process and in documentation which local RECs review for comprehension, applicability to the research population and coherence with local norms, values and priorities.

Greater scientific collaboration means the distance between researchers, the research populations they involve, and local RECs that oversee their studies may be widening. This distance is both literal and metaphoric; literal in that information technologies allow researchers based on different continents to collaborate, and metaphoric in that vast sociocultural differences can separate researchers from the populations they engage, affecting how RECs execute their duties to local populations. Prospective participants learn about relevant benefits and risks primarily during the informed consent process and in documentation which local RECs review for comprehension, applicability to the research to the research population and coherence with local norms, values and priorities.

Research collaboration and centralized review modalities

21st Century innovations in communication and computing have transformed the process of doing science in ways that allow research to transcend institutional, national and international borders. Generation of, and access to biomedical research data have been key drivers of this transformation towards collaborative science. There are strong epistemic and ethical rationales why researchers should collaborate. First, more science can be done when more people are involved.

[9] Oversight of healthcare spending and health research are the jurisdictions of the individual provinces in Canada, for example, despite national guidelines governing each (Canada Health Act and the Tri-Council Policy Statement for the Ethical Conduct of Research Involving Humans, respectively).

[10] See for example Dove ES, Knoppers BM, Zawati MH. An ethics safe harbor for international genomics research? *Genome Med.* 2013;5(11):1-11. doi:10.1186/gm503; Schopper D, Dawson A, Upshur R, et al. Innovations in research ethics governance in humanitarian settings. *BMC Med Ethics.* 2015;16(1):1-12. doi:10.1186/s12910-015-0002-3; van Teijlingen ER, Simkhada PP. Ethical approval in developing countries is not optional. *J Med Ethics.* 2012;38(7):428-430. doi:10.1136/medethics-2011-10012; Klitzman R. How local IRBs view central IRBs in the US. *BMC Med Ethics.* 2011;12(1):13. doi:10.1186/1472-6939-12-13.

[11] Wagner CS, Whetsell TA, Leydesdorff L. Growth of international collaboration in science: revisiting six specialties. *Scientometrics.* 2017;110(3):1633-1652. doi:10.1007/s11192-016-2230-9.

One study found that the scope of international collaboration was positively correlated with impact and scientific productivity, most notably in the field of virology. Collaboration can also imbue the knowledge production process with diverse perspectives and hypotheses. Research shows that more diverse teams produce better science [12]. With more precise methods and powerful tools, “it is becoming harder for any one person, subfield, or field to comprehensively address a scientific question” [13]. Collaboration can thus help researchers tackle harder questions.

Yet despite immense growth in scientific collaboration, the same institution-by-institution approach of ethics approval for single-site studies prevails, without a real evolution in ethics review systems to accommodate multi-site or collaborative research. Growing empirical and anecdotal evidence demonstrates, however, that this approach can be duplicative [14], procedurally inefficient [15], costly [16] and slow [17] without measurably enhancing participant protections [18]. Moreover,

[12] AlShebli BK, Rahwan T, Woon WL. Ethnic diversity increases scientific impact. *Nat Commun*. 2018;9(5163). doi:10.1038/s41467-018-07634-8; Jones BF, Wuchty S, Uzzi B. Multi-university research teams: Shifting impact, geography, and stratification in science. *Science* (80-). 2008;322(5905):1259-1262. doi:10.1126/science.1158357.

[13] Leahey E. From Sole Investigator to Team Scientist: Trends in the Practice and Study of Research Collaboration. *Annu Rev Sociol*. 2016;42:81-100. doi:10.1146/annurev-soc-081715-074219.

[14] Johns AL, Nicol D, Zeps N, Chalmers D, Path T. The Path to Reducing Duplication of Human Research Ethics Review in Australia. *Med Law*. 2017;36(1):7-24; (2) Menikoff J. The Paradoxical Problem with Multiple-IRB Review. *N Engl J Med*. 2010;363(17):1591-1593. doi:10.1056/nejmp1005101; (3) Winkler SJ, Witte E, Bierer BE. The Harvard Catalyst Common Reciprocal IRB Reliance Agreement: An Innovative Approach to Multisite IRB Review and Oversight. *Clin Transl Sci*. 2015;8(1):57-66. doi:10.1111/cts.12202.

[15] Nowak KS, Bankert EA, Nelson RM. Reforming the oversight of multi-site clinical research: A review of two possible solutions. *Account Res*. 2006;13(1):11-24. doi:10.1080/08989620600588845;

(2) Green LA, Lowery JC, Kowalski CP, Wyszewianski L. Impact of institutional review board practice variation on observational health services research. *Health Serv Res*. 2006;41(1):214-230. doi:10.1111/j.1475-6773.2005.00458.x; (3) Hébert P, Saginur R, Stanbrook MB, Flegel K, MacDonald N, Attaran A.

Research ethics review: Do it once and do it well. *Cmaj*. 2009;180(6):597-598. doi:10.1503/cmaj.090172; (4) Christian M, Goldberg J, Killen J, et al. A central institutional review board for multi-institutional trials. *N Engl J Med*. 2002;346(18):1405-1408.

[16] Whitney SN, Schneider CE. Viewpoint: A method to estimate the cost in lives of ethics board review of biomedical research. *J Intern Med*. 2011;269(4):396-402. doi:10.1111/j.1365-2796.2011.02351_2.x; (2)

Seiler CM, Kellmeyer P, Kienle P, Büchler MW, Knaebel HP. Assessment of the ethical review process for non-pharmacological multicentre studies in Germany on the basis of a randomised surgical trial. *J Med Ethics*.

2007;33(2):113-118. doi:10.1136/jme.2005.014605; (3) Ravina B, Deuel L, Siderowf A, Dorsey ER. Local institutional review board (IRB) review of a multicenter trial: Local costs without local context. *Ann Neurol*. 2010;67(2):258-260. doi:10.1002/ana.21831.

[17] Two empirical studies applied a cost-benefit formula to estimate the number of patient lives lost while awaiting REC approval. Christie DRH, Gabriel GS, Dear K. Adverse effects of a multicentre system for ethics approval on the progress of a prospective multicentre trial of cancer treatment: How many patients die waiting? *Intern Med J*. 2007;37(10):680-686. doi:10.1111/j.1445-5994.2007.01451; Whitney SN, Schneider CE. Viewpoint: A method to estimate the cost in lives of ethics board review of biomedical research. *J Intern Med*. 2011;269(4):396-402. doi:10.1111/j.1365-2796.2011.02351_2.

scholars have studied the effects that inconsistencies attributable to *procedure* versus *content* have on fairness and equity in multi-REC decisions - where procedures means that like studies are reviewed using the same procedural standards and principles, and content means that principles means that applied to similar studies yield similar outcomes [19]. In response to growing pressure to make review processes more amenable to collaborative research, researchers and ethicists alike have called for single-time review of multisite research protocols as one of several fundamental reforms to support a more effective REC system [20]. One survey of 31 research ethics regulations/laws/guidelines in Africa, Asia, Latin America and Oceania found 19% mandated single IRB/REC opinion for multisite clinical trial within a country, and 23% allowed for the possibility of single review [21]. The authors affirmed that while respect for national sovereignty is part and parcel of working in global research ethics, they emphasized “it is time to harmonize ethics review processes for international multi-site trials as an effective and low-cost manner to achieve global health” [22]. The proliferation of RECs and their decentralized organization have since motivated some governing bodies to consolidate by centralizing aspects of the ethics review and approval process [23]. Myriad approaches to centralization have been implemented with varying success

[18] Blunt J, Savulescu J, Watson AJM, et al. Meeting the Challenges Facing Research Ethics Committees: Some Practical Suggestions. *Br Med J*. 1998;316(7124):58-61. (2) Hunter D. Efficiency and the proposed reforms to the NHS research ethics system. *J Med Ethics*. 2007;33(11):651-654. doi:10.1136/jme.2006.018424; (3) Smith M, Doyle F, McGee HM, De La Harpe D. Ethical approval for national studies in Ireland: An illustration of current challenges. *Ir J Med Sci*. 2004;173(2):72-74. doi:10.1007/BF02914559; (4) Kenyon GM, David Mendelow A, Gregson BA, Rowan E. Obtaining regulatory approval for multicentre randomised controlled trials: Experiences in the STICH II trial. *Br J Neurosurg*. 2011;25(3):352-356. doi:10.3109/02688697.2010.551675.

[19] Friesen et al argue, for example, the “more procedural consistency one has”, the more likely one is to have content consistency (except in cases in which the procedure is based on chance).” Friesen P, Yusuf ANM, Sheehan M. Should the Decisions of Institutional Review Boards Be Consistent? *Ethics Hum Res*. 2019;41(4):2-14. doi:10.1002/eahr.500022.

[20] Emanuel EJ, Wood A, Fleischman A, Bowen A, Getz K a. Perspective Oversight of Human Participants Research : Identifying Problems. *Ann Intern Med*. 2015;141(4):1-2.

[21] Nakada H, Hasthorpe S, IJsselmuiden C, et al. Recommendations for promoting international multi-site clinical trials—from a viewpoint of ethics review. *Dev World Bioeth*. 2019;19(4):192-195. doi:10.1111/dewb.12245.

[22] Ibid., 19, Page 195.

[23] Note that the empirical literature comparing review time, performance, quality, consistency and cost between single- and centralized RECs is vast, and beyond the scope of this report to meta-analyze. [24] See for example the Ontario Cancer Research Ethics Board Saginur R, Dent SF, Schwartz L, Heslegrave R, Stacey S, Manzo J. Ontario cancer research ethics board: Lessons learned from developing a multicenter regional institutional review board. *J Clin Oncol*. 2008;26(9):1479-1482. doi:10.1200/JCO.2007.12.6441; and the National Cancer Institute Ravina B, Deuel L, Siderowf A, Dorsey ER. Local institutional review board (IRB) review of a multicenter trial: Local costs without local context. *Ann Neurol*. 2010;67(2):258-260. doi:10.1002/ana.21831; Hernandez R, Cooney M, Dualé C, et al. Harmonisation of ethics committees’ practice in 10 European countries. *J Med Ethics*. 2009;35(11):696-700. doi:10.1136/jme.2009.030551.

on the basis of study type (such as clinical trials) [24], specific participant populations (such as children) [25] and in accordance with regulatory reforms. Much of the empirical and conceptual literature on REC centralization reflects the experiences of RECs in North America and Europe [26] and evidence is steadily growing in Central Asia [27], the Middle East [28], South Asia [29], Southeast Asia [30] and in Africa [31].

[24] See for example the Ontario Cancer Research Ethics Board Saginur R, Dent SF, Schwartz L, Heslegrave R, Stacey S, Manzo J. Ontario cancer research ethics board: Lessons learned from developing a multicenter regional institutional review board. *J Clin Oncol*. 2008;26(9):1479-1482. doi:10.1200/JCO.2007.12.6441; and the National Cancer Institute Ravina B, Deuel L, Siderowf A, Dorsey ER. Local institutional review board (IRB) review of a multicenter trial: Local costs without local context. *Ann Neurol*. 2010;67(2):258-260. doi:10.1002/ana.21831; Hernandez R, Cooney M, Dualé C, et al. Harmonisation of ethics committees' practice in 10 European countries. *J Med Ethics*. 2009;35(11):696-700. doi:10.1136/jme.2009.030551.

[25] See for example harmonized REC procedures/templates for pediatric studies from the Maternal Infant Child and Youth Health Research Network., MICYRN, <https://www.micyrn.ca>.

[26] See for example studies discussing the challenges experienced when transitioning from independent, to centralized review of multisite studies based on new regulatory mandates such as: Burr JS, Johnson AR, Vasenina V, et al. Implementing a Central IRB Model in a Multicenter Research Network. *Ethics Hum Res*. 2019;41(3):23-28. doi:10.1126/science.1249098; Lidz CW, Pivovarova E, Appelbaum PS, Stiles DF, Murray A, Klitzman R. Reliance agreements and single IRB review of multisite research: Concerns of IRB members and staff. *American*. 2018;9(3):164-172. doi:10.1080/23294515.2018.1510437; Sodeke S. Using the IRB Harmonization and Reliance Document Can Reduce Review and Regulatory Delays for the Benefit of All

Stephen. *Am J Bioeth*. 2016;16(8):46-48. doi:10.1080/15265161.2016.1187217; Winkler SJ, Witte E, Bierer BE. The Harvard Catalyst Common Reciprocal IRB Reliance Agreement: An Innovative Approach to Multisite IRB Review and Oversight. *Clin Transl Sci*. 2015;8(1):57-66. doi:10.1111/cts.12202.

[27] See for example: Coker R, McKee M. Ethical approval for health research in central and eastern Europe: An international survey. *Clin Med (Northfield Il)*. 2001;1(3):197-199. doi:10.7861/clinmedicine.1-3-197; Gefenas E, Dranseika V, Cekanauskaite A, et al. Non-equivalent stringency of ethical review in the Baltic States: A sign of a systematic problem in Europe? *J Med Ethics*. 2010;36(7):435-439. doi:10.1136/jme.2009.035030. Lévesque, E. and Knoppers, B. M. (2014) 'Management Strategies for Ethics in International Research', *Current Genetic Medicine Reports*, 2(4), pp. 255-260. doi: 10.1007/s40142-014-0056-4.

[28] Hospitals and academic medical centers that do not maintain their own RECs are allowed to be affiliated with RECs and recognize external review decisions as per the Ministry's requirements in Article 7 according to Atallah D, Moubarak M, El Kassis N, Abboud S. Clinical research ethics review process in Lebanon: Efficiency and functions of research ethics committees - results from a descriptive questionnaire-based study. *Trials*. 2018;19(1):1-15. doi:10.1186/s13063-017-2397-2; See also Sleem H, Abdelhai RAA, Al-Abdallat I, et al. Development of an accessible self-assessment tool for research ethics committees in developing countries. *J Empir Res Hum Res Ethics*. 2010;5(3):85-96. doi:10.1525/jer.2010.5.3.85 for a self-assessment tool measuring REC performance and review indicators, including efficiency.

[29] Mathur et al note that new guidelines for a common ethics review for multicentric research have been proposed for the first time, and are expected to "reduce duplication of efforts, save time and improve networking by setting up communication channels between participating ECs of all various study centres:" Mathur R, Thakur K, Hazam RK. Highlights of Indian Council of Medical Research national ethical guidelines for biomedical and health research involving human participants. *Indian J Pharmacol*. 2019;51(3):214-221. doi:10.4103/0253-7613.262456; see also Kandhari R. Justice in jeopardy: a qualitative study of institutional ethics committees in New Delhi. *Indian J Med Ethics*. 2013;10(3):176-183. doi:10.20529/ijme.2013.053

Centralization of REC procedures is often discussed in the context of accelerating reviews for studies during ongoing emergencies or disasters in low- and middle-income countries. The next section reviews this literature and considers the opportunities and challenges of extending the centralized models that enable accelerated review to contexts beyond public health emergencies and for multinational studies.

Accelerated review via centralization during public health emergencies

Streamlining procedures among RECs at the local, national and international levels continues to be a pressing and recurring need as collaboration across the life sciences becomes the norm, rather than the exception. Public health emergencies accentuate this need and intensify pressure on RECs at all levels to conduct timely,

Davalbhakta S, Advani S, Kumar S, et al. A Systematic Review of Smartphone Applications Available for Corona Virus Disease 2019 (COVID19) and the Assessment of their Quality Using the Mobile Application Rating Scale (MARS). *J Med Syst.* 2020;44(9). doi:10.1007/s10916-020-01633-3; Somsekhar H, Prabhakaran D, Tandon N, Roussele R, Fisher S, Stein AD. Review of multinational human subjects research: experience from the PHFI-Emory Center of Excellence partnership. *Indian J Med Ethics.* 2012;9(4):255-258. doi:10.20529/ijme.2012.086; Simpson B, Dissanayake VHW, Douglas-Jones R, Sariola S. Ethical review, remit and responsibility in biomedical research in South Asia. *Indian J Med Ethics.* 2010;7(2):113-114. doi:10.20529/ijme.2010.042; Mahuli A V., Mahuli SA, Patil S, Bhandi S. Institutional ethics committee regulations and current updates in India. *J Contemp Dent Pract.* 2017;18(8):738-741. doi:10.5005/jp-journals-10024-2117.

[30] See for example: Jeon JY, Kim H, Yu KS. The Impact of COVID-19 on the Conduct of Clinical Trials for Medical Products in Korea. *J Korean Med Sci.* 2020;35(36):e329. doi:10.3346/jkms.2020.35.e329; Kim OJ, Park BJ, Sohn DR, Lee SM, Shin SG. Current Status of the Institutional Review Boards in Korea: Constitution, Operation, and Policy for Protection of Human Research Participants. *J Korean Med Sci.* 2003;18(1):3-10. doi:10.3346/jkms.2003.18.1.3.

[31] See for example: Cleaton-Jones P. Commentary on "Measuring the Quality and Performance of Institutional Review Boards." *J Empir Res Hum Res Ethics.* 2019;14(3):200-203. doi:10.1177/1556264618812937; Kirigia JM, Wambebe C, Baba-Moussa A. Status of national research bioethics committees in the WHO African region. *BMC Med Ethics.* 2005;6:1-7. doi:10.1186/1472-6939-6-10; Davies SEH. The introduction of research ethics review procedures at a university in South Africa: review outcomes of a social science research ethics committee. *Res Ethics.* 2020;16(1-2):1-26. doi:10.1177/1747016119898408; Kasule M, Wassenaar DR, Ijsselmuiden C, Mokgatla B. Silent voices: Current and future roles of African research ethics committee administrators. *IRB Ethics Hum Res.* 2016;38(1):13-18.; Silaigwana B, Wassenaar D. Biomedical research ethics committees in sub-Saharan Africa: A collective review of their structure, functioning, and outcomes. *J Empir Res Hum Res Ethics.* 2015;10(2):169-184. doi:10.1177/1556264615575511; Kass NE, Hyder AA, Ajuwon A, et al. The structure and function of research ethics committees in Africa: A case study. *PLoS Med.* 2007;4(1):0026-0031. doi:10.1371/journal.pmed.0040003.

responsive and rigorous REC review without compromising participant protections [32].

History and experience provide key lessons in preparedness and coordination for RECs in this regard [33]. Emergencies such as infectious disease outbreaks and natural disasters justify suspension of standard review procedures including, where applicable, independent and site-specific review. Accelerating research, streamlining information sharing and improving governance capacities were widely supported in response to the Ebola and H1N1 outbreaks, yet drew criticisms for lack of uniformity and coordination across affected areas [34] that inevitably delayed research efforts [35]. The experiences from recent public health emergencies motivated specific REC guidance from the WHO in the early months of the Covid-19 (See **Annex 4**).

Consultative workshops following the Ebola epidemic recommended that RECs should be prepared to activate special standard operating protocols that involve improved coordination among local, regional and national bodies to respond efficiently to pandemic response and management needs for evidence [36]. Schopper et al reflect on the possible benefits of joint pre-review of transnational protocols as a solution to the problem of “double review” during future emergencies: “The lack of joint ethical review for Ebola clinical trials, or at least of proactive communication among ECs reviewing the same Ebola trial protocol(s), may have been a missed opportunity to streamline the different reviews into a comprehensive review (potentially, an advantage for the researchers) and to foster dialogue and mutual learning among the different ECs/IRBs (potentially, an advantage for the ECs/IRBs)” [37]. The authors further note that blinding reviews from different committees involved in reviewing the same study prevented

[32] Hunt M, Tansey CM, Anderson J, et al. The challenge of timely, responsive and rigorous ethics review of disaster research: Views of research ethics committee members. *PLoS One*. 2016;11(6):1-15. doi:10.1371/journal.pone.0157142.

[33] Falb K, Laird B, Ratnayake R, Rodrigues K, Annan J. The Ethical Contours of Research in Crisis Settings: Five Practical Considerations for Academic Institutional Review Boards and Researchers. *Disasters*. 2019;43(4):711-726.

[34] Moon S, Sridhar D, Pate MA, et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. *Health Policy (New York)*. 2015;386:2204-2221.

[35] Equipped with these lessons learned, the WHO and regional bioethics organizations including PAHO released guidance on how to accelerate approvals for Covid-related protocols in the early months of the pandemic.

[36] De Crop M, Delamou A, Griensven J Van, Ravinetto R. Multiple ethical review in North-South collaborative research: the experience of the Ebola-Tx trial in Guinea. *Indian J Med Ethics*. 2016;1(2):76-82. doi:10.21522/tijcr.2014.03.02.art014.

[37] Schopper D, Dawson A, Upshur R, et al. Innovations in research ethics governance in humanitarian settings. *BMC Med Ethics*. 2015;16(1):1-12. doi:10.1186/s12910-015-0002-3.

“exchange of views, shared approaches to new dilemmas and agreement on common review policies” that might have been especially useful during the emergency.

