Human Subjects' Protection

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Arthur L. Caplan and Barbara K. Redman

Federal regulations for protection of human subjects in biomedical and behavioral research have been in place since 1974. Preceded by the Belmont Report, which described ethical principles for human research, regulations known as the Common Rule (common across federal agencies) followed. They may be found at 45 CFR 46 and are administered by the Office of Human Research Protections (OHRP). Updated regulations have been approved and are expected to be in effect by early 2018.

Under these regulations, research is defined as a systematic investigation designed to produce generalizable knowledge; a human subject means a living individual involved in research (46.102). Each institution operates one or more institutional review board(s) (IRB) under policies approved by OHRP. They have the authority to approve, require modification, or disapprove research proposals; decisions are based on minimization of risk to subjects and weighed against anticipated benefits and fair subject selection. The Food and Drug Administration has similar guidelines. Detail of these requirements and description of alternative models for IRB review may be found in tables in Grady (2015). Other sources of guidance include International Ethical Guidelines for Health-related Research Involving Humans prepared by the Council for International Organizations of Medical Sciences (CIOMS), the Declaration of Helsinki by the World Medical Association, and Good Clinical Practice Guidelines by the International Conference of Harmonization.

The goal of IRB review is to assure that subjects will be protected during research. A scoping review of empirical research related to quality and effectiveness of research ethics review found no controlled trials or an underlying framework of institutional review board (IRB) effectiveness, or a systematic research agenda by which to answer these questions (Nichols et al. 2015). Literature on informed consent for research found a similar story – lack of clear evidence of potential research subjects making an informed decision. Many were thought to be enrolling in trials without an adequate understanding of fundamental concepts such as voluntariness or risks of participation, although extended one-on-one discussions appeared helpful. There are few studies of potential subjects who chose not to enroll (Hallinan et al. 2016). Despite these limitations, programs of accreditation provide evidence of quality, widely sought by IRBs.

Many institutions/trials have additional review mechanisms to assure quality. Separate scientific review committees address quality of the science and work collaboratively with the IRB. Data safety monitoring boards (DSMBs) were developed to provide close oversight of the integrity of intervention trials by ensuring objective assessment of accumulating data, monitoring trial results and data quality and safety (DeMets and Ellenberg 2016), and potentially recommending early trial termination. Neither of these mechanisms appears in federal regulations, although DSMBs may be required by funders.

Subjects protection is surely one of the most basic elements of research integrity. It requires not only a virtuous investigator who can solve ethical problems as they arise during research, but as history has taught, an effective oversight system as described above, largely structured as a form of self-regulation by peers. Now 40 years later, it is clear that the system must accommodate new issues also essential to integrity of research. These include recognition of demand on the part of potential subjects for access to clinical trials, over-protection especially of vulnerable groups such as children or prisoners which has stifled research to the groups meant to be protected, and attention to basic constructs such as risk/benefit ratio which depend as much as possible on a stable and reproducible base of prior studies.

Advice: Be informed about the research review boards (IRBs), animal care and use committees, conflict of interest, and biosafety committees in your institution. While your

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mentor will have had much experience with them, do not hesitate to approach IRB staff during proposal preparation with your unanswered questions. It is better to get their advice now rather than after your proposal could not be approved.

4.1 A Scoping Review of Empirical Research Relating to Quality and Effectiveness of Research Ethics Review

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RESEARCH ARTICLE

A Scoping Review of Empirical Research Relating to Quality and Effectiveness of Research Ethics Review

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Abstract

Background

To date there is no established consensus of assessment criteria for evaluating research ethics review.

Methods

We conducted a scoping review of empirical research assessing ethics review processes in order to identify common elements assessed, research foci, and research gaps to aid in the development of assessment criteria. Electronic searches of Ovid Medline, PsychInfo, and the Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED, were conducted. After de-duplication, 4234 titles and abstracts were reviewed. Altogether 4036 articles were excluded following screening of titles, abstracts and full text. A total of 198 articles included for final data extraction.

Results

Few studies originated from outside North America and Europe. No study reported using an underlying theory or framework of quality/effectiveness to guide study design or analyses. We did not identify any studies that had involved a controlled trial - randomised or otherwise – of ethics review procedures or processes. Studies varied substantially with respect to outcomes assessed, although tended to focus on structure and timeliness of ethics review.

Discussion

Our findings indicate a lack of consensus on appropriate assessment criteria, exemplified by the varied study outcomes identified, but also a fragmented body of research. To date research has been largely quantitative, with little attention given to stakeholder experiences,

and is largely cross sectional. A lack of longitudinal research to date precludes analyses of change or assessment of quality improvement in ethics review.

Background

Research ethics review was developed by a post-WWII society to ensure that human subjects were protected from unethical research. Today ethical review is legally mandated prior to the conduct of most human subjects research [1].

While few would disagree with the general need for ethics review, existing review processes are often criticized [2]; common complaints include the amount of paperwork required [3], inconsistency of decisions between review boards, and suggestions that ethics review systems may not be equipped to properly review specific types of research [4–8]. In response to these criticisms, efforts have been made to develop standards of ethics review, and several jurisdictions have implemented accreditation processes to ensure that committees meet requirements, such as those imposed by the US Federal Policy for the Protection of Human Subjects (the 'Common Rule')[9]. However, these largely procedural standards may not necessarily reflect the goals of human subject protection that review processes were established to safeguard. To date, there is no established consensus regarding assessment criteria for evaluating research ethics review [10].

Abstract goals and evaluative frameworks have been described [11], but there remain a lack of operational definitions and consensus regarding criteria against which to perform assessments. Indeed, while there has been much discussion of the need to develop metrics or quality indicators, there has been little progress in terms of identifying and testing meaningful indicators. Despite a recent systematic review to determine what is known about how well IRBs function [12], several existing areas of study were excluded. Indeed, despite the conclusion that there is a need to clarify expectations regarding ethics review processes, and that data on the risks that research participants experience would be helpful in this regard, the authors explicitly excluded stakeholder opinions of IRB performance. Moreover, the review did not explore in detail the different methodological approaches, stakeholders involved, or theories motivating the research.

In order to progress the literature towards evidence-based assessment of ethics review processes, there is a need to examine not just procedural aspects of ethics review, but also a broader range of perspectives and descriptive accounts as well as a range of methodological approaches. In the present review we address this need through an inclusive search of the international literature, and specifically include studies targeting investigator, participant, and research board/committee perspectives with attention given to methodological approach.

Aim

To conduct a scoping review of the relevant literature regarding the evaluation of research ethics review, and to summarize the available evidence in terms of:

1. Applied theoretical frameworks relevant to evaluating research ethics review;
2. Research approaches that have been used to evaluate research ethics review;
3. Subjects of analysis within existing research to evaluate research ethics review; and
4. Research outcomes that have been used to evaluate research ethics review;

Methods

Our choice to conduct a scoping review was necessitated by the disparate body of literature regarding ethics review practices. Scoping reviews are useful to summarize and describe data from a wide range of fields which cross disciplinary and methodological lines [13]. This can include quantitative, qualitative, and review work. In keeping with the aim of scoping reviews, our approach was also informed by a desire to examine the extent, range and nature of research activity so as to provide an initial assessment of the state of the literature and identify research gaps. As per recommended practice [13, 14] we used a five step framework. The five stage process employed was:

1. Identifying the research question;
2. Identifying relevant studies;
3. Study selection;
4. Charting the data;
5. Collating, summarizing and reporting the results.

Identifying the research question

Our main question for the scoping review was: What empirical research exists that addresses the evaluation of research ethics review?

Identifying Relevant Studies

Studies were identified through an electronic search of published literature, together with citation tracking and hand searching. Electronic searches of Ovid Medline, PsychInfo, and the Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED, were conducted. Terms relating to research ethics boards, quality, effectiveness and evaluation were combined with terms relating to research approaches (See S1 File). The search strategy was developed through discussion with experts in the field of research ethics review, a research librarian, a previously published systematic review [12], and a narrative review of the literature. The search strategy included both Meta Subject Heading (MeSH) terms and text words as several articles identified by the narrative review did not have MeSH terms associated with them.

Study Selection

Eligibility criteria were based on the goals of our research question. While there has been much debate with respect to potential indicators of quality in research ethics review, our goal was to advance the empirical assessment of ethics review. As the motivation for the study was to move forward the research agenda on quality assessment in a meaningful way we limited our search to include only manuscripts that had attempted to develop metrics, or evaluate empirically, research ethics review processes or procedures. Studies were therefore excluded if they did not involve empirical research; did not have research ethics review (as opposed to clinical ethics review) as a core element of study; or didn't relate to humans (e.g. studies of animal research ethics). Articles were not limited by date, allowing the assessment of publication trends. Only English language studies were included.

The electronic search was conducted in June 2013 and updated in March 2014. All titles and abstracts were screened by two reviewers (TH, SN). Following the initial screen, the bibliographies of all retained articles were hand searched to identify additional studies. All articles were

imported into Reference Manager 12 for curation. Articles were rejected on an initial screen of titles and abstracts only if the reviewers could determine that the articles did not meet the inclusion criteria. Where abstracts were not available, or where a definitive assessment could not be made, the full text of the article was retrieved. The same two authors reviewed the full texts to make a final determination of inclusion or exclusion. Any disagreements were resolved by discussion. Data extraction was conducted by one reviewer (TH), with a second reviewer (SN) screening a sample (n = 45) for comparison. Each reviewer independently extracted information from the full text manuscript and then results were compared. Differences that were qualitatively different (i.e. there had been different elements extracted) were resolved through discussion as were differences in coding applied to the data.

Charting the data

A data extraction form and process was developed based on the study aim of creating a descriptive account of the research landscape, as opposed to integrated analyses. The content of the form was developed by discussion within the team. Data extracted included: article characteristics (title, author(s), source, date of publication); description of research (type of participants, study design, data collection methods, research question, study size, dates to which data relate, region); and study outcomes.

Collating, summarizing and reporting results

Data were summarized descriptively. Qualitative data, such as individual outcomes from studies or descriptions of approaches, were collated thematically using a process of qualitative description. This is a low-inference approach to coding qualitative data in which the goal is a descriptive account of the content, as opposed to overarching concepts or abstract frameworks [15]. Themes were applied using the constant comparison method in which existing instances are revisited in light of new data. [16] Descriptive statistics were used to explore the quantitative data within the manuscripts. The data extracted are listed in Table 1.

Results

The electronic search resulted in 2939 citations for review. Review of bibliographies for initially retained papers yielded a further 1304 articles. After de-duplication a total of n = 4234 titles and abstracts were reviewed. Screening by both reviewers achieved 94% concordance. Altogether 4036 articles were excluded following screening of titles, abstracts and full text. The main reasons for exclusion were: not research ethics review (n = 3594), not empirical research

Table 1. Extracted information from retrieved articles.

Article Characteristics	Description of Research	Study Findings and Conclusions
Title	Type of Participants	Names of outcomes
Author(s)	Study Design	Results/Findings
Source	Research Questions	Theoretical framework/theory cited? If yes: definition
Date of Publication	Study Size	Authors' Conclusions
	Dates to which data relate	
	Region	
	Definition of quality	
	Definition of effectiveness	

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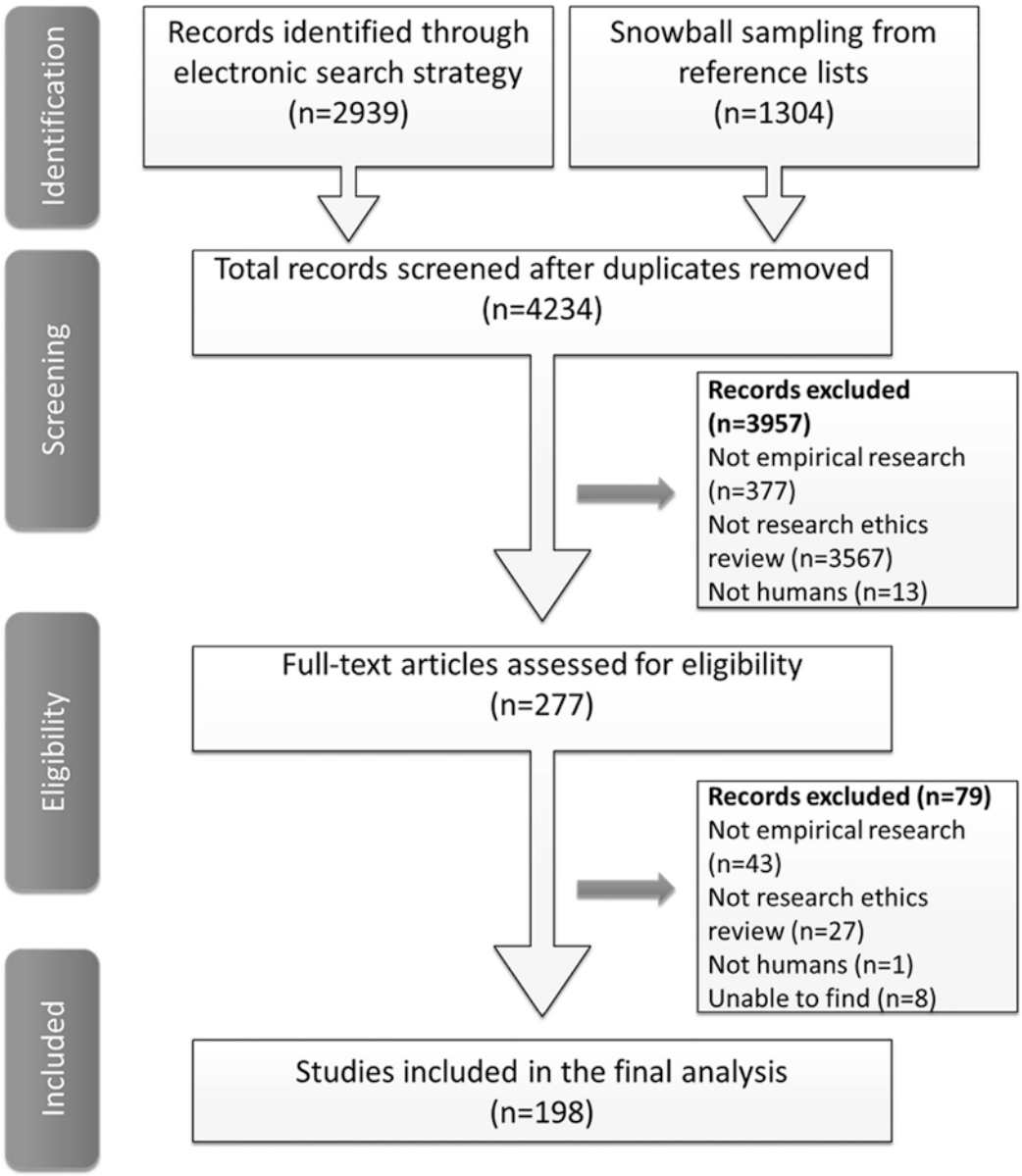

Fig 1. Flowchart of screening process

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(n = 420), not human (n = 14). In addition we were unable to locate the full text of 18 articles. Consequently, a total of 198 articles were included for final data extraction (see Fig 1).

Study descriptors

Publication dates of identified studies ranged from 1979 to 2014. From 1979 through to the 1990s the number of studies identified number one to two per year. There was an increase in the number of articles per year starting in the early 2000s (from n = 6 in 2000 to n = 14 in

2005) with a peak in the latter part of that decade (n = 19 in 2008). Several studies did not include dates to which their data relate, precluding assessment of this. Most studies originated from North America (n = 102) or Europe (n = 62). There were relatively few authors publishing multiple articles.

Theoretical frameworks

No study reported using an underlying theory or framework of IRB quality/effectiveness to guide study design or analyses. Several studies did, however, use theories, such as grounded theory, to analyze data [17–20].

While a number of studies (n = 16) discussed quality or effectiveness of IRB decisions [7, 12, 21–34], none provided explicit operational definitions. In developing their self-assessment tool, Sleem et al., note that "there are no gold standards for determining effectiveness nor are there standards that can actually measure how well human participants are being protected by the use of standards", instead opting to use 'surrogate' metrics that they considered foundations for effectiveness and protection [30]. These surrogate metrics included: availability of policies (e.g. to deal with conflicts of interest), structural elements (such as membership composition), processes (for example, clear processes for the submission of protocols), performance measures (such as whether certain criteria were considered within the protocol review), as well as cost-related information. While the structural organization of review (for example, policies, structural elements, performance measures) is not itself a theory it does provide a framework of aspects of IRB review quality. The development of such metrics, in the absence of explicit operational definitions, was representative of many studies identified by the review.

