**Title: An observational study to assess completion reports for compliance with the institutional ethics committee approved protocol**

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**Abstract:**

**Background:** The protocol non-compliance is common and can affect both patient safety and data integrity. There are no studies published which actively looked for non-compliance in research studies. In the light of this background, the present study was carried out with the objectives to assess the proportion of protocol non-compliance and to evaluate the aspects of protocol that are noncompliant.

**Methods:** The study completion reports that were submitted to the institutional ethics committee for the period January 2017 to December 2017 were compared with approved protocol. A checklist for recording protocol non-compliance was developed, which was validated from 5 experts which consisted of 12-point checklist with responses as yes, no, not applicable and insufficient information was recorded.

**Results:** Out of 193 studies, prospective observational studies were n = 120 (62.17 %), retrospective were n = 39 (20.21%), interventional studies n = 28 (14.51 %) and observational studies with both prospective and retrospective study design were n = 6 (3.11%). The study objective was modified in n=18 (9.32%) studies. Only n=14 (7.24%) modified the selection criteria. 6 studies (3.10%) did not collect the data as mentioned in the protocol. 58 studies (30.05%) did not achieve the calculated sample size, whereas n = 78 (40.41%) did not complete the study as per the study duration. Contrary to 180 protocol deviations found in this study, only 14 protocol deviations were reported by the principal investigator. The aspects like blinding, randomization which are relevant to interventional studies (n=28) showed 100 % compliance.

**Conclusion:** The research protocol is not adhered in all aspects. Adequate training to investigators will help prevent non-compliance and enable us to conduct studies with high ethical and scientific integrity.

**Keywords:** study design, sample size, interventional studies, non - compliance

**Introduction:**

A protocol is an important document in the research that describes the objective(s), design, methodology, statistical considerations, and organization of a trial which is developed based on the evidence-based practice and represents the best method of use of therapeutic regimens (1). The protocols are approved by the institutional ethics committee and the regulatory authorities before the research studies are initiated. The research team must follow the document of protocol religiously if the research project is to be complaint with all the regulations.

Protocol deviations and violations are the terms used for the non-compliance / divergence of study from the protocol approved by IEC. Protocol deviation is a “non-compliance to protocol approved by IEC which does not affect the safety wellbeing of the participant”, also termed as minor deviations. Protocol violation is a “non-compliance to protocol approved by IEC which affects the safety wellbeing of the participant as well as data integrity of the study” also termed as major deviations (2). US FDA defines protocol deviation as “unplanned excursion from the protocol that is not implemented or intended as a systematic change”(3).

Protocol compliance has been a delicate issue in the management of clinical research projects.

Non- compliance to protocol occurs because the research team may not be adequately trained and educated to understand their role in the ethical conduct of research and the need to adhere to the regulations and the study participants for their ignorance and poverty (4). Poor compliance to protocol may lead to unreliable, misleading, conflicting and invalid results. In clinical trials, it may reduce the benefit to the research participants or increase the risk of treatment failure. The therapeutic procedures and the drug treatment mentioned in the protocol follow the standard treatment guidelines, if there are some serious deviations, the study may become non-scientific and unethical (5).

The role of Ethics committee can be very challenging in identifying the protocol non-compliance. It can be carried out passively by reviewing the documents submitted by the investigators to the institutional ethics committee which includes protocol deviation form, study continuing review form and the study completion reports or actively by visiting the clinical trial sites (6). Non-compliance, protocol violations are often under reported by the study team. It is the responsibility of the ethics committee to monitor the activities of approved studies for ethical conduct and adherence to the approved protocol (7). No studies that actively looked for protocol noncompliance were reported in the literature. Against this background, the study was conducted to detect whether the research studies adhered to the approved protocol with respect to the methodology.

**Methods:**

Study protocol was approved by Institutional Ethics Committees (IEC-I and IEC-II) at Seth G.S. Medical College and KEM Hospital.

This was a retrospective observational study. The study involved evaluating all the clinical projects which were completed, and the study completion reports were submitted to the Institutional Ethics Committee for review for the period January 2017 to December 2017. These study completion reports were compared with the approved protocol or protocol amendment to identify non-compliance. The projects which we considered to review comprised of dissertation of post-graduate students, studies other than thesis, government funded research projects and pharmaceutical industry sponsored studies.

