The Quest for Compensation for Research-Related Injury in the United States: A New Proposal

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Introduction

Although occurrences are rare, participants are sometimes harmed[1] and even killed[2] as a result of participating in clinical trials, in studies of the most promising investigational agents or when the participants are healthy volunteers in challenge studies. As the 2011 Presidential Commission for the Study of Bioethical Issues (henceforth, the Commission) acknowledged, "Unintended harm is inevitable in the course of human subjects research."[3] The Commission's International Research Panel advised it to recommend that the U.S. adopt a compensation system for research-related injuries,[4] echoing similar recommendations by many other committees.[5] Instead the Commission endorsed the assertion that human research subjects should not individually bear the costs incurred from research-related injuries and advised the federal government to "move expeditiously to study the issue" and "publicly release reasons for changing or maintaining the status quo."[6] They noted that affirming the moral justification for a system "does not...specify what an optimal system to carry out this ethical mandate would look like."[7] Despite persistent calls from bioethicists to address this issue,[8] the U.S. has not conducted studies or clarified compensation for research-related injuries.

It is unethical that the U.S. does not require all research subjects to receive comprehensive care for injuries they may experience as a result of their participation. In this article, we review how compensation for research-related injuries is currently handled in the U.S., which depends on where the study is conducted, what entities are sponsoring the study, and whether and by whom the participant is insured. We also

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explore various systems of compensation adopted by other countries. The existence of these systems demonstrates both that the U.S. lags behind other nations in its protection of human research subjects and that the establishment of a more comprehensive compensation system is both practical and feasible. We then examine factors that have prevented the U.S. from establishing a comprehensive compensation system. Finally, we consider possible alternatives for the U.S. by examining advantages and disadvantages of both established and proposed systems. We agree with others that a decentralized no-fault compensation system is the best path forward as it minimizes administrative and logistical challenges, and we put forth a new proposal. We suggest mandating and strengthening existing mechanisms for compensating research participants for research-related injuries in the United States. Establishing such a system is not only within reach, it also addresses the justice concerns that compel all research subjects to receive medical care and/or compensation for research-related injuries, and fairly distributes the burdens on various key stakeholders that benefit from the conduct of human subjects research.

We review how compensation for research-related injuries is currently handled in the U.S., which depends on where the study is conducted, what entities are sponsoring the study, and whether and by whom the participant is insured.

Current U.S. system

Federal Requirements

Despite broad consensus that human research participants deserve medical care and/or other forms of compensation if they are injured as a result of research,[9] U.S. regulations do not currently require research institutions or pharmaceutical sponsors to provide medical care or compensation for injured research subjects. The Code of Federal Regulations (CFR) simply specifies that for research above minimal risk, informed consent forms must include "an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs, and if so, what they consist of, or where further information may be obtained" as well as "whom to contact in the event of a research-related injury to the subject."[10] The FDA's guidance on investigator responsibilities sheet does state that the agency expects investigators to ensure that research participants have access to reasonable medical care during their participation in a clinical investigation.[11] And certain federal agencies, such as the Veterans Administration, the Department of Defense, and the NIH Clinical Center, do provide medical treatment for participants in their studies who have research-related injuries.[12]

But in many cases, given the lack of a federal requirement to provide compensation, the tort system is the research subject's main recourse to get compensated by research institutions or sponsors in the event they experience harm as a result of participation in a study. Accordingly, U.S. regulations prohibit exculpatory language in the informed consent forms. At 21 CFR 50 it states "No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."[13] This language is similar to a clause in the International Conference on Harmonisation (ICH) Guidelines.[14] FDA draft guidance on informed consent notes that exculpatory language "has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt."[15]

Dependence on a tort system for compensation raises justice concerns for a number of reasons. The tort system is not equally available or navigable to people without the requisite social and financial supports. Further, those seeking redress specifically for research-related injuries are typically only successful when researchers are negligent or intentionally cause harm.[16] And harms can result from research even if procedures are correctly followed.[17] Even if patients have cases with legitimate malpractice claims, it can be difficult to secure legal representation, legal fees can significantly reduce plaintiff's recovery, and resolution can take years.[18] "Continued reliance on the tort system to compensate injured research participants is morally indefensible" because it is time-consuming,

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adversarial, expensive, and results in disparate outcomes.[19] On its own, the tort system is not an ethical solution since it does not provide a timely, fair or efficient way for harmed research participants to get deserved compensation.

Health Insurance

Since most research sponsors and institutions are not required to provide medical care or compensation to those who experience research-related injuries, insured participants may turn to their health insurance providers for coverage of needed medical care. An executive order signed by President Clinton in 2000 requires Medicare to reimburse for routine patient care costs, which include items and services used to diagnose and treat complications in qualifying clinical trials.[20] To be qualified under Medicare, the trial must have therapeutic intent and fulfill other criteria.[21] There are no federal laws requiring Medicaid to cover clinical trial costs for its beneficiaries, but approximately ten states have laws that do so.[22]