Two studies did describe a general foundation in Procedural- and Interactional-Justice through the use of the Institutional Review Board-Researcher Assessment Tool (IRB-RAT) [35, 36]. *Procedural justice* relates to fairness of process. A fair IRB, it is argued by the authors, might display characteristics that are associated with procedural justice, such as: consistency, lack of bias, accuracy, procedures for correcting errors, representativeness, and adherence to basic ethical standards. *Interactional justice*, on the other hand, relates the behavioral aspects of the decision process. In this respect, the authors of the IRB-RAT argue for the inclusion of this aspect to evaluate the way in which people who receive decisions are treated. In essence, it is an evaluation of communication through assessment of *interpersonal sensitivity*–the degree of politeness or respect–and the substantive *justification*, that is the degree of explanation provided.

Research approaches

We did not identify any studies that had involved a controlled trial—randomised or otherwise–of ethics review procedures or processes. The two most common methods of data collection were surveys, with 92/198 (46%) manuscripts reporting results from survey research, and review of administrative data, with 79 (40%) papers (Fig 2 and S1 Table, for further details). Survey respondents varied, with manuscripts reporting on surveys with several populations. Of the 92 manuscripts reporting survey research, 63 included surveys of ethics committee/board members (69%), 28 included surveys of researchers (31%), and 4 included surveys of research participants (4%). Surveys also often focused on structural aspects of ethics review, with 52 (57%) manuscripts exploring structural or procedural aspects, 43 (47%) elements of membership, and 27 (29%) variation, while 39 (42%) explored ethics committee/board member views. Eighteen manuscripts included researcher views (20%) and 3/92 (3%) papers using surveys included participant views.

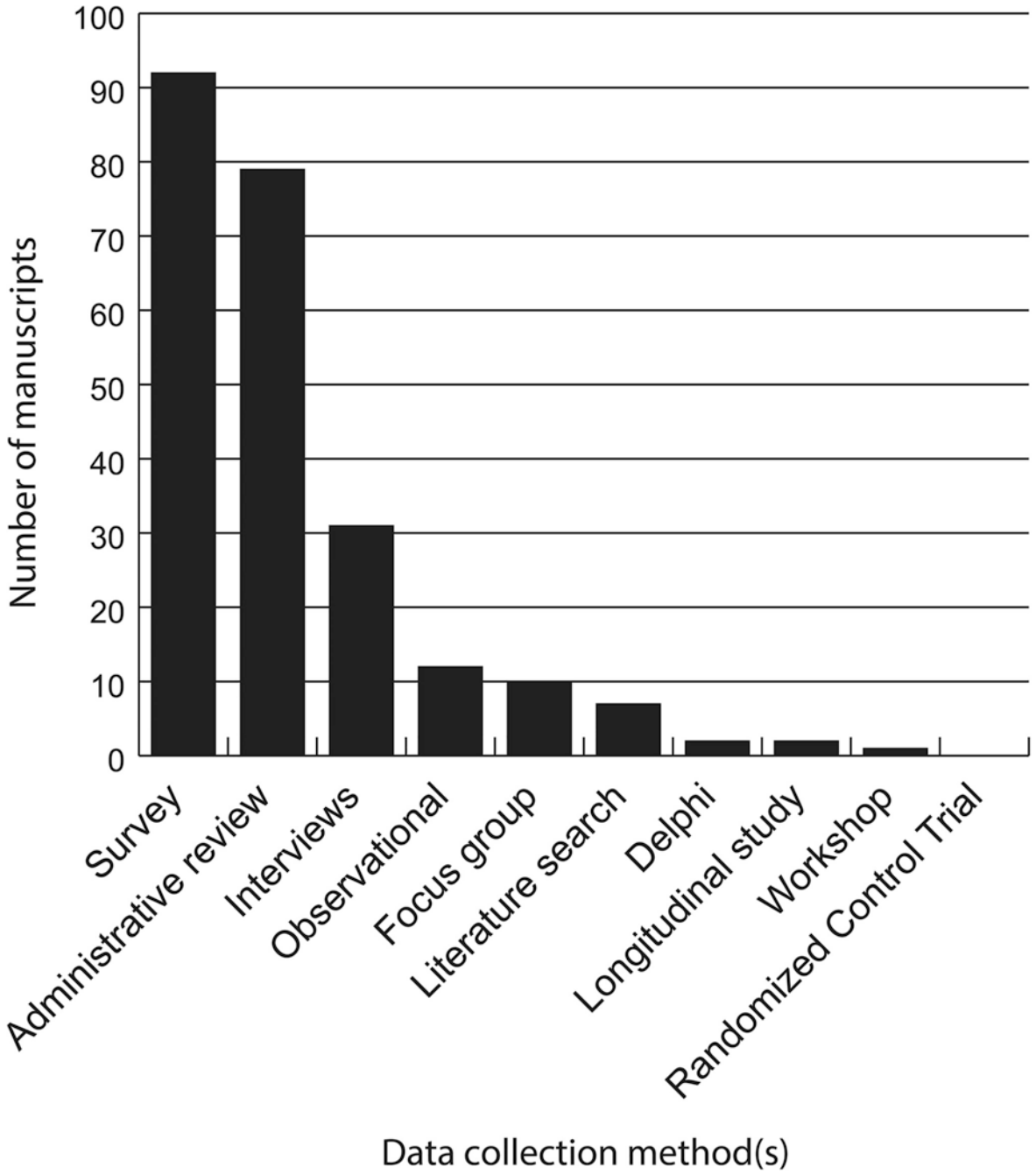

Fig 2. Data collection methods of analysed manuscripts.

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Thirty one papers (16%) reported data collected through interviews. Of these, 4 manuscripts reported interviews with research participants (13%), 8 included researchers (26%) and 24 (77%) were with ethics committee/board members. A handful of studies reported results from

other qualitative approaches such as participant observation (n = 12; 6%) or focus groups (n = 10, 5%).

Seven papers indicated that a literature review had been undertaken: however, in only two instances were detailed search strategies and summaries of the identified literature provided [12, 29].We identified two examples of Delphi processes [26, 37] and only two studies of longitudinal data [38, 39]. Of the two longitudinal studies, Denham et al., reviewed the outcomes of studies reviewed and approved by a single research ethics committee in the UK over the period 1970 to 1978. Based on follow up they found that 43% of projects approved had been completed, 20% had been abandoned, 3% had been suspended and 26% were ongoing [38]. Allen and Waters reviewed the data on number of projects submitted, the types of study, and the numbers approved and requiring modification–including details on the types of modifications or conditions imposed by the ethics committee [39].One manuscript presented a summary of a workshop [40].

Research subject

The research subject referred to what, or who, was the subject of analysis (S1 Table). A total of 147/198 papers reported data where the assessment of administrative processes was the subject of assessment (74%), while 103 (52%) reported the views of IRB members. A total of 45 manuscripts (23%) related to analyses of review board composition, and 37 (19%) explored the views of researchers. A handful of papers included alternative subjects of study. Eight manuscripts explored the views of non-research healthcare workers who may be affected by research [37, 41–47], and only seven papers (4%) identified by the search involved research participants as the subject of study [48–54]. We identified only one study that explored the views of the research sponsors[55].

Outcomes of assessment/thematic analyses

Table 2 describes the themes we identified: Membership; Time; Cost; Variation; Satisfaction; Policy Adherence; Working Hours; Outcome; Training; Knowledge; Structures and Procedures; Number of Protocols; Committee/board Member Views; Researcher Views; Participant Views; Committee/board Decision Making; Post Approval Monitoring; Number of Committee/boards in Region; and Views of Healthcare Professionals (HCPs) (see Table 2 for examples of individual outcomes included within the thematic groupings). Studies often assessed multiple outcomes.

As Fig 3 shows most outcomes were situated within the cluster relating to ethics committee/board processes and outcomes (see also S1 Table). The largest number of manuscripts assessed structures and protocols of review committees or boards (n = 104, 53%). For example, Foster et al. reviewed annual reports of UK Local Research Ethics Committees (LRECs) and sought to determine their size, gender composition, and fees charged for review [56]. Other outcomes in this more common grouping were: Committee decision making (n = 71, 36%), committee/board member views (n = 65, 33%), variation between review committees/boards (n = 61, 31%), ethics committee/board membership (n = 59, 30%); time taken for review (n = 54, 28%), outcome of review (n = 50, 25%).

Within the second cluster of outcomes–which tended to represent assessments of functional aspects of committee/board approval and monitoring—the most popular outcome was the comparison of ethics review performance against existing standards or legislation, such as the Common Rule (n = 26, 13%). Of those assessing performance against existing standards, several studies reported that different IRBs varied in their interpretation and application of the same guidelines [12, 56–59]. Some authors noted that certain criteria–such as informed

Table 2. Examples of individual study outcomes according to thematic groupings.

Thematic grouping	Examples
Membership	**Borovecki et al (2005):**1) IRB membership information: age, sex, occupation 2) Number of members in the committee
	Catania et al (2008): 1) The composition of each IRB committee administered by their office: total members per committee, number of non-institutional members, number of non-institutional members without a science background
Time	**Ahmed et al (1996):** 1) Time taken (days) to obtain ethical approval
	Al-Shahi et al (1999): Delay from application to- 1) Calling an LREC meeting 2) Initial LREC decision 3) Final LREC approval
Cost	**Byrne et al (2006):** Number of units of various resources that were used at a given IRB. 1)Travel 2)Supply and equipment purchases 3) Space used
Cost	**Chakladar et al (2011):** 1) Number of sheets of A4 paper distributed to committee members and used during requested amendments or resubmissions. 2) Paper use during IRB process. 3) Paper use during study conduct
Variation	**Angell et al (2006):** 1) Patterns of agreement in decisions, descriptively and using the kappa statistic.
	Fitzgerald et al (2006) (62): 1) Comparison between centralized and decentralized systems: administrative and the review process
Satisfaction	**Mosconi et al (2006):**1) Average level of satisfaction on the interactions with the REC for each of the following aspects: bureaucratic and secretarial, ethical, scientific and methodological, education aspects and training activities
Policy Adherence	**Abbott et al (2011)** 1) Process studies examining the extent to which federal regulations are implemented by the IRB
	Ateudjieu et al (2010) 1) Difficulties in applying regulations
Working Hours	**Ah-See et al (1998):** 1) Frequency of meetings
	Kirigia et al (2005): 1) Frequency of scheduled meetings 2) Number of times the committee actually met last year
Outcome	**Czarkowski et al (2009):** 1) Number of negative assessments given
	Russ et al (2009): 1) Frequency of formal and content-related objections in the decisions of coordinating ethics committees after first application
Training	**Ateudjieu et al (2010):** 1) Training on research ethics evaluation. 2) Types of Training. 3) Training Content. 4) Perceived importance of targeted groups for training. 5) Training objectives
Knowledge	**Banos et al (2010):** 1) Degree of improvement in the knowledge of those attending seminars
	Borovecki et al (2006): 1) Self assessment of the knowledge of each respondent in the field of biomedical ethics. 2) Participants' knowledge on the field of biomedical ethics, bioethics issues
Structures and procedures	**Foster et al (1998):** 1) Policies regarding multi-centre research
	Jones et al (1996): 1) Policies concerning scientific misconduct
Number of Protocols	**Boyce (2002)** 1) Number of new and continuing applications discussed at each meeting
	Catania et al (2008) 1) Types and volume of protocols received in the past year. 2) Total number of protocols [new and prior] 3) Number of new [all types] and of new full-committee review protocols
IRB Member Views	**Abou-Zeid et al (2009)** 1) Self-rated capacity to perform committee activities
	Allen et al (1983): 1) Present and retired IRB member general attitudes towards ethical committees and their functions
Researcher Views	**Douglass et al (1998):** 1) Researcher experiences of the ethics review process
	Kallgren et al (1996): 1) Student researcher reactions to going through the IRB process
Participant views	**Berry (1997):** 1) Did the patients know that they were research subjects? 2) Had they been given enough information and enough time to give valid consent? 3) Had they been told what to do if there was a problem?

(*Continued*)

Table 2. (*Continued*)

Thematic grouping	Examples
	Karunaratne et al (2006):1) Were there any parts which you found difficult to understand? 1) Which activities do you think ethics committees are involved in?
IRB Decision Making	**Boyce (2002):** 1) Reasons for condition approval/deferral
	Czarkowski et al (2009): 1) Basis on which decisions concerning research projects were made. 2) Basis for reviewing applications
Post Approval Monitoring	**Arda (2000):** 1) Methods used to monitor the progress of projects
	Gibson et al (2008) 1) Assessment of need for ongoing monitoring of registry by REB 2) Types of information that would need to be reported
Number of RECs in Region	**Vulcano (2012)** 1) Assessment of the number IRBs using a database
Views of HCPs	**Allen et al (1983):** 1) Doctors who have never been members of an ethical committee views towards ethical committees and their functions

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consent–received much greater consideration than others, such as risk minimization or data monitoring requirements [58]. Others report variation in the requirements of ethics applications, even within the same jurisdiction [59]. Other outcomes within this cluster were costs (n = 24, 12%), researcher views (n = 23, 12%), post approval monitoring (n = 23, 12%), training undertaken by review board members (n = 22, 11%), working hours (n = 20, 10%), and number of protocols reviewed (n = 18, 9%).

Least studied were outcomes relating to human subjects protections, and the conduct of others involved in the research ethics enterprise. Notably, the views of healthcare professionals not directly involved in research and research participants were rarely studied.

Nine studies identified assessed ethics committee/board member knowledge. As above, multiple approaches were often employed, with seven studies using surveys to explore knowledge, three focus groups, one study using an observational design, and another conducting interviews. These studies ranged with respect to the areas of knowledge being evaluated and how this was assessed. Allen, for example, explored IRB member knowledge of processes and procedures for reviewing genetics protocols [60] while others explored committee/board member knowledge of methodology [42] and ethical principles [42, 61–63] and procedures [55, 63, 64].

We identified four studies (2%) that specifically explored the views of research participants, and one that assessed the views of healthcare professionals not directly involved in research [41]. Studies of participant views ranged in focus, from evaluating IRB consent decisions by exploring participant experiences and understanding of the research in which they were involved [48, 50, 54] to surveying research participants regarding their views as to the roles and purposes of ethics committees [51].

Existing tools

A number of tools were identified that could potentially provide standardized assessments of ethics boards/committees (S2 Table). These include: the IRB-RAT [35, 36], the Training and Resources in Research Ethics Evaluation (TRREE)[65], the Research Ethics Committee (REC) Quality Assurance Self-Assessment Tool[30], an assessment tool developed by Tsan et al., for evaluating research protection programs in the Department of Veterans Affairs [32, 33], and a draft evaluation instrument for use in convened NIH IRB meetings [63].

However, there has been little–if any–validation of these tools. Only one tool–the IRB-RAT–has been used in a replication study, although Tsan et al., have applied their tool at

several time points to evaluate the same population [32, 33]. While the NIH instrument is reported as something that will be used to evaluate four of the NIH's 14 IRBs, no follow up reports were identified by our review.

