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A proposal for a legally enforceable no-fault compensation framework for clinical trial-related injury in Malaysia

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ABSTRACT

Clinical trials play a critical role in the development of life-enhancing and life-sustaining biomedical advances. It is costly and, regardless of how well-designed and ethically conducted, there are always inherent uncertainties which subsequently expose human participants to the risk of injuries or even death. In Malaysia, compensation for clinical trial-related injury has not been incorporated into standard national regulations or policies. Therefore, when clinical trial-related injuries do occur, such participants cannot be compensated by researchers, and with the absence of specific statutory laws governing trial-related injury within the local legal framework, aggrieved parties need to seek legal redress and can only depend on the existing tort laws. To propose a viable compensation framework, the existing compensation regulations and policies implemented in India and South Africa are analyzed, and their best principles have been recommended. This study proposes the implementation of a no-fault compensation framework in Malaysia which should be disbursed efficiently at minimum administrative cost. This proposed approach should be mandated by the amendment of current laws governing biomedical research and, in the interim, should be adopted voluntarily by research sponsors, institutions and investigators conducting clinical trials in Malaysia.

KEYWORDS

Clinical trial-related injury; no-fault compensation; legally enforceable framework; Malaysia; Commonwealth jurisdictions

Introduction

Biomedical science advancements are essentially attained by way of clinical research (CRM 2020). There would be no chemotherapy, vaccinations, organ transplants, or assisted reproduction that we witness today if it were not for research developments. Clinical research can be divided into two broad categories, namely interventional clinical trials and observational (non-interventional) studies, respectively (University of Virginia 2020). An interventional study, or more commonly known as clinical trial, reflects an experiment devised to answer specific scientific questions pertaining to possible new interventional therapies or to acquire new approaches using

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currently available treatments (HSA 2019). Clinical trials are essential in determining whether a new drug or medical device is effective and safe for use by patients. They help physicians decide whether the side effects of a proposed new treatment are acceptable when weighed against its potential benefits (CRM 2017). On the other hand, the main purpose of an observational study is not to assess the potential of new treatments, but instead to develop new knowledge pertaining to specific illnesses and how these may best be treated. In observational studies, the decision to prescribe an interventional treatment is not dictated by a predesigned clinical trial protocol, hence any potential risk pertaining to the use of the medical products in observational studies would be no different from the use of the interventions in a routine medical practice context (Cystic Fibrosis Foundation 2020). Therefore, it is always perceived that the apparent risks of harm a clinical trial patient may potentially experience are relatively higher compared with volunteers enrolled in observational studies due to the *interventional nature* involved in all clinical trials.

Participating in clinical trials may provide both benefits and risks. Potential benefits may include receiving a new innovative therapy prior to it being widely available to the public and at the same time offering valuable information with respect to the effectiveness and safety of the potential treatment under investigation. On the other hand, probable risks may involve incidents of direct physical injury in which more severe cases can result in hospitalization and permanent disability, and indirect psychological, economic and social harms (Thatte, Kulkarni-Munshi, and Kalekar 2009). It should be recognized that it will not be possible to predict and hence minimize all possible risks before a clinical trial begins. In fact, the existing literature shows various instances of clinical trial-related fatalities and injuries. The near disastrous complications of the infamous *Elephant Man* drug trial, a Phase I clinical interventional trial involving humanized monoclonal antibody TGN1412 manufactured by the German pharmaceutical company TeGenero, had received tremendous attention as one of the landmark cases for lethal, life-threatening clinical trial-related injury in March 2006 (Niehoff and Madeleine 2015) when the research caused six healthy young volunteers to become severely ill and experience multiple organ failures (Wood and Darbyshire 2006). In 2017, the *Malay Mail* online newspaper published an article entitled "Clinical trials: Just how safe are they?" (Zahiid 2017). It disclosed that a year prior to the publication date of the article, a healthy man who participated in a clinical trial in France which was sponsored by Bial, a Portugal-based pharmaceutical company, to investigate a mood disorder drug was reported to have died from the administration of the investigational medicinal product (BIA 10-2474) while several other participants suffered brain damage (Funck-Brentano and Joël 2016).

Notwithstanding the clinical trial nightmares that have occurred overseas and having raised critical questions pertaining to the safety of privately contracted drug trials on human subject participants, often by the giant multinational pharmaceutical companies, unfortunately, the Malaysian government still perceives clinical trials as a great opportunity to boost the country's economy (TheSunDaily 2019). Emerging as preferred destinations for multi-center research trials, discussions involving compensation for clinical trial-related injuries are increasingly gaining attention among developing nations, including Association of Southeast Asian Nations (ASEAN) countries. Furthermore, rapid globalization of the research industry is taking place even when there are no established international benchmarks and standards on compensation for trial-related injuries (Chingarande and Moodley 2018).

Therefore, we propose that a study of the compensation system for clinical trial-related injury in Malaysia should be conducted to evaluate whether the current tort-based compensatory framework is still relevant to curtail the abovementioned issues. Such a study will help us determine whether amendments to the current law governing biomedical research are required or to change completely to a *no-fault* compensation framework. A model compensation policy for clinical trial-related injury should be developed from the best elements of policies from different countries (preferably Commonwealth countries which practice Common Law similar to Malaysia) and should be established based on the fundamental bioethical principles of justice, maleficence, beneficence and autonomy (Avilés 2014).

Problem statement

Clinical trials in Malaysia are required to be conducted in compliance with Malaysian Guidelines for Good Clinical Practice (GCP). In accordance with Section 5.8.1, it provides that "[i]f required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence." Notwithstanding the abovementioned provision, two challenges can be pinpointed here. The first would be that in the event the harm to clinical trial participants is caused by the negligence or malpractice of the research investigators themselves instead of the inherent undesirable adverse effects of the investigational medicinal interventions, the sponsors of the research will not be legally liable to compensate the injured participants. The issue is further complicated when the research investigators are not covered with their own professional indemnity insurance that protects against legal liability arising due to their own malpractice or negligence. Additionally, there could also be possibilities in which the insurance premiums taken up by research sponsors are insufficient to cover the required

compensation amount (Mendick 2008), and the sponsor companies enter into a state of insolvency, as seen in the case of TeGenero (Dyer 2006). The second challenge is that the GCP guideline by itself is merely a bioethical research standard instead of a statutory law which is not enforceable through Malaysian courts.

Currently in Malaysia, compensation for clinical trial-related injury has not been incorporated into standard national regulations or policies. Aggrieved injured clinical trial participants who cannot be compensated by researchers and are hoping to seek legal redress can depend only on existing tort laws in the absence of specific statutory law for clinical trial-related injury within the local framework. This creates a significant obstacle to the injured clinical trial participants because to rely on tort laws under civil litigation generally necessitates the aggrieved party establishing all the elements of negligence by the party who has allegedly inflicted the harm. Furthermore, civil litigation poses a particularly challenging compensation route for clinical trial-related injury because the entire burden of proof will be borne by harmed participants. They must prove (1) the existence of legal duty owed by sponsors or researchers to them, (2) when such duty exists, it was breached by the defendants, (3) it was the breach of duty that caused the clinical trial-related injury and (4) there are no other reasons to justify the breach. The inherent nature of research means that aggrieved injured clinical trial participants will have to overcome a very high threshold in proving each of the negligence elements (Mello, Studdert, and Brennan 2003). Clinical trial being an *experimental* procedure as compared with clinically proven medical therapy carries a high proportion of unanticipated risks. Additionally, the responsibility of conducting the clinical trial is often shared between the research sponsor, the institution, and the investigators, hence further complicating the civil litigation case management. The matter becomes even more complicated for multinational clinical trials if in the event that the overseas research sponsor fails to transfer its obligated compensation payment to their local Malaysian affiliate entity, the aggrieved injured participants would then need to seek legal compensation from the alleged party in a foreign international court. Therefore, to resolve these issues, there is a need to review the current local framework governing compensation for clinical trial-related injury.

Conceptual background to the problem

Clinical trial differs from routine medical treatment in a multifaceted aspect (US Food Drug Administration 2018). The intent of clinical trials is often to answer specific scientific questions and, subsequently, to develop new generalizable knowledge relating to the safety and effectiveness of innovative noble treatments. On the other hand, the purpose of medical care treatment

is to address individualized healthcare need and, hence, benefit the specific patient. This would mean that in standard medical care treatment the risks involved in diagnosis and treatment procedures will be carefully considered against the prospective benefits for the individual patient. In contrast, to obtain unbiased trial results, clinical research utilizes study processes which include blinding, randomization, use of placebo, and predetermined protocol designs which restrict flexibility in treatment choice options. Clinical trial procedures are different from routine clinical practice. In terms of assessment, clinical trials involve periodic and systematic assessment of patient data depending on protocol designs whereas routine medical care is based on individual patient assessment which requires real-time decisions. Patient volunteers participating in clinical trials will have to face high uncertainty in the benefits that they may receive since the safety and efficacy of the investigational test procedures and products are still unproven at the stage of research. The trial procedures conducted for scientific purpose may involve possible harm or discomfort risks to trial volunteers without a likelihood of benefit to them. For instance, clinical trial participants allocated to placebo cohorts may not receive any benefit from their participation in the clinical trials. In a clinical research setting, the previous circumstance is justified by the anticipated positive value of new generalizable medical knowledge for the purpose of benefiting society in the future (Hoffman 2000). This differs significantly from standard clinical practice in which the medicinal products and medical procedures used to treat the patients are generally accepted as proven to be safe and effective by the medical professional bodies.

Many researchers and drug developers believe that the main objective of clinical trials is to acquire new generalizable knowledge for innovative treatments, and hence very often the interests and legal rights of the trial participants are not considered with utmost priority during the conduct of the research (Coleman 2005). Concurring with the above discussed literature, the ethical and humanitarian issues become complicated when the clinical trials involve vulnerable populations that include but are not limited to the elderly, minors, mentally incapacitated people and pregnant women (CIOMS 2016). These vulnerable groups of volunteers should be safeguarded with special protections, above and beyond those conferred to the general public.

In the context of clinical trials, safeguarding the interests of trial volunteers should involve an emphasis of the fundamental principles of sustainability, respect of autonomy, justice, proportionality, beneficence, solidarity, and research integrity. Plainly stated, the ethical conduct of research which also encompasses the fundamental moral basis for the compensation of trial-related injury revolves around three of the Beauchamp and Childress principles that are beneficence, respect for autonomy, and justice.

The principle of beneficence implies that the anticipated benefits of clinical trials should always outweigh the corresponding risks. Therefore, the risks of

participating in clinical trials should be minimized. Minimization of risk could be perceived as twofold. First, it represents the necessity to reduce the risk of conducting clinical trials itself. Research sponsors and investigators should ensure that adequate safety precaution measures are included in the design of clinical trial protocols to minimize risks to prospective trial participants. Second, when trial-related injury does happen during the trials, investigators and research sponsors have moral obligations to alleviate the adverse effects implicated on the health of ongoing study participants together with other aspects including economic losses (Chingarande and Moodley 2018).