The objective of the study was:

1. To assess the proportion of protocol non-compliance
2. To evaluate the aspects of protocol that are non-compliant

We developed a checklist to determine whether the principal investigators remained complaint to the protocol or not. The checklist for recording protocol noncompliance was developed using Standard Operating Procedures (SOPs) of KEM Hospital, Declaration of Helsinki 2013 and ICMR guidelines 2017. This checklist had various points which form an integral part of protocol, e.g. study objective, study duration, sample size, inclusion and exclusion criteria data collection tool and technique, mode of treatment, concomitant therapy, efficacy variables, safety reporting, and the statistical tests used (Annexure 1). Any discrepancies observed in these items were noted in the checklist and ticked as ‘Yes’, ‘No’, ‘Insufficient information’ or ‘Not applicable’. The content of the checklist was validated by 5 experts which consisted the members of Institutional Ethics Committee.

No formal sample size calculations were made for the study. All the clinical projects study completion report which were submitted to Institutional Ethics Committee, KEM Hospital for the period January 2017 to December 2017 were selected. The reason for selecting this period was that, the Institutional Ethics Committee, KEM Hospital had adopted a policy of submitting detailed study completion reports as mandatory from the year 2016. Thus, it was possible to compare different aspects of the study protocol with completion reports.

**Statistical analysis:**

The data was expressed as percentages and frequency. Descriptive statistics was used to analyze the data. Strict confidentiality was maintained during the data review and analyses.

**Results:**

For the study, the documents reviewed were study protocol or protocol amendment which ever was applicable and study completion reports. 2 investigators reviewed the documents separately. In case of non-agreement on any point between these 2 investigators, the study team members came together for discussion to resolve the conflict

***Type of studies.* (Figure 1)**

A total of n=193 clinical study completion reports were evaluated which were submitted during the period January 2017 – December 2017. Observational studies formed majority of the studies at n = 120 (62.17 %) which included both cross-sectional studies as well as prospective observational studies. The retrospective observational studies were the second most common with n = 39 (20.21%) followed by interventional studies n = 28 (14.51 %) and observational studies with both prospective and retrospective study design n = 6 (3.11%).

***Non-compliance to aspects of protocol.* (Table 1)**

Of the N = 193 studies, the study objective was modified in n=18 (9.32%) studies, n = 112 (58.03%) remained compliant to the study objective and n = 63 (32.64%) studies did not give enough information in the study completion report to evaluate whether the objective was modified or not.

Further, only n = 14 (7.24%) out of N=193 studies, modified the selection criteria and n = 165 (85.49%) followed strictly the inclusion – exclusion criteria as per the study protocol. However, n = 14 (7.24%) gave inadequate information in the report.

Of all, n = 6 (3.10%) studies did not collect the data as mentioned in the protocol, however most the studies up to n = 186 (96.37%) did follow the data collection method and only n = 1 (0.5%) did not provide adequate date to confirm whether the data collection tool was followed as per protocol.

With regards to the sample size, n = 135 (69.94%) achieved the calculated sample size as mentioned in the protocol. On the other hand, n = 58 (30.05%) did not achieve the sample size out of which 40 studies has sample size lesser than the calculated sample size stated in the protocol.

We found that n = 115 (59.58%) was complaint for the study duration as per the study protocol, whereas n = 78 (40.41%) did not complete the study as per the study duration.

We found 180 protocol deviations in this study, however, only 14 protocol deviations were reported by the principal investigator.

As per the other items in checklist which are specific to interventional studies like randomization, blinding, efficacy variables, safety variables, rescue therapy and withdrawal criteria, all 28 interventional studies (as these aspects are not applicable for observational studies) showed 100 % compliance.

**Discussion:**

The present study being a retrospective observational study to evaluate compliance to various aspects of protocol as submitted to institutional ethics committee shows that different aspects of the protocol were not adhered while carrying out the study.