Discussion

While research ethics review is a cornerstone of ethical research practice, there are no gold standards against which to evaluate research ethics review processes. This lack of standards

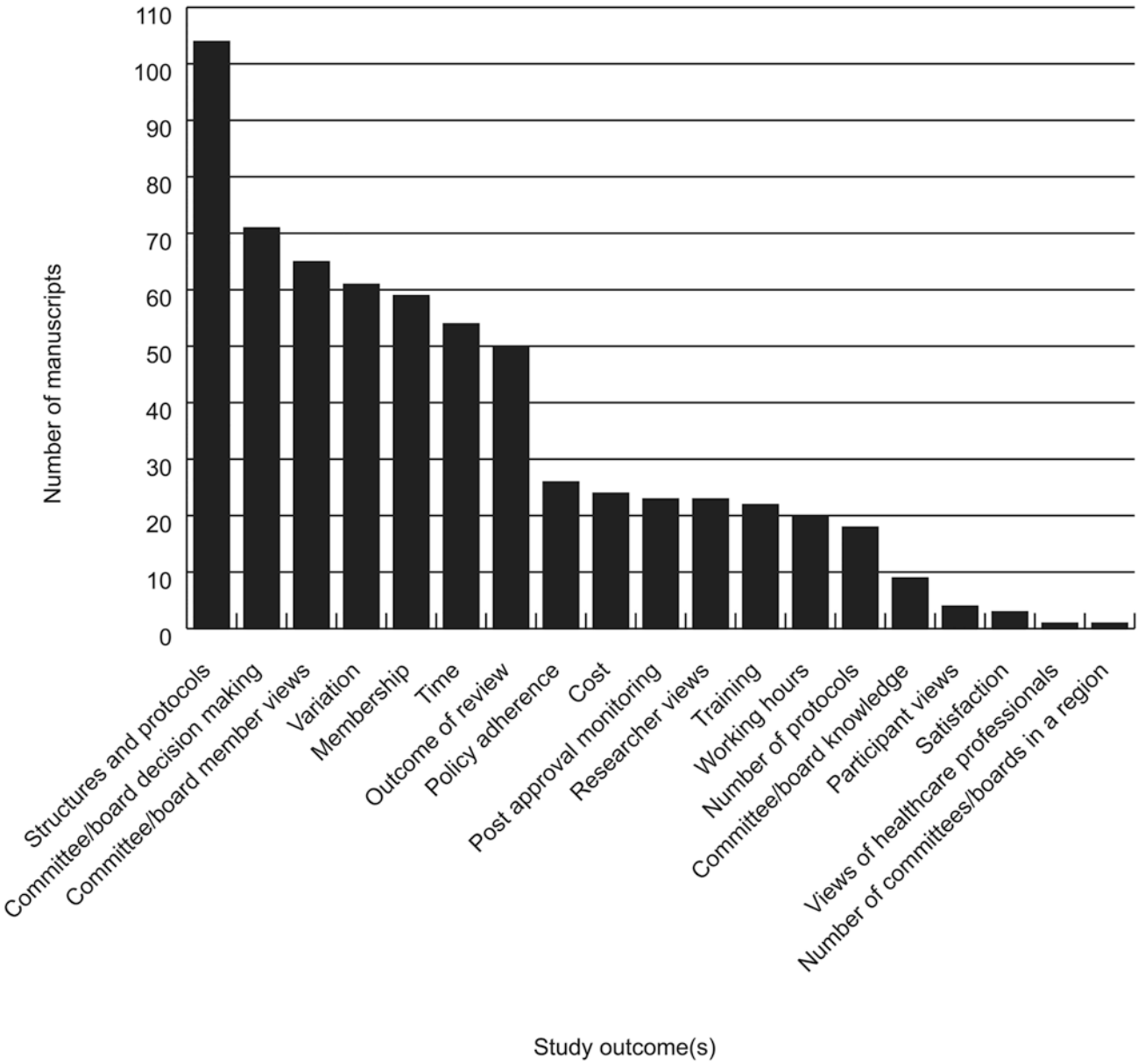

Fig 3. Instances of outcomes present in analysed manuscripts.

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stems, at least in part, from the lack of consensus regarding assessment criteria, but may also indicate a lack of emphasis on the evaluation of ethics review processes.

The findings of our scoping review indicate that until the turn of the 21st Century there has been little in the way of published research on the subject of assessment of research ethics review. What published research there has been has varied in terms of methodological approaches, subjects of assessment, and the outcomes evaluated. Most research has been conducted into procedural aspects of research ethics review such as committee composition, variation in review outcomes or time to approval, and that the majority of research has been conducted using quantitative approaches such as surveys or administrative review of quantitative data. The majority of research that was identified in this review has been conducted in North America and Europe.

Research approaches

The majority of studies retained in our review were quantitative in nature. As a result there has tended to be a focus on descriptive research; studies have documented how committees are composed, and the number of studies reviewed, or the amount of variation between committees reviewing the same protocol. There is much less explanatory research: why do committees make the decisions they do? How do the dynamics of committees play into decisions? Qualitative studies that include ethnographic methods could help to elucidate decision making models or objects of concern that are not easily or readily accessible through structured quantitative approaches.

A second notable gap in the existing literature is the lack of long-term–or longitudinal–assessment. The lack of longitudinal research is problematic if a goal is to protect human subjects or derive a net benefit for clinical research: as the study of de Jong et al., indicates, research outcomes, adverse events, or publications may not be immediately accessible and only through longitudinal studies would these outcomes be amenable to evaluation. Indeed, their finding that studies that had more correspondence with an ethics committee were less likely to achieve publication [66] is something that should motivate a greater degree of research into post approval monitoring.

The lack of longitudinal research may be symptomatic of the lack of a coherent research agenda with respect to developing evaluation frameworks or tools against which to assess research ethics review processes. Moreover, there may be barriers to the conduct of such research. A study by McKenzie et al., that sought to conduct long term follow up of studies receiving ethical approval itself faced difficulties in obtaining ethical approval on the grounds that the researchers were not obtaining informed consent from the trialists to view their ethics application [67].There is a need for leadership in this area, but also greater collaboration. Important questions need to be asked of researchers, administrators and funders. Funding will be central, but will also generate questions of responsibility and management: given the vagaries of short term contract research and associated funding, should the collection of information on ethics review processes be centrally resourced and conducted by ethics review committees themselves? Does this need to be done by an independent oversight body such as the Association for the Accreditation of Human Research Protection Programs (AAHRP), and if so how should this be managed and reported? These questions cannot be addressed in isolation, and need all relevant stakeholders to be at the table.

Research subjects

Our results indicate that there has been limited research with key stakeholders beyond the membership of ethics committees/boards and the researchers that interact with them; the

views of research participants have been largely missing from existing research. If a goal is to develop evaluation tools to assess research ethics review processes against their remit of protecting human subjects, then further research is warranted with those individuals who are subject to research. Indeed, current research is lacking several stakeholders who may be considered relevant to the debate. McDonald et al., have argued that research ethics review is but one part of the research ethics lifecycle, and that there are a broader range of perspectives that need to be considered beyond the researcher-ethics committee/board dyad [68]. We found little research with healthcare professionals outside the research context, and only one study that included the views of research sponsors. Identifying and including all relevant stakeholders in the review process; be they researchers, IRB members, policy-makers, legislators, research funders, institutional-sponsors, or research participants, will be key to identifying shared goals of research ethics review that are appropriate for, and amenable to, assessment. As such, we suggest that more research is needed that includes additional stakeholders beyond the IRB-researcher dyad.

Research outcomes

Given that research ethics review has been established to minimize harms to research participants, and that existing guidelines, regulations and research indicate that the protection of human subjects is a continued goal, we found a paucity of research exploring the experiences of research participants.Greater involvement of participants (and the public) may provide greater support for the decisions made, and could potentially lead to increased trust in the decision-makers and decision-making process as well as improved decisions [69]. Moreover, exploring participants' experiences may identify factors that contribute to potential negative effects, and facilitate modifications to the review process that may mitigate future repetition.

While calls for the development of metrics for measuring the quality of ethics review appear to have been heeded to the extent that some instruments were identified within the review, there has, to date, been little evaluation of these tools. Existing instruments reflect a fragmented research program in which individual researchers have developed custom data collection tools. This has not only limited assessments of reliability or validity, but has led to competing and contrasting data collection tools being developed.

Tools developed in other areas relating to core ethical principles could be useful for the evaluation of ethics review processes and should be considered for evaluation. In a recent review of measurement instruments in clinical and research ethics, Redman identified 10 validated instruments measuring ethical constructs [70].This included two measures of informed consent; the Multi-Dimensional Measure of Informed Choice [71], and the Quality of Informed Consent [72] instruments, but only one instrument that directly related to research. This tool, the Reactions to Research Participation Questionnaires for Children and for Parents (RRPQ-C and RRPQ-P), was developed to evaluate experiences of participating in research, as opposed to incorporating this within a framework for the evaluation of research ethics review [73]. Using tools such as this within a framework to evaluate research ethics review processes could allow for consistent metrics of assessment while specifically addressing the important goals of human subject protections. Moreover, the focus of measures such as this would clearly address the present research gap on participant experiences. However, further development and evaluation is needed to evaluate if such a tool is appropriate, together with consideration of whether this should be a researcher driven evaluation, or something undertaken by review boards themselves.

Limitations

Our results must be interpreted within the context of the limitations of the study. Firstly, our sampling frame was limited to a specific number of databases. As such, some articles, such as

articles from social science databases or grey literature, may be missing based on the limits and boundaries of the included databases. A second caveat is the specificity of the search strategy itself: while steps were taken to ensure that key articles were included, the sensitivity of the search strategy was limited in order to generate a manageable number of articles. However, our review may have been overly-calibrated toward identified key articles. We attempted to mitigate these limitations through reviewing the reference lists of articles, which was not limited by the original databases or the terms within the search strategy. The substantial number of articles achieved through this process indicates the utility of this approach in a heterogeneous area such as the evaluation of research ethics review. Finally, our search strategy was limited to English language publications. This may have biased our results towards countries where this is the predominant language of publication and may account, in part, for the larger number of articles retrieved from certain countries or geographic regions.

Conclusion

There is a continued call for, and interest in, the development of quality indicators for research ethics review. Our review indicates a lack of consensus on appropriate assessment criteria, exemplified by the varied study outcomes identified, but also a fragmented body of research. To date research has been largely quantitative, with little attention given to stakeholder experiences, and cross sectional. On the basis of our review we make the following recommendations for future research developments:

1. Assessment of long-term outcomes following research ethics review to identify variation within and between ethics review committees and to allow time for the identification of potential trends.
2. Engagement with a broader range of stakeholders, including research participants, in order to avoid viewing research ethics solely as ethics review, as opposed to a broader research ethics lifecycle [74].
3. The development of theoretical foundations upon which to base empirical investigations of research ethics review
4. The creation of review strategies and structures that facilitate the systematic search of the diverse literature around the evaluation of research ethics review including high quality databases of peer-reviewed publications across the range of disciplines and a common interface and search language.

Supporting Information

S1 File. Search Strategy.
(DOC)

S1 Table. Articles retrieved.
(DOC)

S2 Table. Identified measures or tools for evaluating research ethics review.
(DOC)

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Author Contributions

Conceived and designed the experiments: SGN JCB DF MM RS CW. Performed the experiments: SGN TPH JCB. Analyzed the data: SGN TPH JCB. Wrote the paper: SGN JCB DF TPH MM RS CW.

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4.2 Pharmaceuticalisation and Ethical Review in South Asia: Issues of Scope and Authority for Practitioners and Policy Makers

Bob Simpson, Rekha Khatri, Deapica Ravindran, and Tharindi Udalagama

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Pharmaceuticalisation and ethical review in South Asia: Issues of scope and authority for practitioners and policy makers

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ABSTRACT

Ethical review by expert committee continues to be the first line of defence when it comes to protecting human subjects recruited into clinical trials. Drawing on a large scale study of biomedical experimentation across South Asia, and specifically on interviews with 24 ethical review committee [ERC] members across India, Sri Lanka and Nepal, this article identifies some of the tensions that emerge for ERC members as the capacity to conduct credible ethical review of clinical trials is developed across the region. The article draws attention to fundamental issues of scope and authority in the operation of ethical review. On the one hand, ERC members experience a powerful pull towards harmonisation and a strong alignment with international standards deemed necessary for the global pharmaceutical assemblage to consolidate and extend. On the other hand, they must deal with what is in effect the double jeopardy of ethical review in developing world contexts. ERC members must undertake review but are frequently made aware of their responsibility to protect interests that go beyond the 'human subject' and into the realms of development and national interest [for example, in relation to literacy and informed consent]. These dilemmas are indicative of broader questions about where ethical review sits in institutional terms and how it might develop to best ensure improved human subject protection given growth of industry-led research.
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From time to time, terms appear in the social sciences which help in capturing a biomedical *zeitgeist*. Notions such as 'medicalization' and 'geneticisation' (Lipmann, 1991; Hedgecoe, 1998; Have, 2001) have in the past provided a simple shorthand for the ways that social, economic and technological changes begin to reshape the landscape of health care and the experience of those that pass through it. In similar fashion, pharmaceuticalisation has entered social science discourse. Williams et al. (2011) provide a critical evaluation of this concept and its utility in understanding the pervasive impact of pharmaceuticals within medical systems, economies and societies (also see (Abraham, 2011)). Consistent with their intention to give greater specificity to the pharmaceuticalisation thesis, we set out in this article to interrogate some of the 'upstream (macro) level processes' (2011: 712) that come within the ambit of pharmaceuticalisation. The arena we consider is one which is increasingly important in understanding the growth and development of pharmaceuticals in society but one that is often lost in a bias towards Euro-American accounts of this process. Here we bring together globalisation, governance and the ethical review of clinical trials involving human subjects in the developing world. The main sites we consider are research ethics committees and the responses of their members to a growing number of protocols for industry-sponsored clinical trials. What we show through this analysis is the way that the growing engagement with pharmaceutical interests across South Asia produces significant tensions for ERC members. Beneath the documentary and procedural claims to standardised measurement, rules and disinterested evaluation in ethical review, industry-sponsored clinical trials generate concerns about scope, legitimacy and authority for those whose job it is to undertake and develop credible ethical review (*cf* Timmermans and Almeling, 2009; Timmermans and Epstein, 2010). Whilst such tensions are likely to be evident in any context where research

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ethics and economic interest coalesce, we argue that in developing world settings there are other factors in play that give these questions a particular urgency and complexity.

Our stepping off point in considering the relationship between ethical review and clinical trials in South Asia is a question posed by Rachel Douglas–Jones in her doctoral thesis on capacity-building in ethical review in Asia: 'what are the problems to which the ethics committee is a solution?' [2013, p34]. The question is an important one. Ethical review committees play a crucial role in the regulation of experimentation involving human beings. In the most basic of terms, the approval of a formally constituted body of experts should ensure that research is beneficial, scientifically valid, and, above all, safe for those who participate. Yet, whereas in Europe and North America ERCs may have reached a degree of institutional integration and stability, they are still very much in a state of development in parts of the world that have only recently been drawn into the rapidly growing demand for experimentation involving human subjects. South Asia is a case in point. Capacity for ethical review is rapidly developing across the region and ERCs currently follow a broadly similar institutional and procedural format. Regional capacity-building has developed in association with organisations like the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP), the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) and the Global Forum on Bioethics (GFB) all of which work to build capacity when it comes to the review of projects locally. Affiliation to these organisations and the establishment of local branches [for example, FERC – Sri Lanka and FERC – India] is an important route to harmonisation and the dissemination of good practice. Arguably however, the more powerful source of standardisation for review of industry conducted trials has been the ICH-GCP guidelines which aim to provide 'a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health' (ICH, 2005). Drawing on a genealogy of crisis reaching back to the Declaration of Helsinki, the ICH-GCP lays down detailed benchmarks for the ethical and scientific conduct of trials. Yet, linking the work of ERCs with a genealogy of universal human rights in this way provides significant cover for the extension of commercial pharmaceutical research (Abraham, 2007; Abraham and Reed, 2002). In this view, ERCs are the handmaiden rather than the governor of trial activity with ethical review seen as essentially procedural, bureaucratic and rule observing. Earlier studies suggest that in countries that have embraced standard guidelines and particularly the ICH-GCP guidelines, ERCs are apt to operate in ways that appear to be more about legal defence of researchers rather than actual protection of subjects (Bosk, 2007; Kleinman, 1999; Stark, 2012). Our analysis confirms these concerns, and shows ethics committee members raising issues that are not limited to human subject protection *per se* but drawing in a range problems which afflict large numbers people in their society [for example, poor access to resources, corruption, illiteracy, inequality to name but a few]. These issues are articulated at a variety of scales [the person, the hospital, the University, the research community, the vulnerable, the nation state, the developing world and so forth]. Yet, the reality faced by many ERC members is one of growing pressure to accomplish human subject protection by narrowing the focus of ethical review such that it is clearly in line with industry specified guidelines.

1. Methods

The data on which this paper is based are drawn from a study of the growth of clinical trials and human experimentation in South Asia [India, Nepal and Sri Lanka].[1] In this study we identified key actors in the conduct, management and regulation of clinical trials in a variety of settings (See Table 1).

Table 1
The BHESA interview data-set.

Category	Nepal	India	Sri Lanka	US, UK	Total
PIs and Co-Is	10	31	11	3	55
Clinical research assistants	14	18	11	0	43
Other trial staff	24	22	39	0	85
Collaborators	0	3	1	1	5
Sponsors and CRO staff	0	35	1	13	49
Ethics committee members	6	14	6	0	26
Regulators	2	7	2	6	17
Other key informants	17	18	9	13	57
Total	73	148	80	36	337

In total we carried out 337 semi-structured interviews, the vast majority of which were recorded, translated into English where necessary, and transcribed. The resulting dataset was entered into Atlas.ti for coding. The codes were generated by an iterative process at a workshop held in Mumbai with all coders present; trial codings were carried out and a selection of interviews was recoded to ensure consistency.