Provisions included in Section 2709 of the Affordable Care Act (ACA) that became effective on January 1, 2014 set a national minimum coverage standard for non-grandfathered health plans for qualifying individuals who participate in approved clinical trials.[23] Again, these include reasonable and necessary items and services used to prevent, diagnose and treat complications arising from participation in a qualifying clinical trial. Qualifying trials include Phase I, II, III, and IV clinical trials that "are conducted in relation to the prevention, detection or treatment of cancer or other life-threatening disease or condition" that are also federally approved or funded, are conducted under an investigational new drug application (IND), or are drug trials exempt from having an IND.[24] Out-of-network coverage for routine clinical trial costs is only required for plans that otherwise cover out-of-network service.[25] Some insurers do exceed these standards. For example, United Healthcare's policy notes that it will cover routine patient costs for members participating in Phase I, II, or III trials for cardiovascular disease or musculoskeletal disorders.[26] Prior to passage of the ACA, many states required health insurers to cover standard of care costs associated with participation in certain clinical trials, but others did not.[27] Whether private insurers cover all care for research-related injuries is unclear,[28] and to our knowledge, there is no publicly available data. The ACA also includes provisions that prohibit group health plans and insurance issuers from denying qualified individuals from participating in clinical trials for life-threatening conditions.[29]

Uninsured subjects may be especially vulnerable should they experience harm as a result of research participation.[30] To shield them from these risks, some researchers may want to exclude uninsured research participants from clinical trials with greater than minimal risk, but this approach "would further disadvantage people who are already disadvantaged."[31] In such cases, the research sponsor could (voluntarily) cover routine costs for uninsured participants, including costs of research-related injury, or the research institution might (voluntarily) ensure adequate liability insurance to cover such costs.[32] There is a concerning lack of information about "what happens when those who are uninsured are injured in research or suffer an adverse event," and ethicists have called for more research on whether uninsured research participants are treated differently than insured participants in high-income countries, including with respect to treatment of and compensation for research-related injury.[33] Other ethicists have called for revised guidance to ensure that those who lack access to health services receive ethical treatment when participating in research in high-income countries.[34]

Another important U.S. regulation relating to research-related injuries is the "Medicare Secondary Payer" rule, which specifies that a sponsor cannot be the secondary payer to Medicare regarding research-related injuries.[35] The rule prohibits Medicare from paying for items and services that are made or reasonably expected to be made by a primary plan, such as no-fault insurers, group health plans, workman's compensation and liability insurance.[36] Medicare also views sponsor promises to pay for research-related injuries as a primary plan.[37] If research sponsors voluntarily agree to pay for research-related injuries in a study, healthcare providers must bill the research sponsor first for any Medicare beneficiaries. If the provider bills Medicare first, they may be liable for double damages for a cause of action under the Medicare statute.[38] Only if the research sponsor or institution does not agree to provide care or compensation for research-related injuries would Medicare accept a role as primary payer.

Voluntary Systems

Notwithstanding the lack of requirement to do so, many sponsors in the U.S. carry trial insurance and/or pay for medical care when injuries occur without being sued.[39] However, not all sponsors do so, and anecdotal reports indicate that sponsors limit these obligations. Typically, sponsors will not pay "for costs incurred due to an institution's mistakes, reckless or negligent behavior, or failure to follow proper protocol for the study…[or] for adverse events or allergic reactions that may have occurred even if the study partici-

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pant was not involved in the study."[40] Of course, causation of adverse events is difficult to determine: they may be caused by an investigational drug or research-associated procedure, by underlying disease, or for a reason unrelated to the study.[41]

Some research institutions have voluntarily developed their own compensation plans. For example, the University of Washington (UW) has a program for research subjects who experience a "medical problem that is more likely than not caused by UW-conducted research."[42] Those who qualify may receive care at a UW facility for up to $250,000 (funded directly by the UW healthcare system) or get reimbursement for up to $10,000 of healthcare expenses incurred outside UW facilities (funded by general UW administrative funds).[43] The plan does not cover lost wages or pain and suffering.[44] UW also typically requires industry sponsors to pay for care for research-related injuries.[45] Wake Forest (WF)'s policy also goes beyond what is legally required: for-profit sponsors must take responsibility for reimbursing reasonable and necessary medical expenses incurred by subjects through the study that are not the result of pre-existing conditions or underlying disease.[46] For studies with non-profit or government sponsors, there is a limited liability insurance policy for payment of reasonable healthcare costs up to $25,000.[47] WF does not allow sponsors to be secondarily liable for any healthcare costs related to treatment of research-related injuries, and all subjects must be provided with the same level of injury liability coverage.[48] Likewise, a University of Chicago IRB policy states, "commercial sponsors of clinical research at the Medical Center must agree to pay for treatment of injuries that are the direct result of the administration of a study drug or device, or any study procedure required to be performed in the study."[49] Sponsors may secure clinical trial insurance and/or self-insure for these liabilities.

Since there is no law requiring such coverage, terms vary from institution to institution and from study to study.[50] A 2012 survey of research-related injury compensation policies of U.S. institutions found that over half did not offer compensation.[51] 36.9% of the policies offered compensation that was conditional on certain factors, for example if the subject did not have insurance or their insurance did not pay, or if there was an agreement in place that the research sponsor would pay.[52] Even when offers to provide care exist, it may be difficult for research participants to receive payment for claims.[53]

In an October 2018 webinar, lawyers from King and Spalding outlined various options available to research sponsors with respect to coverage of research-related injuries.[54] Since there is no legal obligation to provide care or compensation for research-related injuries, leaving such coverage to payers (health insurers) is an option but research sites/institutions often expect sponsors to take some responsibility.[55] Notwithstanding the concern that insurance providers may not always cover research-related injuries due to limits and exceptions, this option raises questions about unequal treatment of insured and uninsured participants. Sponsors cannot agree to pay as secondary payers across the board — the "payer of last resort" option — as this would violate the MSP; however, sponsors may agree to be primary payers for those who are uninsured or covered by Medicare and secondary payers for those with private insurance.[56] Another option is for sponsors to agree to pay for all costs relating to research-related injuries.[57] This standard may be preferred by some IRBs, but it maximizes financial exposure for sponsors;[58] they may push back.

