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.

The text has been revised to read:

A good informed consent form clearly spells out the duty owed by the researcher to the participant. Research related injuries could still occur in spite of the researcher diligently fulfilling his obligations. In such a case, the tort system absolves the researcher. Even in the case where the researcher fails to fulfill the duty owed the participant, the participant must still demonstrate a causal link between the failure and the injury. Demonstrating this is not easy especially considering the fact that in some conditions it is not feasible to trace the occurrence of an injury to a single event. For example, how does one demonstrate that a particular cancer was caused by a specific failure on the part of the researcher when cancer is known to occur in the general population not participating in the research? Where failure is proven and a causal link is demonstrated, if the researcher can proffer a legal justification for the failure, the case falls on this.

Some research related injuries arise from totally unforeseen risks. Since these risks are unforeseen, they cannot be addressed in the informed consent process. The researcher cannot also not be faulted for their occurrence. Such injuries, therefore, fall outside the purview of the tort system leaving the injured participant with no recourse.

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.

The words “are increasing” has been replaced by are significant to read

Research related injuries in these countries are significant.


The text was edited to reflect the latest regulatory framework and read

'the European Regulation no 536/2014 on clinical trials on medicinal products for human use.'

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.

Another column added indicating legal enforceability.

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?

To add clarity the statement was revised to reflect the source of the resolution as the Brazilian parliament by adding the words:

of the Brazilian parliament
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.

The words from the sponsor’s viewpoint were added.

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.

To address this concern a new paragraph was added which reads:

"The silence of the regulations on the issue of economic losses is a disadvantage to the participant. Clarity on this issue helps inform the prospective participant’s decision. In the absence of cover for economic losses the participant has an option to take the risk and enroll on the research without insurance cover or to explore alternative insurance arrangements. Placing the burden of economic losses, which can in some cases be substantial, on the shoulders of the participant is a double whammy. The participant must not only assume the risk of participating in an enterprise meant for the benefit of society, but also carry the burden of arranging at the participant’s cost insurance against economic loss. The society on its part does nothing but reap the benefits of the participant’s benevolence. This patently violates the principle of distributive justice."

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?

The following statement was added to the text:
"To put these figures into context, it is worthy highlighting that according to Rosstat the average annual income of a Russian worker was 257 000 Russian Rupees in January 201621."

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.

The text was revised to reflect that:

"This scheme is thus not a no fault scheme, making it fall short of the minimum required ethical standard."

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

Additional text was added to reflect that:

"When economic losses are substantial and devastating the scales of distributive justice are tipped against the participant."

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.

A brief background to the problem was added as follows:

"Documents presented to the Supreme Court in India in 2013 revealed that between 2005 and 2012 as many as 2868 participants had died during trials of which only 82 had been compensated [21]. The high mortality coupled to the very small proportion of compensated participants gave impetus to the new legal regime."

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.

Extra text was added to address the concern. The text now reads:

"This gives rise to a dilemma. On one hand, the Ethics Committees encroach on the privacy of the participants, while on the other hand they need the information in order to determine the quantum of damages in the event of research related injury. This issue therefore needs to be properly canvassed during the informed consent process."

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 ie 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.

The revision now reads:

"This is atypical and may have been informed by concerns that investigational products were being administered disguised as placebos.

This steers away from the equipoise concern."

Page 17 line 56 – deviant particiants. 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 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.
The concern has been addressed as follows:

"However, from the viewpoint of the participants the stringent legal regime helps to offset the massive power differential between powerless participants and very powerful sponsors."

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!!

The following text was added to make the discussion more complete:

"It can be argued that this departure from orthodoxy is justified in a society where participants are unlikely to independently approach the courts for determination of quantum of damages. This can then be seen not as a new role but just another layer on the REC’s duty to protect the interests of the participants."

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, by definition, 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 experimental stage. But it seems unclear and does not seem the right test.

To shed more light the following statement was added:

"All the sponsor needs to do is to demonstrate that the investigational product was produced in conformity with industry standards."

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.

