Analysis of clinical trial agreement and insurance policy submitted to the ethics committee of a tertiary care teaching institute in central India

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Abstract

**Purpose:** Very few studies conducted in India have analyzed insurance policies and clinical trial agreement (CTA) submitted to ethics committee (EC). This study was conducted to review and find out deficiencies in it.

**Materials and Methods:** This was a retrospective observational study. All the protocols for regulatory clinical trials and academic research sponsored by the Indian Council of Medical Research or other funding agency were included. Insurance documents and CTA submitted with the study protocols were analyzed.

**Results:** A total of seventy CTA and insurance policies were analyzed. CTA mentioned that parties involved in 60 (86%) forms, scope of the agreement in 15 (21%) forms, responsibilities of the party in 68 (97%) forms, and payment details in 58 (83%) forms. Nearly 88.5% of the insurance policies mentioned whether the policy covers the participants for injury due to all clauses and 91% of the policies mentioned the validity period of insurance.

**Conclusion:** It was found that both the documents contained almost all the required elements. This was probably because this institutional EC insisted on and thoroughly reviewed the documents to ensure that adequate compensation of research-related injuries has been provided for and this fact is informed to the trial subject. As very few studies are available in the literature, we could not compare majority of the findings of this study with others.

**Keywords:** Clinical trial agreement, ethics committee, informed consent document, insurance policies

INTRODUCTION

Clinical trials are on the rise in developing countries including India and that has led to increase in the participation of human subjects in the research and thereby a huge responsibility has been placed on ethics committees (ECs) to protect their interests. The process of review of a research study by an EC can be divided into two parts: one is procedural issues such as checking of application form for completeness and other is to review appropriateness of the consent, other study-related documents, and the study proposal by the EC members.
According to the first amendment (of 2013) to “The Drugs and Cosmetics Rule,” payment of compensation is the main responsibility of the sponsor. This amendment has made the EC responsible for recommending the amount of compensation for injuries occurring during clinical trials to the regulators. Provision of medical/surgical treatment of trial-related injuries has to be done by sponsors. How often the sponsors abide by the rules and provide compensation is a matter of debate, but at least the inspection for appropriateness of the related documents needs to be done by the institutional EC (IEC). Therefore, it is essential for the EC members to be aware of clinical trial-related insurance and clinical trial agreement (CTA).

The sponsor must sign CTA with the investigator before the initiation of clinical trial. An agreement manages the relationship between the sponsor and the institution and specifies the financial support, provision of drugs, fees, payment, and honorarium. The duties of a sponsor toward good clinical practice (GCP) compliance, data reporting and recording, and retaining trial-related essential documents are also specified in this legally binding agreement. Description and acknowledgment of responsibilities, terms of collaboration, payment and reimbursement whenever and wherever required, publication terms, subject injury coverage, plans for dispute resolution, grounds for contract termination, and possibility of amending contract terms in future should be made available in a CTA.

Insurance is a way of risk management primarily used to include the risk of unforeseen, uncertain loss. A priori agreement to provide compensation for any physical or psychological injury for participants entitles the sponsor to provide insurance coverage for an unforeseen injury whenever possible. The sponsor decides the amount of insurance cover and thus the premium to be paid in clinical trials. The insurance amount and the annual premium to be paid depend on a variety of factors including the size of the trial being conducted, phase of clinical trial, expected degree of risk and potential untoward adverse events envisaged, financial strength of the company conducting the trial, nature of drug, and the population on which the trial will be conducted.

The GCP guideline of the Central Drugs Standards and Control Organization requires that the protocol should contain a section on “Finance and Insurance,” in which there is evidence that the subjects are satisfactorily insured against any injury caused during the study (2.3.1.12d). The Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical Research Involving Human Participants 2017 have specified the need for provision of compensation of participants for research-related injuries. However, there is paucity of published literature about these issues in India. There are very few studies conducted in India that have analyzed insurance policies and CTA submitted to EC. This study was hence conducted with the objective of identifying the deficiencies in insurance policies and CTA submitted to EC using applicable guidelines and regulation (i.e., ICMR guidelines for ICMR-funded projects and Schedule Y and New Drug and Clinical Trials Rule 2019 for regulatory trials as well as standard operating procedures of IEC).

