SPECIAL ARTICLE

Compensation in Neonatal Clinical Trials: A Perspective

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ABSTRACT

Well conducted clinical trials are the mainstay for generating evidence on preferred treatments. In order to adequately protect the interests of the trial participants, the Central Licensing Authority of India has formulated guidelines to determine the quantum of compensation in cases of regulatory clinical trial related injury or death. However, these guidelines do not address the nuances of trials recruiting children aged under 16 years, within which, neonates are the most vulnerable population. Thus, there is a need for addressing this lacuna in the current guidelines. This article examines the challenges in determining the quantum of compensation in neonatal clinical trials using the current formula, which is a corollary to the challenges faced by the authors in procuring clinical trial insurance for the Probiotic supplementation for Prevention of Neonatal Sepsis (ProSPoNS) trial. Further, it suggests a template for a differential formula using birthweight of infants, which is one of the many important factors impacting neonatal mortality.

Keywords: *Compensation, CDSCO, DCGI, Regulatory trials*

Published online: March 19, 2024; **PII**:S097475591600617

INTRODUCTION

A discernible knowledge gap remains in evidence-based pediatric treatments particularly in neonates, resulting from inadequacies in drug evaluation for children [1]. The practice of extrapolating drug safety and efficacy data from adults for use in neonates is widespread. Such off-label use of drugs in neonates makes their safety and efficacy questionable and puts the neonatal population at a risk of unexpected adverse effects and under / over dosing [2]. Children, in particular neonates, are a unique population with distinct developmental and physiological differences from adults. Clinical trials in neonates are essential to develop age-specific, empirically-verified interventions and therapies to estimate and improvise optimum therapeutic solutions, but these also come with their own set of challenges [3,4]. With respect to drug/ clinical trial participation, neonates show increased vulnerability owing to poor drug metabolism due to hepatic and renal immaturity, larger surface area requiring higher doses, immunological immaturity, limited body responses, clinical symptomatology, dependence on parents etc [5]. The risk is further heightened when a neonate is born underweight / overweight [6].

Special care and protection are required for children participating in clinical trials [7]. In India, the National Ethical Guidelines for Biomedical Research Involving Children by the Indian Council of Medical Research (ICMR), enlist the requirements for conducting clinical trials in the pediatric population [8]. Clinical trials which involve an Investigational New Drug (IND) or a New Chemical Entity (NCE) are governed by the New Drug and Clinical Trials Rules (NDCT 2019). Also, the rules describe in detail every aspect of conducting clinical trials including compensation for trial participants. Justifiable compensation for trial-related injury or death is a priority under the NDCT, 2019, and is considered one of the most important areas of clinical trials in India [9,10].

This article discusses how compensation guidelines related to pediatric clinical trials vary globally and discusses in detail the guidelines in India. An example of a formula based on birth weight, is proposed for calculating compensation in neonatal clinical trials, for consideration

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Received: Oct 13, 2023; Initial review: Nov 19, 2023;
Accepted: March 05, 2024

and further deliberations by the experts and regulatory authorities.

Clinical Trial Compensation for Neonates: Global *vs* Indian scenario

Clinical trial compensation guidelines vary globally. The World Medical Association, Declaration of Helsinki [11] and the International Conference on Harmonization-GCP (ICH-GCP, addendum 2017) [12] require that compensation or treatment be offered for any trial-related injuries. Some others like the Association of the British Pharmaceutical Industry (ABPI, 2014) and the Council for International Organizations of Medical Sciences (CIOMS), provide detailed compensation approaches for various clinical research phases, whereas the US Food and Drug Administration's (FDA) informed consent regulation requires that the participants be informed about the availability of compensation and medical treatment in case of injury [13-16].

In most countries compensation for clinical trial participants is based on the 'Tort's Law'. This implies that the court of law, on hearing from investigator, sponsor, and patient decides on the compensation [17,18]. Globally, compensation in clinical trials also includes the money or reimbursements provided to the participants of the trial [19,20].

India is the only country which protects the interests of its trial participants by awarding compensation in cases of trial-related injury or death by means of rules laid down by the Central Licensing Authority (CLA), the Central Drug Standard Control Organisation (CDSCO). The Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Participants, the Indian Good Clinical Practice (GCP) Guidelines, and NDCT 2019 recommend compensation to be given to clinical trial participants who suffer from trial-related injury [8,9].