The recommendation was incorporated to read:

"This is contrary to the consensus of bioethicists that informed consent to the risks only authorises that research to proceed, and should not be construed as a waiver of compensation[25]."

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 I (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.

Extra text was added to capture the idea that the arrangement is without legal commitment. The text now reads:

"...but the caveat is that the sponsor’s obligation to pay no fault compensation is without legal commitment."

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.

The recommendation was incorporated so that the statement reads:

"Insurance cover, which is important in that it guarantees 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?

The following text has been added:

"A more robust approach should impose an ethical obligation on the sponsor to pay for medical expenses, financial compensation for both long term and short term injuries which should be defined broadly to include both non-physical injuries and compensation for economic losses."

"...and should be adopted as the standard."

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.

The following text has been added.

"The regulations should explicitly state whether the medical expenses will be covered by the compensation package otherwise the participant may benefit unjustly through double recovery."

Page 25 line 53 – there is some suggestion, however, from the BMJ piece above, that sponsors are simply ignoring the law in India.

The concern has been addressed by adding the following statement to the text:

"If the stringent regulations are diligently enforced sponsors may elect to take their projects to more research friendly destinations."

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.

The following statement has been incorporated to address the concern:

"Where injury is caused by the participant’s deliberate non-adherence to protocol the doctrine of contributory negligence and liability should apply as a limit to the blanket no fault compensation
approach. This is likely to dissuade the participants from engaging in non-compliance which neither benefits the participant nor the research enterprise in general."

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.”

The word judiciary has been deleted.

The statement now reads:

"The responsibility to adjudicate compensation claims and to determine the quantum of damages should be vested in a quasi-judiciary entity with experience in determining such matters."

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”

Corrected

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”?"

"The recommendation was incorporated to read:

More protective model."

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

The recommendation has been incorporated to read:

"For the injuries that are related to the clinical trial, over and above comprehensive medical treatment the injured participant or his nominees also receive a financial compensation in the event of death."
Reviewer 2 Dominic Madell

p.1 Line 24 - reference in relation to Ellen Roche and Jesse Gelsinger?
Reference added.

p.4 line 21 - can you provide more explanation about why the nature of research means that research participants will have difficulty proving these elements?
The text has been edited to read:

"A good informed consent form clearly spells out the duty owed by the researcher to the participant. Research related injuries could still occur in spite of the researcher diligently fulfilling his obligations. In such a case, the tort system absolves the researcher. Even in the case where the researcher fails to fulfill the duty owed the participant, the participant must still demonstrate a causal link between the failure and the injury. Demonstrating this is not easy especially considering the fact that in some conditions it is not feasible to trace the occurrence of an injury to a single event. For example, how does one demonstrate that a particular cancer was caused by a specific failure on the part of the researcher when cancer is known to occur in the general population not participating in the research? Where failure is proven and a causal link is demonstrated, if the researcher can proffer a legal justification for the failure, the case falls on this.

Some research related injuries arise from totally unforeseen risks. Since these risks are unforeseen, they cannot be addressed in the informed consent process. The researcher cannot also not be faulted for their occurrence. Such injuries, therefore, fall outside the purview of the tort system leaving the injured participant with no recourse."

Page 5, line 54 "no-fault compensation" (hyphen in wrong place)
Corrected to read no-fault compensation

Table 1 - is there a more straightforward and clearer way of presenting this information given that most of the search terms are the same? e.g. say that "all databases used the following search times" and then state them, and in the table just include the extra search terms that were used for some databases.
Corrected to read "The following search terms were used for all the data bases: research related injury compensation policies; medical related injury compensation; clinical trial related injury compensation; compensable injuries; exclusions. For some data bases extra search terms were used. These are shown in Table 1."

p.12 line 7 - "In Brazilian research..."
Corrected to read “In Brazil research- related injuries”

Some inconsistencies in referencing style In general, I think it is a good, interesting and valuable paper. I think it could do with a read-through by a third party for clear English, as some of the phrasing seems unnecessarily complex. Also, some paragraphs are very long and need reducing.
Revised.