An additional approach to accelerating ethics review through centralization involves a two-tiered system that combines centralized review with expedited authorization from local RECs [38]. The Nuffield Council on Bioethics is the latest organization to substantiate the balance between speed and ethical rigor of REC review of multisite/national studies during a public health emergency [39]. On this point the authors conclude “there is no reason for diverging from the standard principle that research proposals should be subject to ethical scrutiny by an independent body before they should be permitted to go ahead. The *manner* in which this scrutiny is achieved should, however, be sensitive to context, as indeed it should be in non-emergency circumstances” [40]. The report identifies desirable features of ethics review for public health research during emergency settings, namely flexibility, support for local engagement, and scope for expediting genuinely urgent studies. Both centralization and standardization of REC procedures are cited in support of the latter, to emphasize collaboration among national and regional agencies and to bolster the general development and confidence of RECs.

Saxena et al (2019) also underscore this need for standardization and mechanisms for multinational collaboration where, “the consequences of contradictions, redundancies and delays would be particularly harmful for research conducted during outbreaks and other public health emergencies” [41]. Participants involved in a two-day workshop organized in March 2018 by the WHO Global Health Ethics Team and the African coalition for Epidemic Research, Response and Training (ALERTT) called on the WHO specifically to lead in this effort [42] and facilitate development of “a national standard

[36] De Crop M, Delamou A, Griensven J Van, Ravinetto R. Multiple ethical review in North-South collaborative research: the experience of the Ebola-Tx trial in Guinea. *Indian J Med Ethics*. 2016;1(2):76-82. doi:10.21522/tijcr.2014.03.02.art014.

[37] Schopper D, Dawson A, Upshur R, et al. Innovations in research ethics governance in humanitarian settings. *BMC Med Ethics*. 2015;16(1):1-12. doi:10.1186/s12910-015-0002-3.

[38] Cook D, Burns K, Finfer S, et al. Clinical research ethics for critically ill patients: A pandemic proposal. *Crit Care Med*. 2010;38(SUPPL. 4). doi:10.1097/CCM.0b013e3181cbaff4.

[39] Nuffield Council on Bioethics. Research in global health emergencies: ethical issues. 2020

[40] Ibid., Page 145.

[41] Saxena A, Horby P, Amuasi J, et al. Ethics preparedness: Facilitating ethics review during outbreaks - Recommendations from an expert panel. *BMC Med Ethics*. 2019;20(1):1-10. doi:10.1186/s12910-019-0366-x. Page 27.

[42] Specifically, Recommendation (3a) states, “Mechanisms should be explored for (regional) multi-country emergency ethical consultation to support rapid review at country level. Suggested action - WHO should lead a process for a consultation on ‘multi-country rapid ethics review’ in competent and legitimate fora, involving sub-regional mechanisms as appropriate.”

operating procedure (SOP) for emergency response ethical review should be developed and adopted by N(R)ECs and/or in-country competent authority" [43]. The multinational SOP, if developed, could serve as a model for multisite review of research within countries that adopt the WHO standard guidelines for RECs and potentially in non-emergent contexts. Lynch and Cohen argue, in response to Barchi et al [44], the equivalent protections provision offers a "seemingly simple way to capitalize on the existence of robust human subject protection systems internationally, while avoiding the need for formalized efforts at harmonization and the burden of trying to comply with a range of imperfectly aligned research protections" [45]. The authors further hypothesize why regulators have been slow to take advantage of the regulatory permission to establish equivalence, positing that the standards for human research protections may have been set too low, that the variability observed between domestic RECs would scale when international RECs were added, and finally that the burdens associated with full board reviews at local sites might be justifiable in international research specifically because they offer an additional layer of protection [46].

Ravinetto et al. confirm the protective benefits of the additional layer of protection described above when RECs in both the sponsoring and host country conduct what they term 'double ethical review' to correct for power imbalances that collaborations between resource rich- and poor settings in research accentuate [47]. Advocates for double ethical review reject the notion that ethical clearance in the North somehow protects against perceived weaknesses in REC capacities/standards in the South on the basis of moral imperialism. Double ethical review, Ravinetto and colleagues claim, "de facto strengthens the protection of the study participants and their communities, as it takes the specificities of each context into account. Despite their universal character, ethical principles governing clinical research need to be translated into rules, procedures and practices, which may significantly vary among countries and regions." Local REC review is a requisite feature of double ethical review according to the authors, but they acknowledge the implementation challenges the model poses, including delays,

[43] Ibid., Page 27.

[44] Barchi F, Kasimatis Singleton M, Merz JF. Fostering IRB Collaboration for Review of International Research. *Am J Bioeth.* 2014;14(5):3-8. doi:10.1080/15265161.2014.892168.

[45] Lynch HF, Cohen IG. Streamlining Review by Accepting Equivalence. *Am J Bioeth.* 2014;14(5):11-13. doi:10.1080/15265161.2014.892172. Page 12.

[46] Ibid. 19

[47] Ravinetto R, Buvé A, Halidou T, et al. Double ethical review of North-South collaborative clinical research: hidden paternalism or real partnership? *Trop Med Int Heal.* 2011;16(4):527-530. doi:10.1111/j.1365-3156.2011.02732.x.

administrative burdens and increased review volume for multisite/national studies using analyses from a pediatric malaria clinical trials as a case example.

'Double ethical review' typifies the dilemma regulators face in weighing the tradeoffs between the specificity of local reviews and the perceived efficiency of centralized review. In short, can centralized RECs be as responsive as local RECs to community ethical, legal and social values while optimizing procedural efficiency in the review process?

Conceptual challenges to independent, local REC reviews

The indispensability of local REC review dominates the policy debate on whether and how centralization could help REC processes be more efficient, collaborative and effective for multisite/national studies. A recent empirical study found that REC members in the U.S. endorsed local review of a multisite study when at least one participating site was located outside the United States and where sociocultural differences warranted local input [48]. In a separate qualitative-sociological analysis of three institutional research contexts in the Netherlands, Jaspers, Houtepen and Horstman defend the idea that "local context enables ethical review" and that relevant local information is uncovered when RECs arrive at inconsistent decisions [49]. They assert that RECs manage different tensions in ethical review based in large part on their available resources and institutional contexts. Taken together, institutional context and resources lead RECs to develop a kind of "situational authority" that the authors conclude "should be acknowledged, considered a given and not a problem as such."

Jaspers and colleagues grounded their investigation on the conceptual links between trust and regulatory authority in REC review initially proposed by Hedgecoe. Adopting a similar ethnographic approach to study REC decision-making, Hedgecoe claims the "local knowledge plays a vital yet largely overlooked role in how RECs make decisions". Local issues have been traditionally served by localizing the review

[48] Klitzman R, Pivovarova E, Murray A, Appelbaum PS, Stiles DF, Lidz CW. Local Knowledge and Single IRBs for Multisite Studies: Challenges and Solutions. *Ethics Hum Res.* 2019;41(1):22-31. doi:10.1002/eahr.500003; Lidz CW, Pivovarova E, Appelbaum PS, Stiles DF, Murray A, Klitzman R. Reliance agreements and single IRB review of multisite research: Concerns of IRB members and staff. *American.* 2018;9(3):164-172. doi:10.1080/23294515.2018.1510437

[49] Jaspers P, Houtepen R, Horstman K. Ethical review: Standardizing procedures and local shaping of ethical review practices. *Soc Sci Med.* 2013;98:311-318. doi:10.1016/j.socscimed.2013.03.043.

process, but there is growing criticism of the true value add in doing so.

Hedgecoe goes on to note this critique is in “stark contrast to the way in which RECs make decisions and the views of committee members themselves. RECs are still deeply ‘localised’ in their decision-making, and local knowledge is still valuable for helping them think about applicants’ trustworthiness” [50]. The authors argue that the localization of RECs matters most in the face of problematic studies and “where members have other concerns, not being known by members of a committee can make all the difference” [51].

Critics of REC centralization invoke two primary arguments:

- ceding full board review either wholly or in part handicaps local RECs from protecting local interests and can make institutions

more vulnerable to liability

- centralized review removes institutional autonomy from local RECs

Implicit in these arguments are several assumptions that, when investigated empirically, yield mixed results [52]. The first assumption is that only local RECs can hold and apply local knowledge and sociocultural understanding to adequately protect community interests. There is little doubt that local RECs may have more proximal awareness of the social, economic and political environments within which the prospective research study will take place. Rather, proponents of centralization challenge the assumption that full board review at the local site is the only

[50] Hedgecoe AM. Trust and regulatory organisations: The role of local knowledge and facework in research ethics review. *Soc Stud Sci.* 2012;42(5):662-683. doi:10.1177/0306312712446364.

[51] Ibid., 48, Page, 668.

[52] In an ethnographic study of, Stark found that found that multisite studies can result in inconsistent decisions because reviewing members “develop site-specific “local precedents” to work more quickly and to make consistent decisions over time. Different IRBs produce different—but equally legal—requests for modifications based on their different case experience. Stark proposes three recommendations that could support reducing, but not eliminating outright the excess administrative burden multisite reviews can cause, including establishing review networks, incorporating more opportunities for collegial reviews and developing a decision repository. Stark L. IRBs and the Problem of “Local Precedents.” *Hum Subj Res Regul.* 2015:173-187. doi:10.7551/mitpress/9780262027465.003.0015. In contrast, Henrickson et al revealed REC members expressed uncertainty about the roles and responsibilities of reviewing committees, research institutions and study teams to incorporate relevant contextual information to comply with single REC review reforms in the United States. Henrickson NB, Blasi PR, Corsmo JJ, et al. “You Really Do Have to Know the Local Context”: IRB Administrators and Researchers on the Implications of the NIH Single IRB Mandate for Multisite Genomic Studies. *J Empir Res Hum Res Ethics.* 2019;14(3):286-295. doi:10.1177/1556264619850440.

method to acquire this local knowledge. Emanuel et al posit the rigid expectation of institution-specific review has led over time to an incompatible system: “The system of local review may foster local efforts to uphold ethical standards for research and capitalizes on the IRB’s knowledge of the local research environment and community standards” [53]. The authors also note there lacks sufficient “data [to] substantiate the value of such local knowledge or whether it can only be—or is best—gained through institution-based review” [54].

Centralized RECs can use alternative channels to acquire this knowledge that can require amending existing REC workflows [55]. Opportunities for providing necessary local input can be built directly into the centralized REC workflow using electronic REC platforms, such as during online protocol submission, full board review and revision stages. Part of the challenge for ethics review mutual recognition and other centralized

models like it is that they perturb at least three embedded relationships (marked with a star) that have implications for policy adoption between the reliant or centralized REC and the local i) REC, ii) researchers, and iii) communities [56]. Summary findings from four mini case reports corroborate this claim. **Figure 5** depicts graphically where these perturbations occur on a prototypical REC workflow adapted from Hood et al (2005) [57].

Klitzman et al (2019) identified four broad types of local information that REC members considered most important for local RECs to provide a single, centralized REC approving a multisite study, including: cultural and linguistic characteristics of potential participants, geographic and socioeconomic issues, knowledge about particular researchers, and information about differences across

[53] Emanuel EJ, Wood A, Fleischman A, Bowen A, Getz K a. Perspective Oversight of Human Participants Research : Identifying Problems. *Ann Intern Med.* 2015;141(4):1-2.

[54] Ibid.

[55] Centralization is greatly aided by the increasing transition from paper to electronic application submission and review.

[56] Klitzman R, Pivovarov E, Lidz CW. Single IRBs in multisite trials questions posed by the New NIH Policy. *J Am Med Assoc.* 2017;317(20):2061-2062. doi:10.1001/jama.2017.4624.

[57] Hood MN, Gugerty B, Levine R, Ho VB. Computerized information management for institutional review boards. *CIN - Comput Informatics Nurs.* 2005;23(4):190-200. doi:10.1097/00024665-200507000-00005.

[58] Klitzman R, Pivovarov E, Lidz CW. Single IRBs in multisite trials questions posed by the New NIH Policy. *J Am Med Assoc.* 2017;317(20):2061-2062. doi:10.1001/jama.2017.4624.



Embedded relationships in the prototypical REC workflow

Figure 5.

Simplified REC workflow (reprinted from Hood et al (2005) with copyright permission) indicated the relationships ethics review recognition perturbs (marked with colored stars) and that have implications for policy adoption between the reliant or centralized REC and the local i) REC, ii) researchers, and iii) communities.

Part I. / REC oversight

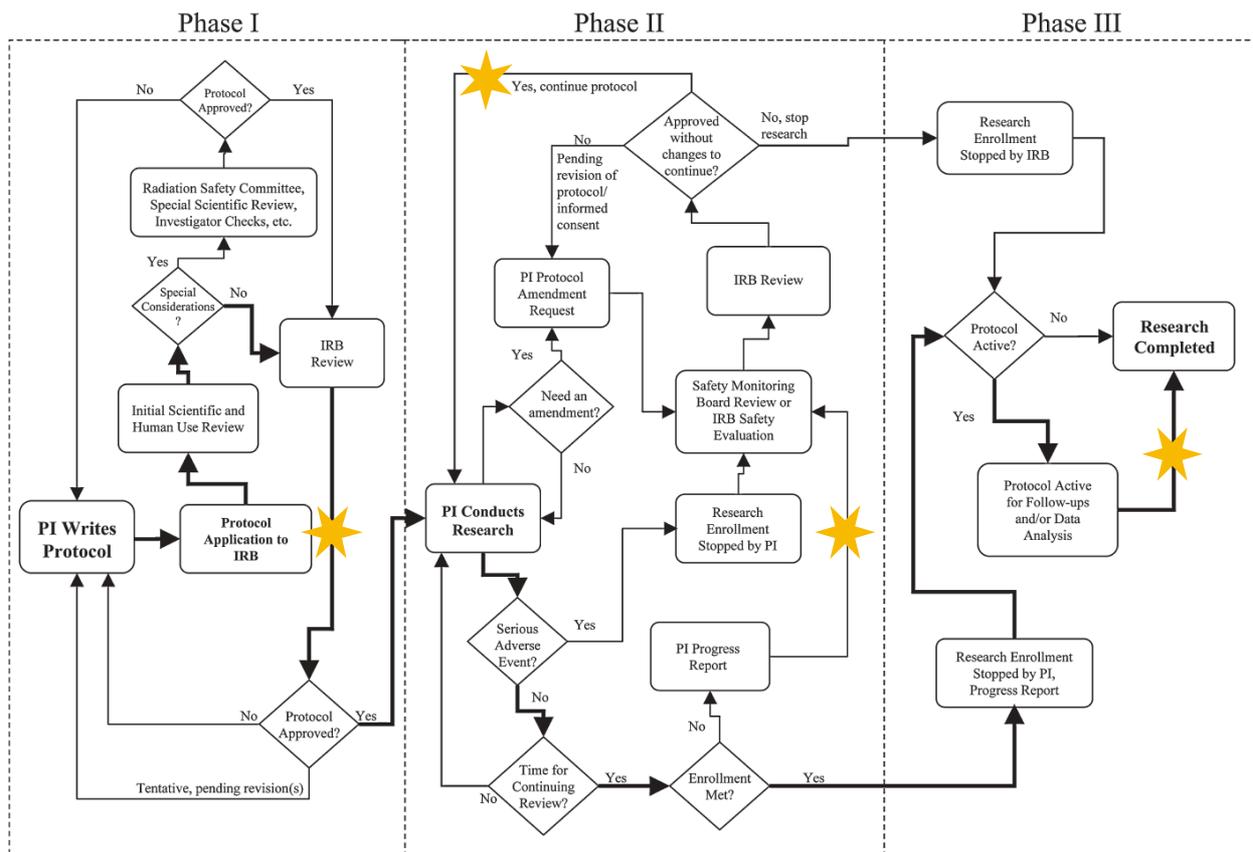


FIGURE 1. A simplified overview of the IRB workflow process depicting the three main phases of activity for a federally regulated and/or funded protocol. Local IRBs vary greatly, thus more specific details have been omitted from this model. The bold arrows depict the simplest path through the IRB research process, starting with the principal investigator (PI) writing the protocol and ending with the completion of the research. Phase I depicts the protocol submission to the IRB and the initial review process of a protocol. Phase II is the research phase where active enrollment and bulk of the research activities are performed. Protocols are reviewed at least annually, more often for higher risk protocols. Phase III is the protocol completion phase. Research protocols should not be considered finished until final reports have been filed and accepted by the IRB.

the study sites in a multisite study [58].

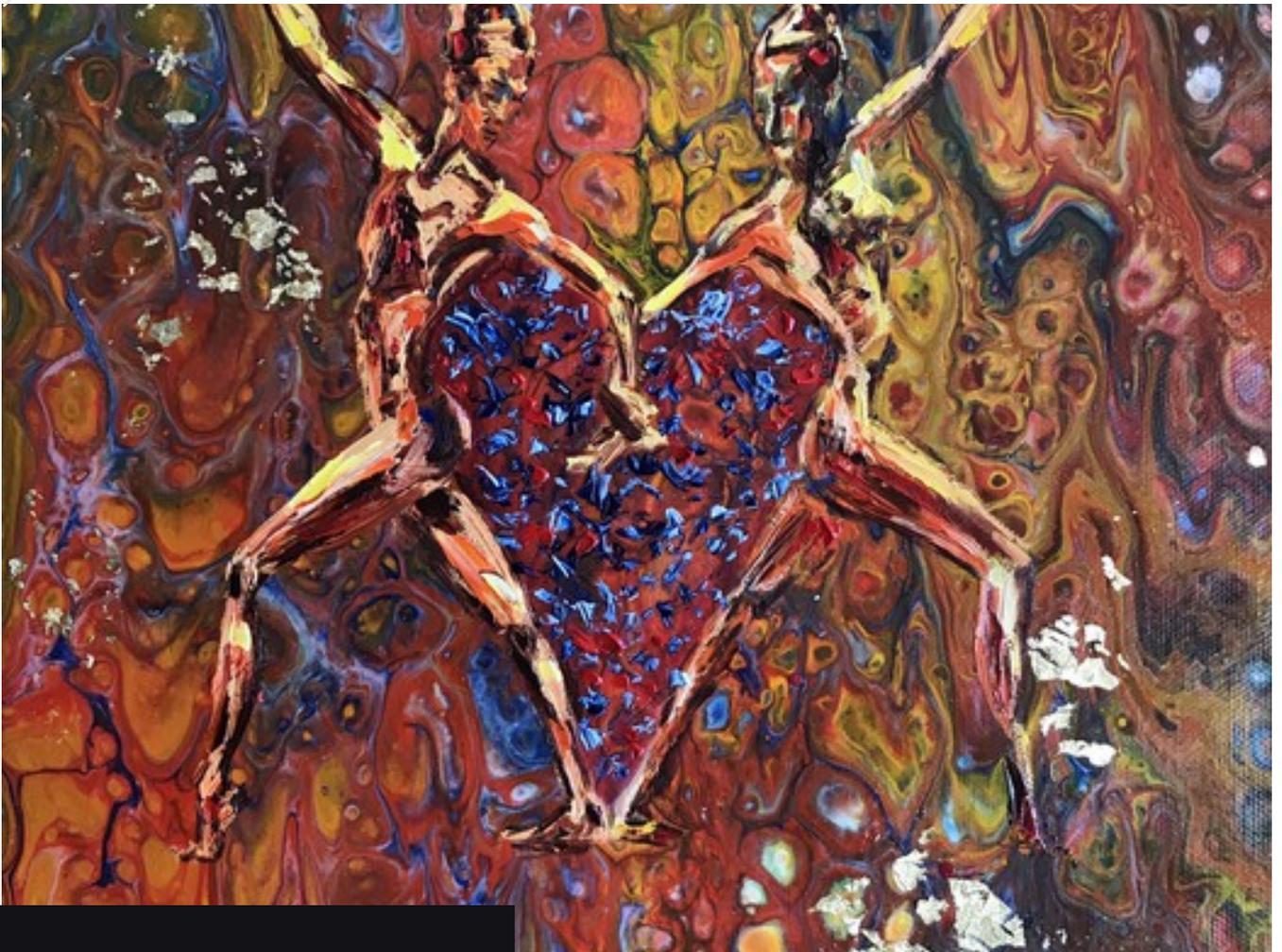
Second, one concern in relation to multisite ethics review is ceding local review and deferring to decisions made on their behalf by a centralized body would be synonymous with ceding institutional autonomy. Townend et al reject this notion, proposing instead that RECs charged with reviewing a multinational study should adopt what the authors call a ‘sounding board’ approach. The conceptual details of this approach, the epistemic and ethical justifications for centralizing REC review at the supranational level and approaches for modeling ethics review mutual recognition will be discussed in greater detail in **Part II**.

Part I. / REC oversight

Part II.

ETHICS REVIEW MUTUAL RECOGNITION

Justifications, Standards and Models



Two regulatory regimes are assessed to be equivalent when the outcomes of a regulatory process are comparable.

The ideas grounding ethics review mutual recognition emerged namely in response to international convergence around the normative ethics principles of respect for persons, justice and beneficence underlying human research protections; the institutionalization of ethics oversight; and the increasingly collaborative nature of biomedical research.