The current U.S. system does offer various means by which research subjects may potentially receive treatment or compensation, including civil tort liability, institutional self-insurance and commercial insurance, individual health insurance, government insurance as well as direct payment by agencies.[59] However, medical care for research-related injuries is not guaranteed for all research participants, nor is compensation for financial losses. Research subjects may be treated very differently depending on which study they are in, its location, and their health insurance status. Lawyers who practice in the area of human subjects research believe there is a growing concern from IRBs about compensation for research-related injuries based on the principle of justice,[60] which relates to the fair distribution of the benefits and burdens of research.[61]

Justification for Establishing a Better System

For many, it seems intuitively obvious that "human subjects who are harmed as a consequence of participation in research should not individually bear the costs of medical care for such harms."[62] Further, it seems unfair that insured and uninsured participants would be treated differently with respect to research-related injuries. The rationale and justifications for the provision of medical care and compensation for research-related injuries have been elucidated extensively in the bioethics literature. We provide a brief review here as determining an optimal system of compensation requires an ethical analysis of what entities ought to bear responsibility for the costs of research-related injuries.

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Professional Obligations to Beneficence and Non-Maleficence

The *Belmont Report* identifies beneficence, the obligation to help others, and non-maleficence, the obligation to do no harm, as core ethical principles for human subjects research.[63] Professional duties of beneficence and non-maleficence stem from the special relationship between the researchers and the research subjects. The obligation of researchers to help injured research subjects has been compared with lifeguards' obligations to rescue swimmers who begin to drown.[64] The principle of professional beneficence obligates those who initiate and conduct research to respond "to the needs of injured research subjects" but does not obligate them to compensate family members in case of the participant's death.[65]

Justice Issues

Most arguments for an obligation to provide care or compensation for research-related injuries are based on the principles of justice and fairness. Perhaps the justification that has received the most support is compensatory justice, which holds that there is an obligation for those benefited by an enterprise to compensate individuals who incur injuries as a result of such an enterprise.[66] Many will agree that those who reap the rewards of research, financial or otherwise, should be responsible for covering its true costs. Therefore, there is a strong case to require research sponsors, investigators, and institutions to provide medical care and compensation to human subjects that experience research-related injuries. However, all members of society benefit from research.

A counterargument explored but rejected by the Commission is that human subjects freely consent to participating in research and as such "have no claim, in justice, for compensation for any harms that befall them."[67] Yet consenting research participants should not be expected to shoulder "avoidable risks before, during, or after research," which include "the cost of medical treatment for unavoidable injuries," the Commission states.[68]

Another argument against compensation is that some human subjects participate in research out of self-interest, such as potential therapeutic benefit. Others may receive payment for participation. Some authors have argued that there is a higher obligation to compensate healthy volunteers with no chance of benefiting from the research than research subjects who participate because it is their best therapeutic option.[69] In France, research-related injuries are treated differently depending on whether the research provides individual direct benefit.[70] In research without individual direct benefit, the sponsor must pay compensation on a no-fault basis, but in research with individual direct benefit, the sponsor must pay compensation unless they can demonstrate that the injury was not caused by negligence on behalf of the sponsor or other investigators.[71]

Interestingly, Medicare and ACA provisions only mandate routine patient costs for certain types of clinical trials, such as those intended for serious disease. While some may argue that distinguishing between types of research is justified, many stakeholders benefit from the knowledge that is gained as a result of human subject participation, even in research that benefits the participant or when participants are paid. Certainly, unexpected harm can be caused by therapeutic research, which generally seeks to better understand risks and benefits of a particular intervention.

Reparative justice is a distinct moral justification for compensating research-related injuries, in that it is a "special duty to redress injuries caused by a wrongful act" that is owed by the "party at fault for the injury."[72] The tort system may best accommodate claims for compensation that are caused by negligence or fault. Yet many (if not most) research-related injuries are not caused by wrongdoing or fault so reparative justice is not sufficient to justify compensation of all claims. Most federal advisory committees have generally agreed that a "no-fault" system would be most appropriate for research-related injuries.[73]

Practical Issues

Aside from concerns about the just treatment of research participants, a comprehensive national system may reduce rather than increase financial liabilities associated with conducting research (i.e., reduce costs of litigation and/or damages awarded through the court system).[74] It may also eliminate confusion and streamline study-specific and case-specific negotiations. A compensation system would also build goodwill and trust in the research community and among would-be participants.[75] People may be more willing to participate in research if assured they will receive medical care and/or other compensation should they experience harm as a result of participation.[76]

Demonstration of the Feasibility of Compensation Systems in Other Countries

Although not a justification per se, the fact that "almost all other developed nations…have instituted policies to require researchers or sponsors to provide treatment or compensation" for research-related injuries demonstrates widespread international support for such systems.[77] Many countries require research sponsors to carry indemnity insurance to cover medical care and compensation for research-related inju-

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ries.[78] As noted above, many research sponsors in the U.S. carry insurance to cover injuries but this is only done on a voluntary basis. We have chosen to highlight and describe a few national systems based on our geographic locations around the world.