Any untoward or adverse medical occurrence in the clinical trial participant that results in hospitalization or its prolongation, permanent disability, or death of the participant is classified as a serious adverse event (SAE). Clinical trial participants who suffer from any SAE which is deemed 'related' to the trial as opined by the expert committee, are entitled to financial compensation; in case of death, their dependents are entitled to financial compensation. Also, the trial sponsor is required to provide free medical care for all trial-related injuries to the participant as long as required (as per opinion of investigator) or till such time it is established that the injury is not related to the clinical trial, whichever is earlier. The amount of compensation in case of injury or death in a clinical trial or bioavailability or bioequivalence study of new drug or investigational new drug is determined by the compensation formula given in NDCT 2019 under Chapter VI, Rule 39 to Rule 43 [9,21].

Genesis of the Clinical Trial Compensation Formula in India

The unique standpoint of India in clinical trial compensation has a long history stemming from the Drugs and Cosmetics Act, 1940 [22]. In 2005/2006, the Drugs Controller General of India (DCGI) established an expert group committee to review and draft the rules for determining compensation in clinical trial injuries in India and a '*No Fault Compensation*' model was adopted for the Indian population as opposed to the '*Tort's Law*' in other countries. The '*No Fault Compensation*' translates as, regardless of the fact that the trial participant has given informed consent (in case of neonates, the parents or the legally authorized representatives) after having fully understood the risks involved in the clinical trial, they will still be entitled to compensation in case of related SAE upheld by the DCGI as a clinical trial injury by virtue of participation in the trial. The committee, took into consideration several factors, including the participant's age, qualification, gender, insurance coverage, urban/rural, place of death/hospitalization, and level of education. Based on their deliberations, the committee unanimously agreed on the following two factors as the basis of the compensation formula:

1. Age: The compensation amount should be proportionate to the productive age group the patient is likely to live in. This means that a younger person with a longer life expectancy and higher earning potential should receive a larger compensation amount than an older person who is likely to live for a shorter period and earn less. This is in accordance with the Workmen Compensation Act which provides a table of compensation based on age [22].

2. Seriousness: The compensation amount should also be based on the severity of the illness or condition suffered by the participant. If a person is suffering from a terminal illness, they are less likely to survive, and therefore should receive lower compensation than someone with a minor ailment, such as a cold or fever. A healthy volunteer with no existing health risks warrants the highest compensation.

Quantum of Compensation for Trial-related Injury or Death

Separate compensation formulas address different types of clinical trial injuries namely permanent disability,

congenital anomaly or birth defect, chronic life-threatening disease, and Reversible SAE in case it is resolved. For example, in case of death of the trial participant, the compensation is calculated as follows:

Compensation = (B x F x R) / 99.37

Where, B = Base amount (i.e. INR 800,000/-); F = Factor depending on the age of the participant (based on Workmen Compensation Act); R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as follows:

0.50 terminally ill participant (expected survival not more than 6 months)

1.0 Participant with high risk (expected survival between 6 to 24 months)

2.0 Participant with moderate risk

3.0 Participant with mild risk

4.0 Healthy volunteers or participants with no identifiable risk

This can be interpreted as follows: If a participant has an expected survival of not more than 6 months, the risk factor (R) can be assigned as 0.5, which translates to half of the maximum compensation amount.

Another factor that was included in the formula was a fixed baseline amount (INR 8,00,000/-) based on the highest average wage/daily wage per months given to a person employed by any of the state governments at that time which was INR 7200 per month. It was assumed that if this money was put into a fixed deposit at 12% interest at that time, it would yield the baseline amount.

Factor F ranges from 99.37 (for age of 65 or more) to 228.54 (of age not more than 16) depending upon the age of the injured. Thus, it can be seen that according to the formula, the compensation amount varies from a minimum of INR 4,00,000/- to a maximum of INR 73,60,000/- depending on the age of the deceased and the risk factor. However, it was decided that in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of INR 2,00,000/- should be given.

Challenges in Assigning Risk Factor in Neonates

Although compensation for clinical trial injuries in adults has been addressed, the issue of compensation for neonates remains unclear. There are several issues that need to be considered in neonatal trials that are not adequately addressed in the compensation formula.

High Risk of Mortality

One such issue is the high risk of mortality among infants in India. It is unclear what risk factor should be assigned to a normal infant - should it be 4 (the value for a normal volunteer), or less than 4? Should socio-economic status be taken into account before deciding the risk factor, and if so, how should this be factored in calculations? These considerations may give rise to moral and ethical debates.