Based on the transnational legal theory of equivalence, ethics review mutual recognition refers to a multilateral system of ethics review and approval in which an REC recognizes the procedural equivalence of another REC in reviewing collaborative, multisite research studies involving humans. This chapter provides an overview of the constituent elements of ethics review mutual recognition and its theoretical aims for streamlining multinational ethics review processes. The chapter also synthesizes the ethical, legal and social justifications invoked in the literature to support ethics review mutual recognition and concludes with how it may be operationalized.

Ethics review mutual recognition borrows from the transnational legal theory of equivalence. Two regulatory regimes are said to be equivalent when the outcomes of a regulatory process are comparable [59]. Equivalence has been applied as an international legal instrument to facilitate financial securities regulation [60] and to enable cross-border transfers of personal data [61] to name two contemporary applications. The overarching goal is to complement national or regional laws/guidelines/policies in enabling timely, quality and effective review of multinational research studies.

Ethics review mutual recognition rests on two interrelated elements to accomplish this goal. The first element determines procedural equivalence. It aims to streamline the review process by standardizing those procedures common to qualified, competent RECs but, when executed at every participating research site, can compound inefficiencies and duplication. These procedures include

- Assessing study design and scientific validity
- Ensuring protection, confidentiality and security of study data

[59] Broude T, Shany Y, eds. *Multi-Sourced Equivalent Norms in International Law*. Hart Publishing; 2011.

[60] Wei T. The Equivalence Approach to Securities Regulation. *Northwest J Int Law Bus.* 2007;27(2):255.

[61] Regulation (EU) 2016/679.):1-2.

- Verifying fair selection of study participants and incentives, if applicable
- Evaluating risks and potential benefits of participation
- Ensuring protection, confidentiality and security of study data
- Reviewing the proposed process of informed consent and relevant documents

Second, mutual recognition aims to leverage these shared procedures to develop reciprocal agreements between and among RECs where their sites are implicated in a collaborative research study. This element *establishes reciprocity*. Taken together, establishing reciprocity following a determination of procedural equivalence form the two-pronged approach that a system of ethics review mutual recognition applies to reduce administrative burden; eliminate unnecessary duplication; and avoid delays that are often associated with multisite review. It is critical to note that procedure, not substantive ethics is the locus of reciprocity. Reciprocal agreements pursuant to mutual recognition of REC procedures do not supplant authorization from local sites, nor do they sidestep community representation that local RECs embed in the review process. Indeed, it attempts to free scarce human and material resources for local RECs to carry out the duties they are best positioned to fulfill i.e. verifying the local feasibility of the study and ensuring it aligns with social, cultural and ethical values of the local population.

Standards

International

The environmental scan unveiled several international standards for operationalizing mutual recognition in guidance documents published by the WHO and Global Alliance for Genomics and Health.

WHO

Under Chapter III: Standards and guidance for members of research ethics committees, the WHO describes the requisite elements of reliance agreements between two cooperating RECs:

Standard 7: Ethical basis for decision-making in research ethics committees

The REC bases its decisions about research that it reviews on a coherent and consistent application of the ethical principles articulated in international guidance documents and human rights instruments, as well as any national laws or policies consistent with those principles. The REC makes clear the specific ethical guidelines on which it relies in making decisions and makes them readily available to researchers and the public. *When an REC develops reliance agreements for review of research under its jurisdiction by another REC, it is the responsibility of the delegating REC to assure that the same ethical principles*

serve as the basis of the other REC's decision-making (emphasis added) [62].

The standard is noteworthy in that it does not specify whether the reviewing and delegating REC must be within the same jurisdiction, but rather that there are equivalent ethical principles guiding the review decision. In this respect, comparable principles can give rise to comparable procedures upon which mutual recognition may effectively be premised.

Global Alliance for Genomics and Health (GA4GH)–Ethics Review Recognition Policy

The GA4GH is a standards-setting and policy harmonization body dedicated to enabling responsible sharing of genomic and health-related data. In response to increasing number of international genomics research consortia, the Regulatory and Ethics Work Stream of the GA4GH developed the Ethics Review Recognition Policy to provide a “common effective baseline of the ethics review process for multi-jurisdictional research involving health-related personal data.” The initial release of the policy (February 2017) preceded some national reforms to research regulations in jurisdictions such as Canada and the United States, and was updated in July 2020 to reflect these changes.

The Policy outlines both Essential (**Box 2**) and Common Elements (**Box 3**) of REC operations that together “should engender trust in the ethics review process followed in another jurisdiction and thereby recognition that the decision rendered by a REC from that jurisdiction is adequate.” Its emphasis on supporting multinational REC review of data-intensive studies is especially useful in pandemic settings when secure access, use and exchange of large epidemiological datasets and vaccine trial results is critically needed to understand disease transmission, rates of infection, therapeutic efficacy and safety to guide public health responses.

National

There are also examples of national regulatory channels that, if utilized to their fullest potential, could allow for mutual recognition of ethics reviews and approvals conducted by international RECs. **Box 4** compares and contrasts two such channels for recognizing external reviews in Canada under Article 8 of the Tri Council Policy Statement [63] and

[62] World Health Organization. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*. 2011. https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=2CB78BE4794C241B287C824F200DA282?sequence=1 (accessed 12/16/2020).

[63] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2018.

Box 2 GA4GH Ethics Review Recognition
Policy— Essential Elements

The following Essential Elements are intended to complement and build upon existing human rights instruments, laws, regulations, guidelines, and practices. They are not intended to supersede any human rights instruments or national laws and regulations. Across jurisdictions, managing authorities of RECs and RECs should work together to achieve these Essential Elements.

- *Norms, Authority and Independence*
- *Resources*
- *Competence*
- *Diligence*
- *Procedures and Forms*
- *Proportionate Scrutiny*
- *Transparency*
- *Fairness and Equity*
- *Oversight*
- *Paediatric and Vulnerable Populations*
- *Indigenous Peoples*

Box 3 GA4GH Ethics Review Recognition
Policy— Common Elements

In reviewing the ethical acceptability of an application for multi-jurisdictional research involving health-related personal data, due regard should be given to the following elements:

- *Expertise and experience of researcher(s)/investigator(s);*
- *Role of the sponsor(s);*
- *Merits and quality of the research protocol (e.g. study design; dissemination of findings/feedback to participants; documentation issues; research impact);*
- *Prior ethics review (if any);*
- *Study context and site(s) information;*
- *Specific health-related data research issues (e.g. relevant regulatory approvals);*
- *Conflict of interest (e.g. financial, organizational, personal);*
- *Potential for waivers of consent;*
- *Consent process (e.g. participant identification and solicitation, information provided; type of consent used – written, explicit, broad, etc.; assent in cases of minors or adults with incapacity; informative material for minors; quality and comprehensibility; withdrawal);*
- *Potential risks and harms for participants, communities, and society;*
- *Potential benefits for participants, communities, and society, including assessment of the project’s social value;*
- *Adequate assessment of the project’s scientific integrity;*
- *Privacy and confidentiality (e.g. protection, access, control, security, retention, and disposal of the data; during and after research conduct and in publications or other reports; possible data reuse, compliance with relevant privacy/data protection regulations);*
- *Considerations for vulnerable populations;*
- *Potential compensation to participants (including assessment of the amount);*
- *Funding (e.g. researcher compensation/benefit; sufficiency and source of funding);*
- *Evidence of training, education, or experience of the researchers relevant to the ethical conduct of research involving health-related data;*
- *Policy for addressing incidental findings or return of results; and*
- *Legacy of the project-generated data, i.e. a plan for how the data generated by the project will be stored, archived, and become accessible for new research uses.*

Canada

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) and its equivalent in the United States under the Common Rule. Whereas the former establishes national guidelines but is legally binding only for researchers who receive national funding, the latter is a requirement irrespective of the source of funding.

Healthcare spending and health research governance are the jurisdiction of the individual provinces in Canada. Most RECs based in Canadian hospitals and universities operate with provincial mandates from Ministries of Health and Education, respectively. Despite their provincial autonomy, REC mandates adhere closely to the TCPS guidelines which outline three possible models of REC review under Article 8.1. Two models address multisite ethics review, specifically,

Research Ethics Review Delegated to an External, Specialized or Multi-Institutional Research Ethics Board– Institutions may allow research on specialized content or research methods to be reviewed by an external, specialized or multi-institutional REB, where such a body exists. External, specialized or multi- institutional REBs may be established regionally, provincially/territorially or nationally, as necessary. Two or more institutions may choose to create a single joint REB, or to appoint an external REB, to which they delegate research ethics review. This delegation of review may be based on geographical proximity or other considerations such as resources, volume of reviews or shared expertise.

Reciprocal Research Ethics Board Review– Multiple institutions may enter into official agreements under which they will accept, with an agreed level of oversight, the research ethics reviews of each other's REBs. This might involve specific agreements between institutions for sharing their workload.

The TCPS acknowledges that “National and international standards for research involving humans are evolving continually, but methods for comparing the precise levels of protection afforded participants in different countries or jurisdictions, and by different institutions within those countries and jurisdictions, have not yet been developed.” For these reasons, Article 8.3 mandates that research sponsored by a Canadian research institution but conducted outside its jurisdiction, whether elsewhere in Canada, or outside Canada, shall undergo prior research ethics review by both the REC

- i. at the Canadian institution under the auspices of which the research is being conducted; and*
- ii. at the research site or other responsible review body or bodies, if any.*

Box 4 *Regulatory channels for multinational ethics review in Canada and the United States*

United States

United States The domestic centralization afforded in the TCPS is paralleled in U.S. research regulations under the Common Rule. 45 CFR 46 details approaches for how institutions conduct initial and ongoing ethical review of research involving humans that reduce the likelihood of research-related harms and provides guidance on maintaining high standards of institutional accountability among primary actors responsible for human research protections. As such, 45 CFR 46 is the procedural implementation of ethical norms and principles codified in international conventions such as the Declaration of Helsinki and CIOMS.

The Common Rule was revised most recently in 2018 to mandate, among other changes, single ethics review for multisite studies within the continental U.S. and its territories. When research covered by the Common Rule takes place in foreign countries, however, a department or agency head may approve the substitution of the foreign procedures pursuant to §46.101(h) if they “determine that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in [the Common Rule]” [emphasis added]. This obscure provision has come to be known as ‘equivalent protections’ clause. It effectively allows for the direct comparison of procedures normally followed in foreign institutions but which “are consistent with guidelines issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized [65]”. An external REC review conducted under a foreign regime where equivalent protections has been determined may therefore obviate the need for duplicate review. A 2003 report conducted by the Department of Health and Human Services, and chaired by Lavery, outlined five steps for determining equivalence based on a review of three previous approaches:

1. *Articulation of the specific protections embodied in 45 CFR 46; Embodied protections include the following:*
 - *Establish norms of ethical conduct and due diligence in review and performance of research within the institution*
 - *Ensure adequate authority and independence of the IRB/Research Ethics Committee IRB*
 - *Protect against biased and arbitrary decisions in research ethics review*
 - *Ensure sufficient quality and comprehensiveness of research ethics review*
 - *Ensure research ethics review and oversight are commensurate with risks to research subjects and vulnerability of the study population*
 - *Ensure research ethics review and oversight are commensurate with risks to research subjects and vulnerability of the study population*
 - *Protect against unnecessary or unjustified risk throughout the course of the study (includes responsibilities of investigator(s))*
 - *Ensure voluntary participation after adequate disclosure of information related to the study (includes responsibilities of investigator(s))*

Box 4 *Regulatory channels for multinational ethics review in Canada and the United States*

United States cont'd

2. *Assessment of the protections provided by the institution's procedures; Comparison of the protections provided by the institution's procedures with those provided by 45 CFR 46 and determination whether or not the institution's procedures provide at least equivalent protections;*
3. *Approval by the relevant department or agency head for the substitution of the institutional procedures in lieu of the procedures of 45 CFR 46; Mechanism of assurance with Office of Human Research Protections*
4. *Assurance from the institution that the substituted procedures will be followed in the conduct of Department of Health and Human Services funded human subjects research. The assurance will be completed and filed with the Office of Human Research Protections.*

The report concludes that "determinations of equivalent protections would offer an important symbolic gesture on the part of the United States to foreign countries, namely the recognition that the same ethical goals can be met through procedures different from those in 45 CFR 46."

Box 4 *Regulatory channels for multinational ethics review in Canada and the United States*

the equivalent protections clause in section §46.101(h) of the United States Common Rule [66]. Both regulatory provisions condition the acceptance of another REC's decision on using equivalent standards and ethical norms such as those outlined in international conventions and guidelines. The regulatory similarities in REC organization and convergent ethical frameworks underpinning the protections outlined in the TCPS inspired one proposal to pilot 'equivalent protections' between Canada and the United States.

Lavery, McDonald and Meslin argue the type of research funded in the United States and Canada—and indeed between two or more countries with common socioeconomic interests—typifies a “cross-border industry in which shared standards might prove beneficial to both countries.” The authors base their proof-of-principle for mutual recognition on conclusions from a commissioned report of the equivalent protections clause. In its report, the Department of Health and Human Services provided a framework for determining equivalence of research protections. Though the 2005 article predates the most recent reforms to human subjects protections in both Canada and the U.S., the authors explain why equivalent protections should be pursued when countries share, among others, scientific and economic goals using an eerily appropriate example: “Given the recent experience with Severe Acute Respiratory Syndrome (SARS) in both countries, the need to remove unnecessary regulatory obstacles to cooperative research and public health practices becomes even more apparent” [67].

Conceptual models

The environmental scan produced three published articles that describe a system of multilateral ethics review and approval for collaborative studies. The models presented therein reflect proposals to centralize reviews at the international level on the basis of research type and geography.

Ethics review mutual recognition for data-intensive studies

In their review of five multinational research consortia, Dove et al identify three models that could “inform a framework for mutual recognition of international

[66] Department of Health and Human Services. *Federal Policy for the Protection of Human Subjects. Final Rule*. Vol 82.; 2018:7149-7274.

[67] Lavery J, McDonald M, Meslin EM. Research Ethics Across the 49th Parallel: The Potential Value of Pilot Testing “equivalent protections” in Canadian Research Institutions. *Health Law Rev.* 2005;2(3):86-96.

review (i.e., the acceptance by RECs of the outcome of each other’s review)” [68]. The framework is intended to facilitate mutual recognition of REC reviews for data-intensive research, of which secondary analysis of clinical trial data of vaccine candidates could be considered, for example, or large epidemiological studies to study disease outbreak and transmission. The three models are summarized in **Box 5**, and founded on two guiding principles consistent with the WHO standards and guidance outlined above. These principles outline i) REC scrutiny should be proportionate to the study risks, and that ii) no further de novo review should be required once a review decision is reached insofar as there are procedural and regulatory alignment between RECs. Importantly, the authors reify the role of local RECs in assessing any local issues and determine whether additional local accommodations are needed to carry out an approved study.

Box 5 *Three models for building ethics review mutual recognition for data-intensive international research organized from most, to least integrative with local RECs [68]*

Most integrative

Federation– *Institutions, funders, or regulators/governments create a central REC with representation from multiple jurisdictions.*

Delegation–*Before review, an institution, funder, or regulator/ government delegates ethics review responsibilities to one or several existing designated RECs through agreement.*

Reciprocity–*An institution, funder, or regulator/government in one jurisdiction accepts the completed ethics review from another jurisdiction and vice versa through collaborative recognition of equivalent processes and/or standards*

Least integrative

Each model affords advantages and poses unique challenges when applied in the context of a public health crisis like the Covid 19 pandemic, and are reviewed in turn below.

[68] Dove ES, Townend D, Meslin EM, et al. Ethics review for international data-intensive research. *Science*. 2016;351(6280):1399-1400. doi:10.1126/science.aad5269.

Time savings is the key benefit of the reciprocal model. As the most minimally integrative model, reciprocity enables local RECs at the participating sites to assess site-specific issues/accommodations and decide whether to authorize the study as approved. Participating RECs build consensus on what research participant protections are most germane to a class of research projects. Once equivalence is reached on one REC decision based on the agreed upon protections, collaborating RECs could ostensibly apply the same standards to an entire class of projects e.g. vaccine trials, human infection challenge trials, and other epidemiological transmission studies. The reciprocal model would not, however, address REC decisions where the study is incompatible with regulations in one or more of the participating countries [69], nor determine which jurisdiction's protections will serve as the reference. Establishing reciprocity is also likely to be time- and resource-intensive at a time when both can be exceedingly limited at the onset of a pandemic.

In contrast, the delegation model could more evenly distribute needed time and resources across one or more designated review bodies. This model consolidates expertise such that more RECs can access experts with specialized knowledge and render more consistent decisions. Collaborating countries within a region could together designate, for example, a special vaccine clinical trial board that would oversee the scientific review and approval of protocols. Unlike the reciprocal review model, however, the outcomes of a delegated review leave little room for alternative decisions. There might also be challenges in determining how post-approval activities will be handled at the respective research sites.

Some countries mandate post-trial access to investigational drugs, for example, and therefore require separate agreements negotiated at the institutional level with the study sponsor. Deciding which existing REC should serve as the delegated review body of record may also inflame political tensions, particularly between large, well-resourced academic medical centers.

Federation of RECs addresses issues in the former two models regarding underrepresentation of local RECs. Federation also promises to reduce duplication and potential inconsistencies in review outcomes given that all decisions are

[69] Some research designs/procedures may be prohibited under national research regulations and therefore not meet jurisdictional standards despite a thorough ethics review by an REC in a country where the design is permitted.

reached via consensus among representatives to the federation. Federated RECs also drive standards improvement by encouraging what the authors term, “herd instinct.” Selecting representatives that ensure a federated REC can be culturally balanced and sensitive to power differences is the main barrier to achieving consensus. Like the reciprocity model, it may be challenging for jurisdictions to agree on reference policies/standards based on which to make federated decisions that will likewise comply with those in the representatives’ home country [70].

Irrespective of the model Dove et al summarize, reviewing RECs must commit to sustaining robust participant protections throughout the lifecycle of the protocol, maintain the integrity of the system as well as that of each participating REC and finally to foster trust in the standards used to render a thorough review decision. And in the absence of internationally recognized bodies to steer data-intensive international research, including during a pandemic, the authors “advocate bottom-up, ad hoc solutions, ideally coupled with official recognition and support by governments and regulators, sponsors, funders, institutions, and data access committees.”

Sounding board model

Using the 2014 European Clinical Trials Regulation as a demonstrative case study, Townend and Dove advocate broadly for how RECs could achieve mutual recognition through adopting a ‘sounding board model’ [71]. In reaching their conclusions, the authors ask explicitly what about the review process makes harmonizing REC procedures difficult when research transcends national borders and interrogate these challenges through a natural justice lens. Like others, they question the position that a multisite/national study must *a priori* receive independent review by a local REC to be responsive to local sensitivities, values and priorities, citing the harms of review duplication and decisional inconsistency. The authors contend that because “ethics has no common language,” substantive ethics discourse should not, and indeed cannot, be the locus of harmonization.

[70] The European Union Clinical Trials Regulation, which streamlines scientific and ethical review of multinational trials within the European Union exemplifies the federated review model. Two assessments run in parallel under this federated model. A study sponsor identifies one Member State to serve as the reporting committee which conducts a thorough risk-benefit evaluation. At the same time, Member States are provided a narrow window in which to submit ethical, legal and social issues relevant to the local context prior to final authorization. See for more information Westra AE, Bos W, Cohen AF. New EU clinical trials regulation: Needs a few tweaks before implementation. *BMJ*. 2014;348(June):10-11. doi:10.1136/bmj.g3710.

[71] Townend D, Dove ES. Approaching Ethics Review Equivalency through Natural Justice and Sounding Board Model for Research Ethics Committees. *Med Law*. 2017;36(1):61-86.

They demonstrate that attempts to harmonize substantive ethics is the primary barrier to mutual recognition because RECs apply different approaches in answering three fundamental questions: "1) Should this research be undertaken at all? 2) Is the science good science? 3) Will the participants be protected in the conduct of this research?"

Instead, the authors place the onus on researchers to defend their own ethical practices. A REC, in turn, acts as a 'sounding board' that conveys whether a researcher has considered the rights, interests and welfare of participants, the scientific integrity of the study, and the likelihood of the study generating the anticipated benefits as described. Using the sounding board mechanisms to promote international systems of mutual recognition,

obviates the need for a harmonised substantive ethics, which we believe is an intractable challenge (in contrast to a harmonised procedural ethics, which we believe is readily achievable). Whilst offering a relatively straight-forward procedural harmonisation (through the three questions), RECs are freed from finding "right" answers to accepting robust approaches to ethics....In multi-centre, multi-jurisdiction ethics review, a lead REC could hold the discussions with the researchers, asking how the researchers have taken into account local sensitivity in the sites where they propose to work, and a report from that lead REC (perhaps including video recording) could be reviewed by other RECs with the questions "are we convinced by the researchers' ethics-by-design and preparedness for dialogue?" Indeed, with the availability of online teleconferencing, the lead REC could facilitate participation of representatives from the other RECs to ensure a consensus around the researchers' preparedness for ethical research and ethics discourse, further streamlining the process [72].