The principle of respect for patient autonomy encapsulates the fiduciary duty to obtain informed consent from volunteers prior to their participation, ensuring their understanding of the risks and benefits of the clinical trials. Also, under the same principle, unless justified by exceptional circumstances such as disclosure to prevent crimes or compelled by the law, the clinical trial participants' confidentiality has to be protected at all times (Malaysian Medical Council (MMC) 2006). This is to ensure that the trial participants will not suffer reputation vulnerability or economic losses from the breach of sensitive personal data confidentiality during their participation in clinical research.

Nevertheless, it is worth highlighting that with respect to the principle of autonomy, there are two main opposing perspectives regarding whether there exists an ethical obligation to compensate injured trial subjects. It is argued that it will be reasonable to have a waiver of claim for compensation in the event of injury, provided that the subjects are fully informed on the risks of research participation and have voluntarily given an informed consent to participate (Hope 1997). This perspective has been firmly refuted by society. It is emphasized that risks disclosure for participating in a clinical trial cannot be assumed to be equivalent to the release of research participants' legal right to trial-elated injury compensation (Robertson 1976). In any circumstances, the main purpose of obtaining prior consent in ethically justified clinical trials is only to allow the progress of research activities involving interference with a participant's body and health, instead of shifting the financial risk burden from researchers to research volunteers (Childress 1976). Hence, the commonly held position since the 1960s has been that voluntary and informed consent provided by a research volunteer to participate in a clinical trial does not eliminate society's moral and ethical obligation to compensate for trial-related injury (Manning 2017).

The bioethical principle of justice applicable for compensation needs for clinical trial-related injury encompasses both distributive justice and compensatory justice. Distributive justice necessitates an equitable distribution of benefits and burdens (Benatar 2001) of clinical research among study participants and society (MMC 2006). The research participants assume disproportionately the

burdens of participating in clinical trials and, hence, the obligations associated with trial-related injury mitigation should be distributed to the research sponsors, investigators and society as a means of balancing the scale (Chingarande and Moodley 2018). On the other side, compensatory justice acknowledges a responsibility to remedy injuries and harms that individuals suffer as a consequence of activities that they partake in *on behalf and at the request* of others. In simpler terms, as the participant endures the burden of a clinical trial-related injury, justice demands that the participant be compensated appropriately (Resnik 2006). The principle of compensatory justice is substantiated by the moral concept of fairness. According to L. M. Henry (2013),

> [t]hose who incur injuries while engaged in a common enterprise have a right to claim compensation from members of the group that has accepted the benefits of that enterprise. It is unfair for the latter group to act as free riders, benefitting from others' efforts but contributing nothing in kind.

Guided by the above bioethical principles, a moral consensus supportive of compensation for trial-related injury has arisen. This consensus is enshrined in several guidance documents, including the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-Related Research Involving Humans and Malaysian Good Clinical Practice Guidelines (CIOMS 2016). Notwithstanding that those who are involved in clinical trials are encouraged to comply with these international ethical guidance documents, they have no statutory force in Malaysia, hence creating a lacuna in local legal and regulatory frameworks on compensation policy for clinical trial-related injury.

The main fundamental ethical basis on the need to implement no-fault compensation for clinical trial-related injury

The distinction between clinical trial and standard medical practice must always be emphasized when considering compensation for clinical trial-related damage (Gainotti and Petrini 2010). As mentioned in the previous section, the main disparity between clinical trial and standard medical practice is that the former is intended to obtain generalizable scientific knowledge for the enhancement of diagnostic and therapeutic treatments in the future (Avilés 2014); whereas medical practice focuses on the provision of proven, available and the best treatment options for patients (Miller and Brody 2003). The disparity becomes significant when injuries have been inflicted and trial participants seek to be compensated. In the case of compensation for injuries in standard medical practice, redress for the damages suffered by patients will occur only if there is proven negligence on the part of the medical practitioners. Similarly, if the same compensation justice schemes were to be applied to clinical trial contexts, then the aggrieved injured participants would be required to establish that the

investigators, institution and research sponsors had been negligent (Jansson 2003). A compensatory justice approach is not appropriate for use within the clinical trial context. The authors agree with the reasoning made by Pike (2012), in which the following was quoted:

> [M]ost injured research participants are unable to show that a duty has been breached, many will have difficulty proving causation, all participants have a signed informed consent document that can limit or preclude recovery in assumption-of risk jurisdiction, and many will be unable to show that their injury was the research's fault. (43 - 44)

The fundamental medical negligence elements should be reformulated as clinical trial-related damage does not conform to the legal features expected in tort litigation and courts should acknowledge the distinctions between experimental procedures and therapeutic medical care practice (Morreim 2003). Therefore, it would be more appropriate to apply compensatory justice schemes in the clinical trial context, in which, irrespective of negligence, it recognizes the social moral obligation to remedy injuries that trial participants sustain as a result of activities that they partake in for the benefit of others (Henry 2013). In other words, compensation should be provided for injuries suffered by human participants in a clinical trial setting even if there is no fault established on the part of the investigators or sponsors. This is fundamental because within the experimental setting substantial harms can be inflicted even if the study protocol design has been approved by the Research Ethics Committees (RECs) and is diligently carried out (Avilés 2014). Whatever safety precaution and risk mitigation procedures may have been taken into consideration during the design and implementation of the study protocol, untoward and unintended harm is inevitable during human clinical trial research.

The compensatory mechanism based on no-fault will not require the establishment of proof of negligence, instead demonstrating the causal connection between the injury damage and the investigational products would suffice to fulfill the legal requirements (Studdert and Brennan 2001). In other words, under the principle of no-fault, an individual involved in a clinical trial should be entitled to receive compensation for any injury suffered regardless of whether there was any negligence on the part of the investigators/institution/sponsors and only if by balance of probabilities the damage is attributed to participation in the research study and could be quantifiable in financial terms. Therefore, within the clinical trial milieu, compensatory justice rather than reparatory justice should prevail in order to ensure a more fair and just treatment of aggrieved participants who are harmed during their participation in research studies (Pike 2012).

Research questions

(1) Do the existing policies, regulatory and legal frameworks governing compensation for trial-related injury in Malaysia adequately protect the legal rights and interests of clinical trial participants?
(2) What are the available compensation regulations and policies in India and South Africa (Commonwealth countries) for research participants who are harmed during the conduct of clinical trials?
(3) How should a legally enforceable no-fault compensation framework for clinical trial-related injury be implemented in Malaysia?

Research objectives

(1) To review critically the adequacy of existing policies, regulatory and legal frameworks governing compensation for clinical trial-related injury in Malaysia.
(2) To analyze and compare the available compensation regulations and policies for clinical trial-related injury implemented in India and South Africa.
(3) To propose how a legally enforceable no-fault compensation framework for clinical trials can be implemented in Malaysia.

Research methodology

This research employed a library desk-based method which incorporated a combination of descriptive, evaluative, comparative and law reform research to achieve the objectives of the study. Under this doctrinal methodology, materials were obtained from the internet and libraries. Primary sources used consisted of relevant statutes, case laws, bioethical research standard guidelines and national policies available in Malaysia, India and South Africa, while the secondary sources were retrieved from a collection of various journals, online newspapers and books. A content analysis technique was employed in which the information retrieved from the primary and secondary sources was compared to analyze the similarities and differences of policy and regulatory procedures currently implemented in the selected jurisdictions. Subsequently, based on the outcomes of the comparative law analysis, a more protective model for the compensation of harmed research participants is proposed for the implementation in Malaysia.

Literature review

Over the past two decades, the development of biomedical science research which encompasses clinical trials has emerged to become a vital source of revenue for the Malaysian government (Ooi and Khalid 2017). Nevertheless, this has led to the escalation of conflicting tension where on one side the government hopes to create an attractive destination that is appealing to international sponsors of global scale clinical trials and, on the other side, realizing their responsibility in ensuring that the interests and rights of their citizens who become human subject participants are not infringed or compromised. With significant growth of the clinical trial industry within the country, Malaysia undoubtedly benefits from the inflow of new innovative technology, infrastructure and monetary resources to its local healthcare system and economy (Ooi and K.F. Khalid 2017). However, it is undeniable that in the midst of a globalization process of the clinical trial industry and the shifting trend in which giant multinational pharmaceuticals and biotech companies now prefer to conduct clinical trials in developing countries due to lower overall administrative costs, various ethical concerns have arisen (Hawkins and Emanuel 2008).

With respect to the presence of wide disparities between developing and developed countries pertaining to healthcare provision, social, economic and educational standings, an imminent danger exists whereby companies from wealthy nations may exploit the resources and human rights of the developing nations (Tangwa 2001). In poor nations such as India, sponsors of clinical drug trials have been known to be less transparent about information provided to the trial volunteers who are mostly poor and are willing to risk their safety in order to be provided with free treatments and be remunerated (Chawan, Gawand, and Phatak 2015).

In Malaysia, other than the Malaysian GCP guideline and several other bioethical research guidelines which are issued by the National Committee for Clinical Research (NCCR) and Malaysian Medical Council (MMC), respectively, there is no well-defined clinical trial legislation that specifically regulates the misconduct of the clinical trial industry stakeholders, including laws pertaining to compensation for clinical trial-related injury (Maisarah et al. 2016). Currently, within the country the human subject protection role lies at the heart of the ethics review process by the REC. In this context, the ethics review process should be able to recognize and account for specific ethical and social concerns that are frequently considered in Malaysia (SCRPM 2016).

Regrettably, Sharon Kaur (2011) has highlighted that the ethics review process in Malaysia fails to adequately confer significant protection to human trial volunteers. One of the main factors emphasized was the lack of systematic and formal training received by the members of the REC. Another

local cross-sectional empirical study data published by See et al. (2019) demonstrated that although most surveyed RECs in Malaysia have written policies for member appointment criteria and procedures, these were found to be inconsistent and not clearly defined. This study further concurred with Kaur in that prior formal training in research ethics is not part of the requirement for appointment and selection of members or the chairman of RECs in Malaysia. Additionally, the study also highlighted the inadequate diversity in membership categories such that there is a dominance of institution-affiliated scientists and physicians with a lack of non-scientific members in the compositions of the existing REC. This poses a major weakness to the current REC's role in providing meaningful legal protection to clinical trial participants in Malaysia. Having a dominant majority of scientific members who are affiliated to the research institutions may induce a potential conflict of interest. Therefore, it is imperative to include adequate laypersons such as community representatives, ethicists and social scientists as well as legal experts in the composition of RECs so as to ensure that the clinical trial is non-exploitative yet socially and culturally sensitive (See et al. 2019).

