UTS IMPACCT Trials Coordination Centre

Standard Operating Procedure

4.5 Protocol Deviations and Violations

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Introduction/Background

Where there is poor compliance with the study protocol, regulatory authorities can reject the data, patient safety can be compromised, and indemnity may not apply.

It is the responsibility of the study Sponsor to ensure compliance with the study protocol. It is essential to record deviations and violations that occur throughout a study so that they can be identified easily and reviewed by the appropriate trial sub-committee. Unavoidable violations may indicate previously unanticipated problems with the study design and if identified early, steps can be put in place to amend the protocol.

Objective

This SOP describes the process for the recording and reporting of protocol deviations and violations. It describes what considerations must be taken into account to assess whether the deviations/violations also meet the requirements for reporting. This SOP also describes how violations are assessed and what remedial or corrective actions are to be applied.

Scope

This SOP applies to all staff involved in clinical studies conducted by the IMPACCT Trials Coordination Centre (ITCC) including Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Symptom Trials (CST), irrespective of individual organisational employment, role, or position.

Ownership and Responsibility

The Principal Investigator and study Sponsor are responsible for recording and reporting of any protocol deviations and/or violations. The task may be delegated to another suitably trained individual, but the responsibility remains with the Principal Investigator and study Sponsor.

Delegation of duties by the Principal Investigator must be recorded in the Staff Signature and Delegation Log (*refer* SOP 4.2.4 Delegation of Duties) prior to the task being undertaken, and only after the designee has completed the relevant study-related training.

Procedure

1. Protocol deviation

A protocol deviation is usually an **unintended** departure from the expected conduct of the trial (with regards to the protocol and/or SOPs). These events may be identified by the trial team during trial conduct and must be continually monitored by the Principal Investigator for repeated occurrences.

The majority of these events are minor and administrative or technical deviations that do not result in harm to the trial participants or significantly affect the scientific value of the reported results of the trial.

All such cases must be **documented in the source documentation or study File Note and in the appropriate electronic Case Report Form (CRF) in the database** and *appropriate corrective and preventative action must be taken to ensure they do not recur*.

Examples of deviations may include, but are not limited to:

- a protocol visit date deviation outside the study visit window, or a visit not conducted that does not have an effect on patient safety or efficacy implications;
- isolated incident of a missed or incomplete study procedure (e.g. laboratory test or completion of a questionnaire) that does not have an effect on patient safety or efficacy implications;
- isolated incident of a missed or incomplete study evaluation (e.g. exam) that does not have an effect on patient safety or efficacy implications.

2. Protocol violation

A protocol violation is **any** departure from the requirements of Good Clinical Practice, the approved clinical trial protocol, trial documents, or any other information relating to the conduct of the study which has the potential to significantly impact the safety or rights of trial participants or the reliability and integrity of the study data and the study outcomes.

Protocol violations are considered to be major deviations and can sometimes be defined as a serious breach. All violations must be reported to the Sponsor as well as to the approving Human Research Ethics Committee (HREC) if it meets the reviewing criteria defined by the committee. The general consensus amongst Australian HRECs is that protocol violations are those variations to a protocol that implicate participant consent, participant safety or data integrity that compromises the ethical acceptability of the project, and, thus, require retrospective notification to or review by a HREC.

Examples of violations may include, but are not limited to:

- failure to obtain informed consent (i.e. there is no documentation of this in source data or a signed Informed Consent form);
- enrolment of participants that do not meet the inclusion/exclusion criteria;

- undertaking a trial procedure not approved by the HREC (unless for immediate safety reasons), or HREC approval not obtained or incomplete (*refer* SOP 6.12 Ethical approval);
- failure to report adverse events, serious adverse events or suspected unexpected serious adverse reactions (SUSARs) in accordance with the legislation and sponsor and protocol requirements;
- investigational product dispensing/dosing error.