The sounding board model lacks the organizational prescription of earlier models described. It does, however, make the case for separating REC procedure from REC duties to ethically deliberate on protocol applications in ways that inform harmonizable elements in the review process. In what follows are summaries of consultative activities in the form of mini case reports conducted with REC stakeholders across low- and middle-income countries from October- December 2020. The consultative activities were conducted to address the perceived opportunities for, and limitations of ethics review mutual recognition from the perspectives of REC reviewers, policy makers, Ministry of Health advisors and WHO Coalition affiliates. Consultative discussions were semi-structured and held in English.

[72] Ibid., 60, page 37.

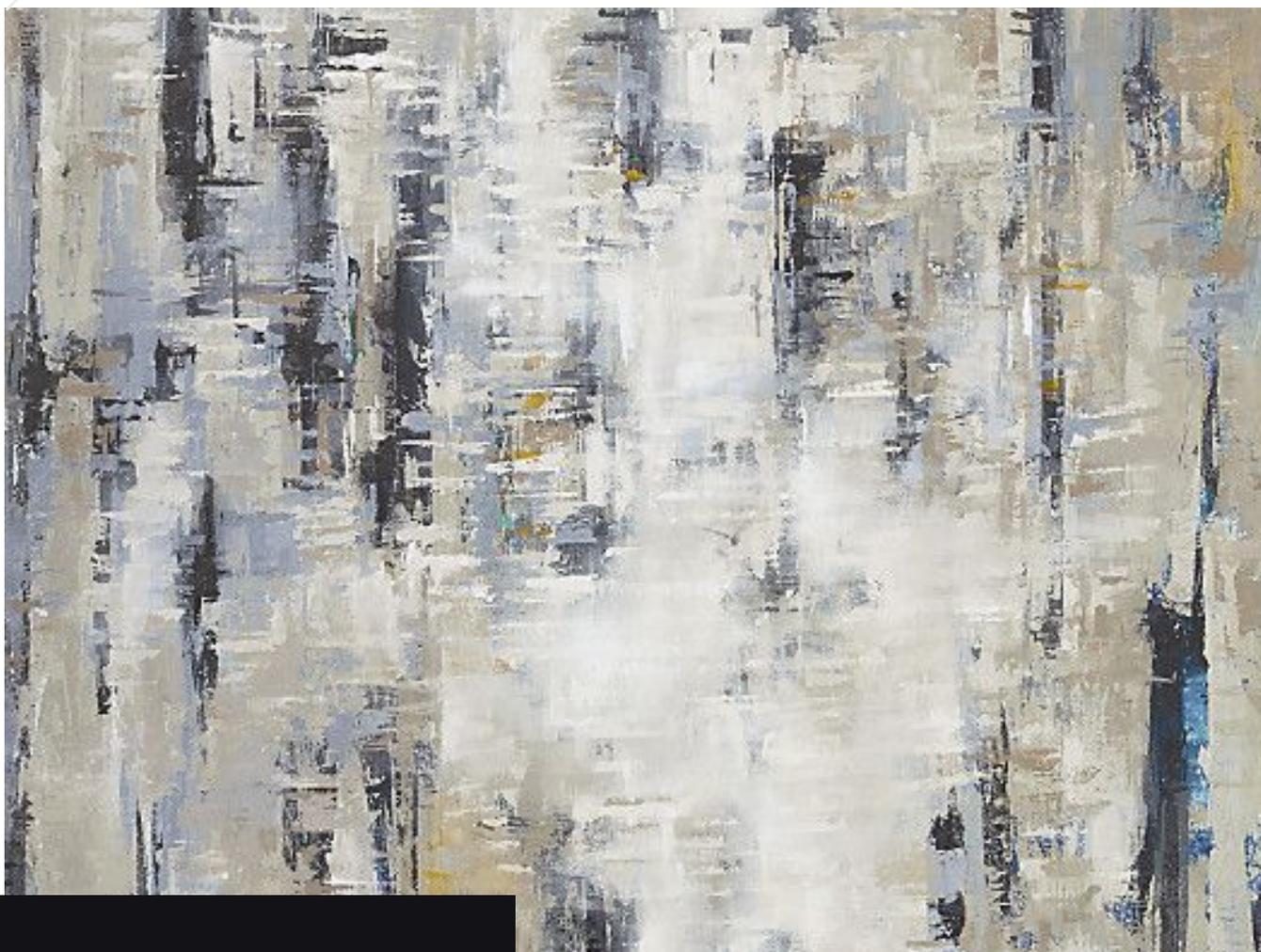
All informants were asked to discuss the following:

- Existing REC infrastructures in their country, including regulatory environments, operations, mandates and resourcing
- Current approaches to reviewing multisite/national protocols before and during the pandemic
- Changes made to REC procedures, including efforts to centralize or otherwise harmonize procedures to accelerate reviews, as well as the lived experience during this transition
- Perceived challenges of centralization, if applicable [73]
- Whether, and how local RECs interact with decisions rendered by RECs in other countries where the same protocol has been reviewed
- Perceived challenges and opportunities of recognizing extra-jurisdictional reviews and implications on review quality, effectiveness and efficiency during the pandemic.

[73] Policies enabling centralized review and approval for multisite studies preceded the Covid-19 pandemic in some countries featured in the case reports, and therefore not explicitly adopted for the purposes of a public health crisis.

Part III.

MINI CASE REPORTS



...shift to standardized clinical trial applications and assessments, and proof of ongoing harmonization initiatives on the continent

Case report 1

African Vaccines REgulatory Forum

The African Vaccines REgulatory Forum (AVAREF) was established by the WHO in 2006 to enhance human research protections, REC capacities and biomedical research collaboration on the African continent (**Box 6**).

Since 2006, AVAREF issued nine consensus guidelines to support quality ethics review and responsible conduct of clinical trials specific to vaccine development. The tools correspond to review processes that span the lifecycle of a prototypical vaccine trial (**Box 7**). They were revised and approved for distribution to 55 African member states as of October 2019, marking a “shift to standardized clinical trial applications and assessments, and proof of ongoing harmonization initiatives on the continent, which will ultimately lead to shorter timelines for product development” [75]. Among the resources available in the AVAREF toolbox are guidelines for joint review of multisite/national vaccine trials. The guidelines provide national regulatory authorities and ethics committees with harmonized procedures for how to plan, organize and conduct joint reviews to reduce redundancies and improve efficiency of clinical trial applications in Africa. The WHO convenes a joint committee with representation from local research sites where a trial will take place, invited experts e.g. from the RECs or regulatory authorities from regional, continental or international countries, a neutral proctor for the meeting and participant observers (if any).

Before a joint review can proceed, the trial sponsor, representatives from the target research sites and the reviewing experts on the joint committee agree to several procedural, transparency and communication requirements. Notably, a candidate medical product must have high public health value to African countries

[74] Tools for Processing Clinical Trial Applications by Ethics Committees and National Regulatory Authorities in Africa: An Introduction to the work of AVAREF. Available at <https://www.afro.who.int/health-topics/immunization/avaref> (Last accessed 12/29/20).

Box 6 *Tools for Processing Clinical Trial Applications by Ethics Committees and National Regulatory Authorities in Africa [74]*

The African Vaccine Regulatory Forum (AVAREF), a Pan African network of National Regulatory Authorities (NRAs) and Ethics Committees (ECs) was established by the WHO in 2006 as a platform for building ethics and regulatory capacity for clinical trials, while promoting harmonization of ethics and regulatory processes in the continent. Recognizing the pressing health needs on the continent, AVAREF's governance and scope was extended during an extraordinary meeting in 2016 in Addis Ababa. AVAREF became one of the Continental Technical Committees of the African Medicines Regulatory Harmonization Initiative. The new mandate covers vaccines, medical products, and medical devices in line with the AVAREF strategic plan 2018-2020.

As an effort to improve clinical trial review practices, AVAREF member states agreed to a maximum 60 calendar day timeline for processing and clearance of clinical trial applications. The AVAREF Assembly, comprising of heads of NRAs and Ethics Committees, met in Accra, Ghana in November 2017 and endorsed this timeline. The Secretariat, which monitors these timelines has established that not all Member States are consistently meeting them due to their different capabilities for assessing clinical trial applications, stressing the need for further harmonization. Through the monitoring of the timelines, member states realized the importance of harmonization of regulatory and ethical review practices to address gaps in the capacities and processes.

Box 7 *Three processes and corresponding tools AVAREF developed to facilitate quality review and responsible conduct of vaccine clinical trials.*

Process for clinical trial applications	Tool
<i>Screening and validation</i>	<i>Clinical trial application form and checklist</i>
<i>Assessment</i>	<i>Joint review guidelines, templates for clinical, nonclinical, quality, and biostatistics assessment</i>
<i>Monitoring</i>	<i>Good clinical practice inspection checklist and good clinical practice inspection guide</i>

before it will be considered eligible for joint review. A prospective Covid-19 vaccine trial would meet this value requirement for AVAREF joint review given it is a “product that addresses a disease for which the Director General of the World Health Organization has declared a Public Health Emergency of International Concern (PHEIC).”

What’s more, the WHO in collaboration with partners recently developed a strategic plan to leverage the AVAREF joint review system to address clinical trials during an epidemic or pandemic. The *AVAREF Strategy and Guidance for Emergency Preparedness* is the product of a tabletop simulation exercise of the MERS-CoV outbreak [75], and is ideally positioned to manage reviews during the current Covid-19 crisis because its “focus is on harmonization of the ethical and regulatory components of emergency preparedness within the continent.

[75] According to the WHO Simulation Exercises Manual, “A tabletop exercise is a facilitated discussion of an emergency situation, generally in an informal, low-stress environment. It is designed to elicit constructive discussion between participants; to identify and resolve problems; and to refine existing operational plans. This is the only type of simulation exercise that does not require an existing response plan in place.”

Implementation of these plans by testing and simulation at country level, within RECs and as a continent, is key to the success of a convergent strategy for Africa.”

The AVAREF joint review model—and its recent adaptation to address public health emergencies—is the only operational, extra-jurisdictional system of ethics review and approval in the world to date. Based on document analysis of available AVAREF guidelines and using the conceptual framework described earlier in this report, the joint review model operationalizes the two foundational premises for ethics review mutual recognition. Participating sites are represented on the joint review panel and apply equivalent procedural standards for REC review of vaccine trials—AVAREF templates, tools, criteria as well as WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations. The joint review model further establishes reciprocity through agreements that have regulatory legitimacy within individual member states named in the joint trial protocol.

As such, the AVAREF joint review model provides a pertinent case study from which the REC community and policy scholars can learn *in vivo* how a system of ethics review mutual recognition could potentially scale for a specific type of research i.e. clinical trials. The WHO and AVAREF Secretariat have also planned for an evaluation of the joint review system using the WHO Simulation Exercise Manual. The AVAREF guidelines identify three key areas that WHO exercises will help to test: in-country preparedness, harmonization of country preparedness at the level of RECs, and the response plan at continental level.

Here again, AVAREF leads the international community aiming to gather empirical policy evidence to design streamlined review procedures. Empirical data from these tests will be valuable to understanding the potential for similar joint review systems elsewhere in the world. These data could enable REC policy researchers to compare, for example, review quality and decision outcomes between joint committees and independent institutional reviews for multinational studies; assess operational, contextual and logistical challenges of coordinating joint reviews, especially between the joint committee and local RECs authorizing the study; and engage community stakeholders on how, if at all, the model could be applied to facilitate other types of research reviews. Based on analysis of available

documents, the AVAREF joint review system will also be the first research ethics review tool to be evaluated using the WHO Simulation Exercises. If successful, the exercises could become a standard test that international REC systems apply to evaluate joint reviews. Testing data could likewise be collected and formatted in a standardized fashion and deposited in a publicly accessible repository as part of the WHO International Health Regulations Monitoring [77].

Finally, evaluators who may in the future look to these findings for evidence on structuring joint reviews in their own regions will need to take into account the AVAREF model is i) specific to a single research type (vaccine trials) and ii) localizes reciprocity to one specific region (African continent). Both features will significantly affect the generalizability of findings from the AVAREF simulation exercises to other review systems. Ethical considerations germane to vaccine trials, while maybe relevant, will differ considerably in scope when reviewing alternative study designs involving human participants e.g. social science research and genetic/genomic research.

The regulatory environments in which RECs and their governing authorities operate in other countries may also not be conducive to, nor permit involvement of representatives from other RECs in the review process. One informant offered a possible explanation. In the West African experience, research ethics review cannot be fully divorced from politics [78]. Conflicts in the quality and independence of reviews, as well as the potential for multinational collaboration among RECs in an extra-jurisdictional system of review and approval likewise reflect this reality. In Ghana, the informant's home country, an estimated 18 RECs are affiliated with institutions and embedded in health systems. Research ethics review is a revenue generating activity and therefore challenges the REC's ability to remain at arm's length.

The informant also identified issues regarding inadequate expertise and conflicts regarding research sponsorships. Improperly reviewed studies often suffered from lack of access to experts with the requisite skillsets. In addition, studies from American or European sponsors tended to receive favorable reviews from local RECs under the impression that review expediency would attract more researchers

[77] International Health Regulations Monitoring. WHO [https://www.who.int/data/gho/data/themes/international-health-regulations-\(2005\)-monitoring-framework](https://www.who.int/data/gho/data/themes/international-health-regulations-(2005)-monitoring-framework) (Last accessed 12/30/20).

[78] Summaries from consultative activity #4 are presented here. See **Annex 3** for full list of activities.

and resources to the institution(s). Greater promotion of intra-African networks was cited as a pressing need to build strong, independent REC system capacities. Current efforts among agencies like AVAREF and the African Centers for Disease Control (CDC) to forge such networks are thus far insufficient because they do not optimize involvement from local communities. The informant shared that research ethics review is an example of complex governing that should give ownership and decision-making agency to communities. There are, inevitably, repetitive elements in complex governing that should be valued and preserved, rather than dismissed as procedural waste in the governance process. Discussions about how well, and by what standards RECs protect the needs and interests of participant communities is incomplete without acknowledging the art of complex governance. Scientists should, according to the informant, appeal to more than pragmatism in their valuation of RECs in this regard.

Case report 2

Philippines [79]

The Philippine Health Research Ethics Board (HREB) is an autonomous, national agency created by law to regulate the ethics of health and health-related research. It is a constituent entity within an integrated national system that is coordinated among the Department of Health, the Department of Science and Technology, the Commission on Higher Education, and the National Institutes of Health. The HREB functions as the governing authority overseeing an estimated 100 local RECs [80]. The RECs are accredited to review studies at three different levels (**Box 8**). Of these 100 boards, nearly 40 are Level 3 accredited. Local RECs can be tied to hospitals, institutions of higher education or are regionally organized. The latter have been established in areas that lack adequately accredited institutions. The membership on regional committees is representative of different institutions but can often be unstable due to difficulties in coordination.

[79] Information used to inform this case study emerged from consultative activities #12. See **Annex 3** for full list of activities. Particular thanks to Professor Leonardo de Castro for providing input.

[80] Approximately half of these also obtained accreditation from the U.S. Federalwide Assurance (FWA) Program. RECs with FWA accreditation have gained a reputation with Philippine investigators who will apply to certain RECs because of the equivalency it affords with research protections in the U.S.

The local, regional and national committees are also complemented by a joint research ethics board based in the capital city, Manila. The Department of Health initially established the joint board to review multicenter trials at hospitals under its purview and, as such, is a hybrid centralization approach typified in Models 2 and 3 (**Figure 4**). The hospitals are government institutions and private hospitals which and are not regular members of the joint research ethics board but can participate in the review process. When the board meets, it includes representatives from the different government hospitals where a particular research study will be done. The members must reach consensus at the joint committee level and all final review decisions are conditional on local authorization. Each representative has the authority to impose additional conditions they consider appropriate for their locality [81]. Most often, approval is conditioned on modifications to the informed consent process to reflect, for example, participant recruitment from certain ethnic groups where community consultation is

requirement. Requested changes to the protocol from the joint committee are sent back to the investigator as is customary in most review systems.

Box 8 *Levels of REC accreditation overseen by the Philippine Health Research Ethics Board*

- Level 1**—accredited to review/ approve minimal research studies
- Level 2**—accredited to review/ approve research with more than minimal risk
- Level 3**—accredited to review/ approve clinical trials

This joint review board has been a primary liaising body for multisite review of Covid-19 studies. Before the joint board issues a final decision on the protocol, it gives local RECs institutional to meet first and grant authorization. At times this approach created procedural redundancies that subsequently delayed the review process and led researchers to wait for two approvals before launching a time-sensitive Covid-19 vaccine or drug protocol. One informant who serves both on joint review board and

[8] Some metro Manila hospitals opted to participate in joint board review, and in this way, established their own system of mutual recognition.

the Philippine HREB reflected that the experience attempting to centralize Covid trials confirms a general sentiment (resistance) in the country towards single review and approval mechanisms. The informant contrasted this position with what occurs in Philippine drug regulation. In specific, the informant described how the Food and Drug Administration of the Philippines tends to look favorably on some foreign drug approvals provided, particularly by the U.S. FDA and its equivalent in Europe.

The case of a vaccine candidate with emergency use authorization in the U.S. was provided as an example of this regulatory contrast. The Philippines FDA could determine it may not have to go through its own procedures after reviewing the grounds for approving the emergency use authorization given by the U.S. agency. Thus, the Philippines FDA accepts responsibility for undertaking an abbreviated review upon mutual recognition of a foreign approval.

Thus far, the experience and precedent during the pandemic suggest the country is not positioned to recognize an ethics approval given for research outside the Philippines in response to Covid19 or otherwise. The informant recalled at a global summit for research ethics committees in Dakar, there was considerable discussion devoted to organizing a WHO body with representation from each country to review protocols and grant ethics approval for multinational studies that met ethical standards. Many attendees were involved in approving Ebola trials and these experiences provided general context for discussions. The consensus principle that emerged was that the WHO could facilitate the multinational process through joint review, but attendees realized the joint committee could not supplant local approval.

Case report 3

PAHO, Brazil, Chile, Caribbean, Peru, Argentina, Columbia

Brazil

Brazil research ethics review system operates as a hybrid model. A national, centralized review body—CONEP—manages local committees—CEPs—which are local, collegiate and independent bodies, most of them linked to hospitals, universities, non-governmental organizations and research institutes. CONEP also maintains a national registry of CEPs and mandates they have at least seven members with various areas of expert knowledge and a community representative.

The National Health Council of Brazil formalized coordination between CONEP and local committees dispersed regionally under Resolution N° 346/2005. The Resolution maintains that CONEP delegates final project approval to the local CEPs, as well as responsibility to oversee protocol modifications requested during centralized review.

CEPs may submit protocols to CONEP if they lack the requisite expertise to conduct a comprehensive review and are required to do so when studies involve indigenous peoples, genetics and international collaborations, among other reasons. The requirement that CONEP review all internationally sponsored research is, according to Brazilian informants, the primary political deterrent to mutual recognition. Informants also highlighted how this requirement was exemplary of how deeply the bureaucratic culture roots within the Brazilian system. CONEP requests documents of ethics approval from the country of origin but does not constitute a waiver of regional and local review. This requirement furthermore applies irrespective of the study's risk profile.

When probed to reflect on the effectiveness of this system, informants confirmed the difficulty of importing solutions from other research contexts. They acknowledged the many ways in which national reform to REC accreditation in recent decades greatly improved the quality and coordination of reviews between

[82] Information used to inform this case study emerged from consultative activities #2, 5-7, 9,14-17. See **Annex 3** for full list of activities. Particular thanks to Professor Sofia Salas and Carla Saenz for providing input.

[83] National Health Council of Brazil, Resolution 196/1996.

CONEP and CEPs. The improvements have not been universally beneficial for reviewing all types of protocols, however, based especially on the perspectives of informants currently serving as RECs members during the pandemic. The procedural reforms have been effective for accelerating interventional studies, and Covid-19 vaccine trials in specific. The improvements were corroborated by a vaccine trialist during an online webinar sponsored by the Pan American Health Organization (PAHO) (**Annex 3**). They described a timely and efficient submission process through the CONEP system and positive experiences working with local CEPs. In contrast to the positive regional oversight CONEP affords for interventional studies, the process added administrative burdens for minimal risk epidemiological studies. Informants felt the lack of risk stratification used to expedite reviews in other countries was a unique operational challenge to a hypothetical system of mutual recognition in Brazil, but also for multisite collaboration within the country given the rise in big data and other types of research where the associated risks are low.

Informants also anticipated that local CEPs would perceive ceding any review authority to an REC other than CONEP as a violation of institutional autonomy and as circumventing the rights of CEPs to weigh in on the ethical deliberation process. Informants were likewise not swayed with the assurance that CEP authorization would still be required under ethics review mutual recognition. Two methods for improving the existing model for within-country multisite reviews were offered to address current inefficiencies. In turn, the recommended improvements could help international RECs gain a clearer understanding of the Brazilian system.