India

Most Indian subjects participating in clinical trials have low socioeconomic status and do not have health insurance. In response to reports that research subjects undergoing harm or even death were not being compensated, the Indian Ministry of Health issued a new rule (122-DAB), "Compensation in case of injury or death during clinical trial," in 2013.[79] The rule specifies that sponsors (pharmaceutical companies, government or non-governmental organizations) are responsible for the compensation of clinical trial related injuries by obtaining insurance coverage or provision for research related injuries or harm in the budget.[80] Further, a December 12, 2014 notification amended rule 122 DAB such that "in case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier."[81] In 2018, India's Ministry of Health and Family Welfare issued Draft Rules to clarify clinical trials requirements and in March 2019, finalized rules were released.[82] Generally speaking, the 2019 rules maintained the "fairly controversial and broad compensation-related requirements" for clinical trials[83] but clarified that free medical management shall be provided "as long as required *as per the opinion of investigator* [emphasis added] or till such time it is established that the injury is not related to the clinical trial or bioavailability or bioequivalence study, as the case may be, whichever is earlier."[84]

Eligible injuries include: adverse effect of the investigational product(s), or due to concomitant medication excluding standard of care, necessitated as part of the approved protocol; violation(s) of the approved protocol, scientific misconduct or negligence by sponsor or its representative or the investigator; failure of the investigational product to provide intended therapeutic effect; use of placebo; injury to child in utero because of the participation of parent in clinical trial and injuries caused by any clinical trial procedures involved in the study.[85] Compensation for failure of the investigational drug or as a result of the use of a placebo can only be granted if a standard treatment was available but not provided. Under the current system, a participant gets compensated even if the injury was anticipated and fully explained in the informed consent process. The "no fault" approach aims at providing compensation without ascribing blame, and as such reduces administrative burden. It enables participants to receive compensation even in situations where negligence cannot be proved. The trial participant or their kin need not prove it was anybody's fault and need not approach a court of law to seek compensation. Further, granting eligibility to injuries that are caused by the failure of the investigational product to provide its intended effect or by the use of placebo creates a relatively liberal causation standard.

The regulations leave the determination of the amount of compensation to the discretion of an Independent Expert Committee (IEC) constituted under the auspices of the licensing authority, the Drug Controller General of India (DCGI). The IEC examines reports from the investigator, sponsor or its representative, as well as the ethics committee that approved the protocol.[86] The committees use formulas to calculate compensation, using information collected in the informed consent forms, such as earnings and occupation. For example, in the case of trial related death, the formula is [Base amount (Rs. 8 Lakhs INR ($11,744 USD)) x Age factor x Risk Factor]/99.37.[87] The formula adopts the Age factor from the Workmen Compensation Act of 1923.[88] The Risk factor is assessed based on the participant's condition at the time of enrollment in the trial, which includes duration, severity, and seriousness of the illness and presence of any other co-morbidity.[89] The Risk factor has five grades ranging from 0.5 (terminally ill patient with expected survival not more than 6 months) to 4.0 (healthy volunteers with no risk).[90] There are different formulas to calculate compensation in the event of serious adverse event other than death.[91]

South Africa

The South African Department of Health Good Clinical Practice (GCP) Guideline provides the framework for dealing with research-related injuries, which is based on the Association of the British Pharmaceutical Industry (ABPI) Compensation Guidelines.[92] All participants in clinical trials must be covered by comprehensive insurance for injury and damage.[93] The Medicines Control Council, ethics committees and other relevant regulatory authorities require that an insurance statement documenting the availability of compensation to participants for trial-related injury be on file with the investigator/institution and with the sponsor before the trial commences.[94] There is no need to prove negligence on the part of researchers or sponsors in order for participants to receive compensation.[95] However, to be eligible, injuries must be attributable to the administration of a medicinal product in a trial or any clinical procedure that was

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part of the protocol. Injuries are also eligible if they are caused by a procedure precipitated by an adverse reaction to a medicinal product under trial.[96] The guidelines specify that damages may only be claimed for bodily injury "of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints."[97] The amount of compensation should be proportionate to the nature, severity, and persistence of the injury, and should be consistent with the damages commonly awarded for similar injuries in terms of South African law.[98] There is no obligation to provide compensation if a medical product fails to have its intended effect, or for injuries caused by licensed comparator drugs or placebo. Sponsors must resolve claims at their own cost under this system, including costs of a mutually acceptable independent expert if agreement cannot be reached between claimant and sponsor.[99] Participants retain the right to pursue a legal remedy, unless they agree not to as part of receiving compensation under these guidelines.[100]

Since research sponsors, research institutions and society at large all benefit from research activities, the Ubuntu framework suggests that they should all contribute to a compensation system "in one way or another."