The governing body entrusted with developing national policy for the local clinical trial industry in Malaysia is the National Committee for Clinical Research (NCCR 2020). The NCCR had initially demonstrated some interest in bringing the clinical research industry under some sort of specific regulation; however, specific knowledge on how this would be accomplished is not possible due to the Official Secrets Act 1972 (Kaur 2011). Nevertheless, it is evident that the Malaysian government does not have any immediate plans to develop well-defined legislation to govern the local clinical trial practices due to various objections from the interested stakeholders, such as the sponsors of the clinical trials (Kaur 2011). In fact, all five terms of reference governing the NCCR are geared more toward the development of a local clinical research industry, rather than safeguarding human subjects as its highest priority. It should be noted that the final term of reference of this committee is "to take pro-active action at all times in enhancing clinical research in Malaysia in tandem with the development in developed nations„ (NCCR 2020).

Globally, a conflict is also noticeable in respect to the issue of compensation for clinical trial-related injury. In the US, it is not mandatory by law for institutions and research sponsors to provide either compensation or free medical treatment for participants suffering from clinical trial-related injury, apart from the general tort law rules that apply to everyone (Resnik 2006). On the contrary, many European countries make the provision of clinical trial insurance cover mandatory, in which participants are often compensated irrespective of fault. Spain, France and Germany have enforceable insurance laws in place with variations in respect to the specific minimum coverage required (Steinbrook 2006). Additionally, countries such as Sweden, Denmark, Finland,

Norway and Sweden advocate a *no-fault* principle in dealing with clinical trial-related injury, relying on insurance compensation schemes instead of civil tort litigation (Thatte, Kulkarni-Munshi, and Kalekar 2009).

The compensation for clinical trial-related injury guideline document issued by the Association of the British Pharmaceutical Industry (ABPI) also proposes that human participants suffering from injuries due to participation in clinical trials should be compensated in accordance with a *no-fault* principle (ABPI 2014). The ABPI compensation guideline has been modified and adopted by many other countries, such as Australia and New Zealand (Manning 2017). Unfortunately, these guidelines expressly mention that obligations of research sponsors in terms of compensation for clinical trial-related injury are of *no legal commitment* and, hence, do not adequately protect human participants.

Kassim (2014) published an article discussing the potential of implementing a *no-fault* compensation system for medical injuries in Malaysia. However, there is no literature available pertaining to the study of a compensation framework pertaining to clinical trial-related injury in the country. This demonstrates the lack of both doctrinal and empirical research conducted in this field of study and, subsequently, this literature gap is worth emphasizing. Furthermore, with the inadequacy of local RECs as highlighted by both Kaur (2011) and See et al. (2019), concomitantly taking into consideration that most of the research guidelines currently being followed by the local clinical trial industry do not have legally enforceable effect, it is argued that the current framework may not be able to confer sufficient legal rights protection for the clinical trial participants, particularly the vulnerable populations such as the mentallyincapacitated patients, elderly, pregnant women and minors in the event of misconduct by the research investigators and sponsors of clinical trials (Kaur 2011). These compelling reasons warrant the necessity to evaluate the viability in proposing law reform to enact legally enforceable subsidiary legislation which comprehensively describes a compensation framework specific for clinical trial-related injury in Malaysia that safeguards the legal rights and interests of clinical trial participants. To the contrary, a balance must be achieved in which the proposed compensation policy and regulation should be comprehensively adequate in protecting the patients' interests and legal rights yet not over-regulated with strict requirements that could eventually deter global research enterprises, especially the multinational pharmaceutical companies, from investing and conducting clinical trials in Malaysia.

Scope of research

This paper focuses only on the use of information gathered through doctrinal methodology and includes data obtained from empirical studies (socio-legal

methodology). The scope of this paper is confined to the viability of a legally enforceable no-fault compensation framework for clinical trial-related injury in Malaysia. The current framework governing clinical trial-related injury compensation is illustrated under the Malaysian guideline on GCP, which itself is not a statutory law in force. Therefore, it is imperative to evaluate to what extent this standard guidance is able to confer protection on the legal and ethical interests of clinical trial participants who are injured or harmed during the conduct of clinical trials. Hence, in this paper the compensation framework for clinical trial-related injury in Malaysia is compared with two other Commonwealth countries, namely India and South Africa, which similarly practice common law principles within their jurisdictions. These two reference countries are selected specifically with respect to the existence of well-defined written compensation policies and regulations implemented for the conduct of clinical research within their jurisdictions (Chingarande and Moodley 2018). Therefore, it will be beneficial to analyze further the gap in the current Malaysian framework as it is anticipated that patients' legal rights and interests may be optimally protected if a no-fault compensation policy for clinical trial-related injury is found to be a more assuring and viable model to be introduced in the country.

Significance of the study

In this paper, it is envisioned that the outcome of this research will benefit clinical trial participants who are not only the vulnerable patient populations, but also the healthy individuals who are enrolled in early Phase I trials. Although it may be argued that Malaysia has an adequate number of standard guidelines in place to govern the conduct of research sponsors and investigators in clinical trials, nevertheless this assumption may not be completely true as most of the currently available standards in the country, including the widely used Malaysian GCP guidelines, are not statutory laws in force. With the existence of lacunae within the local legislation, aggrieved clinical trial participants who are injured parties in irresponsible research misconduct leading to harm and injuries may find that the current Malaysian regulatory frameworks are inadequate for them in seeking compensation claims. It is hoped that this study may inspire discussions among clinical trial stakeholders which include the Ministry of Health, RECs, health institutions, clinical trial sponsors, research investigators, non-governmental organizations, academicians, legal researchers and patient advocate groups on this compelling issue. Subsequently, it is hoped that the Malaysian policymakers would recognize the need to review our current regulatory framework governing compensation for clinical trial-related injury in the country with the primary aim of ensuring that the legal rights and interests of research participants are well-protected.

Results

Current position of regulatory framework for clinical trial-related injury in Malaysia

All clinical trials conducted in Malaysia are regulated by the Medical Device Authority (MDA) and National Pharmaceutical Regulatory Agency (NPRA), in which the latter acts as the secretariat to the Drug Control Authority. Both the MDA and Drug Control Authority are federal statutory agencies of the Ministry of Health (MOH) Malaysia established under Medical Device Authority Act 2012 and Control of Drugs and Cosmetics Regulations 1984, respectively. The MDA governs clinical trials investigating medical devices whereas the NPRA regulates drug clinical trials.

Additionally, the RECs also assist in overseeing the conduct of clinical trials in Malaysia as their approvals are mandatory prior to the commencement of any clinical trial (See et al. 2019). Section 3.1.1 of the Malaysian Good Clinical Practice Guideline provides that a REC, also known as Institutional Review Board (IRB)/Independent Ethics Committee (IEC), should "always safeguard the rights, safety, and well-being of all trial subjects" and that "special attention should be paid to trials that may include vulnerable subjects." In Malaysia, RECs can be categorized into two broad categories known as Central Ethics Committee and Local Ethics Committee, respectively. The Medical Research and Ethics Committee represents the country's Central Ethics Committee which reviews and approves all clinical trials conducted at all MOH institutions and facilities. On the other hand, non-MOH hospitals may have their own in-house RECs and these are known as Local Ethics Committees. In the event that the private institutions or universities do not have their own Local Ethics Committees, clinical trial ethics applications can be submitted to the Medical Research and Ethics Committee for reviews and approvals (Maisarah et al. 2016).

Besides these, there are also other government support bodies and societies which play important roles in ensuring proper clinical trial conducts in Malaysia. The NCCR serves as the steering committee for local clinical research industry through the establishment of strategic policies and clinical trial activities planning for short-, medium- and long-term progress (NCCR 2020). Meanwhile, the clinical research center plays a role in promoting and supporting investigator-initiated research conducted by MOH healthcare providers. One of the important roles of the clinical research center is to organize GCP workshops for potential research investigators. This is in line with the requirement of the Malaysian GCP guideline which mandates all research investigators to attend and pass GCP workshops prior to involvement in any clinical trial. On the other hand, Clinical Research Malaysia was established in 2012 under the National Key Economic Area as a non-profit

entity to establish Malaysia as a preferred destination for internationally sponsored research by attracting foreign investments (Maisarah et al. 2016).

Most of the vision and mission of the abovementioned stakeholders focuses mainly on preventive actions in which they implement various plans to ensure the safe conduct of trial studies and preventing harm to trial participants. These include requiring all clinical trials conducted in Malaysia to comply with the GCP guidelines with concurrent annual inspections on the research institution by the authorities. However, being experimental in nature, clinical trials are filled with multifaceted uncertainties and it is impossible for the stakeholders to guarantee absolute safety for the trial participants. Emphasis on corrective actions such as having a well-defined compensation policy post occurrence of a trial-related injury is undeniably lacking and, hence, more attention from clinical trial stakeholders in this area is warranted in order protect the legal rights of injured trial participants.

Clinical trial agreements, indemnity and clinical trial insurance

Clinical trial agreements are legally binding contracts that formalize the relationship and understanding between parties involved in clinical trials, and these commonly include the research sponsors, the local health institutions and the principal investigators, forming tripartite agreements (SCRPM 2016). In accordance with Section 1.17 of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use GCP Guideline (ICH 2016), it reads:

> [A] contract is a written, dated and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract. (12)

In Malaysia, clinical trial agreements involving MOH employees as the legal parties will require endorsement by Clinical Research Malaysia prior to any contract execution. The Malaysian government has authorized Clinical Research Malaysia to represent the Malaysian MOH clinical research industry for these legal review purposes. On the other hand, for clinical trial agreements involving university hospitals or institutes of higher learning and private hospitals, these organizations will usually have their own in-house clinical research centers which will be responsible for managing, negotiating and finalizing contracts with research sponsors (SCRPM 2016).

The requirement for reviewing clinical trial agreements lies with the contracting parties and their organizations. Research sponsors will usually have their in-house corporate legal departments to ensure that all the clauses specified in the clinical trial agreements adequately comply with their organization policies and regulations in conducting clinical trials. At the same time, the contracting parties of the investigators and institutions will also

need to ensure that the terms in the clinical trial agreements adhere to the local government regulations and laws. Two important sections within the clinical trial agreements which should be reviewed in-depth would be the indemnification and insurance clauses.