First, informants recommended that five or six regional RECs should supplant the one national committee (CONEP) in order to strike enable closer coordination with local review while conferring the benefits of centralization. This recommendation maps onto the typologies presented in **Figure 4**. It exemplifies a transition from model 1—national centralization with local REC authorization—to model 2—regional centralization with local REC authorization. Second, informants recommended that RECs could expedite decision-making if they reduced their rosters, and reduce administrative burden if they implemented a risk-stratified system of review with distinct procedures for minimal, and more than minimal risk studies.

Chile

The Ministry of Health is the governing authority under which twenty-six accredited, local RECs operate in Chile. Like in Brazil, all compliant RECs are accredited. Inconsistencies in the process for obtaining site approval for four Phase III Covid-19 vaccine trials motivated the National advisory committee on bioethics in collaboration with the Ministry of Health to establish an ad hoc committee that issued guidance on all future trials. Representatives from the investigating institutions in the trials were invited to comprise the ad hoc committee that together produced general guidelines to facilitate future review consistency while also allowing for locally specific resource issues to be considered.

One informant who served on this ad hoc committee recounted that the Ministry of Health faced resistance from local RECs despite their representation in the guideline development process. Representatives from some local RECs felt the recommendation to strike an ad hoc committee arrived too late when vaccine trials at their respective institutions were either under review or already approved. RECs that had already approved vaccine protocols were thus encouraged to modify the conditions of the approval retrospectively to accommodate the new guidelines, a process local RECs perceived to be both redundant and time consuming for study sponsors. Moreover, local RECs were reluctant to share the approved protocol for confidentiality concerns.

The ad hoc committee experience proved challenging because it was the first time individuals serving on the committee had worked together. Representatives sometimes perceived local considerations to be too distinct that discussions often lapsed into defending local practices and hindered agreement on common guidelines. At the time of writing, the ad hoc committee continues to meet weekly and provides general recommendations independent of specific protocols in the form of points to consider when reviewing vaccine trials. The recommendations are non-binding.

Several key lessons emerged from providing this guidance that are anticipated to have important implications for future centralization of REC reviews post-pandemic in the country. First, health authorities and RECs disagree on appropriate compensation for REC service, without which the quality of reviews and recruitment of expert members begin to suffer over time. The reluctance on

the part of local RECs and the ad hoc committee was symptomatic of transparency issues that hinder joint reviews. RECs should have access to a dossier of prior reviews, including reviews from other countries, and how the REC came to their decision. Such a dossier is also a valuable training tool to enhance review capacities. Lastly, the informant perceived that the ad hoc committee could have been more effective with a clear procedure on where a principal investigator submitted their protocol and when. An ideal process would proceed from sponsor/PI submission to a national centralized committee for preliminary review—typified by model 1 in **Figure 4**)—and then to local RECs for authorization and site-specific changes if applicable. Instead, the current process is reversed.

Organizing the ad hoc committee also exposed gaps in existing research infrastructures that have since highlighted new areas for reform. In specific, the pandemic underscored the need for a trial registry that could inform investigators about the status of ongoing trials so as not to duplicate research efforts and to allow prospective participants to search available trials for which they may be eligible. A better coordinated REC appeal process was also identified as an unmet need in the current system. Investigators whose trials are denied at one REC may resubmit their application to another REC until they receive a desirable outcome in a practice commonly described as ‘REC shopping.’ The informant could not produce empirical data evidencing the extent to which unsuccessful investigators shop for RECs but reported anecdotally that REC shopping is an increasing issue in the Chilean context. A fair appeals process would incentivize investigators to use established institutional channels to have their applications reassessed by another REC. Such a process accentuates the earlier need to improve inter-REC transparency as quality appeals are contingent on previous RECs sharing their review decisions.

The same opportunities identified for strengthening REC-to-REC trust were also cited as primary reasons why an extra-jurisdictional approval system was not feasible in Chile. Since trust is lacking even between RECs that are accredited by the same body, the informant thought it unlikely that the necessary degree of trust could be forged between RECs from different countries. Institutional bias and its impacts on fair benefit distribution is also a worry. RECs from well-resourced institutions are at measurable advantage in meeting the human and material resources required to maintain good standing in a hypothetical system of ethics review mutual recognition. Ethics review mutual could inadvertently create a tiered

system of RECs where investigators disproportionately elect reputable institutions to submit protocol applications.

PAHO

The country-specific experiences summarized above were corroborated and expanded in a series of online webinars. Throughout November and December 2020, PAHO sponsored six virtual dialogues with regional REC members and administrators around the unique research ethics review considerations for studies investigating Covid-19. The sixth dialogue in the series (December 9th, 2020) summarized key lessons that stakeholders learned in adapting REC procedures to meet the research demands during the public health emergency.

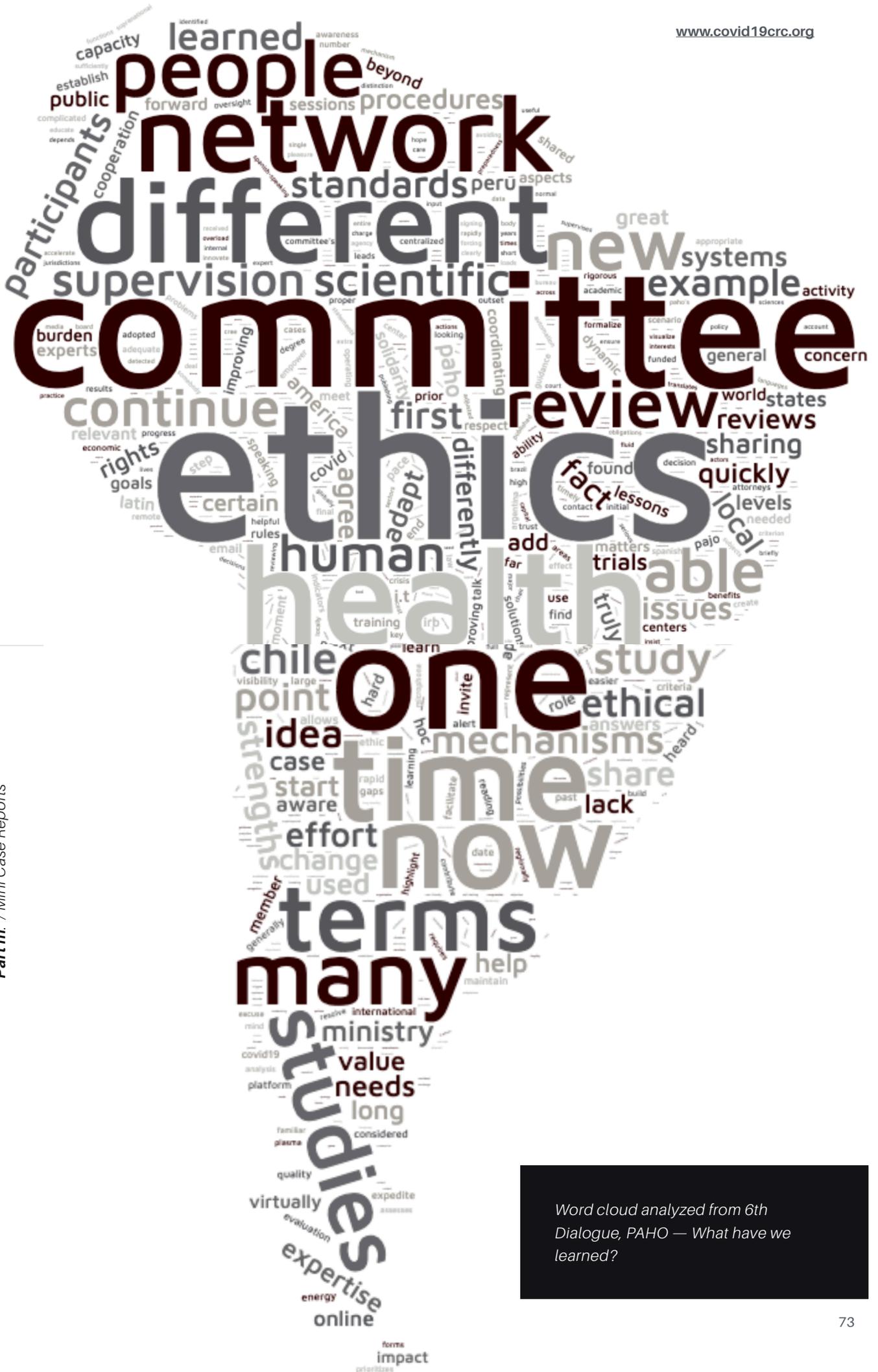
Panelists participating in the sixth dialogue series [85] unanimously agreed that a collaborative 'network' of RECs in the region would allow local RECs to share experiences and address common ethical issues together. One panelist reported Fogarty International had at one time funded such a network among RECs affiliated with institutions in the English-speaking Caribbean. The network is no longer active but was there was interest in applying the network model to facilitate inter-regional collaboration across the Spanish-speaking Caribbean and other South American countries. This network should operate at a supranational level that could implicitly involve governing bodies in collaborative efforts, according to one panelist's perspective [86]: "We need to have a supranational network and this has to be in our entire region because it will also mean our governments become visible and have an effect on recognizing the importance of [RECs] and the work we do in protecting human rights" [87]. Diverting resources from local RECs to organize a supranational network, however, requires additional resources that one panelist was uncertain some countries could afford.

Panelists all reported the state of emergency triggered their RECs to streamline review procedures for Covid- and non-Covid related research. They described various strategies their RECs used to make these procedural changes and were

[85] This series corresponds to consultative activity #15. See **Annex 3** for full list of activities.

[86] Researchers participating in the November 30th PAHO dialogue furthermore emphasized the need for networks in the research community to share information, reduce duplication and learn from the successes and failures of other Covid-related protocols (**Annex 2**).

[87] Excerpt from a dialogue originally conducted in Spanish with professional English translation.



Word cloud analyzed from 6th Dialogue, PAHO — What have we learned?

unanimous in their belief that efforts to streamline should never lessen the quality of the review itself.

When questioned about how the emergency REC procedures and the proposed REC network could be achieved post pandemic, one panelist representing the Chilean experience noted that information technology would play an especially critical role in both regards. In specific, universal internet access and a computerized submission and review platform could support remote work and facilitate a more transparent review process with researchers.

The streamlined procedures were deployed effectively in many countries throughout the region as contingency plans in response to the emergency. Sustaining the procedures throughout the duration of the pandemic—now nearing a full year—has taken a toll on REC professionals. Another panelist reflected on the ways their centralized committee felt especially burdened in adapting their processes to monitor ongoing protocols that obtained accelerated review. Using professional translation, the panelist observed originally in Spanish, “Regarding monitoring, we are not well adapted

to the new situation if we work with centralized committees. The committee rather than researchers absorb this burden. There comes a time when the ability to adapt becomes very burdensome and we need to take this into account for the future if we maintain the same working conditions and maintain the same rigorous approach [to reviews] from beginning to end.” The President of the Ad Hoc Scientific Ethics Committee for Scientific Research on Covid-19 Vaccines of Chile elaborated on the relationship between centralized review and monitoring. Namely, local RECs should be given the responsibility to monitor studies conducted at their site without prejudice to an approval granted from a REC elsewhere. Clear communication and division of responsibilities is key to supporting a centralized system.

Several panelists discussed the effects that streamlining REC processes/ procedures have had on overall workflow. For instance, the pandemic forced many Ministries and local RECs to develop new workflows to fast-track reviews for Covid-related research, commonly referred to as “expedited” or “accelerated” reviews. In the

process of doing so, RECs and governing authorities in the region not only demonstrated that reorganization of internal REC structures was possible but that the reforms were more effective and the level of collaboration among RECs quite inspiring.

Many of the panelists agreed the procedures could be continued post-pandemic with adequate resources. This was particularly true in Peru, Chile and in the English-speaking Caribbean according to invited panelists with representative REC experiences from those countries. One Argentinian panelist, for example, reaffirmed that internal mechanisms to streamline multisite reviews were exhausting to implement but could be sustained post-pandemic if governing authorities committed to resource RECs with the same level of commitment demonstrated during the emergency. There is reason for optimism that this level of support could be achieved. Indeed, one panelist commented the pandemic

made the scientific and social value of REC work more visible to the research community, Ministries of Health/ Science and to the public.

Regarding what could be done differently to prepare for the pandemic, one panelist emphasized forging a stronger sense of solidarity, cooperation and communication within, and between RECs from the region and the world:

Among those of us who are taking on the lions share of the work, there is an unspoken solidarity that we need more of around the world. The idea of sharing the workload and sharing expertise, sometimes called research ethics equivalency having REC that represent different countries or allowing one country to represent the reviews of another or to review jointly particularly because we have so few resources and particularly because in the time of a pandemic or public health emergency of any sort we need to act quickly and we need to work together and share resources. That's what I would like to see, but of course there are many challenges to that happening [88].

[88] Cheryl Cox Macpherson, Director of the CREEi Research Ethics Training Program for the Caribbean, and member of the Anglo Caribbean Bioethics Association, Grenada. PAHO 6th dialogue, "What have we learned so far?" Available at <https://www.youtube.com/watch?v=f3TY3vkWE9g&feature=youtu.be> (last accessed 12/29/20).

Case study 4

Kazakhstan, Azerbaijan, Belarus, Armenia, Kyrgyzstan, Uzbekistan and Ukraine [89]

Since the collapse of the Soviet Union, capacity building and development of research ethics infrastructure has varied considerably across post-Communist countries in Central and Eastern Europe and Central Asia regions. An interview survey with Fogarty International alumni reported that national and institutional commitment to research ethics, as well as dearth in expertise to adequately staff REC were identified as two leading challenges to growth in the region [90]. To date, Kazakhstan, Kyrgyzstan, Belarus and Ukraine have national legislation requiring REC review of human research protections. National priorities to increase both domestic and foreign investment in pharmaceutical research and development were driving factors for the legislations.

Stakeholders involved in research ethics management within this Central Asian caucus met to discuss the ethical and regulatory issues of health research in the context of Covid-19 in a special forum organized by the Kazakhstan Ministry of Health and affiliate NGO 'Forum of Ethics Committees' (see **Annex 3**).

Representatives of national bioethics committees in Russia, Kyrgyzstan, and Ukraine, as well as Ministries of Health in Uzbekistan and a member of the Good Clinical Practice Alliance were in described ongoing efforts to support multisite trials, among other types of research in the region. The representative from the Ukraine discussed the significant effects Covid-19 had on REC operations, including the ability to transition REC personnel to remote work and the challenges of quarantine on this work; lack of an electronic submission system forced face-to-face interaction among some REC members; intense pressures local REC experienced to hasten review processes given the urgency of the public health crisis.

Representatives of all member countries in the Forum reported following WHO

[89] Information used to inform this case study emerged from consultative activities #10 and #13. See **Annex 3** for full list of activities.

[90] Strosberg M, Gefenas E, Loue S, Philpott S. Building Research Ethics Capacity in Post-Communist Countries: Experience of Two Fogarty Training Programs Martin. *J Empir Res Hum Res Ethics*. 2013;8(5):28-39. doi:10.1525/jer.2013.8.5.28. oet. 4600;9(2):74-83.

and UNESCO Statements to guide adaptations of REC procedures, particularly in relation to the SOLIDARITY trial. Although the trial did not receive ethics approval among some RECs in the region, many stakeholders confirmed that Recommendation 7 of the UNESCO Statement on Ethical Considerations for Covid-19 Responses and Recovery motivated temporary reform to accelerated review procedures in their respective countries.

[91].

Leadership within the Ministries of Health in the countries listed above are actively involved in efforts to support legislative development for human research protections in countries without them, namely in Azerbaijan. Here, ad hoc RECs reviews are conducted at the few large academic medical centers under a mandate from the Azerbaijani medical association. Two policy makers representing REC experiences in Kazakhstan and Azerbaijan shared the view that a “Soviet legacy of authoritarian regulation” [92] and governance style is reflected in the bureaucratic, top-down approach to REC structure and review many countries in the region inherited. It was thought that the Ministry of Health in Azerbaijan was especially keen to preserve this dynamic in recent negotiations about adopting national legislation for human research protections. Since so few institutions perform REC reviews, and approvals are granted mostly by a select powerful few, the Ministry of Health in Azerbaijan has been reticent to replace the current system with legislation that could disrupt the de facto centralization and control the system now affords.

[91] UNESCO Statement on Ethical Considerations for Covid-19 Responses and Recovery, Article 7: “There is already an explosion of research activities and clinical trials to find a cure and a vaccine for COVID-19. Most of these activities occur on a local level. However, at the same time, there is a need for coordination of international efforts and the formulation of a common understanding of ethical review processes. In the context of the COVID-19 pandemic, the World Health Organization (WHO) and partners have announced the organization of a study coined “SOLIDARITY” to compare untested treatments throughout several countries since multiple small trials of possible coronavirus therapeutics approaches with different methodologies may not provide the evidence needed. Accelerated review and approval of novel approaches may become necessary so as not to delay research during this public health emergency. An oversight committee for responsible research during this pandemic on a global level needs to be urgently created. Such a committee should gather the results obtained on local levels and coordinate/share the review procedures, which may be exceptional in pandemics and may not follow the regular rules. In this regard, guidance for the local ethics review boards is critical. It is understandable for new practices to be accommodated in the emergency context, considering the nature of the global threat. However, such decisions need ethical justification (see WHO [Guidance for managing ethical issues in infectious disease outbreaks](#) (2016)). Ethical principles should not be transgressed but may be adjusted to exceptional circumstances.” <https://en.unesco.org/inclusivepolicylab/e-teams/ethical-considerations-covid-19-responses-and-recovery/documents/unesco-ibc-comest-statement> (Last visited on 12/20/20).

[92] Famenka A. Ethical review of biomedical research in Belarus: Current status, problems and perspectives. *Rev Rom Bioet.* 4600;9(2):74-83.

Despite this view, stakeholders were optimistic that existing collaboration among REC professionals could support ethics review mutual recognition at least within countries in the region. The common historical, political and economic roots of countries in this region was perceived as both a strength and weakness when asked about whether and how procedural equivalence and reciprocity could be achieved. Whereas both stakeholders reified the need to maintain local autonomy in final review decisions, they identified a possible opportunity to build reciprocity among RECs that mirrors a common economic union that already exists between these countries. Lack of trained personnel and mature REC infrastructure—e.g. adoption of national legislation, formal Ministerial mandate institutionalizing RECs and a system of REC accountability—were among the weaknesses that could prevent some countries from meeting the standards of equivalence required for ethics review mutual recognition. Here too, presents an opportunity for countries with less developed infrastructures to adopt the standard operating procedures, policies and format of RECs in neighboring countries, effectively creating a twin regulatory environment from which procedural equivalence and reciprocity could be established.

Part IV.

OPPORTUNITIES & CHALLENGES

Of Ethics Review Mutual Recognition,
Adoption And Implementation



Window to Reciprocity / Fedor Raki.

Determining that two RECs apply equivalent procedures might entail broad agreement on the scope of REC roles, responsibilities, characteristics and procedures that lead to trustworthy, quality ethics review.

Ethics review mutual recognition is conditional on first determining *procedural equivalence* in the standards, processes and SOPs that two or more REC share, then *establishing reciprocity* between their governing authorities. Determining that two RECs apply equivalent procedures might entail broad agreement on the scope of REC roles, responsibilities, characteristics and procedures that lead to trustworthy, quality ethics review. Namely, RECs must appeal to normative principles of research ethics to protect the rights, interests and welfare of participants and are outlined in international declarations and conventions; that RECs should comprise of members with appropriate scientific, medical, and ethics expertise as well as community representation; and finally, that RECs maintain independence and transparency with the research community. WHO Standard Guidelines (2000, 2011) were mentioned most frequently in discussions with informants about the legislative history of human research protections in their countries, and in helping RECs adapt their operations to manage the volume and complexity of Covid-19 protocol reviews during the pandemic.

Adherence to most, but not all principles and practices of RECs outlined in international guidelines (such as those presented in **Annex 1**) raised some questions during the consultative activities about the extent to which procedural equivalence could be satisfied. For instance, could two countries that adopt different ages of majority for research involving children be deemed procedurally equivalent, or in the case of countries that categorically disallow certain study designs? The determination of procedural equivalence could be premised on the fact that both the reliant and local RECs implement special protections for vulnerable populations participating in research even though the discreet age that distinguishes a minor from an adult participant differs. On the other hand, the review procedures for pediatric versus adult research based on the age of majority, or when a protocol adopts a prohibitive study design could differ too substantially that the outcomes render the procedures inequivalent between reliant and local RECs. Given these nuances, it is plausible that procedural

equivalence for ethics review mutual recognition could be met for some research if shown there was i) international consensus on the foundational standards for RECs, and ii) these standards were broadly adhered to as reflected in national, regional and local REC guidelines and policies. Assuming compliance with national, regional and local guidelines at the independent REC level, the aforementioned conditions generally hold true based on analysis of the environmental scan results and from country-specific experiences learned during the consultative activities. The harmonizable elements which could yield procedural equivalence can be protocol- or committee-based. They were identified based on those procedures and assessments informants reported were common to all reviews regardless of study type (**Box 9**).