Here we draw principally on extended interviews with a small sub-set of Ethical Review Committee [ERC] members from India [14], Sri Lanka [6] and Nepal [6]. In many respects, the sample is unrepresentative of the wider body of reviewers at work in each of these countries as it was self-selecting and therefore tended to be made up of people who were knowledgeable, articulate and keen to express their views on the rights and wrongs of clinical trials, the work of ERCs and their less responsible colleagues. They were also mostly from Institutional [hospital] and University settings. Nonetheless, consideration of their accounts of topics such as ethical review, operation and composition of committees, capacity building, training for reviewers and approaches to informed consent provides a useful indicator of the major challenges faced by committed ERC members in the settings identified. We also draw to a lesser extent on interviews with regulators, policy-makers, academics and investigators involved in developing ethical review infra-structure. Before considering these responses in detail it is necessary to consider briefly the three contexts in which our study took place.

2. India

India has a well-established pharma industry dating back to the 1950s. The thrust of this industry has been the production of generics for local markets. This infrastructure, combined with large numbers of English speaking doctors and technicians, as well as large populations of treatment naive people with a range of disorders of interest in the west [e.g. cancers, cardio-vascular disease, diabetes] has stimulated much interest in clinical trials. Trials are outsourced by western pharmaceutical industries as well as conducted by local companies keen to move into global markets for their products. Acceleration in this sector of activity has overwhelmed existing machinery for ethical review and monitoring which previously catered mostly for locally conducted research. Along with Ethical Guidelines for Biomedical research Involving Human Subjects Indian Council of Medical Research (2000), the

[1] The research was funded by the Economic and Social Research Council of the United Kingdom in collaboration with the Department for International Development [ESRC/DfID nbrRES-167-25-0503]. Ethical approval for the study was initially given by the School of Social and Political Sciences Research Ethics Committee, University of Edinburgh [13/10/2010]. Ethical clearance was then gained from local ERCs for research to be carried out in India, Nepal and Sri Lanka.

ICH-GCP guidelines have provided the framework for the conduct of ethical and scientific conduct of trials. In 2001, ICH-GCP India were created (CDSCO, 2001), adapting the generic guidelines to fit local circumstances. In 2005, the 'Schedule Y' amendment of the Drugs and Cosmetic Act provided further guidance on the constitution and responsibilities of ethics committees. To date, ERCs have largely operated within the institutions in which the trials have taken place. The ICMR has launched various initiatives to encourage the take up of standard operating procedures against a backdrop of poor regulation and variable quality of the review process. The Forum for Ethical Review Committees – India [FERCI] was established under the auspices of FERCAP to improve quality and standards and held its first conference in 2011. In 2007, the ICMR established its own clinical trials registry.[2] At the time of writing, there over 650 ERCs registered via the Clinical Trials Registry of India.[3] The workload of ERCs is unevenly spread with a relatively small number of ERCs dealing with the majority of trials and a disproportionate number using independent ERCs.

3. Sri Lanka

Sri Lanka has neither the population nor the pharmaceutical industry that India has. Not surprisingly therefore, the development of ERCs looks very different. All the major medical faculties and teaching hospitals currently have their own institutional ethical review committees, making for some 15 committees (Dissanayake et al., 2006). The Sri Lanka Medical Association (SLMA) formed its ethics committee in 1991 and began considering research projects carried out by its members in 1999. In 2005, the Forum for Ethical Review Committees in Sri Lanka [FERCSL] was established along with Uniform Guidelines for ethical review (Dissanayake et al., 2006). However, take-up of the guidelines appears patchy with considerable variation in standard operating procedures in evidence. The increase in the number of ERCs and the quality of their capacity to review projects was in part driven by an increase in international collaborative research being conducted in Sri Lanka as well as by the desire to create robust research governance of the kind needed to attract trials in the future. Sri Lanka has also recently created its own clinical trials registry.[4] As in India, ERCs are a key mechanism in the regulation of trial activity but they are also identified as having serious weaknesses that need to be addressed if they are to be effective (Karunananyake, 2012).

4. Nepal

Nepal is by far the smallest player in the emergence of human experimental activity in Asia and consequently has a very recent and modest history of ethical review. The central body regulating research studies in Nepal is the apex Ethical Review Board (ERB) of Nepal Health Research Council. The 20 Institutional Review Committees (IRCs) that operate mostly in the medical schools have been approved by the national ERB. The IRCs came in existence because of increasing volume of local research studies seeking approval from ERB. IRCs are not currently authorised to review international trials which must be reviewed at ERB level. National Ethical Guidelines for Health Research in Nepal were published in 2001. A National Guideline on Clinical Trials with the use of Pharmaceutical Products was published in 2005. Phase I and Phase II trials are not currently allowed and as a consequence Nepal has not been a target for growth in these activities with the increase in research mostly being carried out by international charities, NGOs and academic bodies (Khatri et al., nd).

5. The rise of human experimentation in Asia

> *The earlier attitude was that we should block it [clinical trials development] because as I told you it was a nation of traders at that time and now because our own people are innovating, we want the innovation to be there, we want to be landscaped for the innovation, so the trials are to be permitted but then at the same time the ethical standards have moved up, benchmarks have increased, every trial has to be put on the web and everything has to be on the web, so it is an open system, so in that you don't feel threatened; not at all but the only thing, I feel heavy as a person.* Senior Government of India Official [022]

> *…[the government].. want to promote clinical trials more as a money making exercise than anything else I guess, because clinical trials are big money, and we have a good receptive population here, educated and also the free health care which means that people need not bother about funding health care for the patients with side effects or anything, that automatically falls on the state to fund all that, so it's a very practical place for clinical trials.* Sri Lanka ERC member [71]

> *Before 1990, there are people who brought medicines in bags and distributed but after the formation of Nepal Health Research Council in 1991, every health research in the country should take ethical approval from them. I am dead against clinical trials. My soul just doesn't agree to it. There are vulnerable groups like poor people, army, students, handicapped people who are being tested. We should not encourage it [clinical trials]…[]… Newer biological products should not be tested in humans. There are also DDA regulations to be cleared in Nepal.* NepalERC member [03]

In the three quotations given above, something of the ambivalence that those with responsibility for ethical review feel about clinical trials sponsored by commercial trials organisations is evident. On the face of it, the economics of experimentation are undoubtedly attractive. Saving costs on drug development, opening up new markets and even developing entirely new drugs using local expertise has the potential to reconfigure the shape of the pharmaceutical industry across the globe. In anticipation of such developments, extravagant claims have been made for the contribution that clinical trials will, in due course, make to economies in the region and particularly in India. These claims have stimulated the promotion of trials, training of personnel and capacity building in the knowledge and expertise needed to conduct trials in accordance with international standards. Much of this activity is intended to create a climate in which home-grown as well as outsourced clinical trials will thrive; the promise is nothing short of a pharmaceutical El Dorado.

On the way to this El Dorado, however, serious concerns have been raised. Many of these concerns are by now familiar and well-rehearsed; they draw attention to the potential for abuse and exploitation of 'human subjects' in trials. This may range from the inadequacy of informed consent procedures through to physical

[2] The Clinical Trials Registry India. http://www.who.int/ictrp/network/ctri/en/index.html accessed 23rd July 2013 http://www.who.int/ictrp/network/ctri/en/index.html accessed 23rd July 2013.

[3] Details of registered ERCs can be found on the website of the Central Drugs Standard Control Organisation: http://www.cdsco.nic.in/forms/Default.aspx accessed 5th Feb 2014.

[4] The Sri Lanka Clinical Trials Registry (SLCTR) is a Registry for clinical trials involving human subjects, conducted in Sri Lanka or overseas. The SLCTR is a Primary Registry linked to the Registry Network of the International Clinical Trials Registry Platform of the WHO (WHO-ICTRP). It is a not-for-profit Registry, with free and open access to researchers, clinicians, and the general public'. http://www.slctr.lk/accessed 21st July 2013.

harm and even death as a result of adverse drug reactions for which there may then be little or no compensation, giving rise to charges that local populations are used as 'guinea pigs' with 'double standards' in operation (Macklin, 2004). There are concerns that groups rendered vulnerable by their marginality, poverty and lack of literacy are being caught up in the 'global search for human subjects' (Petryna, 2009). In the ensuing debates, ERCs figure as both a key mechanism in enabling trials as well as a site of potential activism aimed at drawing attention to abuses and the broader issues of inequality that often underpin these. ERC members frequently indicated their awareness of vulnerable research subjects and their duties and responsibilities in ensuring their protection:

> *…. the people who are in the ethics committee, they really see to it that the patient's rights are properly taken care of … because they don't know anything scientifically* India, ERC member [003]

The problems identified, however, were not just downward facing ones. ERC members in each country spoke of their responsibilities to feed issues and concerns up into legal and policy-making machinery. Here, the concerns were much more about 'national' interest and how it might be sidelined, undermined or over-ridden in the quest for viable experimental economies. One informant spoke of 'research coolies', an emotive term intended to invoke parallels with other arena in which domination and exploitation of developing world populations is underway. This was particularly so in India following a change of law in 2005 which allowed easier access to pharmaceutical companies to local populations (see Nundy and Gulhati, 2005). Similar, sentiments were evident in Sri Lanka:

> *… the problem is we need to upgrade our societal knowledge levels, preparedness must be upgraded, if that [successful engagement with international clinical trials] is to actually work in that way, otherwise it won't, it will be a new kind of colonialism. That's the problem.* Sri Lanka ERC member [074]

In response to these problems, members of ERCs spoke optimistically of a progressively stronger, more confident and better organised infrastructure out of which robust and consistent responses could be applied to international and locally sponsored research proposals

> *…… we have a strong procedure right now. Earlier there was hardly any procedures and now we have an application form, even including a standard operating procedure is available for the investigators to check..[].. one of the biggest advantages came for the ethics review parties the ICMR guidelines which came in 2004, '05 which actually helped a lot to formulate how an ethics committee should function in the country.* India ERC member [009]

> *… ethics committees have evolved. The type of questions that we use to ask and the issues we used to raise 10 years ago are different from what we raise now. And by and large the bar has risen. And therefore even investigators have refused trials, I know. And in fact many of them involve me in that pre-nup discussion. You know, before they firm up with the company they will, they have ethical issues they want to know from me also whether these are ethical issues, whether these will cause problems. So they do want to iron it out. …[].. the investigator community needs to be convinced that the ethics committee is a policeman, but a strict policeman, but not somebody who is against us. But [someone] who wants to promote good ethical research. And has ultimately got the patient's good at heart.* India ERC member [002]

Yet, despite these claims to progress, there was a sense in which the work of committee members was a small response in the face of a much bigger problem. Most of the ERC members interviewed were voluntary. Their work involved long hours and exacting work dealing with an unfeasible workload with the threat of possible hostility from researchers in the background should they give unfavourable decisions. Nonetheless, many of those interviewed expressed strong commitment and dedication to their work. Indeed, some spoke with enthusiasm bordering on evangelical zeal about the importance of ethical review and the need to extend its scope and improve its thoroughness.

However, the management of ethical review in practice was likely to be rather more pragmatic and tactical. As a comment from a member of an ethics committee in India makes clear, social and humanitarian concerns are less in evidence as other priorities take over

> *…. according to me if a person is recruited as a subject of research and it is deemed by a component ethical review board and set of researchers, that there is no ethical wrong or scientific wrong in that person being recruited I don't see why Indian subjects can't be recruited for clinical trials. So, yes, ok Indian patients are being made guinea pigs for molecules. If it is being done in the right way I don't see anything wrong…[].. I suppose there are many agencies which are conducting clinical trials which are not earlier into ethical standards or scientific standards that is required. I don't know about that. But as far as we are concerned I don't see anything wrong.* India ERC member [001]

In this rather straight up and down reading of ethical review, the scope and function of ERCs is simple and clearly limited to the research protocol and the assurances given therein. The attraction of this approach, particularly among younger researchers, appeared to be that it offers both procedural efficiency and authoritative outcomes in circumstances where complexity and the sheer volume of work might otherwise overwhelm. In the midst of this tension, our research identified a powerful and emerging alignment. In managing the growing volume of protocols to review, ERCs appeared to be cleaving to ICH-GCP as a route to procedural clarity. At the same time, they also found themselves in competition with a new breed of 'independent' and, indeed, internationally sponsored ERCs.

These organisations were beginning to feature in the ethical review landscape of India and to a lesser extent in Sri Lanka. Constituted and practicing in conformity with ICH-GCP from their inception, they offer a commercial route to ethical approval. Their emergence causes concern to those who have laboured to develop capacity and rigour in the work of institutional review bodies. Concerns expressed were twofold. First, the guidelines followed can be interpreted quite minimally and specifically and whilst scientific rigour is likely to be guaranteed [because otherwise the validity of the data would be compromised] issues of patient safety are likely to be treated in a more procedural fashion.

Furthermore, a route to ethical approval which circumvents a more politicised reading of ethics and what it means to protect a 'subject' is highly attractive to those wishing for a speedy review. This tension is most evident in industry sponsored clinical trials which are likely to be multi-centred. Here industry standards enshrined in the ICH GCP create expectations of high levels of conformity between trials. ERCs have less of a role to play in such trials, primarily because the protocols are less negotiable but also because large pharma companies, particularly foreign ones, have both the resources and the experience to draft scientifically sound and ethically plausible protocols. As one PI on a commercial trial in

India put it: '*Sponsors are very clear. They want safety data, efficacy in the Indian population. That's all. Nothing more*' India Clinical Trial PI [004]. In the drive towards procedural efficiency and auditable outcomes, trialists, both commercial and non-commercial, end up paying less attention to the wider socio-economic contexts in which trials take place. Complex questions of just what is informed consent and how to get it, and what the benefits are for those who participate in research are apt to be occluded in the face of pharma induced proceduralism. This is not to say that these issues are absent from protocols but rather that, in the complex chains of responsibility and accountability that lie between a professionally crafted and ethically approved application and its implementation on the ground, there is much scope for the interests of trial participants to become secondary to the conduct of the trial and the data it sets out to generate. This problem is further compounded by the fact that it is often junior staff with minimal training who are responsible for the implementation of agreed protocols at the level of day to day interaction with research participants.

The emergence of independent ethics committees within the ERC landscape adds further momentum to this process, with concerns being expressed about their independence (Karam and Karandikar, 2012); also see (Emanuel et al., 2006). For many of those interviewed, ethical review was not a legitimate area for commercial activity because of the tension it creates between robustness of review procedures on the one hand and the likelihood of future use of particular ERCs by CROs and their sponsors on the other:

> *.. If an independent ethics committee is very cautious, and they fear that if they don't approve, it [the trial] easily goes elsewhere and they get the approval from there. Like EC shopping. There is nothing to prevent that*. India ERC member [002].

> *The minute they realize that there is something going wrong, when we ask uncomfortable questions, they just go to some other committee* India ERC member [001]

At the time of writing [Jan 2014] the Drug Controller General of India has forbidden independent ethics committees from approving clinical trial protocols following complaints about procedural irregularities.[5] Further steps have been taken by the Supreme Court of India to establish more stringent monitoring of trials including registration and accreditation of ERCs which will, in future, also have increased responsibilities for monitoring and reporting.[6] Neither Sri Lanka nor Nepal has the kind of demand that would currently make independent ethics committees viable. Nonetheless, as we will see in the next section the issues of legitimacy and jurisdiction that their existence raises is much wider than India alone.

6. ERCs and the question of legitimacy and authority

ERCs feature in a complex landscape of interests and concerns. These are at once economic and humanitarian; legal and social; national and international. Procedural legitimacy and authority is drawn from their location within particular institutions. These include Universities, Professional Associations, Hospitals and government departments and institutes with committees assembled out of suitably representative experts. ERCs also derive their authority from a patchwork of guidelines and regulations that emanate from different sources: government, industry, academia and international NGOs. Reference to these sources enables ERCs to gain credibility and acceptance among local and international researchers. They provide members with an ethical charter of sorts which validates and legitimates action.

> *We are SIDCER approved, and basically …[]…, there is the FERCSL national guidelines on writing your standard operating procedures and doing the ethics review and we basically follow that to the letter, so our SOPs is already readily available you can find it or I can give you a copy, everything is in writing and it's very easy to understand, it's all tick boxes and check lists and we are very transparent in the whole review, so really that's what we follow and at the moment we are reviewing our SOPs also, and probably that's of course just our procedures I think you may have to also look at our criteria for review and see whether we can improve on that. It is very standard everybody does the same thing within our* EC. Sri Lanka ERC member [071].