Section 5.8.1 of the Malaysian GCP guideline (NCCR 2018) reads that:

> [i]f required by the applicable regulatory requirement(s), the sponsor should provide or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence. (41)

While Malaysia has no specific legal act governing clinical trial conduct (including clinical trial insurance and indemnification), most of the IECs or IRBs require that all ethics submissions for clinical trials are mandatory, to be accompanied with proof of indemnification either by letter of indemnity from the research sponsors or an insurance certificate (MREC 2006). The above documents *inter alia* should include the specific protocol number and title, coverage period, number of clinical trial participants and the Malaysian trial sites covered. Renewed insurance certificates should be submitted to the IECs or IRBs on an ongoing basis (SCRPM 2016).

For clinical trials involving investigational drugs except for first-in-human studies, the Malaysian Guideline for Application of Clinical Trial Import License and Clinical Trial Exemption (Edition 7.0) issued under the NPRA does not specifically require insurance/indemnity certificate proof documents to be submitted during applications to the authority. However, the principal investigator's declaration form (as per Appendix C of the mentioned guideline) includes a statement clause which provides that the study has indemnity/insurance that will provide cover for my activities in this clinical trial, as required in Malaysia (NPRA 2020). It is mandatory to complete and submit this declaration document during the application to the NPRA to obtain the Clinical Trial Import License/Clinical Trial Exemption as a form of regulatory approval for a particular clinical trial. On the contrary, as mentioned above, only requests for the authority's approvals on first-in-human studies require insurance certificates to be submitted as part of the application dossier.

Similarly, for clinical trials involving medical devices, the MDA's guidance document on Notification of Exemption from Registration of Medical Devices for the Purpose of Clinical Research or Performance Evaluation (first edition) does not expressly require substantial proof of trial indemnification during clinical trial authorization applications from the authority (MDA 2016). However, the research sponsors or investigators are to ensure that the clinical investigational plan (commonly known as protocol) documents have a specific section mentioning the type of insurance which will be provided to the trial participants.

In general, all investigators and institutions involved in clinical trials should be insured or indemnified by the research sponsors for claims arising from clinical trial activities or procedures performed in accordance with the protocol designs, and this should encompass the use of investigational medicinal products by the clinical trial participants. According to the Malaysian GCP guideline, research sponsors are not bound to indemnify against claims arising from negligence and/or malpractice by investigators or institutions. Most research sponsors will expressly specify the non-indemnification clauses in the clinical trial agreements (SCRPM 2016). In the opinion of sponsors, they believe that patient injuries due to negligence or malpractice by investigators should be borne by their own professional indemnities.

Therefore, it is imperative to have all these indemnification and insurance matters ironed out during the negotiation of clinical trial agreements and prior to the initiation of clinical trials to avoid any inappropriate expectations and conflicts between the contracting parties during and after conducting the study. Conducting a multi-center clinical trial in Malaysia can be extraordinarily complex and complicated due to the differing clinical practice and administrative cultures and therefore the requirements of insurance can often be misunderstood and deserve a good insurance underwriter with high expertise to consider all aspects; despite the fact that while some research institutions have well-documented mandatory insurance and indemnity requirements outlining specific conditions and terms which are in place, others do not.

Injury compensation clause in informed consent documents

International bioethical research standards such as the Nuremberg Code, Declaration of Helsinki and Belmont Report emphasize the need to obtain informed consents from clinical trial participants before their participation in a clinical trial (CIOMS2016). Section 4.8 of the Malaysian GCP guideline provides for the requirement of research investigators to obtain prior approvals or favorable opinions from IECs or IRBs for all written information including informed consent forms which must be provided to prospective clinical trial participants. Furthermore, according to Section 4.8.10, both the discussion and written informed consent documents to be provided to clinical trial participants should include *inter alia* matter related to compensation and/or treatment available to the subject, in the event of trial-related injury (NCCR 2018).

Complying with the Malaysian GCP principle, the Medical Research & Ethics Committees release their own informed consent form template which serves as guidance for all research sponsors and investigators who wish to conduct clinical trials at the MOH institutions and facilities. The section in the informed consent form template (MREC 2019) which relates to trial-related injury provides as follows:

> [i]f you are injured as a result of being in this study, you should contact your study doctor. In the event of a bodily injury or illness directly resulting from the study product or a medical procedure required for this study, the sponsor will pay for reasonable and necessary treatment. The sponsor is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or willful misconduct, the negligence or willful misconduct of your study doctor or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

The language for injury compensation drafted in the informed consent form template prepared by the Malaysian Medical Research & Ethics Committees concurs with Section 4.8.4 of the Malaysian GCP guideline which provides that no written or oral information relating to a clinical trial, including the informed consent form documents, should comprise any language which may cause the clinical trial participants to waive any legal rights or release the research sponsors, the investigators along with the institutions from liability of negligence. This clearly shows that the RECs play an important role in safeguarding the legal rights of the clinical trial participants as their prior approval is essential before research investigators can provide these informed consent forms to the prospective trial volunteers. However, it should be highlighted that only the Central Ethics Committee which oversees MOH institutions and facilities has a specific informed consent form language template for trial-related injury, while other respective Local Research Committees have not expressed a specific guideline on the requirement of trial-related injury language to be inserted in the informed consent forms. This inconsistency across RECs in the country may give rise to a significant concern of unequal legal protection of clinical trial participants depending on the research institutions they participate at.

Tort and fault-based system: an option and a hurdle for injured trial participants in claiming compensation

In accordance with the current legal framework in Malaysia, claims arising from injuries related to proper execution of clinical trial procedures or the use of investigational medicinal products will generally be covered under the insurance policies taken up by the research sponsors or investigators (SCRPM 2016). However, issues arise when the injuries inflicted on the participants are due to malpractice or negligence of the investigators. Furthermore, injured participants may also face difficulties in claiming compensation in the event of insufficient insurance coverage purchased by the sponsors or investigators. In these circumstances, the victims may need to resort to the civil litigation route to claim compensation in the event that no out-of-court settlement can be reached, or the research investigators do not have relevant professional indemnity insurance to cover for the injury compensation. The litigation process for clinical trial negligence claims may

demonstrate high similarities to normal medical negligence cases which include high complexity with lengthy and costly administrative legal fees. Despite this, research litigation has not been challenged in Malaysian courts, according to Resnik (2006):

> [m]ost of the causes of action brought against defendants in research litigation have involved various torts, such as battery, negligence, fraud, misrepresentation, conversion, unjust enrichment, breach of fiduciary duty, violation of informed consent, products liability, intentional infliction of emotional distress, and wrongful death. (267)

Taking into consideration the adversarial nature of a tort and fault-based system, the success rate of a case put through the litigation process depends substantially on the respective abilities of the parties' attorneys in construing convincing argumentative evidence (Morreim 2004). This poses a substantial disadvantage to the trial-related injured victims in terms of obtaining the necessary evidence and securing the testimonies of other medical practitioners against the defendant's research investigators. To make things more complicated, the nature of tort action entailing an all or nothing principle will put the plaintiff in a lottery system whereby the injured patients will either receive full damages with the successful proof of causation or get nothing if they fail to establish causation. Even if the eventual verdict goes to the injured patients, the compensation or awards received will often be considered insufficient because a major portion of the damages is offset by the costly administrative court and legal fees (Pike 2012).

In a nutshell, tort law is relatively ineffective at compensating harmed clinical trial participants in comparison with injured patients. The main cause of action in tort law is the proof of negligence, however the prospects of succeeding against research sponsors and investigators are exceptionally limited due to the subject's hurdle in establishing the required elements (Manning 2017). Collectively, the inherent difficulties and complexities in establishing fault for tort claims and, subsequently, the usefulness of a fault-based system in providing adequate and fair reparation to the injured victims warrants the finding of an alternative option to replace the current tort litigation for compensating trial-related injuries.

Assessment on applicability of local product liability law in a clinical trial-related injury compensation framework in Malaysia

In the UK, besides the need to have some form of guarantee, insurance or similar compensation arrangement as in accordance with European Union (EU) regulation, liability of a research sponsor or investigator can also be determined, either by the common tort law of negligence or by strict liability under the Consumer Protection Act 1987 (Manning 2017). The applicability of tort law including its disadvantages in trial-related injury has been

explained in the previous section. Additionally, in the UK there exists an alternative compensatory claim for clinical trial participants, in which the Consumer Protection Act 1987 can potentially be applied. This imposes strict liability on suppliers and manufacturers of defective investigational medicinal products which have partly or wholly caused damage to the consumers, including personal injury or death (Ismail 2015).

Malaysia has similarly enacted the Consumer Protection Act 1999, which was significantly adopted from the UK's Consumer Protection Act 1987. The Part X on Product Liability was integrated into the Consumer Protection Act 1999 pursuant to the report issued in 1992 by the National Advisory Council and Consumer Protection which suggested that the existing Malaysian laws at that point of time, which were the Contracts Act 1950 and tort of negligence, were inadequate in safeguarding the consumers from seeking successful appropriate legal redress from consumption of defective products (Mokhtar and Ismail 2013). This was partly due to the emphasis of doctrine of privity in Contracts Act 1950 and the exceptionally huge hurdle in claims under negligence law which requires plaintiffs to establish the three elements of negligence, namely the duty of care, presence of breach of duty of care and damage or injury.

Notwithstanding that the Malaysian Consumer Protection Act 1999 was greatly influenced by the UK Consumer Protection Act 1987, the question now would be whether the injured clinical trial participants who are enrolled in Malaysian research institutions can potentially institute liability claims from the sponsors or investigators under the local product liability legislation. As yet, there are currently no decided Malaysian case laws that challenge this piece of legislation (Mokhtar et al. 2016). Nevertheless, Section 2(2)(f) of the Malaysian Consumer Protection Act 1999 clearly provides that the Act shall not apply "to healthcare services provided or to be provided by healthcare professionals or healthcare facilities." Additionally, Section 3 also further provides the definition of *healthcare services*, which includes:

[a]ny service for the screening, diagnosis or treatment of persons suffering from, or believed to be suffering from any disease, injury or disability of mind or body or any service for curing or alleviating any abnormal condition of the human body by the application of any apparatus, equipment, instrument or device or any other medical technology.

Taking into consideration that the scope of clinical trial activities may encompass the healthcare services, the Malaysian Consumer Protection Act 1999 may not be successfully invoked by the aggrieved injured clinical trial participants to seek legal recourse.

Nevertheless, in the assumption that the Malaysian courts unprecedentedly allow the invoking of the Consumer Protection Act 1999 in the claim for clinical trial-related injury, the imposition of strict liability may not significantly improve the claimant's prospect in obtaining compensation from the

potential list of defendants in pursuant to Section 68(1) of the same Act. This is because, despite the strict liability under Part X of the Consumer Protection Act 1999, the legislation also provides a state-of-the-art legal defense under Section 72(1)(d) for a manufacturer or in the context of a clinical trial, the research sponsor, in which it states that:

> [t]he state of scientific and technical knowledge at the relevant time was not such that a producer of products of the same description as the product in question may reasonably be expected to discover the defect if it had existed in his product while it was under his control.