Although not a research-related injury compensation system per se, in Sub-Saharan African culture the Ubuntu ethical framework for dispute resolution focuses on consensus-building, reconciliation, and "collective responsibility without blame."[101] Injury to one member of society translates to injury to the whole society. Likewise, blame is shared by the whole society, and there is a norm that everyone should contribute to reparation for the injury.[102] As society at large benefits from the knowledge that is gained from conducting human subjects research, society has a corresponding obligation based on fairness to provide treatment and compensation "as an act of benevolent regard for individuals' willingness to participate in an enterprise of important benefit to the public."[103] Since research sponsors, research institutions and society at large all benefit from research activities, the Ubuntu framework suggests that they should all contribute to a compensation system "in one way or another."[104]

Russia

In the Russian Federation, it is mandatory to provide life and health insurance for research subjects who participate in a clinical trial involving new drugs. According to the Federal Law "On the circulation of medicines" dated March 24, 2010 No. 61-FZ, to obtain permission to conduct a clinical trial, sponsors must purchase insurance for all research participants.[105] According to this law, the insured event under the compulsory insurance contract is the patient's death or deterioration of his health, in the presence of a causal relationship between the onset of this event and the patient's participation in the clinical trial of the drug. The amount of insurance payment under the compulsory insurance contract depends on the severity of the injuries (e.g., death or extent of health deterioration), and ranges from 300,000 to 2.0 million Russian Rubles (RUB).[106]

In order to receive insurance payments, those injured as a result of research must receive a confirmation from the Federal State Institution of Medical-Social Expertise that their injuries were caused by their participation in clinical research. In some cases, this may require a court trial and may include a forensic medical examination, which establishes not only a cause-and-consequence, but also specific causes of harm to health. If harm to the health or death of the research subject has occurred due to natural causes, the insurance indemnity will not be paid. If causal consequence between injury of subject of a clinical trial and the effect of a drug is proved, the subject will be paid an insurance indemnity. However, the insurance does not cover any economic losses incurred by research subjects.[107] The law states that the term of the insurance should be not less than the term of the clinical trial. The claims should be satisfied within the time limit prescribed by the law for civil litigation. This provision could cause a situation when effects related to injury that are discovered later will be not considered as claimable.[108]

Barriers to Adoption of U.S. System

We have established that a compensation system has broad ethical justifications and practical benefits. We have also reviewed systems that have been voluntarily developed by U.S. research institutions and sponsors, and highlighted a few of the many systems that have been put in place in nations around the world. In this section, we consider several barriers that have prevented the adoption of a comprehensive national system for compensation of research-related injuries,

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including logistical issues, moral gridlock, and the complexity of the U.S. health insurance system.

Logistical

Although the ethical rationale for developing a compensation system for injured research participants has been adequately developed and defended by many commissions and independent scholars,[109] there is less agreement about the specific system that best accomplishes this aim. Determinations must be made about the scope of coverage, the qualification of harms, and mechanisms for adjudication of claims.[110] Kenneth Feinberg, an attorney who has administered many compensation funds, including the September 11th Victim Compensation Fund, has expressed caution about the logistical hurdles associated with implementation of such a system.[111] Many practical questions must be answered, including eligibility criteria, how much compensation will be given and what form it will take (money, medical treatment or loss of future wages), who will provide funding, and what methodology will be used for determinations.[112] Aside from logistical hurdles associated with the development of a national system, another significant concern is that placing the burdens of a compensation system on researchers and/or sponsors would threaten or limit the amount of research that they are willing to conduct.[113]

Moral Gridlock

The failure to establish a compensation system in the U.S. can be at least partially attributed to "moral gridlock," [114] which Henry describes as a situation in which "articulation of numerous and sometimes disparate reasons for compensating injured research subjects actually results in incongruent obligations that favor different kinds of compensation systems."[115] In the U.S., lack of consensus about who should pay for research-related injuries may be a barrier to the establishment of clear and comprehensive regulation. Perhaps the ideal system would assign responsibilities to various entities to account for shared responsibilities and obligations.

Complexity of the US health Insurance System

Unlike in some other developed nations, there is no universal healthcare provided by the U.S. government. Yet, many Americans do have health insurance. According to 2017 data provided by the Kaiser Family Foundation, 49% of Americans receive employer-based health insurance, 36% have government-based insurance (Medicare, Medicaid or other public), 7% have non-group insurance and 9% are uninsured.[116] The benefits provided by different insurance providers vary significantly. The fact that different research participants will have varying health insurance status as well as the fact that individuals' policies will vary considerably with respect to coverage of research-related injuries undoubtedly creates confusion. Further, the insurance status of some research participants may change during the course of a study. That some research participants may receive care from health insurers may actually create a disincentive for research sponsors and institutions to assume responsibility. Yet, offering to pay as a secondary payer for all participants could violate the MSP. Any compensation system must be compatible with this complexity.

Possible Solutions

Possible models for compensating injured research participants include a system in which research sponsors fund insurance or self-insurance (the prominent system in many countries); another approach is the establishment of a specialty court or compensation fund.[117] In the end, we favor an insurance-based approach, but believe multiple stakeholders should share responsibility.

Advantages and Disadvantages of Systems in Other Countries

Most international systems rely on an insurance or self-insurance system in which research sponsors buy insurance or simply guarantee that they will compensate injured research participants; whether or not compensation goes above and beyond provision of medical care is variable. Although the socioeconomic, political, and health insurance environments of other countries differ from that of the U.S., it is useful to consider whether any of the compensation systems put in place internationally could or should be adopted by the U.S. or in other countries that currently lack such systems. As detailed above, India, South Africa, and Russia (as well as many other countries) all require that research participants are insured for research-related injuries by research sponsors before ethics committees can allow the research to go forward. In these systems, the research sponsor bears responsibility for compensation for research-related injuries that have a causal linkage with the research, but the definitions of eligible research-related injury, how compensation is determined, and what bodies adjudicate decisions vary.[118] In India, determination of compensation is performed in both a decentralized and centralized manner, in that RECs have a role, but the IEC of the DCGI makes the final determination. In South Africa, it is left to the sponsors to settle claims, including retainer of a mutually acceptable independent expert if necessary. In Russia, there is a

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centralized arbitrator: the Federal State Institution of Medical-Social Expertise must confirm that injuries are research-related.