Severity of Congenital Disease

Another issue is that of correcting mild/moderate/severe conditions in neonates, where neglect or delay can lead to fatal outcomes. The inherent risk in such cases needs to be carefully considered, especially when the neonate is suffering from a condition where mortality could be high if no optimum available treatment is given.

Vulnerability

In vulnerable populations, like children or people with intellectual or mental disabilities, compensation is a special concern. This population is considered as relatively or absolutely incapable of protecting their own interests. The Indian Council for Medical research (ICMR) National Ethical Guidelines for Conduct of Biomedical Research recommend that study protocols involving neonates should take into consideration the vulnerability of this group within the pediatric population in terms of the risk of long-term effects of interventions, including developmental effects.

There are two important challenges in ascertaining the relatedness of SAE and deciding the quantum of compensation in neonates. *Central Drugs Standard Control Organisation* (*CDSCO*) guidelines for adults recommend calculating the compensation amount based on the risk factor assigned based on the expected survival of the study participants at the time of enrollment, the age of the participant, and a base amount of INR 8,00,000/-. However, it is difficult to decide the risk factor in infants delivered preterm or lower than normal birth weight or small for gestational age (SGA) for the following reasons:

i) Despite providing the standard of care, many neonates die due to the co-morbidities associated with pre-maturity and SGA

ii) The majority of these deaths occur within hours to days while surviving neonates may have near normal life expectancy.

The compensation formula of adults considers ages 0-16 years as the same without any differentiation of various weight categories in the vulnerable population. The current formula for compensation is made keeping in mind

the adult population. 'F' is determined by the Workmen's compensation formula which is actually impractical to apply in case of neonates. In actuality, even within the neonates there are subclassifications as mentioned earlier.

Experience from the ProSPoNS trial

Although not many regulatory clinical trials in the pediatric age group have been documented but few examples from vaccine trials [23,24] or the recent Goat Lung Surfactant Study (GLSE) exist where compensation was awarded to some participants [25,26]. But in all these cases the compensation awarded has been based on the adult formula. While conducting the ProSPoNS trial [27] which is a large, phase III multi-centric trial in neonates, currently being conducted at six sites in India, an important aspect of the compensation rules came into light. As the NDCT 2019 rules require sponsors to obtain clinical trial insurance to provide compensation to subjects, we had to calculate the limit of liability to obtain clinical trial insurance, based on the supposed compensation that can be awarded in the trial. This calculation was done based on the compensation formula provided in the seventh rule of NDCT 19 rules [9]. However, it was realised that the compensation formula used does not have any sub-classification for the pediatric population, particularly for the neonates. Thus, it was challenging for the trialists to assign a risk factor and calculate the amount of compensation that should be accounted for in the trial insurance. Therefore, it was realized that a more comprehensive system of determining the compensation in the neonatal population is required to address this lacuna.

Proposed Formula

Based on the mortality and morbidity risk associated with the different categories of birth weight, we propose a template to assign different risk factors for neonates in clinical trials as shown in **Table I** [28]. The compensation amount in case of death can then be calculated according to the earlier formula as: Compensation = (B x F x RA) / 99.37

However, these assumptions need to be reviewed again based on the economic development since the period of their conception, the average salary has increased. However, the interest rates of fixed deposits have decreased.

DISCUSSION

Clinical trials in neonates are faced with multiple challenges and raise some unique ethical considerations owing to the very nature of the population involved. The complexity of research in this population, coupled with the apprehension of causing unintended harm to vulnerable neonates, has led us to propose a modification in the current formula for calculating the compensation involving research in neonates. Further, the inability of this population to provide informed consent and the reliance on obtaining surrogate consent from parents adds to the challenge. There have been instances in neonatal research where the trials have come under the scanner for ethical issues. For instance, the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized) Trial, carried out in the US between 2004-09, had aimed to enhance knowledge on the optimum oxygen saturation level in very premature newborns. The study presented some important findings to the scientific community but simultaneously came under the scanner for a faulty informed consent process with failure to disclose potential risks to participants. It was later that scientific groups and leaders in bioethics and pediatrics came out in support of the trial urging the Office for Human Research and Protection (OHRP) to withdraw the notice given to the institutions involved in this trial as they feared it would set a precedence that would hamper ongoing and future patient-centred outcomes in trials. Such incidences bring to light the difficulty in conducting clinical trials in neonates.