Fundamentally, a research sponsor or medicinal product manufacturer has a good and valid defense in the event that the defect was undiscoverable in the light of contemporary scientific knowledge (Ismail 2015). As generally indicated, unforeseeable risks are predictable in clinical trials, which are experimental in nature, and hence the element of fault is often absent or difficult to establish.

Interim summary remark

In a nutshell, Malaysia has two different regulatory authorities, namely the NPRA and the MDA, which govern human subject participation in drug and medical device clinical trials, respectively. The overseeing of the ethical conduct aspect of clinical trials is further complemented by the Medical Research & Ethics Committees and institutional-specific Local Ethics Committees. Various research guidelines have been issued through these authorities and RECs with the aim to confer protection for the rights, welfare, and safety of the trial participants. However, the existing policy and regulatory framework governing conduct of clinical trials in Malaysia prioritizes the avoidance of exploitation, unethical treatment or harm which is geared toward a prospective preventive approach. With regards to retrospective corrective actions for research participants who have already sustained harm during and after the conduct of clinical trials, there are no well-defined and legally enforceable compensation frameworks available in Malaysia. The identified lacuna in local laws establishes the fact that there is an inadequacy in the protection of legal rights and interest of the aggrieved trial subjects who are already injured through their participation in clinical trials.

Current position of regulatory framework for clinical trial-related injury in India

The Central Drugs Standard Control Organization, led by the Drugs Controller General of India, is the central main regulatory body discharging functions assigned to the Central Government of India under the purview of

the Drugs and Cosmetics Act. The Central Drugs Standard Control Organization is an entity under the Ministry of Health and Family Welfare, which is governed by the Directorate General of Health Services. The major functions of the Central Drugs Standard Control Organization include demonstrating regulatory control over medical devices, cosmetics, importation of pharmaceutical drugs, approval of clinical trials and new drugs (CDSCO 2020). Meanwhile, the Indian Council of Medical Research represents another regulatory body in the country which is responsible for the coordination, formulation and promotion of biomedical research in India ("Clinical Trials in India (Part 1): The early years of regulation" 2017).

The Drugs and Cosmetics Act 1940 represents the consumer protection law of India that is concerned with the quality and standards of cosmetics and drugs (including medical devices), and it regulates their manufacture, import, distribution and sale in the country. Its subsidiary legislation, Drugs and Cosmetics Rules 1945, contains provisions for different drug classifications under given schedules.

Prior to March 2019, clinical trials were required to be conducted in accordance with the requirements set out in Schedule Y of the Drugs and Rules 1945 (CDSCO 2005). In addition to this binding regulation, Indian Good Clinical Practice for Clinical Trials Guidelines (CDSCO 2001) and the Indian Council of Medical Research's ethical guidelines for biomedical research on human participants (ICMR 2017) also serve to provide bioethical guidance to clinical research stakeholders. These guidelines expressly mention that research participants who suffer an injury as a result of participation in research are entitled to compensation for impairment or disability (Singh 2013). Notwithstanding the existence of various bioethical guidance and rules to be complied with in India, a variety of research ethical principles violation cases concerning patient safety and unjust compensation provision for participants suffering from clinical trial-related injury were reported, and eventually debatable issues with respect to the country's clinical trial status were raised by the general public to the parliament of India (Urooj et al. 2017). Specifically, the major areas of concern involved sufficient monitoring of participant safety, ensuring consent is truly informed, increasing occurrence of trial-related death cases and inadequate compensation payment coverage (Kang 2012).

The controversies of ethical issues in the clinical trial field were significantly highlighted in 2012 when *Swasthya Adhikar Manch*, an Indore-based patient-centric non-government organization, filed a Public Interest Litigation plea before the Supreme Court of India ("Swasthya Adhikar Manch, Indore & Anr. Vs. Ministry of Health & Welfare and Ors."). The court filing concerns an allegation of clinical trial conduct malpractices by government and non-governmental organizations including independent research investigators. During the hearing, various regulatory aspects of

clinical trials were deliberated by the Court. Ultimately, the Supreme Court of India issued an order opining that approvals for clinical trials conducted in India should be on the basis of pertinent aspects of efficacy and safety, specifically in terms of assessment on benefit versus risk of the innovation vis-à-vis current available therapeutic options conferred to the general public and unmet medical need in the country (Ashwin, Biplab, and Kartik 2019).

The court verdict subsequently led to several amendments made to the Drug and Control Rules in 2013 to regulate better the conduct of clinical trials in India. As such, the Drugs and Cosmetics (First Amendment) Rules 2013 embodies the addition of Rule-122DAB that provides that in the event of human participants suffering from injury or death during the conduct of a clinical trial, they should be made eligible for financial compensation in addition to free medical management. The quantum of compensation would be determined by the Drugs Controller General of India (Central Licensing Authority). Subsequently, there was a gazettement of the Drugs and Cosmetics (Second Amendment) Rules 2013 with the introduction of Rule-122DAC, which lays down the set of conditions for the conduct of clinical trials in the country in compliance with Schedule Y of the Drugs and Cosmetic Rules, including registration of interventional trials with the Clinical Trials Registry of India, obtaining approval from a REC prior to initiation of research, serious adverse events reporting requirement, etc. Furthermore, guidelines which clarify the required composition and registration of ethics committees were notified through the Drugs and Cosmetics (Third Amendment) Rules 2013.

Despite the series of amendments to the Drugs and Cosmetic Rules, deficiency issues in Indian clinical trial regulations were raised further in a report published by an expert committee headed by Professor Ranjit Roy Chaudhury under the Ministry of Health and Family Welfare (Ashwin, Biplab, and Kartik 2019) and also in the 59th Report of the Parliamentary Standing Committee on Health and Family Welfare on the functioning of the Central Drugs Standard Control Organization (Parliament of India Department-Related Parliamentary Standing Committee on Health and Family Welfare 2012). Taking into consideration the raised deficiency issues, the Ministry of Health and Family Welfare published the draft of the New Drugs and Clinical Trials Rules in February 2018 for feedback from all the relevant pharmaceutical and research stakeholders. This new subsidiary legislation, namely the "New Drugs and Clinical Trials Rules (2019)" which are structured throughout 13 chapters consisting of 107 rules and eight schedules, was finally notified in March 2019. The enforceability of this new law encompasses clinical trials, bioequivalence/bioavailability studies, investigational new drugs for human use, new pharmaceuticals and RECs. The New Drugs and Clinical Trials Rules 2019 supersedes Schedule Y of the Drug and Control Rules and goes into effect immediately (Jain and Chauhan 2019).

Chapter VI of the New Drugs and Clinical Trials Rules 2019 deals with compensation in cases of injury or death in clinical trials or bioequivalence/bioavailability studies of investigational new drugs. Rule 39(1) within Chapter VI provides that in the event of any death occurring during a clinical trial or bioavailability/bioequivalence study, the legal dependents of the trial participants shall be provided financial compensation by the research sponsors or their representatives. On the other hand, Rule 39(2) specifies that financial compensation should be provided by the sponsor to clinical trial participants in the event the latter suffer permanent disability or any other injury during a clinical trial or bioavailability or bioequivalence study. Additionally, Rule 39(3) clarifies that the financial compensation provided shall be in addition to any expenses incurred on medical management of the trial participants.

Rule 41 of the New Drugs and Clinical Trials Rules 2019 expressly sets out the list of considerations behind trial-related injuries that should be compensated by the research sponsor. These include (1) adverse effects of investigational medicinal products, (2) any clinical trial procedures involved in the study, (3) violations of approved protocols, (4) failure of investigational product to provide intended therapeutic effect, (5) adverse effects due to concomitant medications, excluding standard care, (6) injury to children *in utero* due to parents' participation in clinical trials and, last but not least, (7) not providing the required standard of care, though available to the subject as per the research study design in placebo-controlled trials.

Additionally, Rule 42 within Chapter VI of the New Drugs and Clinical Trials Rules 2019 expressly lays down the procedures for compensation in the event of injury or death during the conduct of a clinical trial. The ultimate authority to determine the quantum of the compensation to be paid by the research sponsors or their representatives lies with the Central Licensing Authority taking into consideration in the analysis opinions from the RECs. Hence, the role of the RECs in India extends beyond the standard ethics committees' roles which are to be significantly involved in formulating recommendations for the quantum of damages in the process of compensation claims for clinical trial-related injury or death. Prior to the enactment of New Drugs and Clinical Trials Rules 2019, the superseded Schedule Y of the Drugs and Cosmetic Rules was silent on the details on how the quantum of compensation should be derived. However, with the current new law, it unambiguously provides that the quantum of compensation should be calculated in accordance with the basis of the formula specified in the Seventh Schedule of the New Drugs and Clinical Trials Rules 2019. The research sponsor or its representative shall pay the compensation within 30 days of the receipt of an order from the Central Licensing Authority. Failure of the research sponsors or their representatives to comply with compensation payment in accordance with the order ruling will result in the sponsor

being banned from conducting any clinical trials in India for a certain stipulated period of time at the discretion of the Central Licensing Authority.

Current position of regulatory framework for clinical trial-related injury in South Africa

South Africa has a comprehensive ethical and legal framework regulating clinical trials conducted within the country. The cornerstone of its framework stems from the *guidelines for good practice in the conduct of clinical trials with human participants in South Africa* issued by the National Department of Health. The South African Good Clinical Practice Guideline addresses the local contexts and realities, ensuring that clinical trials which involve South African participants are well-designed and conducted in accordance with local requirements along with ethical and sound scientific standards within the internationally accepted principles for good clinical practice.

The South African Health Products Regulatory Authority, an entity of the Department of Health, is the regulatory authority of South Africa, which is responsible for monitoring, evaluating, investigating, inspecting and registering all health products which include clinical trials. The legislative mandates of the South African Health Products Authority are derived from its Constitution, the National Health Act 2003, the Medicines and Related Substances Act 1965 along with its amendments, namely the Amendment Act 2008 and Amendment Act 2015, and other relevant policies and regulations such as the South African Health Products Regulatory Authority (SAHPRA 2019).

The South African Health Products Regulatory Authority has further released several bioethical research guidelines which provide more detailed guidance on specific GCP matters for clinical trial industry stakeholders to ensure that clinical trial participants are adequately protected and eventually able to gain benefits from their clinical trial participation. In November 2019, the South African Health Products Regulatory Authority released the *Guideline on Liability Insurance for Clinical Trials* (SAHPRA 2019) to clarify insurance requirements for making a submission to obtain review approval for clinical trial applications from the South African Health Products Regulatory Authority. The guideline expressly acknowledges that research sponsors are required to provide comprehensive insurance coverage against damage and injury that participants may experience because of interventional clinical trials. Additionally, the trial sponsors must also indemnify all the research institutions and investigators participating in their clinical trials on compliance with the protocol requirements. In the event where the investigators or site staff were negligent or did not comply with the protocol requirements, their own professional malpractice insurance should apply instead. At the same time, the guidance document also describes the

circumstances and requirements that must be met for participants to claim financial compensation for such trial-related injuries. The principles laid down in the abovementioned documents were developed taking into consideration the current Association of the British Pharmaceutical Industry's Code of Practice for the pharmaceutical industry (ABPI 2014).