At one extreme, the compensation system that India adopted in 2013 is extremely protective of clinical trial participants and burdens fall exclusively on sponsors. Sponsors have to pay compensation for almost all clinical trial injuries, even those resulting from medical negligence of the investigator or when a trial participant violates the protocol, and must provide medical care for as long as required. However, India's broad mandates have created disincentives for sponsors to conduct research there. There has been a drop in the number of clinical trials approved by the DCGI (529 in 2010; 283 in 2011; 253 in 2012; 17 in 2013; and 97 in 2017)[119] and in the number of new drugs approved for marketing (225 in 2010; 143 in 2011; 44 in 2012; 35 in 2013; 63 in 2014; 29 in 2015; 27 in 2016; 42 in 2017; 32 in 2018).[120] There are also ethical concerns about the possibility of creating undue inducement to participate in clinical trials if sponsors have far-reaching obligations to pay for healthcare of the research subjects and/or compensate them if harm arises.[121]

Similar to the system established in India, South African guidelines and Russian law require research participants to be insured for research-related injuries. However, protection of research participants falls short in South Africa, because insurance is only mandated by guidelines that are not codified into regulations.[122] Also, sponsors are not responsible for all clinical trial-related injuries, such as those experienced by participants in arms with comparator drugs. Research participants may not be appropriately protected in Russia, either. The existence of an insurance contract is not an unambiguous guarantee for research participants. In practice, the process of getting insurance payments might take a long time and require research participants (or their relatives) to have some legal literacy. Although there are no data on the success rate of human research lawsuits, most subjects who have research-related injuries will not bring a lawsuit and even if they go to court the plaintiff, will lose most of the time. On the other hand, even though the chances are very small that subjects will bring litigation for injury, the liability risks are a cause for great concern. Lawsuits can be adversarial, cost millions of dollars in legal fees, and continue for many years before resolution (dropped, settled out of court, or adjudicated). Further, it can be difficult to determine whether an injury was caused by a research study and to make an objective conclusion, the Federal State Institution of Medical-Social Expertise should have highly qualified experts, which is not always the case.

Specialty Court and/or Compensation Fund

Another model for compensation is the establishment of a specific specialty court or compensation fund. These can be statutorily created mechanisms for claims adjudication, dispute resolution and compensation relating to a particular source of injury or harm. The Panel to the 2011 Commission noted that a compensation system for human research subjects could potentially be modeled after the U.S. National Vaccine Injury Compensation Program (VICP), which provides compensation to those who are injured by vaccines.[123] Another potential model is the September 11th Victim Compensation Fund (VCF).[124]

There are reasons to believe that establishment of a national specialty court/compensation fund would be a feasible solution for compensation of research-related injuries in the U.S. The VICP is at least partially justified by the fact that society at large benefits when individuals receive vaccinations, as transmission of disease is reduced by herd immunity. Therefore, the rationale shares some similarities with research-related injuries, as research also benefits society at large. Perhaps federal legislation could task the Office for Human Research Protections with responsibility for the administration of such a fund, just as a Division of Health and Human Services (HHS) manages the VICP. The U.S. government could set aside a certain amount of funds from the federal budget to compensate those who experience research-related injuries (similar to the VCF). An alternative is for all research sponsors and institutions to contribute a nominal amount to such a compensation fund on a per participant basis (the amount could be linked to the risk level of the research). Such charges would likely be passed on to the pharmaceutical industry, research institutions, the U.S. government and non-profit organizations.

Some factors make setting up a specialty court or compensation fund for research-related injuries in the U.S. less attractive. Notably, the broad authority and power of the Special Master has been criticized as significant flaw of the system of the VCF system.[125] There have been funding challenges with the VCF.[126] Contrary to statutory expectations, the VICP no-fault alternative compensation system "has struggled to resolve claims consistently or quickly,"[127] challenging notions that no-fault compensation specialty courts can improve upon the traditional court system.[128] The "elemental scientific uncertainty at the root of the causal inquiry" may be the VICP's most significant obstacle,[129] a characteristic that would be shared by a fund for research-related injuries.

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Proposal by Henry, Larkin, and Pike

Building off systems that have been put in place at U.S. institutions and in countries around the world, Henry, Larkin, and Pike have suggested that the U.S. adopt a decentralized system in which sponsors acquire no-fault insurance and/or self-insure to provide medical care and financial compensation for research-related injuries.[130] They outline four steps that research institutions and sponsors would need to take in such a system: securing funds to cover claims by acquiring insurance or self-insuring, appointing an administrator, disclosing the system during the informed consent process, and maintaining records.[131] They suggest that eligibility be based on whether "research participation was more likely than not a factual, or 'but for', cause of the participant's injury."[132] They argue this system would "treat like cases alike, offer fair compensation for the harm sought to be remedied, and disburse compensation with maximum efficiency and minimum administrative cost" as well as harmonize with systems put in place in other countries.[133] They specify that compensation may include monetary payments for medical care necessitated by the research-related injury, as well as reimbursement for lost wages, disability, long-term care, and death benefits. Similarly, in 2018, Lamkin and Elliott called for research institutions and/or sponsors to be legally required to pay for medical care necessitated by research-related injuries as well as to provide compensation for lost wages and suffering.[134]

We agree that a decentralized system would be the most practical and feasible solution. To be effective, we believe that the Common Rule and FDA regulations governing human subjects research would need to be modified, as Henry, Larkin, and Pike suggest. Their fallback option — a voluntary system driven by guidelines and not regulation — may lack effectiveness and may not meet the requirement of justice that all participants are treated consistently. Yet despite its clear advantages, their proposal has potential problems. Requiring research institutions and sponsors to administer such a system and resolve claims without third party involvement may exacerbate inherent conflicts; for example, resolution of claims may be linked to a waiver of the right to pursue future tort claims.