MATERIALS AND METHODS

This was a retrospective observational study which was initiated after obtaining approval from IEC. Administrative approval for accessing the documents from the concerned authorities was obtained and complete confidentiality of the investigators and the study titles was maintained. All the protocols submitted to the IEC from the period of May 2013 to October 2019 were reviewed for insurance policy and CTA. Protocols included those for regulatory clinical trials and academic research sponsored by the ICMR or other funding agency. Protocols for postgraduate thesis and other research protocols that were not funded were excluded from the study.

Insurance documents and CTA submitted with these projects were analyzed. A total of seventy insurance policies and CTA of clinical trial submitted to the IEC during the period of 2015–2018 were analyzed. Out of the seventy insurance policies and CTA, 62 were regulatory clinical trials, four were ICMR projects, and four were sponsored by various funding agencies.

The CTA was analyzed to see whether the following points are mentioned as per the checklist of CTA for legal expert of the IEC:

1. Parties involved
2. Scope of the agreement
3. Responsibilities of the party
4. Payment details.

The insurance policy was reviewed for the following points as mentioned in the checklist for legal expert of the IEC:

1. Whether covers the participants for injury due to all clauses mentioned in rule 122DAB
2. Validity period mentioned or not
3. Countries for which the policy provides cover if mentioned or not
4. Liability limit – per person and total – mentioned or not
5. Whether indemnity covers the liability of investigator and sponsor.
Data were expressed as percentage.

RESULTS

The present study reviewed the protocols submitted to the IEC from the period of May 2013 to October 2019 for insurance policy and CTA.

Analysis of CTA [Table 1] revealed that parties involved were mentioned in 60 (86%) forms, scope of the agreement was mentioned in 15 (21%) forms, responsibilities of the party was mentioned in 68 (97%) forms, and payment details were mentioned in 58 (83%) forms.

After reviewing the insurance document [Table 2], it was found that 62 (88.5%) insurance documents mentioned whether the policy covers the participants for injury due to all clauses mentioned in rule 122DAB, 64 (91%) policies mentioned the validity period of the insurance for the trial, 65 (93%) documents mentioned countries for which the policy provides cover and whether indemnity covers the liability of investigator and sponsor, and 66 (94%) policies mentioned the liability limit (per person and total).

DISCUSSION

The present study reviewed two important documents submitted to EC for protection of trial participants, that is, insurance policy and CTA.

Helping subjects get their compensation is the responsibility of the EC. Members should spend time and effort in understanding the insurance policies placed before them, to make sure that faulty policies will not jeopardize the interest of the subjects. These policies may not cover the entire period of the trial and contain clauses or conditions which would make payment of compensation to subjects difficult. In one of the questionnaire studies, it was found that knowledge of the EC members regarding CTA and clinical trial-related insurance is poor. For this very reason, the knowledge of CTA and insurance document is prerequisite for IEC members.\[1,2\] Reviewing the insurance policies for the mandatory points along with the study protocol by the members should be practiced as insurance policy does not make adequate provisions for paying compensation, and the sponsor will have to bear the costs, but during this period, the subject or nominee may suffer due to delay in payment. Thus, the stakeholders namely the participant and the sponsor will be affected due to lacunae in insurance and may have to face with the above-mentioned consequences. In addition, the EC if not being able to ensure timely compensation will be failing to protect the rights of the participant. In an internationally publicized case, the sponsor did refuse to pay for the trial injuries, citing lack of adequate insurance coverage.

