Reviewer’s report

Title: Disparate compensation policies for research related injury in an era of multinational trials: A case study of Brazil, Russia, India, China and South Africa.

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Reviewer: Joanna Mary Manning

Reviewer's report:

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Page 4 line 23 - short explanation as to why it is so difficult to establish the elements of tort for RRI. Pike has good explanations that can be summarised. Otherwise the point is left hanging. And an explanation is required to link to analysis of no fault v negligence based policies. Eg page 13 in the discussion of Brazil's Resolution.

Page 4 line 38-39 - The stats quoted in the Indian example is insufficient to establish the claim that RRIs in the BRICS countries have increased. It does not even establish this for India. Perhaps claim that the incidence of RRI is significant. It is difficult to find recent studies of the incidence of RRI. Perhaps few have an incentive to undertake this research or the results are hard to access, because pharma will want to keep this information buried. In my article at J Manning, "Does the law on compensation in the UK, Australia and New Zaland meet ethical requirements?" [2017] Med LR Advance Articles I cite to the 1976 US survey of investigators conducting research on nearly 133,000 participants over three years, which showed that of the 93,000 participants in nontherapeutic research, 0.8 % were reported injured; no-one died, one was permanently disabled, 37 were temporarily disabled & 673 suffered trivial injuries. Of the 39,000 therapeutic research participants, 10.8% reported injuries: there were 43 deaths, 13 permanent disabilities, 937 temporary disabilities, & 3,253 trivial injuries. Quoted in DB Resnik, "Compensation for research-related injuries" (2005) 27 Jo Legal Med 263, 265.


Page 9 Table 2 - South Africa. The lack of legal enforceability by the injured subject in SA is a key point, and the legal enforceability of the compensation policies in each of the BRICS
countries deserves noting as a separate criteria. In contract, the Indian ones, enshrined in law, are legally enforceable. See comment below, re South Africa.

Page 12, line 8 - Brazil. State whose Resolution is this? Is Resolution 196/96 a resolution of the Brazilian Parliament? Or a registration authority or REC?

Page 13 line 6 - lack of time limit being a weakness. Presumably the author means from the sponsor's point of view, because its liability remains open and indeterminate into the future. But it is not a weakness but a strength from an injured subject's perspective who suffers a radiation injury after a long latency. Perhaps the Resolution could specifically state that injuries are included within the obligation to provide care, provided a causative link with participation in the research is established, so that even in long latency injuries, the subject could still possibly prove that exposure to radiation caused the injury.

Page 13 line 24 - Comment on the lack of compensation for economic loss, here or later. loss of income from injury is particularly devastating for injured participants. It should at least be clear if it is included, so that if it is not, a subject could decline to enroll or conceivably take out his/her own insurance, but the ethical obligation extends to compensation for these losses. Otherwise the injured subject is left with the burden of injury, to which the sponsor does not have to contribute. Breaches the ethical principles author mentions at the start. So compensation for these losses should be included.

Page 14 line 38 - Russian rupees. Give some idea of the purchasing power of these amounts, or the approximation to annual average wages. To what extent are the specified amounts realistic compensation?

Page 14 lines 53-54 - any comment about the fact that an injured subject can be disentitled from receiving compensation through non-compliance with the protocol (which they may never see or know what is in it) or negligence. This prevents the compensation being no fault compensation, and so it falls below the ethically required threshold.

Page 15 line 25 - same comment as Brazil relating to economic losses. Excellent point on psychological harms not being compensated for.

Page 15 line 45 - India. Perhaps a brief background or a reference as to why India has such stringent laws relating to RRI. See Thousands die in clinical trials in India, but compensation is rarely paid BMJ 2015; 351 (Published 13 November 2015). This suggests that even though the law may be stringent, it is ignored by companies ie it is not being enforced. It is likely that injured subjects cannot afford to enforce it or don't make claims. Hence the need for prison terms and payment of a fine which is double the amount of compensation payable.

Page 17 line 13 - "extra information, such as earnings and occupation that assists the Ethics Committees in their assessments. The investigator therefore acquires private information from
the participant which may not necessarily have any relevance to the study." This information is designed to help pay the income replacement compensation, so while not relevant to the study, it is relevant to the sponsor's ethical obligation to pay proper compensation. It seems like a good idea. It could be stated in the Participant Information Sheet that this information is relevant to the appropriate quantum of compensation in the event of injury, so the potential participant knows whether or not they want to give this information.