In our opinion, the biggest flaw is that such a system does not properly distribute the burdens of research. Henry, Larkin, and Pike acknowledge that "the benefits of research ultimately redound to society," but their system places the entire burden of compensation for research-related injuries on research institutions and industry sponsors.[135] They justify placing the financial burdens solely on research institutions and pharmaceutical sponsors since these entities are "first" to profit or benefit from research; they are also well-positioned to effect such a system and can either "internalize the costs of compensation or shift those costs to society downstream."[136]

However, other stakeholders accrue significant benefits from human subjects research — in particular, those who have access to medical care. Healthcare insurance providers — whether private or public — also benefit from research as it allows evidence-based decisions regarding efficacy, safety, and cost effectiveness of various therapeutic options. Requiring health insurers to cover routine patients costs incurred by a patient in a clinical trial, including the costs to diagnose and treat complications (as Medicare and ACA plans do), is ethically appropriate. Research institutions and pharmaceutical sponsors are already carrying financial burdens by funding the research, even though all research does not directly result in marketed products. Indeed, while some research may "fail," and even harm participants, its conduct may still generate knowledge that contributes to future innovations such as safety improvements. Appropriate allocation of the costs of research-related injuries would increase the perceived fairness of a compensation system, and in turn, increase the chances of its adoption. We therefore believe that it is right for insurance companies and the insured population at large to share responsibility for the compensation for research-related injuries.

A New Proposal

Here, we would like to propose an alternative solution for the ethical imperative to provide medical care and compensation for all those who are injured as a result of participating in research. Adherence to the principle of compensatory justice requires multiple stakeholders to take responsibility for the medical care and compensation of persons who are injured as a result of research participation. Since sponsors, research institutions and society at large all benefit from human subjects research, it is right to expect them all to contribute to compensation "*in one way or another*."[137] Like Henry, Larkin and Pike, we also recognize that practical and logistical barriers have impeded the establishment of a comprehensive U.S. system for research injury compensation. Given the ethical imperative to make sure that all human subjects are not financially burdened by research injuries, the ideal system would be easy to adopt without establishing a large and costly bureaucratic infrastructure or specialty court for the resolution of claims.

Accordingly, our proposal builds upon, strengthens, and mandates mechanisms for compensating research-related injuries that are already in place in the

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United States. Private and government health insurers — not research sponsors — should cover medical care related to research-related injuries as primary payers. The definition of qualifying clinical trials should be expanded and should not be limited to those with therapeutic intent or those that relate to cancer or life-threatening disease. Medicaid should also provide such benefits to all its beneficiaries. It is important to remember that the generalizable knowledge gained from human subjects research mainly benefits the portion of the population that has access to evidenced-based medical care (i.e., the insured population). Therefore, it is justifiable that this population contributes to the costs of research-related injuries. To the extent that both government health insurers (and U.S. taxpayers) and private insurers want to allocate financial resources appropriately, they also benefit from the conduct of human subjects research. Therefore, it is fair that medical care necessitated by research participation is at least partially covered by these entities. An additional benefit for requiring health insurers to pay for medical care for research-related injuries is that it lessens the need to attribute causation to injuries that occur in the context of research. However, the burden of medical care for research-related injuries should not be borne solely by insurers.

Research sponsors and institutions should be *required* to cover medical care for injuries caused by research participation for those who do not have insurance on a no-fault basis (by securing appropriate health insurance for the participants and describing the terms of such on consent forms). Research sponsors and institutions should also be *required* to hold insurance that would provide compensation for lost wages as well as pain and suffering caused by disability or death for all research participants (those with and without health insurance) — on a no-fault basis. The principle of compensatory justice, and in particular a "special duty of fairness," places a duty on researchers to provide financial compensation in the event of a subject's death.[138]

Our proposal is not absolving the investigator or sponsor from professional and ethical conduct of the study. Those who are injured as a result of negligence or fault on the part of investigators, research sponsors, and/or institutions would still be allowed to pursue compensation through a tort claim in the court system, satisfying the principle of reparative justice. Importantly, this proposal would likely simply expand practices and systems that in many places are already being voluntarily put in place. Further, research institutions, sponsors, and health insurers must already negotiate coverage of various medical costs for participants in research; the Clinical Trials Agreement (CTA) details such responsibilities between research sponsors and institutions.[139] The bureaucratic and logistical burden of this system would be minimized.

Ultimately, we have a duty to ensure that no research participants will be left solely responsible for covering expenses for medical care that is necessitated as a result of their participation. We ought to require health insurance companies and government-based health insurance to cover medical care precipitated by injuries from research participation as primary payers, and research sponsors and institutions to cover medical care as secondary payers and to insure all research participants for lost wages, disability, long-term care and death benefits should serious injury or death occur.

Most importantly, by requiring these protections, all research subjects will be treated fairly and consistently no matter where they participate in a study or their health insurance status.