Understanding insurance policies takes time, effort, and a lot of patience. It is often beyond the scope and capacity of lay people as different formats, language, and terminology used by different companies in different policies make it difficult to compare and understand exactly what they offer.\[4\] However, the ECs need to critically examine all policies submitted for approval. Both Schedule Y and ICMR guidelines specify that this be an essential element of the ICD. In this study, validity period was mentioned in 64 (91%) out of the 70 policies. Most policies examined by us were for a period of 1 year, while trials are for a longer period. Only two policies had a validity period of 2 years and three policies had a validity period of 3 years. Similar findings were reported in a study by Ghooi and Divekar.\[4\] In most of the cases, it is expected that the insurance will be renewed; however, there is no guarantee that it will be. In case there are a large number of trialrelated serious adverse events (SAEs), and compensation mounts, the insurer may refuse to extend the period of insurance. Another insurer may not be too keen to take up the responsibility, if it is known that large amounts of compensation have already been paid.\[4\]

In most policies that we analyzed, liability limit per person and total was mentioned, which was a positive finding. In general, policies specify the liability per claim and the aggregate liability, which seems to be the norm, but not all policies follow this. Similarly, majority of the insurance

### Table 1: Analysis of clinical trial agreement (n=70)

| Parameter                  | Mentioned (n=70), n (%) | Not mentioned (n=70), n (%) |
|----------------------------|-------------------------|----------------------------|
| Parties involved           | 60 (86)                 | 10 (14)                    |
| Scope of agreement         | 15 (21)                 | 55 (79)                    |
| Responsibilities of the party | 68 (97)             | 2 (3)                      |
| Payment details            | 58 (83)                 | 12 (17)                    |

### Table 2: Analysis of clinical trial insurance (n=70)

| Parameter                                           | Mentioned (n=70), n (%) | Not mentioned (n=70), n (%) |
|-----------------------------------------------------|-------------------------|----------------------------|
| Whether covers the participants for injury due to all clauses mentioned in rule 122DAB | 62 (88.5)               | 8 (11.5)                   |
| Validity                                            | 64 (91)                 | 6 (9)                      |
| Countries for which the policy provides cover       | 65 (93)                 | 5 (7)                      |
| Liability limit per person and total                | 66 (94)                 | 4 (6)                      |
| Whether indemnity covers the liability of investigator and sponsor | 65 (93)                 | 5 (7)                      |
documents mentioned whether the policy covers the participants for injury due to all clauses mentioned in rule 122DAB and the countries for which the policy provides cover, which was again a positive finding.

All the CTAs submitted to EC were either tripartite or quadripartite and the responsibilities of various parties were mentioned in majority of the forms (97%). The reason for CTA being tripartite or quadripartite was that it was the requirement of EC. Details of the payment to various stakeholders should be mentioned in the CTA. However, in our study, we found that payment details were mentioned in 83% of forms.

Overall findings of this study about the analysis of CTA and insurance policies were positive because majority of the required elements were covered in all the three documents except for few deficiencies. This was probably because this IEC insisted on and thoroughly reviewed the documents. As very few studies are available in the literature, we could not compare majority of the findings of this study with others.

**CONCLUSION**

One of the primary responsibilities of EC is protection of participant’s safety, rights, and well-being. The present study focused mainly on two documents, that is, CTA and insurance policies reviewed by the ECs for compensation. It was found that both the documents contained almost all the required elements. This was probably because this IEC insisted on and thoroughly reviewed the documents to ensure that adequate compensation of research-related injuries has been provided for and this fact is informed to the trial subject. As very few studies are available in the literature, we could not compare majority of the findings of this study with others and findings of this study are not generalizable as it include data from only one EC. ECs should insist on submission of a compensation plan for research participants and go through the documents for appropriateness in trials and should ensure that adequate compensation for research-related injuries has been provided. EC members must be trained to review this process carefully.

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**Conflicts of interest**

There are no conflicts of interest.

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