Box 9 *Harmonizable elements at the protocol and committee levels to support coordinated reviews for multinational studies based on feedback from consultative activities*

Protocol-based

- *Assessment of consent disclosures, including relevant benefits and risks of participation; summary of study objectives and procedures; participant compensation (if any).*
- *Evaluation of the study design and scientific value*
- *Confirmation of investigator's expertise and experience*
- *Fair participant selection*

Committee-based

- *Appropriate accreditation of the REC or official recognition/mandate from a governing authority*
- *Independence of the REC and free from financial conflicts of interest related to the institution, researcher or study sponsor*

Missing from the protocol-based elements is a harmonizable process for assessing study benefits and risks. Informants reported diverse risk assessment approaches, namely involving Covid-19 vaccine trials. The dynamic nature of the pandemic and evolving molecular understanding of the novel SARS-CoV-2 made precise assessment of research risks difficult in the early months of the outbreak. Informants explained that foreseeable risks to participation in a multinational vaccine trial differed significantly depending on availability of ancillary care resources, healthcare personnel and standard therapies, all of which could be exceedingly limited during the crisis. Two informants shared their experiences reviewing the WHO Solidarity Trial to exemplify the differences in risk assessment. RECs adapted their assessment as more became known about the virus' transmission and the physiological factors conferring higher risk of infection and death.

Rather, the intractable barrier to operationalizing ethics review mutual recognition at present lies in meeting the second condition: *establishing reciprocity*. Neither the urgency for, nor the increased volume in multinational research collaboration in response to the Covid-19 pandemic significantly lowered this barrier according to informants engaged for this report.

Key mediating factors influencing whether, and how to pursue a multilateral system of mutual recognition in ethics review differed extensively by region. The chief barriers to *establishing reciprocity* identified primarily through consultative engagement can be summarized in the following themes a) lack of conceptual clarity on the protected roles of local RECs, the b) heterogeneity of regulatory environments within which RECs currently operate and c) perceived inequities in North-South research collaborations.

Protecting the roles and authorities of local RECs

Conversations with informants reinforced the prevailing view that decision-making authority to approve any study involving human participants remains with the local REC. Many informants agreed that the volume of multisite/multinational studies related to Covid-19 stressed local REC resources and acknowledged that some processes became overly bureaucratic. When asked to describe how RECs modified their pre-pandemic processes to meet the demand for more multisite studies during the crisis, every informant reported centralizing some component of the review with local authorization. Yet, most informants expressed grave

concern that a proposed system of ethics review mutual recognition would remove local input entirely from the decision process absent full board review of the multinational study from a local REC. Engagement with REC stakeholders during the consultative activities suggested there remains conceptual ambiguity about the harmonizable elements of ethics review recognition. Namely, ethics review mutual recognition harmonizes at the level of procedure, not substantive ethical deliberation. Informants were furthermore unclear how local input would be integrated into the final authorization of a multinational study at a participating research site, the roles of local RECs in providing this input, and the extent of community engagement.

Regulatory organization of RECs

The complexity of regulatory environments within which RECs embed were also a predominant theme that informants invoked in their reasons why establishing reciprocity was unrealistic at best and, at worst, incompatible with regulatory sovereignty of human research protections in their respective countries. Brazilian informants explained, for example, how establishing reciprocity would require concordant oversight of researchers as well as healthcare professionals because RECs are co-regulated with healthcare delivery in Brazil. Research and healthcare systems are similarly embedded in Nigeria and Ghana, where informants also indicated challenges in adapting one system of governance for two otherwise distinct professional sectors within the Ministry of Health.

A comment on the social construction of 'reciprocity' as it relates to cooperation between regulated bodies is worth noting here. Scholars have previously commented that the litigiousness of a regulatory environment can be projected onto the norms, actions and rules governing REC activities. The litigious character of a regulatory regime is frequently cited in policy debates critiquing how local RECs preserve institutional interests and protect themselves against legal liability for research harms incurred when a study was approved elsewhere [94]. Establishing reciprocity can therefore take on predominantly legalistic and contractual meanings in these environments. RECs and their governing authorities are conditioned to look to the law legitimize reciprocity, and which is typically manifest in reciprocal agreements negotiated between the reliant and local RECs

[94] Townend D, Dove ES, Nicol D, Bovenberg J, Knoppers BM. Streamlining ethical review of data intensive research. *BMJ*. 2016;354(August):1-2. doi:10.1136/bmj.i4181.

for multisite reviews conducted domestically [95]. Townend and Dove liken the responsibility of REC members to those in public office: “Even though the (principal) issue at hand with RECs is ethics rather than law, and the appointment is non-stipendiary, the activity of research ethics review and monitoring constitutes an exercise of an accepted public office, and as such a number of expectations of administrative law - probity in office - would seem to follow” [96] (Page 74).

Research impact, precedent and benefit sharing, in contrast, were among the most influential factors shaping perceptions of reciprocity among stakeholders consulted from the English-speaking Caribbean, Ghana and Nigeria, primarily [97]. These factors are elaborated in the subsequent section on equity relations in North-South research collaborations.

Equity relations in North-South research collaborations

Nearly all authors of published articles, key organizations and institutional policies supporting ethics review mutual recognition are based in North America and Europe. This finding, while inconclusive on its own, gives pause for reflection on how the problems of multinational review are framed, from whose perspectives, and what values and priorities are being served in advancing ethics review mutual recognition. Many informants expressed healthy skepticism to this effect during individual meetings. The efficiency-driven motives of ethics review mutual recognition were not in general perceived to enhance equity relations between reliant REC and local communities. They instead precipitated fears that ethics review mutual recognition might further limit opportunities for meaningful engagement and community prioritization in REC decision-making in North-South research collaborations, in particular.

The consultative activities affirmed that centralizing elements of the review workflow perturbs at least three embedded relationships in the research institution, namely between the reliant or centralized REC and the local i) REC, ii) researchers, and iii) communities. **Figure 6** shows where these perturbations lie within a prototypical REC workflow. If pursued, the future scalability of mutual recognition would require at a minimum, equal representation from research

[95] United States Office of Human Research Protections typifies such an environment.

[96] Townend D, Dove ES. Approaching Ethics Review Equivalency through Natural Justice and Sounding Board Model for Research Ethics Committees. *Med Law*. 2017;36(1):61-86.

[97] Consultative activities #4 and 11.

systems with highly integrated as well as newly developing REC infrastructure in modeling approaches to establish reciprocity. It would also require representation from stakeholders with experience at all levels of the REC review pipeline e.g. from administrators, committee members, REC policy makers, Ministries of Science/Health and researchers.

Moreover, select informants critiqued the ways that standardizing REC procedures in line with values, priorities and norms of highly resourced research contexts could be construed as imperialistic. For them, the basic problem confronting multinational ethics review was, as Christakis articulates, “which ethics should govern transcultural clinical research?” [99]. The theoretical frameworks that produce REC procedures and which ethics review mutual recognition aims to standardize skew inevitably toward principlism and other predominantly Western-centric paradigms of ethics. Informants objected particularly to the ways ethics review mutual recognition could further instantiate the ethical paradigms of powerful countries through standardizing procedures. Implicit in these objections was that power differences would lead organizations to disproportionately peg REC equivalence to standards that aligned with jurisdictions in the North at the exclusion of alternative, transcultural paradigms of research ethics, including indigenous ways of knowing, traditional Chinese medicine, and Ayurveda to name but a few examples.

Barchi et al. underscore the resource and power asymmetry between RECs in the Global North and South. They posit the current environment for U.S. oversight of international research is “fertile terrain for mistrust” when “U.S. IRBs assume that host-country IRBs are unable to conduct adequate reviews, and the latter are skeptical that U.S. IRBs will be sensitive to their national concerns or place the needs of a local population above the imperatives of the U.S. research enterprise” [100]. The authors identify four thematic challenges in fostering mutual recognition, including lack of familiarity with the research setting, procedural challenges, limited review capacity, differences in review criteria and lack of trust. They propose a continuum of approaches that range from entirely

[98] Klitzman R, Pivovarova E, Lidz CW. Single IRBs in multisite trials questions posed by the New NIH Policy. *J Am Med Assoc.* 2017;317(20):2061-2062. doi:10.1001/jama.2017.4624

[99] Christakis NA. Ethics are local: Engaging cross-cultural variation in the ethics for clinical research. *Soc Sci Med.* 1992;35(9):1079-1091. doi:10.1016/0277-9536(92)90220-K.

[100] Ibid. 19, Page 4.

independent to entirely collaborative to streamline multinational reviews of studies that involve collaborators from resource-rich and poor countries [101].

REC coordination and communication

Significant issues in coordination and communication between reviewing RECs, local RECs and researchers were unanimously cited by informants with experience reviewing multisite/national studies related to Covid-19 in countries with and without centralized models of ethics review. Because communication was perceived to be so poor even among RECs from the same region, informants expected these communication challenges to scale if RECs from different countries were required to collaborate as part of a system of ethics review mutual recognition. Two articles identified in the environmental scan spoke to this issue directly. In a combined documentary review of special standard operating procedures for public health emergencies and interview study of Jamaican REC stakeholders, one researcher determined “hubris is likely to be an issue as each research ethics committee would not wish to regard itself as being subservient to another, or to give up control over its current areas of jurisdiction” [102].

Saxena et al also corroborate the negative effects that territorial local RECs may have on communication and coordination. Since RECs do not proactively communicate with other RECs evaluating the same protocol, the authors claim there is a

missed opportunity for a mutual learning process among ethics committees from different contexts. Proactive communication would offer the opportunity to build collaborative partnerships among the committees, beyond partnerships between clinical researchers. Such committee partnerships could provide a space where agreement is reached on common ethical practices and standards, e.g., on informed consent, on indemnity and on harmonization of administrative requirements, where more efficient models and schedules for international ethical reviews are built and the submission schedule is optimized (e.g. parallel or consecutive submission, differentiation between detailed and expedited review etc.) and where cases of conflicting opinions in different countries are resolved [103].

[101] The proposal for ethics review mutual recognition evaluated in this report is situated closer to the collaborative pole of this spectrum.

[102] Aarons D. Research in epidemic and emergency situations: A model for collaboration and expediting ethics review in two Caribbean countries. *Dev World Bioeth.* 2018;18(4):375-384. doi:10.1111/dewb.12157.

[103] *Ibid.*, 47 Page 529.

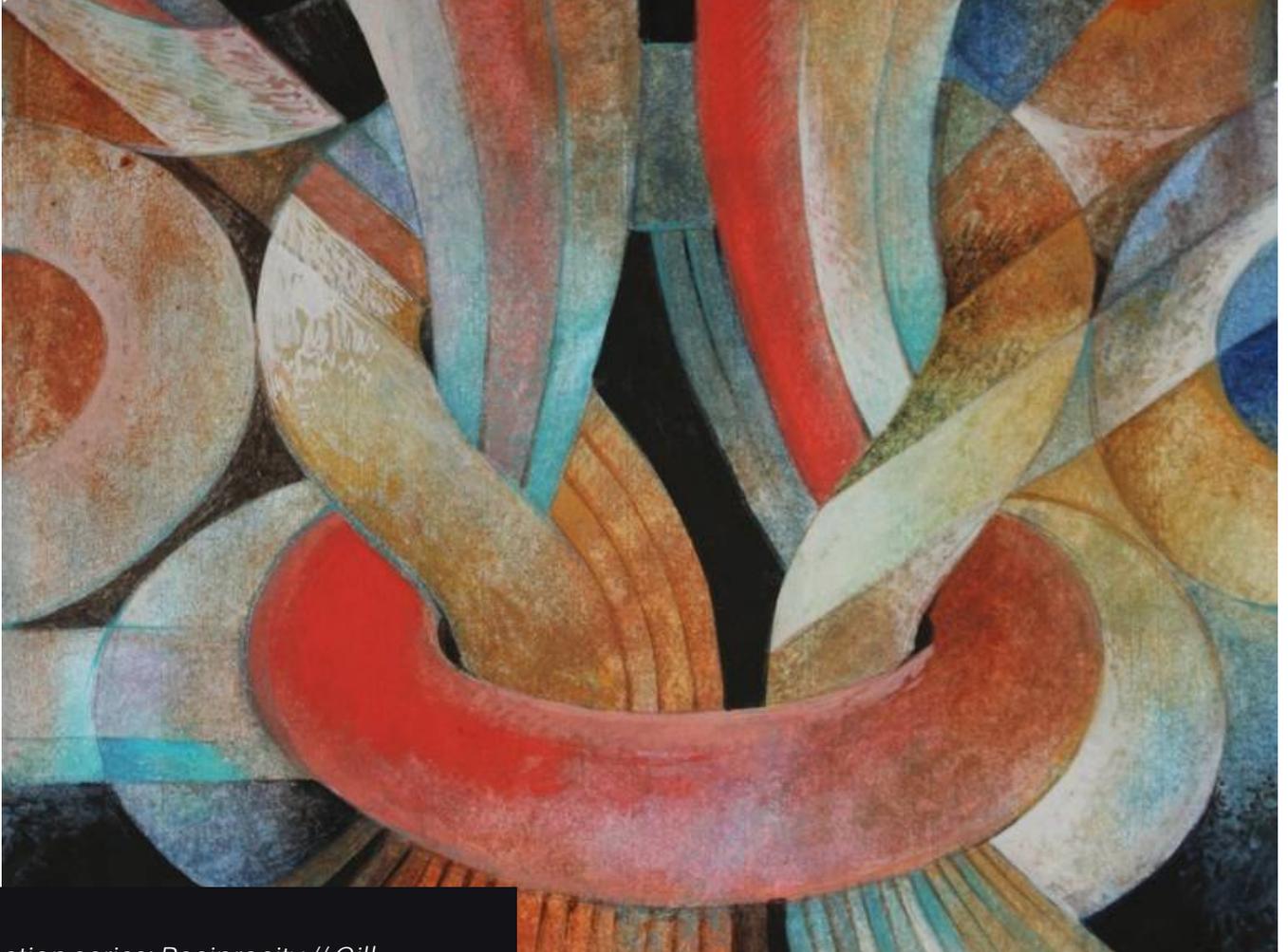
Improved coordination and communication were also areas of reform that have been supported by North-South research funding collaborations, including from the Fogarty International Institute [104]. Continued efforts to strengthen communication, reporting and collaborative partnerships among RECs and their governing authorities across countries is a necessary first step to promoting multinational REC harmonization.

[104] Investigators involved in a collaborative project between the Public Health Foundation of India and Fogarty International launched an internal audit of the multinational ethics review process and piloted a parallel review system. The authors published five recommendations to promote seamless, thorough and efficient review of collaborative research, including ways to “increase communication among multiple [ethics review committees] responsible for review of US sponsored research conducted in other countries, perhaps through an annual meeting of the chairs of the [ethics committees] from collaborating countries; and to develop a system of coordination among investigators and local ERCs. Somsekhar H, Prabhakaran D, Tandon N, Rousselle R, Fisher S, Stein AD. Review of multinational human subjects research: experience from the PHFI-Emory Center of Excellence partnership. *Indian J Med Ethics*. 2012;9(4):255-258. doi:10.20529/ijme.2012.086.

Part V.

NEEDS IDENTIFIED TO AUGMENT TRUST & COOPERATION

Among International RECs



Perspectives shared in this report point to a growing asymmetry in procedures for conducting multinational reviews.

Summary of findings

The Covid-19 pandemic was an important catalyst for reflection among REC actors in the regions surveyed for this report regarding the effectiveness of current review models for multisite research. The pandemic also served to ‘stress test’ these models under mounting pressure to inform quick, but well-evidenced decisions about public health responses and management. In countries working to attract research investment through fortifying REC capacities, and in countries hoping to correct the gross underrepresentation of diverse populations in biomedical research, the pandemic has been an unique opportunity for taking the temperature of existing REC mechanisms and consider improvements where applicable.

Perspectives shared in this report point to a growing asymmetry in procedures for conducting multinational reviews. There is universal agreement that reviews should be conducted by competent experts, with community representation and local interests in mind, and in a transparent, independent manner. In contrast, there is considerable divergence in the extent to which ceding reviews in part or in whole to centralized RECs threatens the ability of local RECs to protect community interests. All models of ethics review mutual recognition summarized in this report aim to balance the need for quality and expedience in multinational reviews based on shared REC standards while preserving local input required to ensure a given study can be conducted effectively at the proposed site.

Findings from the consultative activities suggest, without being conclusive, that recommendations guiding how to operationalize ethics review mutual recognition are premature at this juncture. Rather, improving trust among RECs is a pre-requisite to better functioning ethics review systems generally, and towards fostering inter- and intra-national research collaborations that are equity-enhancing. Despite overwhelming skepticism of ethics review mutual recognition as a foreseeable policy option, informants identified ways RECs across countries could foster greater trust. It was widely held among informants that trust-building

was an incremental step in the right direction towards raising the standards of multinational reviews everywhere. What follows are practical points to consider in taking this initial step based on experiences, perspectives and needs shared during the consultative activities.

The practical points situate equity at the center of their REC trust- and capacity-building outcomes. The practical points should thus be interpreted as approaches RECs can take to limit the harms created by asymmetries in power that can evolve when researchers from resource-rich and poor contexts collaborate during the pandemic.

Practical points

1. **When RECs coordinate, they engage in mutual learning, build collaborative networks and better understand the common ethical practices and standards of research ethics in other social, cultural and political contexts.** Greater understanding of the procedures and models of review facilitates reflexive practice and can strengthen solidarity among REC actors who share in the responsibility to gatekeep

rigorous science and play an active role in the public health response to the crisis.

2. **Making prior REC decisions available for review by participating RECs is not unique to multinational studies nor to studies related to Covid-19.** The recommendation

is furthermore consistent with Standard 6.6 in WHO Operational guidelines and should be reinforced in future guidance to facilitate multinational review. Informants testified that improved transparency and communication between reviewing RECs either within, or external to the national system is a recurring need that has not resulted in substantive action. REC personnel from jurisdictions where transparency between RECs is legislatively mandated likewise shared this view.

3. **Develop and maintain a registry of REC committees reported to the WHO on an annual basis.** The registry could serve as a valuable resource for REC members and institutions to facilitate communication and collect demographic data on REC. Minimum reporting

requirements could allow for systematic study of REC volume and operations and support empirical-based assessments of centralized review for multinational studies. The registry would also enable researchers to identify international collaborators, and proactively familiarize themselves with the regulatory and legislative environments within which they hope to conduct their research. This requires infrastructures that rely on both soft and hard-ware to prop them up. Researchers should also be encouraged take on some of the responsibility for consistent reviews by sharing prior REC experiences and decisions if such a policy does not exist at the REC to which they are applying.

4. For countries that meet, and sustain the procedural equivalence determination, reciprocity should be established and recognized bilaterally. Bilateralism distinguishes ethics review mutual recognition from other regulatory models where a designation of equivalence only flows one way i.e. *from* a determining body to a corresponding body, but not the reverse. This feature is critical to raising REC standards globally, and to addressing concerns about inequity that can arise when

multinational collaborations involve countries with better- and less developed REC infrastructures. It also facilitates more equitable benefit sharing.

- 5. Clearly delineate responsibilities between reliant RECs and local RECs.** Both RECs retain responsibilities to protect human participants in a system of ethics review mutual. Local RECs, for example, will be relied on to report protocol issues, adverse events, manage conflicts of interests, hold researchers accountable and ensure adequate member training. Explicit terms of reference should outline what responsibilities rest with whom and how conflicts are resolved.
- 6. Regional experiments to centralize multinational reviews, such as through AVAREF or under the EU Clinical Trials Regulation, should be empirical studied and evaluated.** Numerous studies have investigated quality and performance indicators of multisite/national REC reviews, including time from submission to decision, review cost, as well as the frequency and general type of requested changes to the protocol. Claims that ethics review mutual recognition and related models will improve procedural efficiency and streamline processes remain, however,

largely theoretical. Regional efforts to implement standardized, concurrent review of a multinational study among RECs based in collaborating countries should be treated as policy experiments from which to learn and compare review systems. Empirical data should be systematically collected and analyzed on the review process, implementation and outcomes. Interdisciplinary researchers with expertise in social science and statistical methods should be equally engaged in this evaluation given the complex social, political and economic dynamics that the mini case studies this report briefly highlight.

Future Directions

Issuing WHO guidance on how to operationalize ethics mutual recognition is, at present, premature based on broad opposition from informants who contributed to this report. Instead, several practical points are offered to help RECs limit the harms created by asymmetries in power that can evolve when researchers from resource-rich and poor contexts collaborate during the pandemic. In addition, the WHO could consider the following future directions in advancing the theory and practice of ethics review mutual recognition.

Any future attempt to promote mutual recognition must therefore

be collaborative, cooperative and proceed from a bottom-up approach. Commitment to health services and policy research that adopts this participatory approach is needed to empirically test the various models of mutual recognition presented herein. The exceptional circumstances brought on by the public health emergency will serve as a catalyst for some, and deterrent for other countries to experiment with centralized REC review models in this regard.