Protocol deviations may affect scientific integrity or affect safety or wellbeing of the participants. Hence guidelines state that the investigator should promptly reports to the ethics committee, the monitor and the sponsor deviations from or changes of, the protocol to eliminate immediate hazards to the subjects (8). The authors are members of the ethics committee and while review of completion reports we identified protocol deviations which were not reported by investigators. Also, while carrying out monitoring we came across deviations from protocol. This prompted us to look at the literature, to find original studies on protocol deviations. Thorough literature search revealed the original research in the area of protocol deviation/ non-compliance. However the methods or study designs used by these researchers to identify these protocol non compliances are different i.e. review of published clinical trials (9), study monitoring reports (10,11) or review of deviations submitted to IECs (5,12) etc. A study conducted by *Jones et al* who evaluated 45 monitoring reports found that end point deviations (38%) and ICD deviations (17%) were common (10) and *Yashashree et al* identified Informed Consent Document (ICD) related violations in 8 of the 12 sites monitored by them (11).Whereas a study conducted by *Jalgaonkar et al* which evaluated protocol deviation reports submitted to IEC, reported maximum study procedure related deviations (68%) of the total deviations reported to IEC (12). Submission of completion report for the study is after completion of the study and is at the final stage of the study. We did not find any study actively studying protocol deviation that are unreported by investigators at the final stage of the study. Thus, we planned the study where we evaluated the completion reports and identify the protocol non compliances.

Study objective states the overall aim of the study. A clearly defined objective directs the researcher to discover answers to questions through application of scientific procedures. In our study, we found that 9.32% modified the study objectives. For example, the study objective was to determine a ‘correlation’ between two variables, the study objective was modified to determine the ‘association’ between the variables. Further, in other study, the objective was to study the ‘prevalence’ of a particular outcome, the objective was changed to ‘proportions’. Also, in few other studies, the number of objectives stated in completion reports were more than the number of objectives stated in the protocol.

In our study we found that 32.64% of the studies did not give enough information regarding study objectives in the study completion report. The study completion report according to ICH guidelines must mention the salient features which include study objectives (8). The lack of this component in high number of submitted completion reports indicate that there is a need for changing practices in institutional ethics committee regarding submission of completion reports. It is necessary to physically ensure that important components of the study are stated in the completion reports before they are accepted for review. Also, ethics committee members need to review these completion reports thoroughly and ask for relevant information from the study team.

Inclusion and exclusion criteria are one of the most critical aspect of the protocol. It helps identify the right research participant for the study. Any violation in the eligibility of the right research participant questions the validity and ethical conduct of the study (13). Similar findings were observed in 7.24% (n=14) studies in this study. To enumerate, few inclusion criteria were not considered while recruiting the research participants. In one study, the research participant enrolled into the study were beyond the age group that was mentioned in the protocol. Out of the 14 studies that breached the selection criteria we found that 2 studies were interventional studies. As breach in selection criteria can directly impact the safety of the participants especially if the study is interventional in nature, we identified the investigators and reprimanded them to undergo retraining in GCP. Also, their ongoing interventional studies were tagged for monitoring.

Data collection tool helps in achieving the aims and objectives of the research study. We found that the data collection tool stated in protocol and study completion report to be different in about 3.10 % of the studies. In these studies, the variables evaluated in the protocol and the study completion report were not the same.

Data analysis tool were found to be modified in 6.73% of the studies where different statistical tests were applied than the ones mentioned in the protocol. For e.g. tests for association was used as per the completion reports instead of tests for correlation. Also, statistical tests were used that were not specified in the protocol, for example, test for regression was specified as a statistical test to be used, however, the same it was not applied.

With reference to sample size, we identified that the sample size stated in protocol and study completion report did not match. 58 studies did not achieve the sample size as calculated in the protocol which constitutes 30% studies. Whereas, there were 40 studies in which the sample size achieved was less that is 20% of the studies. This finding raises serious concern on scientific validity of the findings as taking lesser sample size than was planned may reduce the power of the study. Such studies are difficult to be inferred to the reference population. In a similar study conducted by An-Wen Chan et al in 1994-1995 in Denmark found that 11/62 trials described the sample size estimation consistently in the protocol and publication (14).

Out of 193 studies, 40.41% of the studies did not complete the study as per the study timelines specified in the protocol when compared with the study completion reports. This finding indicates that there may be reduced relevance of the study findings due to undue increase in time to complete the study.

