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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.

Keywords:

Ethical review

South Asia

ICH-GCP

Clinical Trials

Capacity-building

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

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 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 of problems which afflict large numbers of 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.

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 One].

TABLE ONE ABOUT HERE

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.

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 [eg 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 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.ⁱⁱ At the time of writing, there over 650 ERCs registered via the Clinical Trials Registry of India.ⁱⁱⁱ 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.

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, Lanerolle and Mendis, 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, Lanerolle and Mendis, 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.^{iv} 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).

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, Raj Jeevan and Harper,nd].

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 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 any thing 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 Emmanuel, Lemmens and Eliot, 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.^v 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.^{vi} 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.

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 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 an 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, pp4-5].

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.

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 work load 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 ethics 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.^{vi} 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, p495]. 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.

Notes.

ⁱ The research was funded by the UK's 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.

ⁱⁱ The Clinical Trials Registry India. <http://www.who.int/ictrp/network/ctri/en/index.html> accessed 23rd July 2013.

iii. Details of registered ERCs can be found on the website of the Central Drugs Standard Control Organisation: <http://www.cdsc.nic.in/forms/Default.aspx> accessed 5th Feb 2014

iv 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.

v. <http://pharmabiz.com/ArticleDetails.aspx?aid=76984&sid=1> accessed 13th August 2013.

vi. 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.

vii Panel recommends sweeping changes in clinical trials, The Hindu sept 18, 2013.

<http://www.thehindu.com/sci-tech/health/panel-recommends-sweeping-changes-in-clinical-trials/article5141590.ece> accessed 20th Jan 2014. Also see Jesani 2102 & 2013

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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

Table One. The BHESA interview data-set.

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

Research Highlights

- In the review of trial protocols, tensions surround the scope, functioning and authority of ERCs
- ERC members expressed specific concerns about responsibilities towards vulnerable populations
- ERC members face pressure from the constituencies they serve.
- ICH-GCP and evidence-based approaches to ethics narrows the parameters for ERC concerns,
- these developments suggest a novel impact of pharmaceuticalisation in the developing world.