Page 17 line 47 - "This is atypical and violates the ethical principle of equipoise." Incorrect statement. The compensation requirements on the sponsor in the event of injury, even if caused by placebo, do not affect the requirement for equipoise at the start of the study. It is unusual for there to be compensation obligations to pay for injury caused by placebo, but I strongly suspect that this results from the drafters of the law being concerned that placebo will be used unethically when there is a standard treatment for the condition available. I agree it is unusual for the law to require compensation for failure of the trial product to achieve a therapeutic effect, because the point of the trial is to see if there is a therapeutic effect, and it is usually argued by the sponsor that failure to achieve a therapeutic effect means that the subjects underlying condition was the cause of the harm. Causation arguments can be a huge hurdle for the injured subject, and I suspect that the Indian law's drafters wanted to spare the injured subject from being turned down because of insoluble causation arguments made by the sponsor.

Page 17 line 56 - deviant participants. Same comments as above. How does a participant know they have deviated from the protocol when they haven't seen it, been given a copy, or had it explained to them? Statement about draconian and punitive needs to be seen in the context of the massive power differential of the multi-national company and the injured subject. It looks like the Indian law is creating a no fault scheme in the law (ie compensation payable regardless of the subject's fault). The NZ ACC system has such a scheme for RRI on publically funded trials.

Page 18 line 20 "The role of the REC extends beyond prosaic REC roles to include formulating recommendations on the quantum of damages." While unorthodox, the key role of the REC is to protect subjects, so seems like a good idea in a country where injured subjects are unlikely to be able to get a court to decide quantum, and it is certainly better than relying on the sponsor to determine quantum, given its conflict of interest!!

Page 19 line 13 - "incompliance to industry standard. If manufacturer of a defective product that causes harm or injury can prove that the said product meets the national or industry standard, such a manufacture would be absolved of any wrong doing. Furthermore, if a drug is approved by the State Food and Drug Administration agency, bydefinition, it cannot be defective and therefore no claims against it can be made." I am not sure I agree. Presumably the F and D Admin only approves licensed drugs, not those undergoing clinical trials. I would have thought there was no industry standard for a new trial medicine, since it is at the experiemntal stage. But it seems unclear and does not seem the right test.
Page 19 line 30 - interesting discussion of "Equitable Liability Doctrine" as a matter of comparative law. A pragmatic response, which tries to ensure that the subject gets something.

Page 22 line 37 - "a signed informed consent document properly canvassing the risks inherent in the study as absolving the sponsor from the obligation to pay compensation." This is contrary to the consensus of bioethicists that informed consent to the risks only authorises that research to proceed, and does not constitute a waiver of compensation. See my Med L Rev article.

Page 20 line 37 - "The sponsor should pay compensation to patient-volunteers suffering bodily injury, including death." I think the key point which needs highlighting is that the sponsor's obligation to pay no fault compensation is without legal commitment. The author does note this at p 22 line 43. See DOH, Good Clinical Practice Guidelines 2006, compliance with which is compulsory, see para 1.4. See para 4.11, which replicates the UK ABPI Compensation Guidelines, which I critique in my article (above Med L Rev). The UK Compensation Guidelines for Phase I studies are legally enforceable by the injured participant, but the ABPI ones for Phase II-IV studies are legally unenforceable by the injured subject, and the obligation to compensate on a no fault basis is a moral one only. Para 4.11 also states that the sponsor's responsibility to pay no fault compensation is "without legal commitment." Because para 4.11 does not state which phases the para applies to, I suggest that it applies to all phases including Phase 1 (the riskiest, where no benefit is derived by the subject), unlike the UK ones applicable to Phase I trials, which as stated, are legally enforceable.

Otherwise discussion of SA rules is very good. There is more discussion if the features of the ABPI Compensation Guidelines in my Med L Rev article.

Page 23 line 33 - author doesn't explicitly state why compulsory insurance is important ie it guarantees that the sponsor will be able to pay compensation.

Page 23 line 35 et seq - the author states the differences in compensation quantum and items for compensation eg economic losses, but makes no comment at all about what is a preferable arrangement ethically. This make it just information of little use except interest to the reader. Likewise to the third area of dissimilarity - which is preferable?

Page 25 line 23 - "some of these participants may require medical treatment until death." If the trial product causes disability until death, why is it "overkill" for the sponsor to compensate the injured person for that? I take the point about double recovery, but compensation would presumably exclude medical care if the sponsor was providing it.

Page 25 line 53 - there is some suggestion, however, from the BMJ piece above, that sponsors are simply ignoring the law in India.
Page 26 line 25 - if the subject can lose compensation for non-compliance with the protocol and contributory negligence, the policy is not truly a no-fault one.

Page 26 line 43 - Does the author recommend investing this in the judiciary, when he later says in the Conclusion "court based systems are often too slow."

Otherwise I agree with much of the Discussion, which makes very good points.

Typos
Page 5 line 37 - should read "compensation policies for research-related injury"

Page 5 line 37 - probably no such as an "ideal" model, since the balance between compensation for RRI and encouraging research will be subjective. Select better word. Eg "more protective model"?

Page 16 line 16 - should read "injured participant or his nominees also receive a financial compensation in the event of death."

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