3. Persons responsible

The Principal Investigator is responsible for:

- Recording and reporting any deviations and violations to the ITCC as soon as the deviation/violation is identified using Template 7: Protocol Deviation/Violation Report Form.
    - In addition, for violations deemed to be a potential serious breach or an urgent safety measure, the Principal Investigator is to report the violations to the approving HREC and/or local Research Governance Office (RGO) as per the requirements of the committee and local site policy.
    - The definition of protocol deviation and violation may differ between different HRECs so sites should always consult and follow the reporting timeline and procedures specified by the relevant committees when reporting deviations/violations to the approving HREC and/or RGO.
    - Protocol deviations or violations that are anticipated to occur need prior approval from both the Sponsor and the approving HREC.
        - For example, if a potential participant does not meet, or only partially meets, one of the eligibility criteria, the inclusion criteria cannot be waived without prior approval of the HREC unless this is to address immediate safety considerations or if changes involve only logistical or administrative aspects of the trial.
        - In cases where a deviation occurred to eliminate immediate hazards to participants, the deviation should be reported to the HREC retrospectively as soon as possible after the event occurred.

The ITCC National Project Officer/Monitor/Designee is responsible for:

- Ensuring all protocol deviations reported by the site, including those identified during monitoring activities are adequately recorded in the source documentation/participant files and eCRF.
- Logging all violations on a Protocol Violation Log, assigning a de-identifying ID number, and completing a Protocol Violation Form with a code for the violation.

- Ensuring that the violations are reviewed by an appropriate committee and the decisions recorded. Updates to the eCRF in the study database may also be required.

The Coordinating Principal Investigator (CPI), along with the appropriate committee, is responsible for:

- Reviewing and assessing each protocol violation and to ensure that a decision about the violation with respect to the integrity of the study data is made.

4. Identification of deviations and violations

The judgment on whether a deviation meets the definition of a violation and is likely to have a significant impact on participant safety and affect the scientific value of the trial depends on a variety of factors (e.g. the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis, etc.).

Once a deviation or violation has been identified, it is important that the site notifies the ITCC of what corrective and preventative actions they have taken so that a formal plan of corrective and preventative actions can be devised.

Other deviations or violations can be identified during on-site monitoring visits, or through central monitoring (*refer* SOP 5.18 Monitoring, or protocol specific Monitoring Plan). Deviations are recorded in the Corrective Action Sheet. Violations are recorded using the monitor Protocol Violation Form (Template 8).

4.1 Deviations

Recording: Deviations are recorded in the participant data collection worksheet (*refer* SOP 5.23.2 Data Collection Worksheet Completion), study File Note (*refer* SOP 4.9.2 File Notes), other source documentation, in the electronic Case Report Form (eCRF) in the database, and/or an email discussion.

Appropriate records should be kept in the essential documents (for example if staff training, a change to internal procedures, etc., are required) (*refer* SOP 8.0 Essential Documents), or in the patient's study records (study folder). Any corrective and preventative action should also be documented and retained in the site file.

Reporting: To fulfil ICH GCP requirements, any protocol deviation is required to be reported to the Sponsor. Deviations are reported by the site to the Sponsor through data entry in the eCRF and by email (as required).

4.2 Violations

Recording: Violations are recorded in the participant data collection worksheet or other source documentation, in the eCRF, Protocol Violations Log and study File Notes, if necessary.

Reporting: Violations of Good Clinical Practice (GCP), protocol and regulations must be reported to the Sponsor within three calendar days of staff becoming aware of that violation. Violations, if identified by the site, are to be reported to ITCC using the protocol Deviations/Violations Report Form (Template 7) for further assessment and onward reporting if required.

Sites should report violations including serious breaches to the approving HREC and/or local RGO as per the requirements of the committee and local site policy.

Escalation: Corrective and preventative actions should be implemented for violations.