REC stakeholders on the frontlines of reviewing multisite/national Covid-19 studies should be encouraged to widely disseminate and share their experiences adapting REC procedures during the crisis. Importantly, many of the special SOPs and strategies adopted to accelerate multisite/national reviews during this pandemic were taken directly from guidance documents and lessons learned from previous pandemics, namely from the Ebola and H1N1 outbreaks. The WHO Health Ethics and Governance Unit, in collaboration with the Global Coalition, International Association of Bioethics, UNESCO and others should **co-organize a global summit of bioethics committees** to facilitate international dialogue and provide a shared platform for

exchange.

Conclusions

The Covid-19 pandemic—and public health emergencies generally—shines a bright light on the scientific and social value of collaboration. Scientific progress needed to reestablish social order following such emergencies is possible only when individuals agree to participate in research and development. For this reason, Article 27 of the UN Declaration of Human Rights protects the rights of citizens to benefit from science, and of scientists to be recognized for their contributions. Public health emergencies are also among the rare phenomena in which time can be directly proportionate to lives saved, and lost. Timely, quality and effective ethics review and continuing oversight are necessary to maximize these benefits while ensuring the rights, dignities and welfare of individuals are universally respected. RECs play critical gatekeeping and balancing roles in this regard. Enhancing REC capacities to effectively, efficiently and equitably review collaborative research studies has direct implications on the quality of the science and on the experiences of participants who help to inform it.

This report clarifies the organizational and ethical bases of a system of extra-jurisdictional review and approval for multinational, collaborative studies involving human participants. It adds conceptual clarity to the literature regarding such a system, termed ethics review mutual recognition, by defining its two constituent elements: determining procedural equivalence and establishing reciprocity. Ethics review mutual recognition requires, but is distinct from models of centralized REC review that have been implemented with success in many countries and summarized in this report. The models identified through the environmental scan and consultative activities centralized REC review in whole or in part namely by study type, participant population, and geography.

No national, regional or local regulation/law/policy/guideline as yet mutually accepts without additional review a REC decision provided by a competent, qualified REC from another jurisdiction for a multinational study. The costs and benefits of a supranational system of ethics review and approval are largely theoretical. The report captures perspectives of REC stakeholders across low- and middle-income countries using the Covid-19 pandemic as a specific lens to explore opportunities and barriers to meeting the conditions of a proposed, but not yet operational system of ethics review mutual recognition. The series of

consultative activities lend evidence that political sensitivities couched in local ethics review of multinational, collaborative studies are substantial but not insurmountable in meeting the first condition: *determining procedural equivalence*.

Recent capacity building efforts among REC informants in former Soviet-controlled nations in Eastern Europe and Central Asia also demonstrate promise in establishing reciprocity at least at a regional level. Regional interoperability in REC review could be achieved if mutual recognition were built prospectively into the legislative frameworks of countries where REC policies are currently being negotiated. Countries with more developed REC infrastructures have taken active roles in helping neighboring countries mirror such development. Consultative activities with REC stakeholders in Kazakhstan and Azerbaijan highlight this type of REC 'mentoring' that could in the future lay a strong foundation for ethics review mutual recognition in the region.

The intractable barrier to operationalizing ethics review mutual recognition at present lies in meeting the second condition: *establishing reciprocity*. Neither the urgency for, nor the increased volume in multinational research collaboration in response to the Covid-19 pandemic significantly lowered this barrier according to informants engaged for this report. Lack of conceptual clarity on the protected roles of local RECs, the heterogeneity of regulatory environments within which RECs currently operate and the perceived inequities in North-South research collaborations were found to be key mediating factors precluding reciprocity. More engagement with local RECs, their governing authorities, researchers and ethicists is needed from countries with and without centralized systems for multinational reviews to better understand why. It is hoped that this report provides preliminary insight into some of these questions, in particular where the key barriers and opportunities lie for ethics review mutual recognition.

The report's findings highlight a policy tension where the promises of a nimble ethics review system must be juxtaposed against deep mistrust of the research enterprise based on human rights abuses. REC stakeholders charged with protecting participants implicated in this history, particularly in the Global South are thus unlikely to cede oversight or governance role. The more coordination that can be achieved between RECs at levels most proximal to the prospective participant populations would go a long way to minimizing the concerns about

'helicopter' reviews i.e. the perception that decisions are being imposed upon local sites without proper engagement or input.

Supporting countries in building coordination and adaptive capacities to develop streamlined procedures for in-country, multisite reviews during the pandemic is a feasible first step towards regional or international harmonization given that many countries allow for centralized reviews currently. There is cause for optimism in that the pandemic is spurring movement towards procedural integration as several of the consultative activities unveiled. Standard operating procedures for accelerated reviews from the WHO and other regional networks could be highlighted as examples from which ethics review mutual recognition models could draw to enable review efficiency and quality in non-pandemic settings. Empirical assessment of the extent to which these regional initiatives were successful is not only informative for future crises, but necessary if regulatory authorities are to make evidence-based decisions about effective REC policy and harmonization.

Taken together, the consultations and review of the policy literature summarized in this report open the door to further inquiry into how institutions, individual countries, and regions innovate REC systems that are harmonizable, equitable and forward-facing to combat the current Covid-19 pandemic and to promote ethical biomedical research in the years to follow.

Research ethics committees defend human rights and international agencies should act to empower their ability to continue doing so.

—President of the Ad Hoc Scientific Ethics Committee for Scientific Research on Covid-19 Vaccines of Chile

References

- Aarons, Derrick. 2018. "Research in Epidemic and Emergency Situations: A Model for Collaboration and Expediting Ethics Review in Two Caribbean Countries." *Developing World Bioethics* 18(4): 375-84.
- AlShebli, Bedoor K., Talal Rahwan, and Wei Lee Woon. 2018. "Ethnic Diversity Increases Scientific Impact." *Nature Communications* 9(5163).
- Angell, E., A. J. Sutton, K. Windridge, and M. Dixon-Woods. 2006. "Consistency in Decision Making by Research Ethics Committees: A Controlled Comparison." *Journal of Medical Ethics* 32(11): 662-64.
- Ataguba, Ochege A., and John E. Ataguba. 2020. "Social Determinants of Health: The Role of Effective Communication in the COVID-19 Pandemic in Developing Countries." *Global Health Action* 13(1). <https://doi.org/10.1080/16549716.2020.1788263>.
- Atallah, David, Malak Moubarak, Nadine El Kassis, and Sara Abboud. 2018. "Clinical Research Ethics Review Process in Lebanon: Efficiency and Functions of Research Ethics Committees - Results from a Descriptive Questionnaire-Based Study." *Trials* 19(1): 1-15.
- Bambra, Clare, Ryan Riordan, John Ford, and Fiona Matthews. 2020. "The COVID-19 Pandemic and Health Inequalities." *Journal of Epidemiology and Community Health* 74(11): 964-68.
- Barchi, Francis, Megan Kasimatis Singleton, and Jon F. Merz. 2014. "Fostering IRB Collaboration for Review of International Research." *American Journal of Bioethics* 14(5): 3-8.
- Blunt, Jennifer et al. 1998. "Meeting the Challenges Facing Research Ethics Committees: Some Practical Suggestions." *British Medical Journal* 316(7124): 58-61.
- Broude, Tomer, and Yuval Shany, eds. 2011. *Multi-Sourced Equivalent Norms in International Law*. Hart Publishing.
- Burr, Jeri S et al. 2019. "Implementing a Central IRB Model in a Multicenter Research Network." *Ethics and Human Research* 41(3): 23-28.
- Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2018*.
- Christakis, Nicholas A. 1992. "Ethics Are Local: Engaging Cross-Cultural Variation in the Ethics for Clinical Research." *Social Science and Medicine* 35(9): 1079-91.
- Christian, Michael et al. 2002. "A Central Institutional Review Board for Multi-Institutional Trials." *New England Journal of Medicine* 346(18): 1405-8.
- Christie, D. R.H., G. S. Gabriel, and K. Dear. 2007. "Adverse Effects of a Multicentre System for Ethics Approval on the Progress of a Prospective Multicentre Trial of Cancer Treatment: How Many Patients Die Waiting?" *Internal Medicine Journal* 37(10): 680-86.
- Cleaton-Jones, Peter. 2019. "Commentary on 'Measuring the Quality and Performance of Institutional Review Boards.'" *Journal of Empirical Research on Human Research Ethics* 14(3): 200-203.
- Coker, Richard, and Martin McKee. 2001. "Ethical Approval for Health Research in Central and Eastern Europe: An International Survey." *Clinical Medicine* 1(3): 197-99.
- Coleman, Carl H., and Marie Charlotte Bouësseau. 2008. "How Do We Know That Research Ethics Committees Are Really Working? The Neglected Role of Outcomes Assessment in Research Ethics Review." *BMC Medical Ethics* 9: 1052-61.
- Cook, Deborah et al. 2010. "Clinical Research Ethics for Critically Ill Patients: A Pandemic Proposal." *Critical Care Medicine* 38(SUPPL. 4).
- De Crop, Maaike, Alexandre Delamou, Johan Van Griensven, and Raffaella Ravinetto. 2016. "Multiple Ethical Review in North-South Collaborative Research: The Experience of the Ebola-Tx Trial in Guinea." *Indian journal of medical ethics* 1(2): 76-82.
- Davalbhakta, Samira et al. 2020. "A Systematic Review of Smartphone Applications Available for Corona Virus Disease 2019 (COVID19) and the Assessment of Their Quality Using the Mobile Application Rating Scale (MARS)." *Journal of Medical Systems* 44(9).

- Davies, Simeon E.H. 2020. "The Introduction of Research Ethics Review Procedures at a University in South Africa: Review Outcomes of a Social Science Research Ethics Committee." *Research Ethics* 16(1-2): 1-26.
- Department of Health and Human Services. 2018. 82 Federal register *Federal Policy for the Protection of Human Subjects. Final Rule.*
- Dove, Edward S. et al. 2016. "Ethics Review for International Data-Intensive Research." *Science* 351(6280): 1399-1400.
- Dove, Edward S., Bartha M. Knoppers, and Ma'n H. Zawati. 2013. "An Ethics Safe Harbor for International Genomics Research?" *Genome Medicine* 5(11): 1-11.
- Edwards, Sarah J.L., Tracey Stone, and Teresa Swift. 2007. "Differences between Research Ethics Committees." *International Journal of Technology Assessment in Health Care* 23(1): 17-23.
- Emanuel, Ezekiel J et al. 2015. "Perspective Oversight of Human Participants Research : Identifying Problems." *Annals of Internal Medicine* 141(4): 1-2.
- Falb, Kathryn et al. 2019. "The Ethical Contours of Research in Crisis Settings: Five Practical Considerations for Academic Institutional Review Boards and Researchers." *Disasters* 43(4): 711-26.
- Famenka, Andrei. 2011. "Ethical Review of Biomedical Research in Belarus: Current Status, Problems and Perspectives." *Rev Rom Bioet* 9(2): 74-83.
- Friesen, Phoebe, Aimi Nadia Mohd Yusof, and Mark Sheehan. 2019. "Should the Decisions of Institutional Review Boards Be Consistent?" *Ethics and Human Research* 41(4): 2-14.
- Gefenas, E. et al. 2010. "Non-Equivalent Stringency of Ethical Review in the Baltic States: A Sign of a Systematic Problem in Europe?" *Journal of Medical Ethics* 36(7): 435-39.
- Green, Lee A., Julie C. Lowery, Christine P. Kowalski, and Leon Wyszewianski. 2006. "Impact of Institutional Review Board Practice Variation on Observational Health Services Research." *Health Services Research* 41(1): 214-30.
- Hébert, Paul et al. 2009. "Research Ethics Review: Do It Once and Do It Well." *CMAJ* 180(6): 597-98.
- Hedgecoe, Adam M. 2012. "Trust and Regulatory Organisations: The Role of Local Knowledge and Facework in Research Ethics Review." *Social Studies of Science* 42(5): 662-83.
- Hernandez, R. et al. 2009. "Harmonisation of Ethics Committees' Practice in 10 European Countries." *Journal of Medical Ethics* 35(11): 696-700.
- Hood, Maureen N., Brian Gugerty, Richard Levine, and Vincent B. Ho. 2005. "Computerized Information Management for Institutional Review Boards." *CIN - Computers Informatics Nursing* 23(4): 190-200.
- Hunt, Matthew et al. 2016. "The Challenge of Timely, Responsive and Rigorous Ethics Review of Disaster Research: Views of Research Ethics Committee Members." *PLoS ONE* 11(6): 1-15.
- Hunter, David. 2007. "Efficiency and the Proposed Reforms to the NHS Research Ethics System." *Journal of Medical Ethics* 33(11): 651-54.
- . 2015. "Is Research Ethics Regulation Really Killing People?" *Medical Journal of Australia* 202(6): 338-40.
- Jaspers, Patricia, Rob Houtepen, and Klasien Horstman. 2013. "Ethical Review: Standardizing Procedures and Local Shaping of Ethical Review Practices." *Social Science and Medicine* 98: 311-18.
- Jeon, Ju Yeun, Hyeikyung Kim, and Kyung Sang Yu. 2020. "The Impact of COVID-19 on the Conduct of Clinical Trials for Medical Products in Korea." *Journal of Korean medical science* 35(36): e329.
- Johns, Amber L et al. 2017. "The Path to Reducing Duplication of Human Research Ethics Review in Australia." *Medical Law* 36(1): 7-24.
- Jones, Benjamin F., Stefan Wuchty, and Brian Uzzi. 2008. "Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science." *Science* 322(5905): 1259-62.
- Kandhari, Rohini. 2013. "Justice in Jeopardy: A Qualitative Study of Institutional Ethics Committees in New Delhi." *Indian journal of medical ethics* 10(3): 176-83.

- Kass, Nancy E. et al. 2007. "The Structure and Function of Research Ethics Committees in Africa: A Case Study." *PLoS Medicine* 4(1): 0026-0031.
- Kasule, Mary, Douglas R. Wassenaar, Carel Ijsselmuiden, and Boitumelo Mokgatla. 2016. "Silent Voices: Current and Future Roles of African Research Ethics Committee Administrators." *IRB Ethics and Human Research* 38(1): 13-18.
- Kenyon, Gillian M., Alexander David Mendelow, Barbara A. Gregson, and Elise Rowan. 2011. "Obtaining Regulatory Approval for Multicentre Randomised Controlled Trials: Experiences in the STICH II Trial." *British Journal of Neurosurgery* 25(3): 352-56.
- Kim, Ock Joo et al. 2003. "Current Status of the Institutional Review Boards in Korea: Constitution, Operation, and Policy for Protection of Human Research Participants." *Journal of Korean Medical Science* 18(1): 3-10.
- Kirigia, Joses M., Charles Wambebe, and Amido Baba-Moussa. 2005. "Status of National Research Bioethics Committees in the WHO African Region." *BMC Medical Ethics* 6: 1-7.
- Klitzman, Robert. 2011. "How Local IRBs View Central IRBs in the US." *BMC Medical Ethics* 12(1): 13. <http://www.biomedcentral.com/1472-6939/12/13>.
- . 2019. "Local Knowledge and Single IRBs for Multisite Studies: Challenges and Solutions." *Ethics and Human Research* 41(1): 22-31.
- Klitzman, Robert, Ekaterina Pivovarova, and Charles W. Lidz. 2017. "Single IRBs in Multisite Trials Questions Posed by the New NIH Policy." *Journal of the American Medical Association* 317(20): 2061-62.
- Kontis, Vasilis et al. 2020. "Magnitude, Demographics and Dynamics of the Effect of the First Wave of the COVID-19 Pandemic on All-Cause Mortality in 21 Industrialized Countries." *Nature Medicine* 26(12): 1919-28.
- Lavery, James, Michael McDonald, and Eric M. Meslin. 2005. "Research Ethics Across the 49th Parallel: The Potential Value of Pilot Testing 'Equivalent Protections' in Canadian Research Institutions." *Health Law Review* 2(3): 86-96.
- Leahey, Erin. 2016. "From Sole Investigator to Team Scientist: Trends in the Practice and Study of Research Collaboration." *Annual Review of Sociology* 42: 81-100.
- Lidz, Charles W et al. 2018. "Reliance Agreements and Single IRB Review of Multisite Research: Concerns of IRB Members and Staff." *American* 9(3): 164-72.
- Lynch, Holly Fernandez, and I. Glenn Cohen. 2014. "Streamlining Review by Accepting Equivalence." *American Journal of Bioethics* 14(5): 11-13.
- Mahuli, Amit V., Simpy A. Mahuli, Shankargouda Patil, and Shilpa Bhandi. 2017. "Institutional Ethics Committee Regulations and Current Updates in India." *Journal of Contemporary Dental Practice* 18(8): 738-41.
- Mathur, Roli, Kalyani Thakur, and Rajib Kishore Hazam. 2019. "Highlights of Indian Council of Medical Research National Ethical Guidelines for Biomedical and Health Research Involving Human Participants." *Indian Journal of Pharmacology* 51(3): 214-21.
- Menikoff, Jerry. 2010. "The Paradoxical Problem with Multiple-IRB Review." *New England Journal of Medicine* 363(17): 1591-93.
- Nakada, Haruka et al. 2019. "Recommendations for Promoting International Multi-Site Clinical Trials—from a Viewpoint of Ethics Review." *Developing World Bioethics* 19(4): 192-95.
- Nowak, Kristin S., Elizabeth A. Bankert, and Robert M. Nelson. 2006. "Reforming the Oversight of Multi-Site Clinical Research: A Review of Two Possible Solutions." *Accountability in Research* 13(1): 11-24.
- Nuffield Council on Bioethics. 2020. "Research in Global Health Emergencies: Ethical Issues." *Nuffield Council on Bioethics* (January).
- Okoi, Obasesam, and Tatenda Bwawa. 2020. "How Health Inequality Affect Responses to the COVID-19 Pandemic in Sub-Saharan Africa." *World Development* 135: 105067. <https://doi.org/10.1016/j.worlddev.2020.105067>.

- Ramanathan, Kollengode et al. 2015. "Since January 2020 Elsevier Has Created a COVID-19 Resource Centre with Free Information in English and Mandarin on the Novel Coronavirus COVID- Research That Is Available on the COVID-19 Resource Centre - Including This for Unrestricted Research Re-Use A." *Health Policy* (January): 19-21.
- Ravina, Bernard, Lisa Deuel, Andrew Siderowf, and E. Ray Dorsey. 2010. "Local Institutional Review Board (IRB) Review of a Multicenter Trial: Local Costs without Local Context." *Annals of Neurology* 67(2): 258-60.
- Ravinetto, Raffaella et al. 2011. "Double Ethical Review of North-South Collaborative Clinical Research: Hidden Paternalism or Real Partnership?" *Tropical Medicine and International Health* 16(4): 527-30.
- Regulation (EU) 2016/679 of the European Parliament and of the Council. 2016.
- Saginur, Raphael et al. 2008. "Ontario Cancer Research Ethics Board: Lessons Learned from Developing a Multicenter Regional Institutional Review Board." *Journal of Clinical Oncology* 26(9): 1479-82.
- Saxena, Abha et al. 2019. "Ethics Preparedness: Facilitating Ethics Review during Outbreaks - Recommendations from an Expert Panel." *BMC Medical Ethics* 20(1): 1-10.
- Schopper, Doris et al. 2015. "Innovations in Research Ethics Governance in Humanitarian Settings." *BMC Medical Ethics* 16(1): 1-12.
- Seiler, Christoph M. et al. 2007. "Assessment of the Ethical Review Process for Non-Pharmacological Multicentre Studies in Germany on the Basis of a Randomised Surgical Trial." *Journal of Medical Ethics* 33(2): 113-18.
- Silaigwana, Blessing, and Douglas Wassenaar. 2015. "Biomedical Research Ethics Committees in Sub-Saharan Africa: A Collective Review of Their Structure, Functioning, and Outcomes." *Journal of Empirical Research on Human Research Ethics* 10(2): 169-84.
- Simpson, Bob, Vajira H.W. Dissanayake, Rachel Douglas-Jones, and Salla Sariola. 2010. "Ethical Review, Remit and Responsibility in Biomedical Research in South Asia." *Indian journal of medical ethics* 7(2): 113-14.
- Sleem, Hany et al. 2010. "Development of an Accessible Self-Assessment Tool for Research Ethics Committees in Developing Countries." *Journal of Empirical Research on Human Research Ethics* 5(3): 85-96.
- Smith, M., F. Doyle, H. M. McGee, and D. De La Harpe. 2004. "Ethical Approval for National Studies in Ireland: An Illustration of Current Challenges." *Irish Journal of Medical Science* 173(2): 72-74.
- Sodeke, Stephen. 2016. "Using the IRB Harmonization and Reliance Document Can Reduce Review and Regulatory Delays for the Benefit of All Stephen." *American Journal of Bioethics* 16(8): 46-48. file:///C:/Users/Carla Carolina/Desktop/Artigos para acrescentar na qualificação/The impact of birth weight on cardiovascular disease risk in the.pdf%0Afile:///Users/paulagamero/Downloads/nihms772425.pdf.
- Somsekhar, Hemalatha et al. 2012. "Review of Multinational Human Subjects Research: Experience from the PHFI-Emory Center of Excellence Partnership." *Indian journal of medical ethics* 9(4): 255-58.
- Stark, Laura. 2015. "IRBs and the Problem of 'Local Precedents.'" *Human Subjects Research Regulation*: 173-87.
- Strosberg, Martin, Eugenijus Gefenas, Sana Loue, and Sean Philpott. 2013. "Building Research Ethics Capacity in Post-Communist Countries: Experience of Two Fogarty Training Programs Martin." *Journal of Empirical Research on Human Research Ethics* 8(5): 28-39. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf>.
- van Teijlingen, Edwin R., and Padam P. Simkhada. 2012. "Ethical Approval in Developing Countries Is Not Optional." *Journal of Medical Ethics* 38(7): 428-30.
- Townend, David et al. 2016. "Streamlining Ethical Review of Data Intensive Research." *BMJ (Online)* 354(August): 1-2.