Both the South African Good Clinical Practice Guideline and the Guideline on Liability Insurance for Clinical Trials provide that trial participants may seek compensation if it can be demonstrated on a balance of probabilities that the administration of a study procedure or investigational medicinal product has eventually caused serious bodily injury of a disabling and enduring nature that would not have happened but for partaking in the research study. This would also mean that no compensation would be paid for temporary and less serious discomfort or pain. The research sponsors are under strict liability with respect to the injuries caused by the inclusion of the participants in the clinical trials irrespective of whether the claimant can prove that the administered investigational medicinal product is defective or negligence exists on the part of the sponsors.

Section 6 of the Guideline on Liability Insurance for Clinical Trials specifies that the patient information leaflets and informed consent discussion provided to participants prior to participating in a clinical trial (which should subsequently be condensed into a written document) must include clear instructions on prompt reporting of trial-related adverse harms and also information on compensation and treatment available to them in the event of trial-related injury including details for submitting a claim (SAHPRA 2019). Furthermore, these compensation claims for clinical trial-related injury should be submitted to the research sponsors through their respective investigators.

The Guideline on Liability Insurance for Clinical Trials also specifies that whenever there is an adverse reaction attributable to the investigational medicinal product under clinical trial and the subsequent injury is exacerbated by a rectifying procedure used to treat the initially experienced adverse reaction, participants should be compensated for such injury as if it were caused directly by the initial trigger cause. Additionally, for a child injured *in utero* through the participation of the biological parent in an interventional clinical trial, compensation should be paid as if the child were a trial volunteer. Accordingly, the research sponsors should pay compensation to research volunteers suffering bodily injury, including death. However, it should be emphasized that the stipulation as per the guideline is that the obligation of the sponsor to pay no-fault compensation is without legal commitment (Slack et al. 2012). In terms of the amount of compensation to be paid, the guideline provides that it should be commensurate with the severity, nature and persistence of the clinical trial-related injury. Furthermore, the compensation should consistently be aligned with the

quantum of damages commonly awarded by the South African courts for similar medical injuries in cases where legal liability is admitted (SAHPRA 2019).

It is also worth highlighting that the guideline also laid down several clauses that describe certain circumstances in which research sponsors have no obligation to pay compensation for the injured trial participants. These include situations in which (1) injury is caused by other licensed pharmaceutical products administered to the participants for the objective of comparison with the trial products under investigation, (2) failure in receiving therapeutic benefit taking into consideration that the participants are allocated to the placebo groups, (3) failure of the investigational medicinal products to exert their intended therapeutic effects, or (4) the injury has actually been caused by a deviation from the agreed study protocol by the investigators or through contributory negligence by the trial participants themselves. For the latter, the research sponsors may consider providing compensation for ethical reasons on a case-by-case basis (SAHPRA 2019).

Additionally, the undertaking provided by the research sponsors only extends to injury resulting from administration of all protocol procedures and interventions taking place within the duration of the clinical trial, not to any treatment extended beyond the end of the research study. The use of unlicensed medicinal products beyond the agreed clinical trial duration will be wholly the responsibility of the treating physicians (DoH SA 2006).

It is worth noting that the fact a research sponsor has agreed to comply with the compensation stipulations in both the South African Good Clinical Practice Guideline (2006) and Guideline on Liability Insurance for Clinical Trials will not diminish the right of a clinical trial participant to seek legal recourse for injury alleged to have been suffered as a result of partaking in the research study. Additionally, Paragraph 6 of Section 4.11 of the South African Good Clinical Practice Guideline 2006 also expressly mentions that:

> [n]either the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the participant has freely consented (whether in writing or otherwise) to participate in the trial should exclude a participant from consideration for compensation under these guidelines.

However, contrary to the above clause, the case law of ("Venter v Roche Products (Pty) Ltd" 2014) (hereafter *Venter*) indicates otherwise. The issue to be considered by the learned judge in this case was

> [g]iven that the informed consent document expressly limited compensation to medical costs, in dispute was whether Mr Venter was entitled to claim for non-medical costs such as pain and suffering, loss of income, and general damages (Strode and Singh 2014, 760).

The *Venter* case which was decided based on English case law of *Morton James Wylie v Dr Donald Grosset and Greater Glasgow Health Board* demonstrated that claims for clinical trial-related injury will not be successful if the claimants have agreed to limit their own rights through signing an informed consent document which limits the scope of compensation (Strode and Singh 2014). This is indeed conflicting to the consensus among bioethicists in which informed consent only authorizes that research can proceed and should not be regarded as a waiver for any form of trial-related injury compensation (Manning 2017). South African courts are hence more predisposed to a signed informed consent document appropriately conveying the risks inherent in a clinical trial study as a means in absolving the research sponsor from the obligation in providing compensation for injury inflicted on the participants. The provision in the South African Health Products Regulatory Authority 2019 guideline which states that compensation should be according to the ABPI guidelines will not be helpful in this respect as "the guidelines recommend compensation without legal commitment and therefore payments which may be made in terms of the guidelines, are to be made *ex gratia*" (Chingarande and Moodley 2018, 9). The South African guidelines hence leave a substantial burden on the injured clinical trial participants. Additionally, the guidelines do not specify the crucial role which can be assumed by the RECs in overseeing and ensuring appropriate compensation for clinical trial-related injury (Mamotte, Wassenaar, and Singh 2013).

Discussion

Comparative law analysis on Malaysia, India and South Africa

A comparison of the clinical trial-related injury compensation regulatory frameworks across the three Commonwealth countries, namely India, South Africa and Malaysia, reveals that there is a substantial collection of regulations which exist on a continuum in these analyzed jurisdictions. At one extreme, India has by far the most stringent and comprehensive regulations which are codified into laws. Centrally, South Africa has at least a well-defined national regulatory authority-endorsed compensation guideline and, at the other extreme, there is Malaysia, which does not have specific laws regulating clinical trial-related injury or any well-defined regulatory authority-endorsed compensation guideline. The similarities and differences across the three jurisdictions are discussed in the following paragraphs and summarized in Table 1.

Mandatory insurance provision

Both national GCP guidelines of South Africa and Malaysia, respectively, require research sponsors to provide insurance cover to all trial

Table 1. Summary of comparative law analysis on existing clinical trial-related injury compensation regulatory frameworks across Malaysia, India and South Africa.

Country	Specific written policy on compen-sation	Mandatory insurance provision	Mandatory consent language	Requirements for indemnification to research institutions and investigators	Types of compensable injury	Exclusions	Entity responsible for determining responsibility for injury (adjudicators)	Legal enforceability	Entity responsible for compensation/source of funds for managing harm
Malaysia	No	Yes	Yes	Yes	No clear written guidance	No clear written guidance	No clear entity assigned (unless via civil court claim)	No (yes only if claims filed via civil court processes)	Sponsor/local clinical trial applicant (except for claims that arise from malpractice and/or negligence which should be borne by research investigators themselves via professional indemnity)
India	Yes (New Drugs and Clinical Trials Rules 2019)	No	Yes (as per New Drugs and Clinical Trials Rules 2019)	Yes (Indemnity Policy as part of supporting documents for Ethics Committees' Review)	All injuries including non-trial-related and economic losses	No	The Licensing Authority; REC and Expert Committee (quantum of compensation is required to be calculated on the basis of the formula specified in the Seventh Schedule of the New Drugs and Clinical Trials Rules)	Yes	Sponsor (whether a pharmaceutical company or an institution) or its representative or the investigator or the institution or center where the study was conducted
South Africa	Yes (South African Guidance on Liability Insurance for Clinical Trials 2019)	Yes	Yes (as per South African Guidance on Liability Insurance for Clinical Trials 2019)	Yes (as per South African Guidance on Liability Insurance for Clinical Trials 2019)	Bodily injuries; enduring injuries	Psychological injuries; non-enduring injuries	Mutually acceptable independent medico-legal expert (should be consistent with the quantum of damages commonly awarded for similar injuries by a South African court in cases where legal liability is admitted)	No (yes only if claims filed via civil court processes)	Sponsor/local clinical trial applicant (except for claims that arise from malpractice and/or negligence which should be borne by research investigators themselves via professional indemnity)

participants. Nevertheless, the clinical trial insurance does not indemnify against malpractice or negligence caused by the research investigators and institutions. Furthermore, the payment of medical expenses and provision of insurance cover do not prevent an injured trial participant pursuing legal recourse through the civil litigation process against the research sponsors or investigators claiming compensation for harm or loss not covered by the insurance. In South Africa, an insurance certificate with an explicit set of requirements listed in the Guideline on Liability Insurance for Clinical Trials is a mandatory document that must be submitted to the South African Health Products Regulatory Authority for obtaining regulatory approval before conducting clinical trials (SAHPRA 2019). In Malaysia, it is not required for an insurance certificate to be submitted to the NPRA for the purpose of clinical trial approval. However, a written undertaking from the principal investigators must be provided to the local authority declaring that the clinical trials conducted are covered by insurance (NPRA 2020). However, the individual RECs in Malaysia require the research investigators to present an insurance certificate as part of the requirement to obtain ethics approval for a clinical trial. Indian jurisdiction contains legally binding provisions on compensation for clinical trial-related injury in their New Drugs and Clinical Trials Rules 2019; however, it does not explicitly require provision of insurance cover for human trial participants. In accordance with South African regulations, the quantum of compensation is to be commensurate with the severity and persistent nature of the trial-related injury. Additionally, compensation should consistently be aligned with the quantum of damages commonly awarded by the South African courts for similar medical injuries in cases where legal liability is admitted. In India, the New Drugs and Clinical Trials Rules 2019 dictates that the amount of compensation should be calculated in accordance with the formula specified in the Seventh Schedule of the New Drugs and Clinical Trials Rules 2019 that is derived from the local Workmen Compensation Act. Malaysian laws are silent with respect to the area pertaining to determination of quantum of compensation.

Types of compensable injury

The local regulation is silent on the types of compensable injury in Malaysia. Both South Africa and India have regulations that cover financial compensation over and above the medical treatment expenses involved in treating clinical trial-related injury (Chingarande and Moodley 2018). Notwithstanding the absence of legal commitment, South African regulations adopt a strict liability approach that bears a resemblance to a no-fault approach (SAHPRA 2019); however, compensation will be confined to bodily injuries of a disabling and enduring nature requiring medical treatments

(Agar and Burgess 2018). The Indian jurisdiction implements a strict no-fault liability approach whereby all types of injury are compensable.