> *… we have developed our SOP's based on ICMR, ICH and FERCAP guidelines, so we follow those. And now because we have a SOP we are stronger in saying certain things* — India ERC member [156].

Unlike in Sri Lanka and Nepal, there is an expectation in India that the responsibilities that figure in a research application will be legally recognised and approved:

> ***Interviewer**: In India CRO PI, investigator and director all sign an agreement relating to the collaboration?*

> ***Respondent:** Yes. That is reviewed. But it comes to the ethics committee; it also goes to our legal expert. You have a (hospital ethics committee) legal expert. He also clarifies that, gets things done the way the hospital is supposed to have it legally and it also comes to the ethics committee to have a final look at that. This goes simultaneously; when they put in support for the scientific review they will immediately send the CTA to the legal expert office*. India ERC member [156].

Whilst these forms of regulatory triangulation increase confidence, they also raise concerns about over-excessive and disabling regulation among researchers. ERCs as mechanisms that enable and facilitate better research, give way to rather more antagonistic readings of the role of ERCs among researchers with concerns expressed that ERCs address problems that are not within their sphere of responsibility:

> *I mean we are talking about ethics; we are talking about bad science which is impeaching on ethics. They do ask, 'who are you, what is this? This is (name of the respondent)'s EC please, we should try to avoid it'. So we have people like that. So it's not that simple. … whoever has to work as regulators are never popular people, by definition*. India ERC member [002]

However, in contexts where authority is weak and mistrust is high, invoking rhetorics of legitimacy, such as audit, monitoring, surveying and certification by higher authorities, is one of the few strategies available to persuade outsiders of the committee's authority to make legitimate pronouncements on the ethics of research. Such credentials are essential when it comes to an ERCs ability to act as what Stark has referred to as a 'declarative body', that is, one capable of making judgements and evaluations but, most critically, decisions which will be accepted as emerging from a democratic process (Stark, 2012, pp. 4–5).

[5] http://pharmabiz.com/ArticleDetails.aspx?aid=76984&sid=1 accessed 13th August 2013.

[6] Government set to tighten clinical trial norms. Times of India 3/01/2014. http://articles.timesofindia.indiatimes.com/2014-01-03/india/45834762_1_clinical-trials-accreditation-council-ethics. accessed 10th Jan 2014.

The power of ERCs is, therefore, largely negotiated rather than absolute, based on guidelines rather than laws and persuasion rather than instruction. Whilst great strides have been made in channelling more research through ERCs and cultivating the confidence of researchers, there remain anxieties about the limits of their power and a sense that all their good work might be undone once the project passes beyond the ERC and into its implementation phase. For example, in Nepal and Sri Lanka, once a project is approved it is very much a matter of trust and investigators' willingness to self-report on how the trial is implemented. For one of our informants, this issue was further linked with lack of capacity within the committee:

> *… there's no training, we don't have people who have trained in it [ethical review], it needs training, monitoring, for the moment we have done the consent monitoring and then we have depended on adverse events from the investigators, ..[]… We do not have the staffing or the training.* Sri Lanka ERC member [076]

For this ERC member, establishing a functioning ERC, simply served to highlight the partiality of the process; there was an awareness that many further steps would need to be taken to ensure that monitoring was both comprehensive and rigorous. The committee simply made apparent the magnitude of the problem of policing projects once approved.

Problems of ERC scope, however, are not just about jurisdiction. Other concerns arise for ERC members when they consider the limits of their roles and responsibilities towards subjects who they will never know. The moral complexity of the issues that they are expected to deal with are substantial. As one of our Indian informants candidly put it:

> *…. I find it very difficult to put myself in the feet of the completely uneducated women from Uttar Pradesh. I find it impossible to do so. Which means to know how she would think and how she would react to a situation is impossible for me? Which means then we need them [ERC members] to discuss this, to come up with a guidance document. Like I told you, to talk to this cancer survivor, completely different thought process came in to my mind, that you have to think of it from too many different sources.* India ERC member [002].

What this quotation points to, is a profoundly humanistic conception of the role of ERCs but one that is often lost to procedure and pragmatism. The starting point for any application is a research protocol. The style of the protocol is invariably technical and constructed in such a way that researchers and 'subjects' are described impersonally and with maximum detachment – socially and culturally these documents are flat, and intentionally so. It is the skill of the person drafting the research protocol, and particularly in pharmaceutically sponsored multi-centred trials, to produce such documents. However, through ethical review, there is some presumption that the social imagination of the reviewers will be brought into play. It is, in theory at least, the task of the ethics committee to animate the protocol, that is, to try to imagine the people who are likely to end up in the trial and the worlds in which they live. Arguably, this is why social scientists and lay people are brought on to ERCs and why there is currently a great deal of interest in community advisory boards as ways of amplifying the voice of those who end up in trials (Weijer and Emmanuel, 2000). The purpose of such a mechanism is precisely to help stimulate acts of imagination and empathy capable of invoking the people and relationships with which the protocol will ultimately engage.

> *… you can't define risk only as physical risk. People just forget social risks, economic risks and psychological risks.* India ERC member [002].

However, putting oneself in another's shoes in the context of a busy ERC is both challenging, time consuming and deemed by some to be wholly misplaced. Consequently, there is a danger that the human subject that features at the heart of an ERC's deliberations will not be any actual person in a real place and time but the trans-cultural, trans-historical, universal subject which features in all protocols. At this juncture, ICH-GCP offers an attractive route to consistency in the conduct of clinical trials and particularly its focus on the informed consent transaction as the primary index of ethical conduct. However, the economic and cultural questions that exercise some ERC members are apt to be obscured or overlooked.

In India in particular, limitations in terms of resources, training and the absence of clearly defined statutory duties render the limits of ERC responsibilities fuzzy at the margins. Indeed, the scale and complexity of activity means that the possibilities for breaches of regulation are rife. A current concern of a number of informants was the potential for moving activity to the edges of regulatory reach whether this be in terms of the regions in which trials are conducted or the committees through which trials are put. As a result there have been calls for ERCs to have 'teeth' and a clearer articulation with law and state regulation. Proposals to amend the Drugs and Cosmetics Act [1940], as mentioned above, have specified that ethical approval for clinical trials can only be given by ERCs that have been registered with the licensing authority. This development further ties in the practice of clinical trials with the ICH-GCP India Guidelines via the formal registration of ERCs. The amendment also gives the Central Drugs Standard Control Organisation the power to inspect the documentation of an ERC at any time.

7. Conclusion

We began our considerations of ERC members' views with a question: if ethics committees are the solution what is the problem? In reflecting on the impacts of industry sanctioned models and strategies for ethical review in the developing world it would seem that there are a range of problems, some of which extend the business of human subject protection beyond the immediate engagement between a trial participant and a treatment being tested in an RCT. In this article we have provided insights from those who are, in many respects, at the eye of the storm when it comes to the governance of clinical trial activity. On the one hand, ERC members articulate a need for contextualisation and localisation in the attempt to render trials ethical in developing world settings (cf Emanuel et al., 2004; Lavery et al., 2007). Here, ERC members we interviewed, allude to issues that confound their efforts to protect subjects, such as poverty, literacy and structural inequality. Achieving a satisfactory ethical review might, in other words, inspire advocacy and social critique. On the other hand, however, they face considerable pressure. Their workload is substantial, they are under-resourced and there is a strong push to standardise and regularise the work of ethical review in ways that remove the independence of reviewers to set the scope of their concerns.

These tensions are not just national or indeed regional phenomena but are fuelled by changes that are taking place in Europe and US which are aimed at increasing research capacity and velocity by means of an alignment between ethical review and industry standards and procedures. For example, at the time of writing, the EU is proposing to replace the existing clinical trials directive with a new regulation aimed at accelerating application procedures and harmonising administrative requirements for multi-centre trials across the European Union and in countries participating in trials beyond the EU (Den Boer and Schipper, 2013). In the US, Food and Drugs Administration (FDA) proposed that the

International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) be designated as the new regulatory standard which in effect sidelined the Declaration of Helsinki for trials carried out outside the US (Goodyear et al., 2009). Both of these developments have significant implications for the role that ethical review might play in attempts to safeguard trial participants from harm and exploitation. Given that ethics committees may not be able to provide the kinds of protection that vulnerable people need we ought to ask a further question: if ethic committees are the problem, what is the solution?

That ethics committee are currently a problem in the countries considered might be inferred from the ways in which clinical trials activity has generated debate, stimulated activism and stirred those responsible for the governance of research to put forward improved regulatory responses. For example, since our data was collected, responses to public concerns over clinical trial regulation in India have resulted in a wide range of new regulations coming from the Supreme Court, the Office of Drugs Controller General of India and a series of expert panels. Registration of ethics committees, audio-video recoding of the informed consent procedures and clearer rules regarding compensation for deaths and injuries that occur during clinical trials are all now mandatory.[7] In Sri Lanka, the drafting of a new Clinical Trials Act has provoked controversy as it is believed by some to lower the regulatory threshold thereby making it easier to conduct clinical trials (Siribaddana and Bandara, 2013). In Nepal, whilst debates about commercial trials have only just begun, there is much interest in regulating research activities and promoting ethical standards in the conduct of both clinical and public health research. Significantly, in each of these places, ERCs are identified as the problem but they are also identified as the solution when it comes to better research governance.

Yet, when it comes to what constitutes effective and legitimate ethical review, the language of ICH-GCP is a strong card to play. One of the reasons for this is the ease with which techniques of verification such as monitoring, audit, record keeping, documenting and other evidence making procedures familiar to scientists, can be imported into the practice of ethical review. However, the failure of ethical review to protect human subjects beyond the informed consent transaction does not result in a change of method but typically better monitored replications of the same process (cf McGoey, 2010). One consequence of this move in the US has been a tendency to replicate the evidential turn in science through an evidence-based ethics in that it would similarly, '…. emphasize the importance of data in informing decision and decision-making about the ethical issues inherent in clinical medicine and research' (Sugarman, 2004, p. 495). The tendency to instrumentalise ethics in this way was evident in the accounts of a number of researchers interviewed. Rather than seeing the directives of an ERC as the beginning of an ongoing awareness of the wide-ranging vulnerability of their subjects, many researchers spoke of ethics as a kind of object; something obtained from, or 'given' by, the ERC which then enabled them to continue with a clear conscience.

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4.3 Understanding the Functions and Operations of Data Monitoring Committees: Survey and Focus Group Findings

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Recommendations for data monitoring committees from the Clinical Trials Transformation Initiative

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Abstract

Background/aims: Use of data monitoring committees to oversee clinical trials was first proposed nearly 50 years ago. Since then, data monitoring committee use in clinical trials has increased and evolved. Nonetheless, there are no well-defined criteria for determining the need for a data monitoring committee, and considerable variability exists in data monitoring committee composition and conduct. To understand and describe the role and function of data monitoring committees, and establish best practices for data monitoring committee trial oversight, the Clinical Trials Transformation Initiative—a public–private partnership to improve clinical trials—launched a multi-stakeholder project.

Methods: The data monitoring committee project team included 16 individuals charged with (1) clarifying the purpose of data monitoring committees, (2) identifying best practices for independent data monitoring committee conduct, (3) describing effective communication practices, and (4) developing strategies for training data monitoring committee members. Evidence gathering included a survey, a series of focus group discussions, and a 2-day expert meeting aimed at achieving consensus opinions that form the foundation of our data monitoring committee recommendations.

Results: We define the role of the data monitoring committee as an advisor to the research sponsor on whether to continue, modify, or terminate a trial based on periodic assessment of trial data. Data monitoring committees should remain independent from the sponsor and be composed of members with no relevant conflicts of interest. Representation on a data monitoring committee generally should include at least one clinician with expertise in the therapeutic area being studied, a biostatistician, and a designated chairperson who has experience with clinical trials and data monitoring. Data monitoring committee meetings are held periodically to evaluate the unmasked data from ongoing trials, but the content and conduct of meetings may vary depending on specific goals or topics for deliberation. To guide data monitoring committee conduct and communication plans, a charter consistent with the protocol's research design and statistical analysis plan should be developed and agreed upon by the sponsor and the data monitoring committee prior to patient enrollment. We recommend concise and flexible charters that explain roles, responsibilities, operational issues, and how data monitoring committee recommendations are generated and communicated. The demand for data monitoring committee members appears to exceed the current pool of qualified individuals. To prepare a new generation of trained data monitoring committee members, we encourage a combination of didactic educational programs,

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practical experience, and skill development through apprenticeships and mentoring by experienced data monitoring committee members.

Conclusion: Our recommendations address data monitoring committee use, conduct, communication practices, and member preparation and training. Furthermore recommendations form the foundation for ongoing efforts to improve clinical trial oversight and enhance the safety and integrity of clinical research. These recommendations serve as a call to action for implementation of best practices that benefit study participants, study sponsors, and society.

Keywords

Data monitoring committees, clinical trials, data and safety monitoring boards

Introduction

The use of data monitoring committees (DMCs) to oversee clinical trials has increased and evolved since the concept was introduced in 1967 by the Greenberg Report.[1] Initial recommendations in that report were applied in National Institutes of Health (NIH)-sponsored cardiovascular trials to monitor trial conduct and safety and to recommend trial modifications or closure. Today, DMCs are occasionally used across therapeutic areas to oversee single trials, groups of trials, or entire portfolios of research related to an investigational intervention. Safeguarding clinical trial participants and monitoring interim safety and efficacy outcomes data in ongoing trials remain paramount responsibilities for DMCs, but variation in the structure and organization of DMCs exist. Membership and responsibilities of DMCs also may vary depending on the nature and goals of the trial.

The Clinical Trials Transformation Initiative, a public–private partnership whose mission is to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials, initiated the DMC Project to address the identified issues in understanding the role, importance, and conduct of DMCs, and to recommend best practices for DMCs and for sponsors working with DMCs. The DMC Project Team included 16 representatives from a broad cross section of the clinical trials enterprise, including regulators, government and industry sponsors of clinical research, academics, contract research organizations, patient representatives, and clinical investigators. The project team developed recommendations for DMC use and conduct (Supplementary Appendix 1) based on their expertise and analysis of the findings from the project's evidence-gathering activities. Our recommendations may apply to any DMC that is charged with monitoring an interventional trial regardless of sponsorship or funding source. While these recommendations focus on external DMCs (defined as an independent group of individuals, external to the sponsor, that conduct its activities outside of the sponsor organization), many of the principles and recommendations may also apply to internal DMCs that conduct similar activities within the sponsor organization.[2]

The objectives of the DMC Project were to (a) clarify the purpose of DMCs and the rationale for their use; (b) develop best-practice recommendations for the operation and optimal conduct of independent DMCs; (c) describe effective communication practices between independent DMCs and trial stakeholders (e.g. sponsors, investigators, and institutional review boards); and (d) identify strategies for preparing the next generation of DMC members.[3]

Methods

Approach

To address the objectives, the DMC Project Team employed three research strategies: a survey of 143 DMC members and organizers, a series of focus group discussions with 43 participants, and a 2-day expert meeting. Detailed methods and results of the survey and focus group discussions are described elsewhere.[3]

The expert meeting[4] was conducted in July 2015 among 54 stakeholders representing academia, government agencies, industry, contract research organizations, patient representatives, and professional societies. Findings and key themes from the survey and focus group discussions were presented. The DMC Project Team used discussion from the meeting to refine recommendations through an iterative process based on consensus-building guidelines[5] that focus on core values of inclusiveness, shared control, and flexibility.

Described herein are the primary outcomes of the DMC Project with emphasis on consensus-based, multi-stakeholder recommendations (Supplementary Appendix 1) for optimizing the operation and conduct of contemporary DMCs.

Results

Clarifying the role of the DMC

As use of DMCs has increased and evolved, confusion has emerged regarding the role of the DMC, which may contribute to unclear expectations between DMCs and other trial stakeholders. We sought to clarify the unique

role of DMCs relative to roles of other groups involved in oversight of clinical trials.

The key difference between a DMC and other research oversight groups is that DMCs perform periodic benefit–risk assessments using available efficacy and safety outcomes data gathered during the course of a trial in order to provide the most optimal recommendations and advice to the sponsor and trial leadership. This necessitates close monitoring of the trial for "early definitive evidence of benefit, convincing evidence of harm, or sufficient evidence of no potential benefit to render continuation of the trial to be futile."[6] To adequately perform this important function, DMC members require full access to the unmasked safety and efficacy outcomes data during the course of the trial. The DMC must be able to review the accumulating data by treatment group to assess the benefit–risk balance for trial participants. We emphasize that interim analyses of unmasked trial data require thoughtful consideration and the utmost of care. Various statistical monitoring methods exist but were not discussed in this project and are beyond the scope of this article.

