COMMENTARY

# Research Subject Injury Compensation: The Ongoing Search for Fairness, Consistency and Clarity

*Mark Barnes, Jamie Flaherty, and Barbara E. Bierer*

Chapman *et al.* analyze important ethical, political, and logistical considerations underlying research injury compensation models, ultimately proposing a blended approach for the U.S., including both personal insurance (private and government plans) and insurance/self-insurance by research sponsors.[1] Research injury compensation continues to be a complex issue; different countries have taken very different approaches, with some, like India, mandating strict, pro-participant research injury compensation rules and others, like the U.S., remaining silent, leaving such policies optional and to be determined by research sponsors and institutions on a case-by-case basis. In proposing a research injury compensation model for the U.S., much can be learned from other countries' rules. It is worth noting, however, that given the increasingly globalized nature of research, with most phase III trials being multicenter and trans-national, a clear model mandating research injury compensation in the U.S. — though an important step forward in terms of advancing the U.S. research legal framework — would leave unaddressed a need for consistency in approach among these transnational, multi-regional trials.

Unlike in the U.S., many countries require — at least in some form — compensation for subjects injured in connection with research. In light of basic principles of fairness and justice, and given the limitations associated with U.S. tort law and the desire to assure and encourage potential participants to engage in research, the U.S. research regulatory regime would benefit from standardized research injury compensation rules. The question, however, explored by the authors is what those rules would substantively entail (no-fault, coverage for physical and non-physical injuries, etc.) and the ideal manner of establishing such rules (through guidance, binding regulations, etc.).

Research injury compensation models must strike a balance: the rules must be robust enough to safeguard the rights of human participants, while not being so onerous or burdensome on sponsors so as to hinder or stifle research, as has — the authors note — happened in India in response to mandatory clinical trial injury compensation not tied to a causational principle. The approach to research injury compensation in India perfectly illustrates this delicate balance and the risks associated with overly broad compensation provisions. India's clinical trial rules generally require compensation for research subject injuries deemed related to a clinical trial, and also require sponsors to provide free medical care for injuries that occur to trial participants regardless of whether the underlying injury was caused by participation in the clinical trial, at least until it is established that the injury is not related. The Indian government developed a formulaic approach to research injury compensation, with distinct formulae in case of death or for various injuries, which ensures all participants are entitled to the same compensation based on certain individual characteristics, such as illness and age. These compensation formulae introduced transparency and predictability to a system formerly lacking limitations on liability. As has been well documented in the literature, India had ini-

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tially adopted an extremely broad approach both with respect to compensation for research related injuries and free medical management — having included, for example, adverse effect of the investigational product and failure of the investigational product to deliver the intended effect as injuries deemed related to the clinical trial. This expansive approach toward defining "relatedness," coupled with the broad free medical management provision, ultimately deterred sponsors from siting clinical trials in India. This not only cut-off sponsor access to a diverse research population, but also deprived those in India from access to important investigational drugs, as in oncology studies.

Over time, however, Indian regulators through official notifications and new clinical trials rules have sought to clarify and scale back certain onerous requirements, including now essentially re-instating a causation requirement for compensation for clinical trial injuries. For example, compensation for an investigational product that fails to achieve its intended effect is now limited to situations where the standard of care, when available, was denied. In March 2019, the government finalized its 2019 clinical trials rules, which eliminated a proposed rule that would have required sponsors to pay an interim compensation of 60 percent of the full compensation to be awarded in the event the injury was determined to be "related to" the trial and therefore compensable.[2] This interim compensation would have been irrevocable, meaning the sponsor would not have been reimbursed even if it were later determined that the death or injury was not related to participation in the clinical trial.