- If the violation is determined to be a potential safety concern or meets the reporting criteria of the approving HREC, this violation must be reported to the competent authority and HREC within regulatory timelines.
- If the violation is identified by the ITCC during remote or on-site monitoring, the violation is to be recorded within the Corrective Action Sheet (if appropriate) and completion of a Protocol Violation Form (Template 8) and then logged into the Protocol Violation Log. The CPI is notified of the violation via email of the Protocol Violation Form. The CPI may then form a sub-committee based on the seriousness of the violation. Retrospective reporting of the violation by the Principal Investigator to the approving HREC and/or RGO may be required depending on the requirements of the committee and local site policy.
- A violation may trigger a monitoring visit. All major violations must be resolved to conclusion. Depending on its nature, the violation may constitute a Serious Breach of Good Clinical Practice (GCP) and further follow up and reporting may be required by the ITCC in line with current regulations.

Reoccurring violations must be discussed at any meetings with the site team and/or at the relevant Scientific Advisory Committee and detailed in the clinical study report (if required).

4.3 Assessment by the ITCC

The ITCC will form a Trial Sub-Committee to consider study specific protocol violations. If there is more than one violation, these will usually be discussed in a batched manner, unless the Principal Investigator considers any individual violation serious enough to form a specific meeting urgently.

The Trial Sub-Committee will generally consist of the following members:

- Chair of the PaCCSC/CST Trials Management Committee
- The study CPI, unless the CPI is also the Principal Investigator where the urgent protocol violation occurred

- The study statistician
- At least one other clinician/protocol investigator with expertise who can assess the clinical implications of the violation
- PaCCSC/CST National Manager and/or ITCC National Project Officer.

4.3.1 Corrective and Preventative Actions (CAPA)

The Trial Sub-Committee must agree on the appropriate corrective and preventative action to be taken and this should be documented and detailed within the body of the initial notification report.

Follow-up reports

Follow-up reports should be made in writing and should:

- be clearly identified as a follow-up report
- identify the unique ID allocated when the initial report was generated
- document the outcome of the decision
- detail any follow-up to the discussion (e.g. additional site staff or Principal Investigator training, exclusion of the participant data, protocol amendment)
- be placed in the central record of the participant file.

4.3.2 Escalation and dissemination process

Internally:

The protocol violations or the summarised outcomes are reported to the following committees:

- Relevant Scientific Advisory Committee
- Relevant trial Data Safety Monitoring Committee (if the protocol violation is considered to be a breach of participant safety and/or will impact on the overall quality of the study data).

Externally:

External reporting will be dependent on the nature of the violation and may include reporting to Ethics Committees, local RGO, other sites and pharmacies affected etc.

The violation should be circulated to relevant staff so that it is included as relevant information in the study report or publications. Serious violations relating to investigator sites, laboratories, etc., should also be made available to relevant staff during the process of site selection for future studies (i.e. careful assessment should be made before using a non-compliant site in future studies).

Related SOPs

4.2.4 Delegation of Duties

4.9.2 File Notes

5.18 Monitoring

5.23.2 Data Collection Worksheet Completion

6.12 Ethical Approval

8.0 Essential Documents

Related documents

Template 7: Protocol Deviation/Violation Report Form

Template 8: Protocol Violation Form

References

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). November 2016 (accessed 23/10/2017)

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

NHS Lothian and The University of Nottingham, Academic and Clinical Central Office for Research and Development Standard Operating Procedures. Management of Protocol Deviations and Violations. 24 Feb 2011.

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 17/10/2017)

https://www.tga.gov.au/sites/default/files/ich13595an.pdf

Praxis Australia

History			
Version	Date	Author	Reason
1.1	23/02/2016	B Fazekas	New procedure
1.2	28/02/2018	B Fazekas, S Kochovska	Periodic review Publication of the ICH GCP E6 (R2)
1.3	16/03/2020	C Strauss	Periodic review
1.4	06/01/2022	C Strauss	Periodic review

Approval		
Version	Approval Name	Approval Signature
1.4	Meera Agar