- Townend, David, and Edward S. Dove. 2017. "Approaching Ethics Review Equivalency through Natural Justice and Sounding Board Model for Research Ethics Committees." *Medical Law* 36(1): 61-86.
- Tully, Joanna, Nelly Ninis, Robert Booy, and Russell Viner. 2000. "The New System of Review by Multicentre Research Ethics Committees: Prospective Study." *BMJ* 320(7243): 1179-82.
- Wagner, Caroline S., Travis A. Whetsell, and Loet Leydesdorff. 2017. "Growth of International Collaboration in Science: Revisiting Six Specialties." *Scientometrics* 110(3): 1633-52.
- Wei, Tzung-bor. 2007. "The Equivalence Approach to Securities Regulation." *Northwestern Journal of International Law & Business* 27(2): 255.
- Westra, Anna E., Wendy Bos, and Adam F. Cohen. 2014. "New EU Clinical Trials Regulation: Needs a Few Tweaks before Implementation." *BMJ* 348(June): 10-11.
- Whitney, S. N., and C. E. Schneider. 2011. "Viewpoint: A Method to Estimate the Cost in Lives of Ethics Board Review of Biomedical Research." *Journal of Internal Medicine* 269(4): 396-402.
- "WHO Simulation Exercise Manual. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO." 2554.
- Winkler, Sabune J., Elizabeth Witte, and Barbara E. Bierer. 2015. "The Harvard Catalyst Common Reciprocal IRB Reliance Agreement: An Innovative Approach to Multisite IRB Review and Oversight." *Clinical and Translational Science* 8(1): 57-66.
- World Health Organization. 2011. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*.

Annex 1.

Database search and literature review

PubMed search strategy

Search number	Query	Search Details	Results	Date/ Time
2	(((((((committee, research ethics[MeSH Terms]) OR (ethics committee[MeSH Terms])) OR (board, institutional review[MeSH Terms])) OR (research ethics review[MeSH Terms])) AND (single review)) OR (centraliz* review)) OR (mutual recognition)) OR (ethics review equivalen*)	(("ethics committees, research"[MeSH Terms] OR "ethics committees"[MeSH Terms] OR "ethics committees, research"[MeSH Terms]) AND (("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields]) OR "single person"[All Fields] OR "single"[All Fields] OR "singles"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]))) OR ("centraliz*"[All Fields] AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])) OR (("mutual"[All Fields] OR "mutuality"[All Fields] OR "mutually"[All Fields]) AND ("recognition, psychology"[MeSH Terms] OR ("recognition"[All Fields] AND "psychology"[All Fields]) OR "psychology recognition"[All Fields] OR "recognition"[All Fields] OR "recognitions"[All Fields])) OR (("ethic s"[All Fields] OR "ethicality"[All Fields] OR "ethically"[All Fields] OR "ethics"[MeSH Terms] OR "ethics"[All Fields] OR "ethic"[All Fields] OR "ethics"[MeSH Subheading] OR "morals"[MeSH Terms] OR "morals"[All Fields] OR "ethical"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) AND "equivalen*"[All Fields])	5,607	12/16/20 13:48:03
1	(((committee, research ethics[MeSH Terms]) OR (ethics committee[MeSH Terms])) OR (board, institutional review[MeSH Terms])) OR (research ethics review[MeSH Terms])	"ethics committees, research"[MeSH Terms] OR "ethics committees"[MeSH Terms] OR "ethics committees, research"[MeSH Terms]	9,446	12/16/20 13:42:47

Annex 2.

International guidance documents

Multisite REC standards, responsibilities, procedures and operations

Convention/guideline / policy	Reference	Text
<p>Council for international organizations of medical sciences (CIOMS). International Ethical Guidelines for Health-Related Research Involving Humans (2016), https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-ethicalguidelines.pdf (last visited 12/16/2020).</p>	<p>Guideline 23</p>	<p>Multi-centre research. Some research projects are designed to be conducted in a number of centres in different communities or countries. To ensure that the results are valid, the study must be conducted in a methodologically identical way at each centre. However, committees at individual centres must be authorized to adapt the informed consent document provided by the sponsor or the lead institution in the multi-centre trial in order to make it culturally appropriate. To avoid lengthy procedures, multi-centre research in a single jurisdiction (state or country) should be reviewed by only one research ethics committee.</p> <p>In cases of multi-centre research, if a local review committee proposes changes to the original protocol that it believes are necessary to protect the research participants, these changes must be reported to the research institution or sponsor responsible for the whole research programme for consideration and possible action. This should ensure that all persons are protected and that the research will be valid across sites.</p> <p>Ideally, review procedures should be harmonized, which may decrease the time needed for review and accordingly, speed up the research process. In order to harmonize review processes and to maintain sufficient quality of these processes, ethics committees must develop quality indicators for ethical review. Appropriate review must be sensitive to increases in risk of harm or wrongs to local participants and populations.</p>
<p>Global Alliance for Genomics and Health, Ethics Review Recognition Policy (2017), https://www.ga4gh.org/wp-content/uploads/GA4GH-Ethics-Review-Recognition-Policy.pdf (last visited 12/16/2020).</p>	<p>Common and Essential Elements</p>	<p>Policy wide</p>

Convention/guideline / policy	Reference	Text
UNESCO, <i>Universal Declaration of Bioethics and Human Rights</i> (2005), http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights (last visited 12/16/2020).	Article 19	<p>Article 19 - Ethics committees</p> <p>Independent, multidisciplinary and pluralist ethics committees should be established, promoted and supported at the appropriate level in order to:</p> <ul style="list-style-type: none"> (a) assess the relevant ethical, legal, scientific and social issues related to research projects involving human beings; (b) provide advice on ethical problems in clinical settings; (c) assess scientific and technological developments, formulate recommendations and contribute to the preparation of guidelines on issues within the scope of this Declaration; (d) foster debate, education and public awareness of, and engagement in, bioethics.
World Health Organization. <i>Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants</i> . 2011 https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=2CB78BE4794C241B287C824F200DA282?sequence=1 (Last visited on 12/16/2020).	Standard 1	<p>Standard 1.3</p> <p>Procedures exist to ensure clear and efficient communication, harmonization of standards, networking, and cooperation among national committees and between different levels of committees, as applicable. These procedures enable RECs to learn about prior decisions by other RECs that may be relevant to the proposed research under review. In addition, procedures exist for the coordinated review of multi-site research, whether within a country or in more than one country.</p>

Annex 3.

Consultative Activities

Summary

Activity #	Date	Activity type	Informants*
1	10/21/20	Meeting	Covid-19 Clinical Research Coalition Ethics Working Group, monthly meeting
2	10/26/20	Meeting	Cheryl Cox Macpherson* , Director of the CREEi Research Ethics Training Program for the Caribbean, and member of the Anglo Caribbean Bioethics Association, Grenada
3	11/2/20	Meeting	Francis Crawley* , Good Clinical Practice Alliance of Europe (GCPA), Belgium
4	11/9/2020	Meeting	Caesar Attuire* , University of Ghana Jantina de Vries* , Chair of Ethics Working Group; Associate Professor of Bioethics, University of Cape Town, South Africa
5	11/13/2020	Meeting	Carla Saenz , Bioethics Advisor the Pan American Health Organization (PAHO)
6	11/10/2020	Webinar PAHO dialogue—a REC procedures	Aldo Vivar , Peru's national transitory REC for COVID-19 trials, Perú Mike Cambell , REC of University of West Indies - Cave Hill and Barbados Ministry of Health and Wellness, Barbados Marianela Sánchez Rojas , Central REC from Costa Rica's Social Security System, Costa Rica Dorian E. Ramírez Flores , Guatemala's National Ethics in Health Committee, Guatemala
7	11/18/2020	Meeting	Covid-19 Clinical Research Coalition Ethics Working Group, monthly meeting
8	11/18/2020	Presentation	EULaC PerMed Technical Workshop
9	11/20/2020	Meeting	Sofia Patricia Salas Ibarra* , Center of Bioethics, Faculty of Medicine, Clínica Alemana-Universidad del Desarrollo; Chair of the National Commission for Research Ethics, an advisory Commission for the Chilean Ministry of Health

10	11/23/2020	Meeting	<p>Francis Crawley*, GCPA Belgium</p> <p>Bakyht Sarymsakova, Head of the Regional Training Center for Health Research Astana Medical University, Kazakhstan</p> <p>Nariman Safarli, President of the Azerbaijani Medical Association</p>
11	11/24/2020	Meeting	<p>Chiedozie Ike, Public Health Physician, Certified Research Ethics Professional, Irrua Specialist Teaching Hospital, Benin City, Nigeria</p>
12	11/26/2020	Meeting	<p>Leonardo de Castro*, Chair of the Philippine Health Research Ethics Board; Member of the National Ethics Committee of the Philippines</p>
13	11/26/2020	Presentation	<p>NGO 'Forum of Ethics Committees, Kazakhstan Ministry of Health</p>
14	11/30/2020	Webinar PAHO dialogue– Researcher perspectives	<p>Silvina Kuperman, Argentina</p> <p>Juan Manuel Anaya, Colombia</p> <p>Ricardo Palacios, Brasil</p> <p>Jose Gotes Palazuelos, México</p>
15	12/9/2020	Webinar PAHO dialogue–What have we learned so far?	<p>Sandra Tapia, President of the Ad Hoc Scientific Ethics Committee for Scientific Research on Covid-19 Vaccines of Chile</p> <p>Adriel Jonas Roitman, Member of the Central Committee of Research Ethics, Ministry of Health of the City of Buenos Aires, Argentina</p> <p>Cheryl Cox Macpherson*, Director of the CREEi Research Ethics Training Program for the Caribbean, and member of the Anglo Caribbean Bioethics Association, Grenada)</p> <p>Juan Villacorta, Member of the Transitory Committee on Research Ethics for the Covid-19 Emergency of Peru</p>
16	12/15/2020	Meeting	<p>Eimy Minowa, Clinical site manager, PAREXEL, New South Wales, Australia</p> <p>Guilherme S. Julian–Director RWE/HEOR/Market Access at IQVIA, São Paulo, Brasil</p>
17	12/21/2020	Email correspondence	<p>Ludmila Macêdo Naud, Epidemiologist, Ministry of Health, Brasil</p>

Annex 4.

Multisite ethics REC guidance

for ethics review during Covid-19 and other public health emergencies

Convention/ guideline /policy	Reference	Text
<p>Nuffield Council on Bioethics. (2020). Research in global health emergencies: ethical issues. https://www.nuffieldbioethics.org/publications/research-in-global-health-emergencies/read-the-short-report (Last visited on 12/16/20).</p>	<p>Ethical review processes Capacity of ethics committees to respond in emergencies 6.23-6.42</p>	<p>6.28 In addition to review by either local or national committees in the country (or countries) where the research is taking place, research in emergencies will often involve research institutions or funders based in other jurisdictions, with their own review requirements. This presents a further challenge: even where all such committees are in place, coordinating responsive and timely reviews is clearly more complex and time-consuming across multiple committees, with scope for duplication and contradiction. Further difficulties arise in circumstances such as where emergencies are linked with internal conflict, where there may be no body available with local legitimacy to undertake ethical scrutiny. Alternative suggested approaches in such cases include seeking input from local advisory groups, or from local academics able to provide a complementary structured review of protocols</p> <p>6.29 The value of multi-country review, including the opportunities for complementariness through sharing of different perspectives, and potential for mutual learning, was emphasised by a workshop of REC members from across five continents, convened in 2018 by WHO and the African coalition for Epidemic Research, Response and Training (ALERT) network (see paragraph 3.28 and Box 3.9) to explore effective review in infectious disease outbreaks.⁵¹⁷ Participants highlighted the importance of definitive national approval before a study could go ahead, rather than supporting a single multi-country approach, and recommended that individual national RECs, or other in-country competent bodies, should prepare by developing standing operating procedures for emergency review.⁵¹⁸ They also emphasised the value of greater harmonisation of criteria and procedures, particularly at regional level, supported by legitimate umbrella bodies such as the African Vaccine Regulatory Forum (see also Box 6.7 for a Caribbean example). It was also noted that such a regionally harmonised approach to review procedures need not be limited to infectious disease emergencies</p>

UNESCO (2020). *Statement of Ethical Considerations in Covid-19 Research and Recovery*
<https://en.unesco.org/inclusivepolicylab/e-teams/ethical-considerations-covid-19-responses-and-recovery/documents/unesco-ibc-comest-statement>
 (Last visited on 12/20/20).

Recommendation
 7-8

There is already an explosion of research activities and clinical trials to find a cure and a vaccine for COVID-19. Most of these activities occur on a local level. However, at the same time, there is a need for coordination of international efforts and the formulation of a common understanding of ethical review processes. In the context of the COVID-19 pandemic, the World Health Organization (WHO) and partners have announced the organization of a study coined "SOLIDARITY" to compare untested treatments throughout several countries since multiple small trials of possible coronavirus therapeutics approaches with different methodologies may not provide the evidence needed. Accelerated review and approval of novel approaches may become necessary so as not to delay research during this public health emergency. An oversight committee for responsible research during this pandemic on a global level needs to be urgently created. Such a committee should gather the results obtained on local levels and coordinate/share the review procedures, which may be exceptional in pandemics and may not follow the regular rules. In this regard, guidance for the local ethics review boards is critical. It is understandable for new practices to be accommodated in the emergency context, considering the nature of the global threat. However, such decisions need ethical justification (see WHO Guidance for managing ethical issues in infectious disease outbreaks (2016)).

Ethical principles should not be transgressed but may be adjusted to exceptional circumstances. It is also important that research under these circumstances must not be carried out purely for financial gain. Transparency, sharing of data, and sharing of benefits of research for all humans need to be recognized as central values (see Report of the IBC on the Principle of the Sharing of Benefits (2015)). The IBC and COMEST applaud the rapidly growing number of funding agencies and scientific journals that have responded to the call by Wellcome Trust to commit to make COVID-19 related scientific publications available in Open Access in times of public health emergencies.

World Health Organization. (2016). *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*. <https://apps.who.int/iris/bitstream/handle/10665/250580/9789241549837-eng.pdf?sequence=1&isAllowed=y> (Last visited 12/16/20)

Chapter 8 Research during infectious disease outbreaks

Role of local research institutions – When local researchers are available, they should be involved in the design, implementation, analysis, reporting and publication of outbreak-related research. Local researchers can help ensure that studies adequately respond to local realities and needs and that they can be implemented effectively without jeopardizing the emergency response. Involving local researchers in international research collaborations also contributes to building longterm research capacity in affected countries and promoting the value of international equity in science.

Addressing limitations in local research ethics review and scientific capacity – Countries' capacity to engage in local research ethics review may be limited during outbreaks because of time constraints, lack of expertise, diversion of resources to outbreak response efforts, or pressure from public health authorities that undermines reviewers' independence. International and nongovernmental organizations should assist local research ethics committees to overcome these challenges by, for example, sponsoring collaborative reviews involving representatives from multiple countries supplemented by external experts.

Providing ethics review in time sensitive circumstances – The need for immediate action to contain an infectious disease outbreak may make it impossible to adhere to the usual timeframes for research ethics review. National research governance systems and the international community should anticipate this problem by developing mechanisms to ensure accelerated ethics review in emergency situations, without undermining any of the substantive protections that ethics review is designed to provide. One option is to authorize the advance review of generic protocols for conducting research in outbreak conditions, which can then be rapidly adapted and reviewed for particular contexts. Early discussion and collaboration with local research ethics committees can help ensure the project is viable and can facilitate local committees' effective and efficient consideration of final protocols when an outbreak actually occurs.

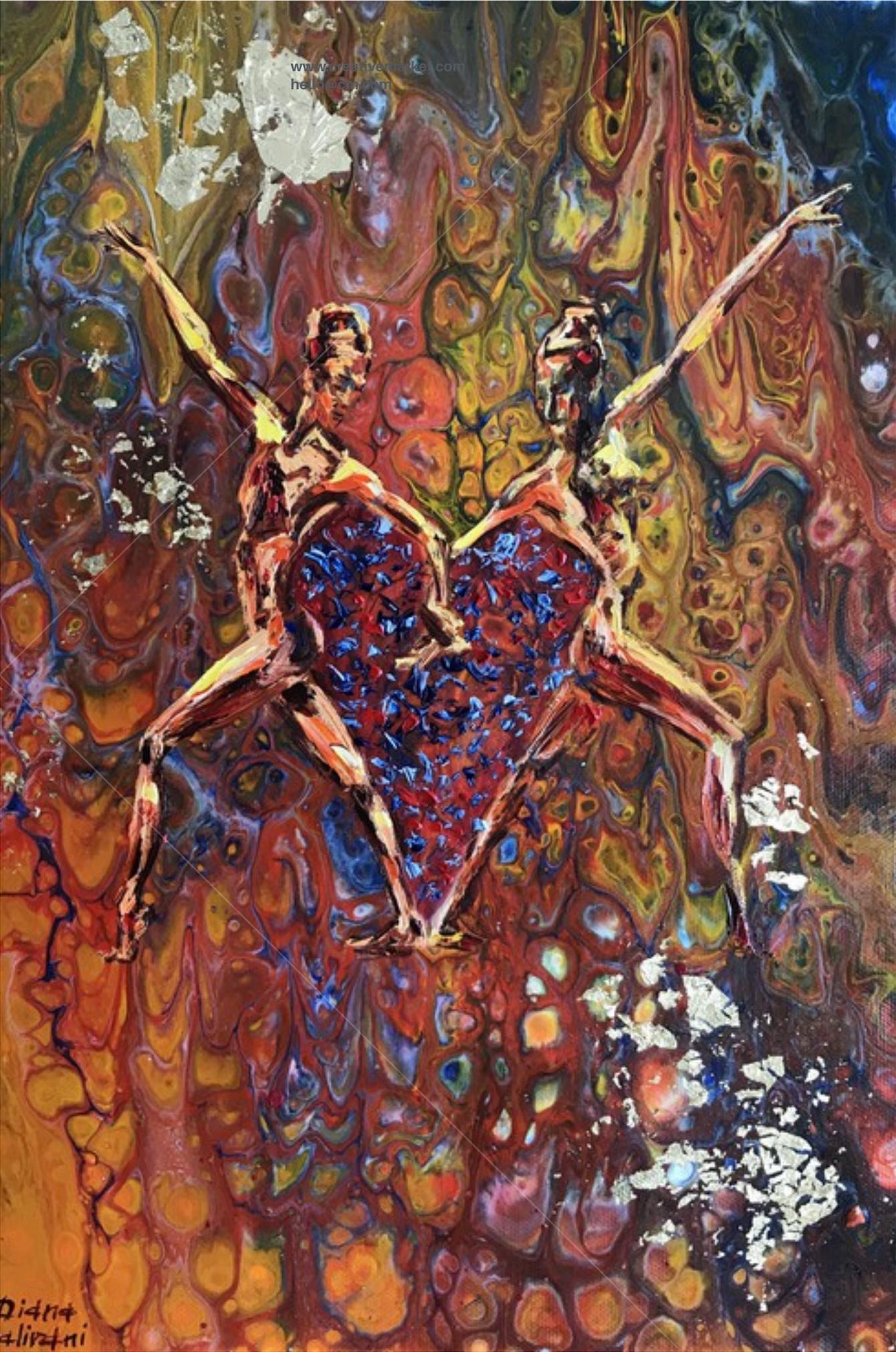
World Health Organization. (2020). *Guidance for research ethics committees for rapid review of research during public health emergencies*

Recommendation 3

To prepare for the review of emergency research, research ethics committees should agree on a process for rapid review (this would mean reviewing protocols as and when they are submitted rather than waiting for a scheduled meeting). This process should be communicated to the researchers. Any anticipated delays for non-emergency research should also be communicated to all principal investigators who had previously submitted such research projects.

Annex 5.

Report Art.



Samuel Kane.





Ginny Gaura.

Window to Reciprocity //
Fedor Rakic, Serbia