Establishment of such a comprehensive compensation system would require the passage of federal legislation that compels government (Medicare and Medicaid) health insurers to cover medical care related to research-related injuries as primary payers; the Medicare Secondary Payer rule would need to be modified. Further, the definition of qualifying clinical trials should be expanded. It would also require passage of federal legislation to compel research sponsors and research institutions to secure health insurance that would provide medical care for research-related injuries for subjects without health insurance.

Ideally, legislation would also compel research sponsors and institutions to secure insurance that would provide compensation for lost wages as well as pain

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and suffering caused by disability or death that would not have resulted but for participation in research on a no-fault basis — for all research participants. To facilitate claims adjudication, the law may even provide some guidelines for amounts or formula that can be used for such compensation. The VICP, VCF, and even the system in India may provide at least a starting point for the development of these guidelines. An independent oversight or advisory committee that includes representatives from insurance companies, research institutions, pharmaceutical companies, and patient advocates could also potentially be created, to assist with liability assessment. This body could also maintain a national database of research-related injuries — important information that is not currently available.[140]

Informed consent standards should also be raised. Although FDA guidance prohibits exculpatory language in ICFs, they should instead be required to delineate responsibilities of types of potential costs emanating from research-related injuries as outlined in the CTA and any related insurance contracts. The consent form should not only identify what forms of compensation are available and whom to contact, it should also be specific about which entities are responsible for which clinical trial-related costs, including those that may result from research-related injuries. Calls for transparency around responsibilities for clinical trial costs are not new and extend to the provision of products and services associated with participation.[141]

Ultimately, we have a duty to ensure that no research participants will be left solely responsible for covering expenses for medical care that is necessitated as a result of their participation. We ought to require health insurance companies and government-based health insurance to cover medical care precipitated by injuries from research participation as primary payers, and research sponsors and institutions to cover medical care as secondary payers and to insure all research participants for lost wages, disability, long-term care and death benefits should serious injury or death occur. Our proposal satisfies the ethical principle of compensatory justice that compels the establishment of a compensation system in that it distributes the burden of compensation for research-related injuries amongst all the stakeholders who benefit from human subjects research. As a hybrid and decentralized system, it would also present minimal administrative burden to adopt.

Limitations

Our proposal has several limitations. First, it is presented as a high-level idea; for this approach to be feasible, specific details would need further refinement and study. For example, most insurance plans in the U.S. incorporate cost sharing in the form of deductibles and co-pays. Should claims for research-related injuries be insulated from cost sharing, or should injured participants also bear some of the financial cost of their participation? We favor the latter approach, since this would not preference medical care that is necessitated by research participation over medical care that is precipitated by any other cause. Also, research participation is voluntary. Likewise, it is possible that adoption of this proposal may require insurers to pay for medical care that they would not be obligated to cover if the care was not caused by research participation; although we hope insurers would provide broad coverage for all medically-necessary care, this discrepancy may be justified by the fact that research participants are contributing to society. There is also a possibility that participants who experience injury will have uneven access to tort remedies should their insurance company fail to meet obligations, as potential judicial remedies may depend on the type of insurance and/or state laws;[142] if so, this unevenness in tort access would likely not be specific to disputes about research-related injuries. Some may argue that by shifting some of the burden of compensation for research-related injuries away from research institutions and pharmaceutical companies, they may be less incented to ensure that risks are minimized. This is a legitimate concern; however, all human subjects research must go through independent review in the United States to make sure that potential benefits of research outweigh its potential risks. Further, research institutions and pharmaceutical companies would still share some of the burden for research-related injuries — they must provide for lost wages, compensation for pain and suffering, and medical expenses for those without insurance.

Conclusion

In this paper, we have reviewed why the U.S. should adopt a comprehensive national system that requires all research participants to receive medical care and compensation for harms they experience as a result of their participation. We have reviewed the problems and injustices associated with maintaining the status quo in the U.S., and we have considered systems put in place in other nations around the world as well as voluntary systems that have been set up within the United States. The existence of these systems proves that many view a comprehensive compensation system as ethically important and demonstrates their feasibility. We analyzed barriers to the adoption of a U.S. system before examining solutions for the U.S.

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As suggested by others, we believe that a decentralized, hybrid, no-fault compensation system would be the appropriate path forward, as it would minimize the administrative and logistical burden associated with initiating such a system. Here, we suggest that research institutions, pharmaceutical sponsors, and health insurers all share in the responsibility to provide medical care and compensation for research participants who experience harm as a result of participation. Although it would require the enactment and/or modification of federal legislation, our solution would rightly provide all research participants with the treatment and compensation they deserve, and appropriately distribute the burdens of research to all those who benefit from it.

Note

All the co-authors have a connection to WCG; however WCG did not fund this project and WCG employees did not research, write, or even read the manuscript. The paper solely reflects the research and opinions of the co-authors. Dr. Sukumaran, Dr. Tsegaye and Dr. Shevchenko were all fellows in the 2018 WIRB International Fellows Program. Dr. Chapman organizes and teaches in the NYU component of the program. NYU receives a grant from WCG for conduct of this program. Dr. Caplan is a paid member of an advisory board for WCG on human subjects research standards. Dr. Chapman and Dr. Caplan have provided consulting and/or educational services to pharmaceutical companies. Dr. Caplan's online disclosure form can be found at https://med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/medical-ethics/sites/default/files/population-health-medical-ethics-long-form-disclosure-arthur-caplan.pdf.

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