When reviewing trial data, bias must be minimized particularly in the assessment of study outcomes and attribution of adverse events. Therefore, independence from the trial sponsor is critical for the DMC to fulfill its central role of protecting vulnerable study participants from unpredictable harm that may arise during the course of a trial. Occasionally, this may require unscheduled meetings of the DMC and/or additional analyses without alerting the sponsor or study investigators.

Best practices for DMC conduct

Composition. The composition of a DMC must be carefully balanced to ensure effective monitoring of clinical trials. Representation on a DMC, at minimum, should include a clinician with expertise in the therapeutic area being studied and a biostatistician with expertise in statistical monitoring plans and analysis of clinical trial data. The designated chairperson—whether a clinician or statistician—must have experience with clinical trials and data monitoring. Other types of expertise (e.g. pharmacology, toxicology, and behavioral science) also may be required, and some trials by nature have challenging social, cultural, and ethical implications and may benefit from added expertise and diverse perspectives for effective evaluation and monitoring. In light of the increased complexity of clinical trials and interventions being evaluated, the inclusion of bioethicists and patient advocates should also be considered, particularly for trials evaluating high-risk interventions or involving vulnerable populations. Knowledge of research methodology and data analysis, and experience in clinical research are skills generally considered essential for any DMC member.

Selection of an effective DMC chairperson is critically important. The pivotal role of the DMC chair is not limited to trial monitoring, but extends to organizing the operational aspects of the committee and ensuring that DMC members have adequate resources and flexibility to do their work without hindrance or undue interference, particularly from sponsors and others with a vested interest in the trial outcome. Prior experience as a DMC member is essential for the chair. Importantly, the chair should be an accomplished leader and effective communicator who can skillfully manage meetings and create an environment that encourages cooperation and active participation of all DMC members. The chair should be capable of bringing consensus without being overbearing or forceful with personal conclusions or opinions. In addition, the DMC chair should have the necessary interpersonal skills to draw from the collective talents of all members in order to thoughtfully and effectively guide the process of monitoring and oversight.

Conflicts of interest. Prospective DMC members may have potential financial or intellectual conflicts of interest that could compromise their ability to objectively monitor a trial. Thus, conflict of interest must be regularly disclosed, assessed, and managed for all DMC members. At each meeting, members should be asked to declare any new conflicts, and report activities or connections with any parties that may introduce bias and influence their conduct. Activities or relationships deemed to have the potential to undermine independence of DMC members may result in disqualification from DMC service; therefore, both actual and perceived conflicts should be disclosed. Even the perception of a conflict of interest can damage the credibility of the DMC and raise questions about its conduct and recommendations.

Conversely, it is important to note that not all previous interactions with a sponsor are necessarily disqualifying. In some cases, identifying experts with highly specific skills and knowledge but without any connections to the study sponsor or investigators can be difficult. If concerns about conflicts of interest are taken to extremes, few qualified members would be available to serve on DMCs. Many minor conflicts that are unlikely to introduce bias (e.g. prior DMC service for the same sponsor for a different treatment intervention) can be addressed and managed by proper disclosures to the sponsor and other DMC members. However, some conflicts are so significant that they cannot be mitigated by the usual means and may require exclusion from DMC service for certain trials.

It should be emphasized that not all conflicts of interest are financial in nature. Scientists can have vested intellectual or research interests in the results of a given trial, which might impede their impartiality.

Such conflicts must also be addressed on a case-by-case basis and may preclude service on a DMC.

Statistical Data Analysis Center. To support the DMC in fulfilling its role, a Statistical Data Analysis Center capable of preparing reports for or performing additional analyses that may be requested by the DMC is typically utilized. For the DMC to make optimal recommendations regarding the trial to the sponsor and trial leadership, planned interim analyses (based on the DMC Charter, trial protocol, and the statistical analysis plan) may necessitate unplanned analyses to provide insight regarding the interim safety and/or efficacy findings. Therefore, the Statistical Data Analysis Center should have access to all accumulating trial data beginning at trial initiation, possibly necessitating coordination between the Statistical Data Analysis Center and the trial's data management group. It is not acceptable for the sponsor—either by requirement or by financial contract—to limit the scope of statistical work that is to be conducted by the Statistical Data Analysis Center. Instead, the Statistical Data Analysis Center contracts should allow for reasonable adjustments after trial initiation to ensure the sponsor does not unduly influence or restrict the type of work the Statistical Data Analysis Center conducts in support of the DMC. This approach would also minimize the chance that a sponsor is inadvertently informed about additional analyses requested by the DMC in the course of trial monitoring.

The Statistical Data Analysis Center should receive scheduled data transfers both prior to scheduled data reviews and during the period between reviews. Flexibility in the timing of these transfers is essential to aid the DMC in fulfilling its responsibilities. The tables, listings, and figures to be provided to the DMC during its meeting should be specified in advance and the templates approved by the DMC prior to its first data review. Changes to these templates may be requested during the trial, and there should be enough flexibility by the Statistical Data Analysis Center to implement these modifications.

DMC meetings. A best practice for DMC meetings is to hold an initial organizational meeting in order to orient and familiarize DMC members with their roles and responsibilities. All DMC meetings should be held at a neutral venue, avoiding sponsor offices or lavish accommodations. The inaugural meeting should ideally be held in person prior to the start of patient recruitment to allow DMC members to meet each other and review the DMC charter, protocol, and planned Statistical Data Analysis Center report templates. The protocol and statistical analysis plan should be readily available. The DMC members should have minimal sponsor interactions outside of the formal DMC meetings.

In addition to the DMC members, another key participant in the DMC meetings is the Statistical Data Analysis Center biostatistician. As the Statistical Data Analysis Center reports to and serves the DMC directly, the Statistical Data Analysis Center biostatistician should have an in-depth understanding of the data and how it is acquired, as well as comprehensive knowledge of the statistical analysis plan and protocol.

We recommend a face-to-face DMC meeting at least annually, but other meetings can be held via teleconference or web-based conferencing. Meetings can consist of open sessions (meetings in which individuals not directly involved in the DMC operations may attend) or closed sessions (meetings in which only DMC members and the Statistical Data Analysis Center statistician are permitted). Only blinded data are reviewed in open sessions. Regardless of trial sponsorship (i.e. commercial, government, or private foundation), review of unblinded data can only occur in the closed sessions without any representation or undue influence from the sponsor. Even during open sessions in which blinded data are reviewed and study progress is discussed, sponsor and trial leadership attendees generally should be limited to a few designated officials who are directly responsible for overseeing the trial for the sponsoring organization.

Effective communication practices

Charter. To inform DMC communication practices and address the overall oversight process, a charter that is carefully aligned with the research protocol and the statistical analysis plan should be developed by the sponsor in collaboration with the trial executive committee and with substantive input from the DMC. This important document should be agreed upon by the sponsor, executive committee, Statistical Data Analysis Center, and the DMC members prior to patient enrollment. After careful review of the charter, the protocol, and the statistical analysis plan, feedback from the DMC should be incorporated into the charter. The charter should clearly state the rationale for use of a DMC, broad goals, and the roles, responsibilities, and operational structure of the DMC relative to other clinical trial oversight groups. In addition, the charter should clearly describe the decision-making process of the DMC, describe how DMC recommendations are made, and include the following items: (1) composition, including the number and expertise areas of its members; (2) scheduled data transfers from the trial's data management group to the Statistical Data Analysis Center; (3) the format (face-to-face, tele- or video-conference, open and closed session, etc.) and frequency (e.g. every 6 months) of meetings; and (4) the relationship and communication between DMC and Statistical

Data Analysis Center, and other trial committees and stakeholders, including the trial sponsor.

The content of a DMC charter and the principles underlying it are not identical to those of the protocol and statistical analysis plan. By design, the latter documents are meant to be strictly followed, and any deviations need to be documented with substantive changes requiring amendments. In contrast, the DMC charter should be a succinct and user-friendly document that outlines a set of guiding principles for conduct of the DMC. While clearly aligned with the protocol and statistical analysis plan, the charter should avoid rigidity and legalism since it is not possible to anticipate and address all potential scenarios that could emerge during the course of an ongoing trial. Lengthy elements, such as table and figure templates to be included in DMC reports, should be relegated to the appendix section of the charter. Given the broad and flexible nature of the charter, amendments to this document should be infrequent. A critical aspect of the DMC charter is the monitoring guidelines for efficacy and safety outcomes.

DMC recommendations. The recommendation to continue, modify, or terminate a trial is the most important communication provided to the sponsor and trial leadership by the DMC. The DMC makes its recommendations based on benefit–risk assessments, and it is the sponsor who is ultimately responsible for acting upon these recommendations. Consensus should be sought among DMC members, and voting is generally discouraged. If differences of opinion persist, these are documented in the DMC minutes, and it is acceptable to describe these differences without attribution when issuing a statement or other formal communication.

As previously described, sponsors—and particularly the project team(s) directly involved in trial operations—often have a vested interest that may lead to a biased perspective on the research. Therefore, DMC trial recommendations and proposed modifications should be provided to a steering committee or sponsor leadership group authorized to act on these recommendations, and not to those directly involved with implementation of the trial.

The primary and preferred method of communicating the DMC's recommendations to the sponsor is in written form. The DMC may also verbally brief the sponsor and/or trial leadership after the closed session, and the recommendations should be conveyed clearly and concisely.

When in agreement with the DMC's recommendations, the sponsor should report these within an appropriate time period to institutional review boards and, in the case of trials performed under regulatory guidance, to the relevant regulatory authorities. Minor operational recommendations do not necessarily require regulatory reporting. Procedures for managing disagreements between the sponsor and the DMC should be described in the charter. Although consensus between the sponsor and DMC with respect to the recommendations is highly desirable, in case of an impasse, it is the sponsor's decision whether to accept or reject the recommendations. The sponsor may choose to respond to the DMC through written comments, especially in the case of disagreement with the DMC's recommendations. If the sponsor rejects the recommendations, this decision and its rationale should be reported promptly along with the written DMC recommendations to institutional review boards and to the appropriate regulatory agencies if the trial is under regulatory purview. Based on the information provided, the regulatory agencies and institutional review boards may reach their own independent conclusions and act accordingly within their respective authorities. At the end of the trial, all minutes and reports from the DMC meetings should be made available to the sponsor and trial leadership, as needed.

Preparing the next generation of DMC members

The pool of qualified individuals available to serve as DMC members may soon be inadequate to meet the current needs of the research enterprise, as demand for trained and qualified DMC members has risen and may continue to grow. In 2013, the Office of Inspector General at the US Department of Health and Human Services reported that the NIH faces challenges in the recruitment and training of DMC members. As a result, the Office of Inspector General[7] recommended that NIH develop ways to recruit and train new DMC members. Although training is highly desirable prior to serving on a DMC, the vast majority of our survey respondents indicated that they had not received training and were unaware of DMC-specific training programs.[3]

The DMC Project also identified a growing need to prepare a new generation of qualified DMC members so that the pool of properly trained and experienced individuals does not dwindle. Preparing individuals to serve as DMC members is challenging because of the complexity of data monitored in clinical trials and the interpretation relative to the monitoring guidelines. Knowledge of research, familiarity with the study design, and unstructured on-the-job training are not sufficient to ensure that prospective DMC members are adequately qualified to serve on a DMC. While the skills needed for prospective DMC members are described in the literature, to date, nationally recognized training programs have not been established.

Effective training for DMC members should consist of a combination of didactic educational programs and practical experience. Didactic elements could include a review of the fundamentals of clinical trials, study design, data analysis, and the functions and

responsibilities of DMCs. They should also focus on the aspects of DMC work that are different from the work conducted by those who operate the trial. One of the realities of DMC operations involves the real-time analysis of emerging study data that has yet to undergo the full quality-control checks to ensure completeness and accuracy of the data.

However, didactic training and review of case studies, alone, may be insufficient. Effective training of prospective DMC members should also incorporate formal, supervised longitudinal apprenticeships in the setting of actual DMC proceedings, including closed sessions during which the most critical and sensitive issues are addressed. The adoption and endorsement of this type of comprehensive training by sponsors and other key stakeholders will help ensure that a new generation of DMC members is adequately prepared.

To advance this effort, stakeholders with an interest in the role and function of DMCs (e.g. professional, scientific, and medical societies and organizations) should consider developing and maintaining databases of qualified DMC members that include a listing of their experience and relevant expertise.[8] In compliance with confidentiality provisions for a given trial, DMC members should also be encouraged to submit interesting and instructive DMC case studies to peer-reviewed journals in order to raise awareness of important issues and challenges that can arise during a clinical trial. Legal and contractual issues concerning service on a DMC (e.g. indemnification) require thoughtful discourse but were not formally addressed in our DMC project.

Discussion

The rationale for using a DMC in clinical trial monitoring is predicated on the need for periodic assessment of the risks and benefits in an ongoing trial guided by a well-defined DMC charter that is aligned with the research protocol and statistical analysis plan. Similarly, our recommended best practices for DMC oversight and communication are intended to ensure the validity and sensitivity of this monitoring process to detect early evidence of avoidable harm, futility, or benefit, and to communicate DMC recommendations in a manner that is actionable when necessary and maintains trial integrity to the greatest extent possible.

An independent, knowledgeable, and well-trained DMC serves the trial sponsor, trial leadership, investigators, and study participants through this periodic assessment of risks and benefits. DMCs have an important and unique role in trial oversight that is substantially distinct from institutional review boards, ethics committees, or trial steering committees, which do not see unblinded interim results. Thus, the role of the DMC cannot be delegated or shared with other entities without the potential for substantially increased risk to trial integrity, and thus also to study participants and sponsors.

The choice of DMC members should be thoughtfully considered, and the role of the chair should never be bestowed on an individual solely by virtue of their position or status in academia or as a key opinion leader. Previous experience acting as a member of a DMC should be a primary consideration, as this experience is invaluable for effectively leading the DMC and providing guidance to newly trained members. Our recommendation for apprenticeship and mentoring necessitates close interaction among DMC team members.

The composition of the DMC is especially important in light of its responsibility to make the best possible recommendations unbiased by the sponsor or commercial interests with relatively sparse information, given that their recommendations often result in irreversible actions being taken. For example, if a trial is stopped and the sponsor and trial leadership is unmasked to treatment assignment, that action cannot be undone. Even if trial enrollment is only suspended for a potential safety concern, it is often difficult or impossible for the prior rate of patient enrollment or investigator enthusiasm to be regained should trial enrollment be resumed.

While our recommendations for DMC use, conduct, communication, and member training form the foundation for improved oversight of clinical trials and enhanced participant safety, it is the effectiveness of the implementation of these recommendations that will determine whether the potential benefits are realized. Several recommendations proposed by us are well aligned with those of the NIH, specifically regarding the importance of DMC access to the unmasked trial data, the need to identify and adequately train new DMC members, and the restriction of attendance at the closed sessions to DMC members only.[7] Our recommendations should, ideally, serve as a call to action, encouraging all those involved in clinical trial design and conduct to ensure the DMC structure, charter, membership, and implementation are all consistent with these recommendations. Doing so will ultimately benefit study participants, study sponsors, investigators, and society.

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4.4 Women and Fetuses First? An Ethical Case for Giving Priority in Clinical Research Testing of Zika Vaccines to Pregnant Women

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Unpublished.

Women and fetuses first:

An ethical case for giving priority in clinical research testing of Zika vaccines to pregnant women

Introduction

The rapid emergence of the Zika virus has been described as "unprecedented" because the virus can spread through both a mosquito vector and sexually, causing severe neurological birth defects and miscarriages in humans.[1] Though 80 percent of people infected with Zika are asymptomatic, Zika virus infection can cause microcephaly and other severe birth defects in developing fetuses and neurological developmental defects in infants.[2] The long-term effects of Zika virus infection on both mother and child are not yet known, but it is likely that some deleterious effects in children born to mothers with Zika virus infection will not be apparent until later in their childhood.[3] Additionally, Zika virus infection has been associated with an increase in the number of cases of Guillain-Barré syndrome in Rio de Janeiro, Brazil, and Puerto Rico.[4,5]

Because Zika virus infection can lead to these severe health problems, it is prudent for the public health community to develop a vaccine prior to the next major outbreak. As of September 2017, there were approximately 32 vaccine candidates in various stages of the drug development pipeline.[6] However, Zika vaccine development has slowed in recent months for several reasons. The summer of 2017 saw a decrease in the number of documented Zika virus infections in the Americas,[7] which means that researchers face difficulties in reliably determining the efficacy of vaccine candidates as herd immunity has likely contributed to a decline in Zika infections. In November 2016, the World Health Organization (WHO) stated that microcephaly and other neurological disorders caused by Zika were no longer a public health emergency of international concern.[8] Vaccine developers may have interpreted the November statement as a "downgrade" in the seriousness of the problem. Indeed, Sanofi Pasteur, one of the only major pharmaceutical company working on a vaccine, withdrew from developing its candidate in September of 2017.[9]

And phase II vaccine testing that was scheduled to take place in Puerto Rico will likely be temporarily halted as the region recovers from extensive damage from Hurricane Maria in 2017.