Much can be learned from the experience in India. First, the Indian government's strict rules prompted important ethical and legal discussions regarding the rights of research subjects, and reflect the country's focus on ensuring compensation and fairness for its research participants. Second, Indian regulators developed clear timelines for reporting research participant injury or death and adjudicating the likelihood of its relatedness to participation in the trial and, as mentioned previously, detailed compensation formulae — details that could benefit and inform other countries' research injury compensation rules. Third, India's compensation rules were adopted with the country's political and socioeconomic climate in mind. Specifically, much of the Indian population does not have access to health insurance; thus, the regulations go beyond simply relying on insurance mechanisms to assist research participants with research-related injuries.

The ideal U.S. model would strike a balance between protecting research participants, while being sufficiently narrow and flexible so as to not deter or overly burden those sponsoring and conducting important scientific research. (Chapman *et al*., in fact, fail to note that in many cases, academic medical centers act as both sponsor and investigator — meaning that obligations imposed on research sponsors of the sort that the authors advocate would apply not only to private industry sponsors of research, but also to not-for-profit medical centers and foundations that sponsor research.) A preferred compensation methodology would also establish clear mechanisms in terms of scope and process. Assuming — as many do — that a no-fault approach would best reflect considerations of justice and fairness for research participants, an ideal approach would also need to address causation and relatedness; after all, it may be that most "injuries" in clinical research may relate not to research interventions, but rather to the natural history and expected course of disease, or to expected adverse events from novel therapies that effectively decrease other adverse events. Finally, from a practical perspective, the proposed methodology should reflect — and be feasible under — existing U.S. regulations and policies.

The approach proposed by the authors, which blends aspects of both personal insurance (through private and government health insurance plans) and insurance/self-insurance by research sponsors, reflects these myriad factors; however, it still is unclear whether and how the approach would assess causation and research-injury relatedness. It is also unclear what role — if any — institutional review boards or research ethics committees will play, *i.e.*, whether they will be responsible for assessing the scope and

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adequacy of the insurance policy adopted by the sponsor. One potentially problematic consideration is that with such a blended approach, sponsors may seek out populations more likely to have their own insurance, so as to avoid the need to take out the sponsor's own insurance, thereby reducing access of uninsured populations to clinical trials.

Looking beyond the question regarding the ideal U.S. model, even if clear rules were established in the U.S., we note that those conducting research in multiple countries still will find themselves subject to and grappling with many different compensation rules. Authors George Rugare Chingarande and Keymanthri Moodley have described the issues associated with these international discrepancies:

> Disparate standards create problems in the resolution of injury claims which, in a globalized industry, will likely emanate from different countries. It becomes imperative for sponsors of global research to familiarize themselves with local standards before they choose the destinations of their research activities … Imagine a hypothetical scenario involving five adverse events leading to death in a multi-center clinical trial conducted in the BRICS [Brazil, Russia, India, China and South Africa] countries, with one trial related fatality occurring in each country. The sponsor is faced with five different conundrums and the quantum of compensation, all things being equal, if any, will be different in each case. A system in which participants who suffer similar injuries receive differential compensation patently violates the ethical principle of fairness.[3]

As this conversation continues, thought should be given to efforts to standardize certain fundamental research injury compensation rules on a global scale, such as establishing certain consistent minimum compensation requirements and consistent methodologies for causation or relatedness determinations.[4] Efforts to streamline or harmonize different countries' approaches would result in increased international harmonization and a more clear and uniform approach, which could better reflect and accommodate the increasingly globalized nature of clinical trials.

## Note

Mr. Barnes reports income from Ropes and Gray, LLP, from the Multi-Regional Clinical Trials Center of Harvard University, and Brigham and Women's Hospital, outside of this submitted work.

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3. G. R. Chingarande and K. Moodley, "Disparate Compensation Policies for Research Related Injury in an Era of Multinational Trials: A Case Study of Brazil, Russia, India, China and South Africa," *BMC Medical Ethics* (2018), *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5816510/> (last visited November 13, 2019).
4. *See id.* ("There is need for consistency and even harmonization of such regulations at a global level. A model policy on compensation for research related injuries should borrow from the best aspects of the different policies of the BRICS countries and should be informed by the cardinal ethics principles of autonomy, justice and beneficence.")



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