Taking into consideration the lessons learnt from the *Venter* case, South African jurisdiction is inclined more toward obtaining a properly signed informed consent document which has detailed the inherent risks of a clinical trial as absolving the research sponsors from legal obligation to pay compensation for the cost of non-medical injuries such as general damages including suffering and pain, loss of earning capacity and mental anguish (Strode and Singh 2014). On the other hand, Indian regulations include provisions for compensation of non-trial-related and economic losses (Chingarande and Moodley 2018). Correspondingly, it should also be emphasized that Rule 40(1) of New Drugs and Clinical Trials Rules 2019 provides that:

> [w]here an injury occurs to any subject during clinical trial or bioavailability and bioequivalence study of a new drug or an investigational new drug, the sponsor, shall provide free medical management to such subject as long as required as per the opinion of [the] investigator 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.

Additionally, inclusion of injury due to the use of concomitant medications, failure of investigational medicinal products to provide intended therapeutic effect and failure of standard care provision in placebo-controlled trials are unique features of the Indian regulations. The ethical soundness of mandating research sponsors to compensate for injuries inflicted due to the use of concomitant medications is debatable. Concerning these concomitant medications, the sponsor has no control over the pharmaceutical formulations as most of the time they are produced by other pharmaceutical manufacturers not affiliated with the research sponsor. The Indian laws do not take into consideration that, in some circumstances, clinical trial participants may also contribute to their own injuries through their own non-compliance or other acts of commission or omission. Therefore, where contributory liability may be applicable, the current Indian New Drugs and Clinical Trials Rules 2019 seemingly disregard the faults and unreliability of trial participants and place the entire burden on the research sponsors (Chingarande and Moodley 2018).

Furthermore, the requirement for free medical treatment provision for an indefinite period until proven otherwise and the provision of financial compensation to the same aggrieved participant under Rule 40(1) of the New Drugs and Clinical Trials Rules 2019 could be viewed as unreasonable since some of these injured participants may require medical treatment until their end of life. It should be ethically accepted that when the injured participants have already been sufficiently compensated by the research

sponsors, they should use the compensation received to access further medical care. It may be recommended to revise Rule 40(1) to state expressly whether the medical treatment expenses should be covered under the financial compensation package. Otherwise, the aggrieved participants may unjustly benefit from double recovery. Nevertheless, from a human rights perspective, the stringent regulatory regime helps to offset the substantial power differential between the powerless trial participants and very powerful research industries (Chingarande and Moodley 2018).

Compensation process claim

In Malaysia and South Africa, the responsibility for compensation payment lies either with the research sponsors or with the institutions and their investigators, depending on whether the injury arose due to the trial procedures and/or administration of investigational medicinal products or malpractice and negligence caused by the researchers in the institutions, respectively. In India, the ultimate responsibility for compensation payment resides in the research sponsors regardless of fault. Malaysian regulations do not offer any explicit guidance on how compensation claims should be handled, while the South African regulations suggest claims should be made preferably through the research investigators. Requiring injured trial participants to file their compensation claims through research investigators fails to consider the potential conflict of interest that can arise due to the relationship between the research sponsors and the investigators. Furthermore, an investigator may also assume the role of the research sponsors and, hence, create further conflict of interests (Kamalo, Manda-Taylor, and Rennie 2016).

In South Africa and Malaysia, local guidelines dictate that a compensation payment will be made available through the insurance cover policy in place. However, it should be noted that these local guidelines do not have legal enforceability in the event of non-compliance or an unsuccessful insurance payout. The Indian New Drugs and Clinical Trials Rules 2019 list a step-by-step compensation claim process with well-defined timelines and penalties for non-compliance by the research sponsors or their representatives. This legally binding process implemented in India facilitates expeditious compensation claim resolutions and should be adopted as the standard for other countries (Chingarande and Moodley 2018).

Role of the Research Ethics Committees

The New Drugs and Clinical Trials Rules 2019 require the RECs to provide an analysis of the injury caused and forward their opinions on the quantum of compensation even though the final decision will be made by the Central Licensing Authority.

Both Malaysian and South African regulations are silent on this matter. Special expertise is required to determine injury cause or injury leading to death. As an example, in the event of injuries due to concomitant medications, pharmacology expertise may be necessary, whereas in the case of death, post-mortems may be required. Quantum of compensation determination, being highly complex, may not be the forte of most of the members of the RECs. Therefore, to fulfill their mandate, the REC members in India require additional skills which may not be necessary in other countries (Munshi and Thatte 2013).

Differential compensation for early and late phase trial participants

The three jurisdictions analyzed do not distinguish between early phase trials involving healthy volunteers and late phase clinical trials involving patient participants. It is ethically argued that a same-size-fits-all approach does not pass the fairness test in morality because healthy volunteers who will not obtain direct benefit from the investigational products ought to be compensated better than patient volunteers who may participate in clinical trials due to the exhaustion of other alternative standards of care. Moreover, patient volunteers who enroll in clinical trials further benefit from closer attention and monitoring, an added advantage not experienced by non-clinical trial patients on standard medical care (Chingarande and Moodley 2018). As a result, the ABPI (ABPI 2014) recommends the adoption of a differential compensation approach depending on phases of the clinical trials.

Elements of an efficient and fair no-fault compensation framework in a clinical trial setting

The no-fault compensation framework could represent the standard compensatory approach for individuals who suffer injury participating in clinical trials (therapeutic or non-therapeutic), where negligence cannot be established because information regarding all possible risks and harm was explicitly conveyed during the informed consent process, and the duty of care was not breached (Avilés 2014). Regardless of whether individuals participate in biomedical research studies selflessly or in exchange for payment, having the disease under investigation, compelled by law, and irrespective of whether the trial is successful or not since clinical trials represent collective activity conducted *on behalf and at the behest of others*, the public has a social moral obligation to safeguard these good Samaritans who are harmed by advocating a no-fault compensation framework.

To establish successfully an efficient and fair no-fault compensation framework in a clinical trial context, there are four fundamental commitments which research sponsors and institutions must embrace. First, sufficient funds should be secured for financial compensation and free medical care

provision for the aggrieved participants suffering from clinical trial-related injuries either through acquiring sufficient insurance or through self-insuring; second an independent external administrator should be appointed to evaluate and manage filed compensation claims; third, to ensure that sufficient, explicit and easy-to-understand information pertaining to the compensation framework is disclosed during the informed consent process; and finally, adequate records detailing the compensation system and all successful and unsuccessful claims should be maintained in a systematic manner for future reference to treat similar circumstances alike (Henry, Larkin, and Pike 2015). A precise formula to calculate the quantum of compensation for clinical trial-related injury should be established from data collected from precedents set in previous compensation claim cases to achieve consistent and harmonized compensation amounts for different types of injury based on the nature, severity and persistence of the injury.

It is crucial at the initial roll-out phase to establish a clear scope of accountability and responsibility for establishing, funding, and maintaining the no-fault compensation framework. In situations where research institutions engage in clinical trials without sponsors from pharmaceutical industry, these institutions will be responsible for administering the claim system and provision of compensation and medical care. However, when research institutions collaborate with industry sponsors both stakeholders should negotiate and allocate duties in administrating the claim system and accountability for the costs of clinical trial-related injuries. For clinical trial studies that are purely industry sponsored and not conducted at research institutions by third-party contract research organizations, the industry sponsor should bear the full accountability for claim system administration in addition to providing compensation and medical care to aggrieved injured participants (Morreim 2003).

Regardless of the clinical trial-related injury rate, an ideal national policy governing clinical research should sufficiently protect human trial participants who have suffered from unexpected, unfortunate, and unintended injuries. Mandatory insurance coverage purchased by research sponsors should be included as part of the no-fault compensation framework before clinical trial studies with greater than minimal risk are allowed to proceed.

Under the no-fault compensation framework, there will be no compensation provided for damages with an established non-causal relationship to clinical trial participation (Gainotti and Petrini 2010). Correspondingly, the question of which injuries are caused by clinical trial participation is extraordinarily complex and has its roots in the traditional scientific and legal concept of causation. Questions of causation are more challenging to analyze where participants are involved in therapeutic research, especially in pragmatic studies or clinical trials that involve standard of care treatments. When verifying whether a clinical trial-related injury has occurred, one factor to

consider is whether the trial participants were deprived of the standard of care therapy for their medical illness. In pursuing the causation, the assigned evaluator should weigh the distinctions between what occurred because of the clinical trial procedures and what would have in fact happened in the event that the required standard of care treatment had been administered. A limitation in terms of redressable causes of injuries is essential as an issue of compensatory justice and policy. Having a no-fault compensation framework with limitations not only ensures the coverage for injuries suffered while accepting risks for the benefit of others, but also limits the coverage to injuries that are within the scope of risk in which the compensation scheme is designed to address. Owing to the absence of tortious conduct in defining the scope of liability within a no-fault compensation scheme, it will be more appropriate to identify the scope of liability by assessing the types of risk which the compensation scheme was developed to guard against (Henry, Larkin, and Pike 2015).

Propositions for a no-fault compensation framework

The traditional fault-based negligence framework barely detects or prevents systems failures and cannot completely prevent non-intentional errors (Weisbrot and Breen 2012). Furthermore, it discourages adverse event and error reporting, hence impeding the contemporary focus on universal patient safety. In fact, a no-fault compensation framework may demonstrate potential to be a swifter, fairer and no more costly strategy which can contribute to patient safety (Weisbrot and Breen 2012).

From the perspective of professional indemnity, a no-fault compensation scheme may confer potential benefits in altering the research investigators' mindset concerning patient safety issues and, subsequently, learn from their own and others' mistakes to prevent future errors (Studdert and Brennan 2001). The main intention of a no-fault approach is to restore aggrieved trial participants to the state they enjoyed prior to their inflicted injury instead of finding fault in any party. Hence, it can be anticipated that a no-fault approach will encourage a more robust adverse event reporting, eventually leading to efficient and more thorough data collection (Avilés 2014). Additionally, it should also reduce the practice of defensive medicine and at the same time foster good clinical practice (Mikkonen 2004).

Moreover, due to the non-adversarial nature and non-involvement of a peer expert panel in a no-fault regulatory framework, the approach will put an end to the challenges for civil courts from hearing biased or poorly qualified expert witnesses. Furthermore, it may also prevent the inclination of experts to judge performance of the research investigators primarily on the occurrence of adverse event outcomes instead of the actual care delivered (Hugh and Douglas Tracy 2002).