Even much before this controversy, in the 1970s, many acts and guidelines like the Belmont Report, issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research,1978, were passed in the US, to protect children's rights during research. But these impeded clinical trials and pediatric drug development for the next two decades until new measures were implemented. It took another decade and

Table I Risk Factor Assigned by Birth Weight

Weight category	*Risk*	*Risk factor assigned (RA)*
Micro preemie < 800 gm	Very high risk (Expected survival not more than 48 hrs)	0.5
Extremely low birthweight (ELBW 800-1000 g)	High risk (expected survival between 48 hrs – 2 months)	1.0
Very low birthweight (VLBW 1000-1500 g)	Moderate risk	2.0
Low birthweight (LBW 1500-2500 g)	Mild risk	3.0
Normal birthweight (NBW 2500-4000 g)	Lowest risk (Healthy neonates with no underlying conditions)	4.0
Higher than normal (HBW > 4000 g)	Mild risk	3.0

new laws and funding passage for good research to begin. India experienced a similar scenario after specific amendments were introduced in the Drugs & Cosmetics (Amendment) Bill in August 2007. Subsequent amendments vide Gazette Notification G.S.R. 53(E) came in 2013. These regulatory changes brought about stricter rules for conducts of clinical trial and compensation in India and hampered clinical trials in India for almost a decade for the fear of compensation, etc. Thus, thoughtfully designed government regulations are needed to guide and promote ethical research: In context of compensation for neonates in trials, it is essential that the compensation safeguards the interests of participants in concordance with the Declaration of Helsinki, while simultaneously safeguarding the interest of scientifically and ethically conducted clinical trials in neonates for advancement in medical sciences.

Compensation in case of clinical trial-related injury or death is an important aspect of conducting regulatory trials in India. The present formula given in the NDCT 2019 rules for calculating compensation does not address the issues of the pediatric / neonatal population and the various risk factors associated with various categories in the pediatric age group within which neonates form the most vulnerable sub group. This results in calculation of a broad compensation which may not be appropriate for that age group.

Although, in this example, we have proposed a new marking system for 'R' in the formula based on the risk assigned to neonates according to their birthweight, the base line amount 'B' and 'F' also need to be re-evaluated in the current context. The Workmen's compensation formula which forms a part of the compensation clause, assigns equal weightage to all ages between 0-16 years ('F' = 228.54). We suggest that children as the future citizens of the country should be assigned a 'value of life' to be considered in the compensation formula. Adaptation to the neonatal context while estimating the quantum of compensation for trial-related injury/death among neonatal participants has been suggested by Sivanandan et at 2019 [25]. They suggested an adaptation of 'R' factored in the calculation for severity of neonatal diseases, prematurity, comorbidity and presence of risk factors. We have suggested a method of assigning value to 'R' based on risk associated with birth weight. For calculating the 'F' factor for children, other methods can be used for instance 'Life tables'. Life tables give estimates of the mortality which can be used to find the remaining period of expected life of children [29,30]. Another method could be determining the statistical value of life [35]. The formula proposed here in this manuscript has certain limitations as mentioned above. Considering the uncertainty of outcomes in this population owing to multiple biological and socio-economic factors etc, there is a need for deliberation by experts from the fields of neonatology, pediatrics, biomedical statistics, ethicists, etc. and a more comprehensive formula needs to be developed for determining compensation in trials involving neonates as participants.

CONCLUSION

Considering the paucity of the data available from neonatal trials in Indian population and the dire need for tailor-made drugs for the neonatal population, it is imperative to set an environment more conducive for conduct of drug trials for the neonatal population in India. The ICMR is contributing by creating national facilities such as centralized ethics committees for multicenter trials, Indian Clinical Trial and Education network (INTENT) etc. Given the vulnerability of this population, they are at a high risk of facing adverse events. In case of SAEs, a broad formula as per the Clinical Trial Regulations of India seems insufficient. We therefore suggest a differential formula for trials specific to the neonates.

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Funding: ICMR, UKRI-MRC; *Competing interests*: None stated.

Disclaimer: The authors would like to declare that this formula should not be considered prescriptive and further deliberation on the matter by an expert committee is required to create a comprehensive formula that can be adapted to the needs of the neonatal population.

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