Nevertheless, Zika remains a public health concern and could re-emerge in the foreseeable future. How to effectively prepare for a Zika outbreak and identifying which target populations should receive a vaccine before its received regulatory approval remain open questions. An editorial in *The Lancet Infectious Diseases* argues that Zika vaccine development must receive higher strategic planning priority from the World Health Organization so that vaccines can be rolled out quickly in the event of an outbreak.[9] Delays in vaccine development now may lead to hastening the enrollment of participants for trials later, so it is still very important to consider who should be enrolled. Recent population-level modeling data suggest that Zika virus vaccination with a moderate to highly effective vaccine could virtually eliminate prenatal infections if a vaccine were to be approved.[10]

As of April 2018, no Zika vaccine trials were enrolling pregnant women. Because the population most affected by Zika are infants and unborn children, the public health and clinical research communities are presented with difficult ethical challenges in developing safe and effective prophylactic vaccines. This challenge is especially acute given the "vulnerable" subject status of pregnant women and fetuses as research participants. The Common Rule, a set of federal ethical regulations that U.S. government-funded research sponsors must follow, states that vulnerable populations, including pregnant women and neonates, should receive additional protections in order to enroll them in research to ensure their welfare.[11] In April of 2018, the U.S. Food and Drug Administration (FDA) released new draft guidance on the safe and ethical inclusion of pregnant women in clinical research, which states that failing to study the safety and

efficacy of new drugs on pregnant women creates uncertainty that may damage their health and that of their fetuses.[12]

Zika vaccine development raises several important questions about the ethical conduct of research. First, do women and fetuses belong in Zika vaccine trials? Others in the bioethics community have responded to this important question with a resounding "yes." The Ethics Working Group on ZIKV Research & Pregnancy has established a set of recommendations that put first the needs of pregnant women, who have historically not been represented adequately as research participants.[13,14] We agree with their recommendations, particularly that researchers should "pursue and prioritize development of ZIKV vaccines that will be acceptable for use by pregnant women in the context of an outbreak."[13] To augment this group's influential work, we believe it's important to answer a set of related questions: Why should pregnant women be prioritized as a population to study in these trials? How does this priority affect public health responses in future outbreaks of the virus? How should researchers handle priority enrollment?

Justifying the inclusion of pregnant women and fetuses in Zika vaccine trials

Testing a vaccine candidate in pregnant women may be ethically justifiable. Indeed, others have made this claim.[13,14] The goal of priority enrollment of a pregnant population is to ensure that only vaccines that are expected to be safe for testing during pregnancy and that have been thoroughly examined on a pregnant population should receive regulatory approval for general usage. We believe that pregnant women should be included in trials and receive priority access to enrollment in clinical trials that test the safety and efficacy of Zika vaccine candidates, at phase II or later, which is reflected in these guidelines.

Several guidance documents provide ethical justification for the safe inclusion of pregnant women in research that can guide future study design. FDA draft guidance issued in April of 2018 states that pregnant women should be included in clinical research when nonclinical research on pregnant animals has been previously conducted, and there is a prospect of direct benefit for the pregnant mother and/or the fetus.[12] Guideline 19 of the International Ethical Guidelines for Health-related Research Involving Human Subjects, updated in 2016, asserts the need to study certain interventions that can specifically benefit pregnant women: "Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted."[15] The CIOMS guideline states that research ethics committees "may permit a minor increase above minimal risk" when the social value that the research will provide is strong enough to improve to lives of pregnant women or their fetuses; short-term and long-term follow-up may be required, depending on the study intervention's potential risks. This guideline responds to the obligation of researchers to enroll members of populations in research studies that are expected to benefit from the results of the study. However, none of these guidelines provide justification for how to *prioritize* the involvement of pregnant women in research for a situation like Zika vaccine trials.

A moral imperative to prevent vertical transmission of infectious disease justifies the priority inclusion of pregnant women and fetuses in Zika vaccine trials. Verweij *et al.* describe pregnancy as an "immunologically altered state that can render women more susceptible to infections than they are when they are not pregnant."[16] Maternal immunization is justified if the vaccination provides direct protection for pregnant women, prevents disease transmission, can provide passive immunity to the newborn child, and/or can reduce infant mortality that results

from infectious disease transmission.[16] The authors justify these claims by suggesting a more reasonable version of the precautionary principle, which dictates that for activities that may cause irreversible harm, precautionary measures are warranted.[16] In the case of maternal immunization, the authors suggest that adverse event reporting and disease surveillance measures be strengthened so that vaccination be offered when there are "concrete, severe risks of disease for mother and child."[16] The risk of severe birth defects, as occurs with Zika, fits this description.

Why do pregnant women and fetuses deserve priority enrollment in Zika vaccine trials?

The statement that pregnant women and fetuses deserve priority enrollment in Zika vaccine trials does not answer the most pressing questions for sponsors of these trials: Why is priority enrollment necessary, and how exactly should it work? Adding to the work of the Ethics Working Group on ZIKV Research & Pregnancy, we argue that pregnant women should be enrolled first and that spots for enrollment in these trials be reserved specifically for pregnant women.

To strengthen the argument for the inclusion of pregnant women in Zika vaccine trials, it is prudent to consider that unapproved vaccine candidates may need to be authorized for emergency use in the event of an outbreak in the future. In such an instance, available doses of Zika vaccine candidates that have been made for usage in clinical trials could fall short for covering the entire at risk population. Available doses will need to be rationed. In the case of a Zika outbreak, those that are at the greatest risk for serious health issues related to the virus have the strongest need for access to a vaccine that may help. A just and fair public health regulatory authority will provide those in dire need with the resources to meet that need.

Because of the aforementioned risks of viral infection, pregnant women and fetuses should be first in line to receive experimental Zika vaccine candidates in an emergency situation. The plausibility of such an outbreak is not unreasonable to envision in the near future. Hurricane recovery efforts in Puerto Rico and the U.S. Virgin Islands, in the wake of 2017's Hurricane Maria, have been slow. A lack of electricity and standing water, combined with increasing global temperatures, could create optimal breeding conditions for disease-carrying mosquitos.

Furthermore, women of childbearing age in areas of the world where Zika has been endemic often do not have safe or legal access to abortion if they were to become pregnant while infected with the virus. Thus, if a pregnant woman believes she may be infected with Zika, she may have no choice but to carry her child to term, which may lead to lifelong financial, medical, and social challenges that particularly affect socioeconomically disadvantaged communities. According to the Pew Research Center, 26% of countries included in a recent analysis of abortion regulation worldwide only allow abortions to save the life of the mother.[17] 42% of countries, including Brazil, only allow abortions when the mother's life is at risk or for at least one other specific reason, such as the desire to terminate a pregnancy that resulted from rape or incest.[17] If abortion is not a feasible option for pregnant women who have contracted a Zika virus infection, it is ethically required to offer them an experimental vaccine that is believed to have some chance of protecting a fetus from neurological devastation or birth defects.

Finally, if there is going to be emergency use authorization of an experimental Zika vaccine, more data gathered from pregnant women and fetuses would be helpful, or perhaps necessary, to guide the administration of the vaccine in an outbreak. In some cases of compassionate use, where a pharmaceutical sponsor makes its product available to patients without other treatment options outside of a clinical trial setting, sponsors are unwilling to

provide an experimental product if there is no data on a specific population that may desire early access to an intervention in development (personal communication). Thus, in preparing for public health responses in the future, it is important to gather data before the anticipation of emergency use authorizations.

Discussion

We believe that giving pregnant women and fetuses priority enrollment, first and foremost, in Zika vaccine trials is a sensible path forward for countermeasure development in the event that the virus re-emerges to cause an outbreak. In general, it is ethically sound to conduct research on populations that would need access first in an emergency situation. Public health emergencies, though unanticipated, are not unforeseeable. Setbacks in timely Zika vaccine development, combined with the exclusion of pregnant women from phase II and III testing of the candidates that are moving forward in the development pipeline, will only further contribute to healthcare injustices for the populations most affected by Zika.

One might ask why it is necessary to further justify that pregnant women need to be enrolled in Zika vaccine trials first. Developing a transparent rationing strategy of available vaccine doses ahead of an outbreak will balance the competing approaches of utilitarianism and egalitarianism and will garner more public support than leaving these decisions to the last minute. Pregnant women carrying developing fetuses will be first in line to receive an experimental vaccine, so the public health community needs to know with some degree of confidence if a vaccine candidate demonstrates some efficacy in those populations.

The argument for priority enrollment of populations likely to be most affected by a particular infectious disease is applicable to other areas of public health concern. For example,

H7N9 avian influenza is zoonotic and spreads from human contact with infected birds. If this virus is able to spread between humans, it will become pandemic.[18] Immunocompromised individuals, the elderly, and the very young are particularly susceptible to mortality from influenza.[18] Research studies that test new interventions against the standard of care should be sure to enroll members of these groups first, after phase I studies in healthy volunteers demonstrate a feasible immune response. In the event that pandemic flu results, it has been suggested vaccines be rationed according to medical neediness first, followed by random selection for the rest of the population.[19] This method of rationing follows an egalitarian principle that is rooted in social justice, which could similarly be applied for a Zika vaccine rationing strategy.[19]

Ultimately, priority enrollment of the most at-risk populations in research studies for interventions that may benefit them is not just an argument that relates to Zika vaccine development. When sponsors consider populations from which to sample in the development of therapeutic agents for infection disease, they should put first the people who are most likely to benefit from the experimental intervention. This is important because institutional review board (IRB) professionals need to understand priority enrollment as well. Though IRBs mostly are concerned with the protection of human participants from risks inherent in biomedical research participation like undue inducement, exploitation, and coercion, there is a role for them to facilitate safe access to research that will benefit populations with unmet medical needs that are at high risk for an infectious illness.

The prioritization argument challenges the precautionary principle, which dictates that in the absence of scientific understanding of the safety and efficacy of an intervention, the potential risks of that using that intervention should be diminished by any means possible. A strict

interpretation of this principle may leave pregnant women in Zika-endemic areas – or to give other examples, those with a high risk of influenza mortality or those who are at risk of acquiring resistance to HIV medication – with little to no options to meet their medical needs.[16] A softened version of the precautionary principle would balance the needs of these populations with facilitated access to experimental interventions in emergent situations, in which quick regulatory decisions must be made based on available evidence. Priority access to research participation must become an essential component of public health policy strategy so that these decisions can be made with as much information possible. Inclusion is important, but frequently in vaccine research eligibility is not enough to ensure enrollment in a study. Public health officials, sponsors, and regulators need to also determine who goes first.

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4.5 Rethinking the Belmont Report?

Phoebe Friesen, Lisa Kearns, Barbara Redman, and Arthur L. Caplan

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Rethinking the Belmont Report?

Phoebe Friesen, Lisa Kearns, Barbara Redman & Arthur L. Caplan

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Rethinking the Belmont Report?

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This article reflects on the relevance and applicability of the Belmont Report nearly four decades after its original publication. In an exploration of criticisms that have been raised in response to the report and of significant changes that have occurred within the context of biomedical research, five primary themes arise. These themes include the increasingly vague boundary between research and practice, unique harms to communities that are not addressed by the principle of respect for persons, and how growing complexity and commodification in research have shed light on the importance of transparency. The repercussions of Belmont's emphasis on the protection of vulnerable populations is also explored, as is the relationship between the report's ethical principles and their applications. It is concluded that while the Belmont Report was an impressive response to the ethical issues of its day, the field of research ethics involving human subjects may have outgrown it.

Keywords: research ethics, Belmont Report, autonomy, beneficence, justice, human subjects research

As the new revisions to the Common Rule take their place, it seems timely to reflect on the significant document that gave shape to the regulations both at its inception and now. Since its release in 1978 and publication in 1979, the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979) has had an enormous impact on the way research with human subjects has been conducted in the United States and in many other nations. This article explores some of the more significant criticisms that have been raised in response to the report, as well as changes that have reshaped many questions central to research ethics since its publication, and asks whether the report still holds up nearly four decades later. Part I briefly summarizes the central components of the Belmont Report, describes the ethical climate at the time, and provides clarification about what the report was and was not meant to achieve. Part II explores several criticisms that have been leveled against the report and situates many of them within the dynamic landscape of biomedical research. Finally, Part III offers a discussion of whether the Belmont Report is in need of a 21st-century overhaul.

PART I: THE BELMONT REPORT

The 11 members of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research who authored the Belmont Report worked on it from 1974 to 1978, including four intensive working days at the Smithsonian Institution's Belmont Conference Center in 1976. The Secretary of Health, Education, and Welfare (now Health and Human Services [HHS]) gave them four primary tasks: identify the boundary between research and practice, determine the role of risk–benefit analyses in human subjects research, outline appropriate guidelines for subject selection, and provide criteria for what constitutes truly informed consent (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). Both the organization and the content of the Belmont Report reflect these directives. The first section of the report addresses the first task; it defines "practice" as an intervention solely meant to enhance a patient's well-being, and "research" as "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The second section describes three ethical principles that are "particularly relevant" to research involving human subjects: respect for persons, beneficence, and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The third links each of these principles to the remaining three tasks, suggesting that respect for persons should be the guiding principle behind informed consent, that beneficence should underlie

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risk–benefit analyses, and that justice ought to be the central principle behind subject selection.

To understand the Belmont Report, one must understand the ethical climate in which it was written. Three decades earlier, the Nuremberg Code, a set of research ethics principles to guide human experimentation, had been promulgated, at the conclusion of the "Doctors Trial" of Karl Brandt and 22 other Nazi defendants (The Nuremberg Code 1949). The verdict, with some modifications, was later endorsed by the World Medical Association as a code of ethics meant to guide research involving human subjects: the Declaration of Helsinki (WMA General Assembly 1996). While there is certainly ethical overlap between these documents and the Belmont Report, the ethical emphases of the latter are drawn from particular concerns that were paramount in the United States at the time. Especially important were the revelations contained in the now famous exposé on subject abuses penned by Henry Beecher in the *New England Journal of Medicine* and the publicity surrounding the Tuskegee Syphilis Experiment, which continued to track the progression of untreated syphilis in hundreds of poor black men long after a cure had become widely available (Beecher 1966). The public outcry in 1972, triggered by an African American whistleblower at the Centers for Disease Control (McCallum et al. 2006), led Congress to establish the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The content of the Belmont Report reflects the committee's fears that research subjects would continue to be deceived, harmed, or otherwise exploited by investigators, a point that has often been overlooked by critics. As one Belmont author explains, the Belmont Report was meant to be "a proclamation that had to ring true in the ears of scientists, policymakers, politicians, ethicists, journalists, and judges" (Jonsen 2005). As well as being a proclamation, the Belmont Report was primarily intended to be a statement of a general, principled moral framework that would help prevent abuses such as Tuskegee from occurring in research involving human subjects in the future (Beauchamp 2008). Although some have expressed concern that the report is "not easily understood or fathomed" (Vanderpool 2001), and that its principles are often misinterpreted as direct action guidelines (Levine 2005), the authors maintain that there "was never any ambition or attempt to make this document specific and practical" (Beauchamp 2005) and that the report "was not to be a philosophical treatise nor was it to be a set of guidelines" (Jonsen 2005). The Belmont Report was not written as an extension of any particular moral theory (Levine 2005), and was both principlist and casuist at the same time (Beauchamp 2005).[1] This may seem somewhat unambitious given the stakes involved, but the goal of the report was only to offer a preliminary, protective ethical framework. A national Ethics Advisory Board was meant to act as a standing agency to continue to grapple with practical ethical issues related to human subjects research (Jonsen 2005; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978, January 13), and indeed many remaining issues were explored in 16 volumes the National Commission later produced (Beauchamp 2008). Despite its modest goal, the Belmont Report was an impressive response to the ethical issues facing human subject researchers when considered in the very troubling context in which it was written.