Arguments against a no-fault compensation framework

It is anticipated that there will be an increasing number of opposing critiques against a no-fault compensation framework, whereby some may be legitimate while others more inclined toward self-interest. Advocates of the status quo may contend that a fraction of those who successfully secured reparative compensation under the traditional fault-based system could potentially end up financially worse off if they were to be compensated under the no-fault scheme approach instead (Productivity Commission 2011). If this is indeed true, it will only demonstrate the inequalities of the fault-based legal framework. To magnify the assumed risk of creating an expensive bureaucracy in the long-term progress of establishing an entirely new no-fault framework, status quo advocators may also criticize that there will be potential risk in which administrators appointed for a no-fault system may be susceptible to influence from the major funder such as research enterprises to reduce and limit the compensation coverage (Productivity Commission 2011). It is argued that these aspects can be addressed with an emphasis on achieving an impressive design for an effective, independent no-fault regulatory framework right from the beginning.

Nevertheless, the potential increase in cost to be borne by the local government and research enterprise due to the anticipated increase in claim frequency under this type of no-fault compensation system will undeniably represent a legitimate critique. Whether the above speculation will indeed occur is not easily predictable because this depends on multiple factors, such as the local culture of seeking compensation and the set limit of scheme coverage (Weisbrot and Breen 2012). To overcome the potential increase in cost, it may be appropriate for funding to be raised collectively by the research enterprise (local and overseas pharmaceutical companies) instead of tapping from the national budget. This is the viewpoint that research sponsors who are also the pharmaceutical manufacturers should demonstrate corporate social responsibility as they will be the first to gain substantial financial benefits once their investigational medicinal products are successfully commercialized in the market. To gain considerable support from the research enterprises on the proposed fund acquisition approach would necessitate the government introducing an incentive constituting appropriate adjustments in tax reduction for these research entities.

Additionally, as the main intention of a no-fault scheme is to mitigate the harm inflicted by the wrongdoer without the assigning of blame, it may also be argued that this approach will delay or prevent the identification of problematic and unethical research investigators (Weisbrot and Breen 2012). Notwithstanding, it is consensually agreed that a no-fault framework approach must not incidentally defend substandard, underperforming and unethical research investigators from being identified and properly managed (Weisbrot and Breen 2012).

Suggestions and recommendations on how a legally enforceable no-fault compensation framework for clinical trial-related injury can be implemented in Malaysia

It is hereby recommended that to fill the lacuna in current Malaysian law, a no-fault compensation framework should be codified into local legislation rather than merely having bioethical guidelines circulating in the research industry which have no legal enforceability. Fundamentally, to avoid placing an excessive financial burden on the central government, the recommended no-fault compensation scheme should take the form of mandatory clinical trial insurance purchased by the research enterprises instead of depending on fund allocation from the national tax revenue.

Moving forward, it is strongly urged that the proposed regulation should require all research sponsors who would like to conduct human clinical interventional studies in Malaysia, irrespective of early or late phase trials, to submit a valid insurance certificate with sufficient coverage to the authorities. Inspired by the South African policy, the insurance coverage should not have any co-payment or deductibles for which the participant is liable (SAHPRA 2019). Furthermore, the criteria and list of requirements for an insurance certificate to be submitted to the regulatory authorities should be explicitly set out in the proposed new laws. The period for insurance coverage should span from the initial approval date of the clinical trial to a reasonable timeline for the emergence of late injuries after a clinical trial has concluded. Annually renewed insurance coverage and the current effective certificate should be promptly submitted to the regulatory authorities by the research sponsors, in which failure to do so may result in the halting or termination of the corresponding clinical trial.

Additionally, encouraged by the Indian regulations, the explicit reporting timeline of adverse outcomes by the research investigators and sponsors to the RECs and authorities should be well-defined ("New Drugs and Clinical Trials Rules 2019"). The proposed new laws should comprise a schedule that clearly describes the formula to calculate the quantum of compensation in the evens of injury and death ensuing from the conduct of clinical trials. Like the Indian New Drugs and Clinical Trials Rules 2019, RECs should assume the assessor role for reported clinical trial-related injuries and deaths. Subsequently, the RECs should forward their assessment reports to the authorities for final decisions on the compensation amounts. In the event that the calculated quantum of compensation exceeds the insurance coverage, research sponsors should undertake to pay the remainder financial amounts, and failure to do so within the stipulated timeline should result in a penalty as described by the Sales of Drug Act 1952, which provides that:

> [A]ny person who commits an offence against this Act, or any regulation made under this Act for which no penalty is expressly provided shall be liable on

> conviction to a fine not exceeding twenty-five thousand ringgit or to imprisonment for a term not exceeding three years or to both, and for a second or subsequent offence he shall be liable on conviction to a fine not exceeding fifty thousand ringgit or to imprisonment for a term not exceeding five years or to both.

For drug clinical trials which are regulated by the NPRA, a legally binding guideline on compensation for clinical trial-related injury should be issued by the Director of Pharmaceutical Services as authorized under Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984.

Whereas, for medical device investigational clinical trials which are regulated by the MDA, the Minister, in the interest of the trial human participants, should issue a new compensation regulation in exercise of his power conferred by Subsection 77(1) of the Medical Device Act 2012. For non-compliance issues, the criminal punishments imposed under the abovementioned Act are heavier in comparison with the Control of Drugs and Cosmetics Regulations 1984. Section 79(30) of the Medical Device Act 2012 provides that:

> [t]he regulations made under this Act may provide for any act or omission in contravention of the regulations to be an offence and may provide for penalties of a fine not exceeding two hundred thousand ringgit or to imprisonment for a term not exceeding two years or to both.

Implementation of legally enforceable clinical trial-related subsidiary legislation which incorporates heavy criminal penalties for non-compliance may help prevent and deter irresponsible research sponsors or investigators from exploiting human participants involved in clinical trials conducted in Malaysia. Furthermore, with clearly written regulations incorporating well-defined compensation claims procedures, the aggrieved injured trial participants and their legal dependents will be adequately compensated for injury, damage or death arising from their participation in clinical trials, without the requirement to go through difficult hurdles in seeking legal remedy through civil litigation. Therefore, the proposed new NPRA guideline and Medical Device Act should, respectively, embody a comprehensive and fair compensation framework with relevant no-fault characteristics. Likewise, the proposed new subsidiary legislations should grant powers to relevant governing authorities, namely the NPRA and the MDA, to control interventional research activities through demand for specific improvements, issuance of temporary suspensions or complete discontinuation of clinical trials that fail to comply with the authorities' published guidelines and regulations.

Concluding remarks

Undeniably, clinical trials play a crucial role in the development of life-enhancing and life-sustaining biomedical advances. However, this scientific progress does not happen without cost. Clinical trials, regardless of how well-

designed and ethically conducted, will always have their uncertainties and, subsequently, expose human participants to risk of injury or harm and even death in more severe cases. In the event that injury is unfortunately inflicted, compensatory justice tied with the other well-accepted cardinal ethical principles of non-maleficence and professional beneficence require that trial participants should never be left worse off as a result of their participation in clinical research studies.

The chances of proving negligence are lower in clinical research because research injuries are not a form of ordinary negligence. Hence, ordinary legal recourse actions are perceived to be inappropriate as the prospects for aggrieved participants to obtain financial compensation through civil litigation are inherently rare. The compensation of clinical trial-related injuries represents a substantially significant issue in the progressive development of ethically acceptable biomedical research. However, it is worth highlighting that even as of today, the ethical arguments revolving around the most ideal and workable regimen of compensation for injuries caused to individuals participating in clinical trials remain unclear.

The authors hence propose a no-fault compensation framework which aims to offer equitable compensation for inflicted harm injuries for which remedy is sought and to treat like cases similarly. Within this framework, compensation should be disbursed with maximum efficiency and at a minimum administrative cost. This proposed approach should be mandated by amendment of the Malaysian laws governing biomedical research, and in the interim should be voluntarily adopted by all the research sponsors, institutions and investigators involved locally in the conduct of clinical trials. By explicitly setting the eligibility of claimants, defining injuries which are compensable, establishing the type of remedies which will be offered, including quantum of compensation in accordance with established calculation formulae and setting forth a standardized procedure for claims evaluation, the framework proposed in this paper pursues the resolution of a long overdue ethical weakness in the country.

The imposition of a legally enforceable no-fault compensation framework in Malaysia for trial-related injury would culminate in a more comprehensive and consistent level of protection for voluntary human participants in clinical trials conducted locally. Additionally, the proposed no-fault compensation framework may help to achieve a fair apportionment of the benefits and risks inherent in clinical trial research studies and eventually promote effective research subject protection.

Limitations of the research

The main limitation encountered in completing this legal research paper is the lack of recent local empirical data and Malaysian journal literature pertaining to

the issue of compensation schemes for clinical trial-related injury. Most of the available local information focuses only on the operational aspects of conducting clinical trials with the objective of mitigating prospective injury risk to the participants while placing minimum emphasis on a compensatory mechanism in the event that the participants suffer harm. Furthermore, to the authors' best knowledge, there is no local case law available to use as a reference authority or precedent. Moreover, the regulations and policies of both referenced jurisdictions (India and South Africa) described in this paper are based on primary and secondary sources which are currently available online. While the authors endeavored to obtain the current policies and laws of these jurisdictions, there is a possibility that some law reform activities that are currently happening within the referenced countries are as yet not publicly available online and, hence, the abovementioned information would be excluded from the current research analysis work.

Another limitation is that the current legal research work is based on a pure doctrinal analysis which studies what the law states instead of evaluating the effectiveness of the law in a real life social context. Doctrinal methodology often focuses on legal sources and does not challenge or question the application of the proposed laws, rather, it only analyzes the law in the context of inherent consistency. This methodology is therefore often criticized for being disengaged from reality as it does not evaluate the social and economic practicability of the suggested law reform. Nevertheless, it is believed that this doctrinal analysis-based study outcome will provide an essential precursor for the policymakers to conduct further studies examining the practical applicability of the proposed compensation policy through empirical studies, including survey-based or questionnaire study methodologies.

Future research

A substantial series of quantitative and qualitative research studies is imperative in determining whether the proposed law reform approach is well accepted by the clinical trial stakeholders, including but not limited to the pharmaceutical companies both local and multinational, research sponsors, health institutions, research investigators, non-governmental organizations, academia and patient advocate groups. This represents a task that perfectly fits within the NCCR's authority and expertise. With the proposed no-fault compensation framework, the possibility of increasing numbers of compensation claims may be anticipated, nevertheless, this has not been proven locally. The only answer to such speculation is through the presence and subsequent evaluation of empirical data. Therefore, it is strongly urged that the Government of Malaysia should consider requesting the NCCR along with support by Clinical Research Malaysia to undertake the mentioned further research initiative.

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