Above all this, when the number of protocol deviations reported to the institutional ethics committee by the investigators were evaluated, we realized that meagre 14 protocol deviations were reported voluntary by the investigator’s contrary to the 180 deviations that were identified in all the 193 studies that submitted completion reports in the year 2017.

However, in contrast to the observational studies, the compliance to the protocol of interventional studies was satisfying. These studies remained compliant to study design with respect to randomization and blinding procedures. This also implies adequate measures were taken to reduce the bias in the study population. The efficacy and safety variables were evaluated as stated in the protocol and the same was reflected in the study completion report. The rescue therapy was followed throughout the study duration as described in the protocol, similarly the withdrawal criteria was followed as and when the situation arises during the conduct of the study.

The study is limited by the fact that it was a retrospective study and the studies whose completion reports were reviewed had completed the study. Had the study been a prospective wherein the studies were actively monitored, we would be able to capture the non-compliance issues at the earliest without jeopardizing the patient’s safety and maintaining the overall ethical and scientific conduct of the study. Furthermore, it was not possible to contact each investigator to ascertain specific reasons for being not compliant to the study protocol which would have helped develop mitigations for prevention of future occurrence of protocol non-compliance. Another important aspect after identifying the protocol noncompliance is to analyse its impact on patient’s safety & data integrity which is not assessed in this study. A study by *Ghooi et al* categorized the protocol deviations in five grades (5). The authors reported that when PDs were analysed on the basis of their impact, it was noted that deviations with minimum impact had high incidence, whereas those with maximum impact were very few. The other studies quoted above, have not only used different methodologies but in each of these studies authors have categorised observed protocol noncompliance in their own categories thus indicating the fact that there is no uniform classification system for protocol deviations. For this reason it was difficult for us to compare these studies with our study.

**Conclusion:**

This study highlights the need to create awareness amongst the study team members about the non-compliance to study protocol and its implications. There is a need to sensitize the investigators in their early post graduate training about protocol compliance and Good clinical practice. They also need to be trained with respect to seeking institutional ethics committee approval for protocol amendments and timely reporting of non-compliance. A little more effort from the ethics committee members for being extra vigilant and ensuring the study completion reports submission is as per the guidelines. The institutional ethics committee members need to improvise on adequate monitoring and review practices of the documents for detecting protocol non-compliance.

Conflict of interest : *None*

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Competing Interest: *The authors declare no competing interest.*

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**Figure 1: Type of study designs**

**Table 1: Aspects of protocol that are non-compliant (N=193)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sr. No.** | **Aspects** | **Yes**  **(n)** | **No**  **(n)** | **Insufficient information**  **(n)** |
| 1 | Objective Modified | 18 | 112 | 63 |
| 2 | Selection criteria Modified | 14 | 165 | 14 |
| 3 | Data collection tool Modified | 6 | 186 | 1 |
| 4 | Data analysis tool modified | 13 | 175 | 5 |
| 5 | Sample size compliance | 135 | 58 | - |
| 6 | Study duration compliance | 115 | 78 | - |

**Annexure 1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Points to be checked in the study report** | **Yes** | **No** | **NA** | **Insufficient**  **Information** |
| * Was there any alteration with the objective after initiation of the study |  |  |  |  |
| * Were new objectives added in the study |  |  |  |  |
| * Was the sample size achieved?   less  more  or  enrolled than approved by EC |  |  |  |  |
| * Was the inclusion and exclusion criteria stringently and scientifically followed |  |  |  |  |
| * Was the data collection tool carried out in the manner mentioned in the protocol |  |  |  |  |
| * Whether the following point followed * Study design * Blinding * Randomization |  |  |  |  |
| * Was rescue therapy given as stated in the protocol (if given) |  |  |  |  |
| * Was the reason for withdrawal of patient (if any) according to the withdrawal criteria stated in the protocol |  |  |  |  |
| * Were the methods followed to achieve the efficacy variables were in accordance with the protocol |  |  |  |  |
| * Were methods to assess safety and tolerability of the drug were in accordance with the protocol |  |  |  |  |
| * Was the data analyzed in the manner mentioned in the protocol |  |  |  |  |
| * Was the study completed as per the time mentioned in the protocol |  |  |  |  |