1. One of the authors of the report, A. R. Jonsen, has noted that the Belmont Report was written as if guided primarily by principles, but constructed on the basis of casuistry (Jonsen 1988.)

PART II: CRITICISMS AND CHANGES

Several significant changes have occurred within the field of human subjects research since the publication of the Belmont Report, and many concerns about the adequacy of the report have been raised in the literature in the intervening years. Five key themes that arise are the distinction between research and practice, harms to communities, the importance of transparency, implications of protectionism, and the relationship between Belmont's ethical principles and their applications.

Research and Practice

Although the commission knew it could not adequately delineate the complicated boundary between research and practice, it did manage to capture paradigmatic features of each. The report states that research is meant to contribute to generalizable knowledge, while practice is meant to contribute to patient well-being. The authors recognized that there often could be overlap between the two; for example, practice could contain significant risks and require oversight, or could involve goals beyond the well-being of individual patients (Beauchamp and Saghai 2012). However, in the decades since the publication of the report, the line between research and practice has become even more vague.

Institutional review boards (IRBs), charged with the protection of human research subjects, have long relied on the report's distinction to determine what is and is not within their purview, but today face an increasing number of examples of novel "practice" involving significant risks and therefore in need of significant oversight (e.g., preapproval, or "compassionate" access to drugs; innovative treatment design; innovative surgeries), as well as a growing number of cases of "research" involving only minimal risk (e.g., retrospective analysis of deidentified data, some forms of survey research, the use of biospecimens) (Faden et al. 2013). These examples illuminate the difficulties in drawing a boundary between research and practice on the basis of the aim of either creating generalizable knowledge or seeking patient well-being. This boundary also limits what information is gained, since practitioners often abstain from collecting data during routine care or innovative practice as a result of the perceived burdens of research oversight (Rhodes 2010). As a result, risky interventions take place with no oversight and no data

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collection, while minimal-risk research is delayed or forgone due to the difficulty of securing regulatory approval. In response, some have argued that unique guidelines for innovative practice are needed (Taylor 2010), especially since disadvantaged groups are particularly at risk of being enrolled in such therapies (Sherwin 2005). Others suggest that research and practice should be integrated into a single, comprehensive learning health care system (Faden et al. 2013).

Harms to Communities

Another criticism of the Belmont Report is that it fails to account for the unique harms to communities that can occur due to research (Weijer 1999; Weijer and Anderson 2002; Emanuel and Weijer 2005). These are not simply the aggregate of harms to individuals within a community, but harms suffered by a community as a whole. Many communities have endured a long history of abuses at the hands of researchers, leading them to doubt the likelihood that they will be beneficiaries of research conducted on them, while others do not share the goals of the researchers. These groups include poor communities, racial and ethnic minorities, those living with mental or physical illness or disabilities, and other stigmatized groups. Harm to these groups cannot be mitigated simply by securing informed consent from individuals according to Belmont's principle of respect for persons. This principle fails to take into account the unique harms that can be done to communities *qua* communities, such as violating widespread trust or taking ownership of a community's stories. For example, in the case of the controversial Human Genome Diversity Project, several indigenous communities expressed reluctance to help researchers in their development of a theory that may offer them no benefit and may serve as evidence to debunk their beliefs about their creation beliefs and histories (Weijer and Anderson 2002). This has led some to argue that there are "special issues related to the religious beliefs, cultural traditions, and history of aboriginal communities" that are not addressed by the report (Weijer and Anderson 2002). Others suggest adding a principle of respect for cultures (Levine 1982) or expanding respect for persons to "respect for persons and communities" (Lebacqz 2005).

Transparency in Research

Concerns about transparency in research have become paramount in the years since the publication of the Belmont Report. Protocols submitted to IRBs have become increasingly elaborate, while biomedicine has become much more commodified, raising issues of conflicts of interest.

When the report was written, most submissions to IRBs were for government-funded, National Institutes of Health (NIH) projects taking place at a single site. Now committees often review complex protocols that are privately sponsored and global in scope (Emanuel 2015). Further issues complicating transparency are worries about the composition of IRBs and their scope of responsibilities as additional committees devoted to research oversight have been created, such as data safety and monitoring boards (DSMBs) and institutional biosafety committees (IBCs). Biomedicine has also seen tremendous growth in the value of patents, devices, and stock.

The majority of biomedical research in the United States is funded by industry, tying the profit motive to every stage of the research process (Taylor 2010), and making transparency much more difficult to attain. This has made the task of identifying and managing conflicts of interest increasingly important (Dumit 2012). Some have argued that the principles offered by the Belmont Report are unable to uphold research integrity, since they do not provide "a clear basis for investigators to keep promises, tell the truth, and avoid killing" (Veatch 2005).

Another significant development that compromises transparency has been the rise of new technologies that pose novel and sometimes unpredictable risks to research participants' privacy and confidentiality of data. These risks can arise throughout all stages of research: participant recruitment through social media, the development of digital monitoring devices that collect data on unwitting bystanders, the use of vast amounts of data being collected and analyzed by companies without individual consent, and the potential to reidentify data using the wealth of personal information available online or through the use of genetic data (Kelly et al. 2013; Gelinas et al. 2017; Benitez and Malin 2010; Metcalf and Crawford 2016).

Critics have noted the Belmont Report's limitations with regards to transparency, suggesting that the report pays little attention to the importance of trust and openness within research (Faden, Mastroianni, and Kahn 2005). Many of these issues, unheard of in the 1970s, threaten the ethical principles espoused in the report, especially that of beneficence. Obstacles to transparency may limit the ability of members of IRBs, DSMBs, and IBCs to adequately analyze the risks and benefits involved in a given study, if they lack access to a significant portion of past research, as a result of publication biases or trade secrets, or if they are unaware of all known risks to participants, as a result of a lack of full disclosure by private sponsors.

Implications of Protectionism

Given the Tuskegee Syphilis Experiment's role in the creation of the Belmont Report, it is understandable that the protection of vulnerable populations took center stage in the report, including those who are vulnerable due to a lack of autonomy, such as children and individuals who are mentally disabled, and those vulnerable for other reasons, such as "racial minorities, the economically disadvantaged, the very sick, and the institutionalized" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). Certainly, protecting vulnerable research participants from exploitation or abuse is an essential task of any research ethics framework. In retrospect, however, the weight the report places on protectionism has both helped

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and hindered epistemic and ethical progress in research. One negative result of the emphasis on protectionism is that some groups considered vulnerable have been left out of the research process and health data relevant to them are now lacking (e.g., pregnant women, children, embryos, the institutionalized, the elderly) (Beauchamp 2008; Rhodes 2010; Sherwin 2005; King 2005). Additionally, as the AIDS epidemic showed, being protected from research is not always desired by members of vulnerable groups (Beauchamp 2008; King 2005; Rogers and Lange 2013).

Today, the desire in many communities to move away from protectionism can be seen in the increasing demands for pre-approval access to investigational drugs, in participants' insistence that they receive active agents and not placebos in clinical trials, and in concerns about the underrepresentation of minorities in late-stage clinical research (Rogers and Lange 2013). This raises questions about how much autonomy those interested in participating in research should be allowed and whose interpretation of risk/benefit analysis—the IRB member's, the researcher's, or the potential participant's—should take precedence.

Concerns about how groups are characterized as "vulnerable" in the report have also been voiced. Some worry that the term is not explicitly defined (Rogers and Lange 2013; Levine et al. 2004) and that the reasons for particular groups' vulnerabilities are not explored (King 2005; Luna 2009), leading to a widespread assumption that all individuals in a vulnerable group lack autonomy (Rhodes 2010). Others have suggested that identifying groups or individuals as vulnerable can trigger paternalism and stereotyping (Rogers and Lange 2013; Luna 2009), while others note the failure of the report to spell out different guidelines for groups facing consent-based and fairness-based vulnerability (Nickel 2006).

Ethical Principles and Applications

A final criticism concerns the relationship between ethical principles and their applications. Belmont advocates for a deductive relationship, in that each principle is matched with one aspect of the research process: Respect for persons applies to informed consent, beneficence to risk/benefit analysis, and justice to subject selection.[2]

Many criticisms of the report stem from this deductive relationship, as they unpack the implications of putting forward principles with such a narrow scope. For example, several authors suggest that the principle of respect for persons is often taken to represent autonomy, consent, and individual choice, when in fact it ought to have (and some say it used to have) a much broader meaning—concern for a patient and respect for the dignity of each individual, regardless of his or her capacity for autonomous choice (Lebacqz 2005; Faden, Mastroianni, and Kahn 2005; Cassell 2005). A narrow focus on autonomy ignores the way in which people are embedded in relationships, and so does not capture the lived experience of many potential participants (Lebacqz 2005). Similarly, the report's concept of beneficence has been criticized for failing to encompass the related principle of nonmaleficence (Beauchamp 2005; Lebacqz 2005), or for being ambiguous in terms of whether it includes non-maleficence (Veatch 2005). It has also been observed that beneficence has shifted away from meaning the good of the whole patient over time toward a much narrower meaning, measured by the good done in the short run to some dimension of the patient (Cassell 2005). Likewise, the report's discussion of the principle of justice has received heated criticism for its lack of breadth and its narrow focus on subject selection (King 2005). The principle, it has been argued, fails to take into account social justice, including historical patterns of oppression and domination (Shore 2006; Sherwin 1992), and compensatory justice for those injured in research and for groups excluded from the research process (Vanderpool 2001; Lebacqz 2005; King 2005). Justice Belmont-style also does not address procedural justice such as involving vulnerable groups in the process of establishing research agendas (Sherwin 2005; King 2005), or key aspects of distributive justice, especially how the benefits of research will be made available to participants and to underserved populations (Vanderpool 2001).

Questions about how to apply the report's ethical principles are especially pertinent to discussions of IRBs. In an empirical exploration of how IRBs function, investigators found a significant portion of committee discussion revolved around the process of informed consent, while issues related to confidentiality, subject selection, risk/benefit analysis, adverse event reporting, and the minimization of risks were overlooked (Lidz et al. 2012).[3] Transcripts from meetings of the National Commission show its concern for mechanisms for the evaluation and monitoring of IRB performance, yet its suggestions include only process measures (site visits, audits of IRB records, and the like), and they were never addressed or published (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978, March 10–11).

2. It should be noted that there is some disagreement among members of the commission about whether the principles were meant to have a deductive relationship with the applications (Beauchamp 2008; Levine 2005). The report itself, however, is quite explicit about the relationship: "Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects." The report also suggests that "other principles may also be relevant", but maintains that these three are comprehensive in themselves (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979).

3. See also Klitzman (2015).

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PART III: MOVING BELMONT INTO THE 21ST CENTURY—IS A TOTAL OVERHAUL NEEDED?

The Line Between Research and Practice Is Insufficient

Defining research and practice as interventions aimed at knowledge and interventions aimed at well-being is incompatible with Belmont's own principles of respecting persons, maximizing beneficence, and ensuring justice. The boundaries around what requires oversight should be defined pragmatically, so that knowledge production and benefits to all communities are maximized and harms to participants are minimized. Oversight should be required for any research or intervention involving novel, significant risks that are not part of the standard of care. This would encourage low-risk data collection during routine practice and ensure that innovative therapies are regulated and their findings disseminated. Investigators ought to be permitted to engage in low-risk or minimally risky research with minimal oversight, while regulatory mechanisms for experiments with significant risks should be kept in place. Regulation ought to be proportionate to novelty and level of risk, rather than derived from intent.

Unique Harms to Communities Remain Unacknowledged

The Belmont Report's failure to consider the potential for harms to communities should be taken into account in the design of any research protocol. This oversight could be overcome if harms to communities were explicitly acknowledged, whether as a new principle or as an extension of the principle of respect for persons. Such a principle "would obligate researchers to respect the values and interests of the community in research and, wherever possible, to protect the community from harms" (Weijer and Anderson 2002). These goals can be achieved by conducting research that is more participatory, by taking into account the needs and interests of the community involved throughout the development of a research agenda, in stages of research collection and analysis, and during the dissemination of results (Weijer and Anderson 2002). A move toward this goal was taken in the recent Common Rule updates, which state that the official governing body of American Indian/Alaska Native tribes can establish additional protections and use of a single IRB (Federal Policy for the Protection of Human Subjects 2017). There is no simple way to define a community, but relevant factors would include self-definition, shared health data and outcomes, group-based vulnerabilities, and historical relationships with prior research.

The Report Fails to Address Current Concerns Involving Transparency

In order for regulatory agencies to operate with the principle of beneficence in mind, they must understand, to the fullest extent possible, the risks and benefits involved in a given research protocol. To achieve this goal, each stage of the research process must strive for greater transparency. By adopting an additional principle of transparency, or making explicit the principle of nonmaleficence, a revised framework could better address issues that arise in the wake of the commodification of biomedicine. Some advances toward this goal are already taking place, such as the Food and Drug Administration (FDA) requirement that details of all clinical trials be reported on ClinicalTrials.gov (Piller 2015). As industry funding continues to outpace government investments in research, transparency will remain an important tool for minimizing conflicts of interest.

A Focus on Protectionism Is Incompatible With Today's Emphasis on Participation

The Belmont Report's emphasis on researchers' duty to protect participants is admirable and necessary. Yet this duty should be augmented by a duty to include individuals from excluded and vulnerable groups in the research process. Inclusion should be understood to mean including those who have been left out not only as participants but as research partners who can help shape the research goals and protocols. This broader understanding of inclusion is likely to be more effective at reducing the inequalities in both knowledge and opportunity to obtain benefits that exist between those who have been overly protected and those who have not. This move away from protectionism and toward participation, from subjects to partners, is supported by both the principle of beneficence, since it may lead to greater positive health outcomes, and the principle of respect for persons, since many individuals desire to be more involved in research. This also aligns with the recently released Common Rule updates, which now exclude pregnant women and those with physical disabilities from those "potentially vulnerable due to undue influence" (Federal Policy for the Protection of Human Subjects 2017), and the revised Council for the International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans, which recognize that a judgment of vulnerability "requires empirical evidence to document the need for special protections" (CIOMS 1993). Of course, care must still be taken to ensure that each stage of the research process is not exploitative. Especially important is that participants receive reasonable compensation for harms and injuries they might sustain within an experiment, a problem that remains unsolved to this day.

The Deductive Relationship Between Single Ethical Principles and Applications Espoused by the Report Is Too Limited

Although the Belmont Report suggested that the relationship between individual principles and applications be understood as a deductive one, this unnecessarily

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limits the principles to narrow aspects of the research process; the principles instead ought to be understood as applying broadly to all aspects of research involving human subjects. Each principle should be kept in mind by investigators, oversight committees, and regulators throughout each stage of research design, development, implementation, and distribution. Respect for persons should no longer be thought of as a principle that is captured merely by the process of informed consent, but as one that guides the entire research process. In practice, this would involve determining eligibility criteria with this principle in mind, so that individuals are not excluded for trivial reasons (e.g., extra time required for a translator) and those deemed eligible would be likely to benefit from the results (e.g., individuals living below the poverty level are less likely to benefit from an investigation of a novel device not covered by Medicaid). This would also imply that specific informed consent can sometimes be forgone in favor of "broad consent" (Federal Policy for the Protection of Human Subjects 2017; Council for International Organizations of Medical Sciences 2002).[4] Similarly, follow-up should be conducted with the principle of respect for persons in mind; test results should be given directly to a participant's primary care physician when requested, and someone from the study team should be available to answer questions for a reasonable period of time once data collection is complete.

CONCLUSION

The Belmont Report was an impressive and inspiring response to the ethical issues of its day. Since its release, the field of research involving human subjects has developed in complex and unexpected ways, challenging the report's ethical framework to respond not only to the fears related to research abuses that it stemmed from, but also to the increasing commodification of biomedicine, the exclusion of many groups from research, the globalization of research, the desires of many to have access to experimental drugs, the lack of generalizability and reproducibility of many research findings, and the unique harms and histories that communities have experienced as a result of research. While these challenges are likely to continue to shift and expand in the coming years, there are several areas where the report comes up short today. Considering the important role the Belmont Report has played and continues to play in research ethics today (Federal Policy for the Protection of Human Subjects 2017), it is time for a tune-up, if not a complete overhaul. ■

4. In fact, the recently released Common Rule acknowledges that feedback on the previously proposed policy of requiring informed consent for the use of biospecimens was insufficient in that it emphasized "respect for persons with little regard for the principles of beneficence and justice" (Federal policy for the protection of human subjects 2017).

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