



## Standard Operating Procedures

### 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 change 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 PaCCSC 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 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 appropriate Case Report Form (CRF) or study File Note** and *appropriate corrective and preventative action must be taken to ensure they do not recur*. In addition, a notation within the database may be required.

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

- A case where a potential participant does not meet, or only partially meets, one of the eligibility criteria, and the issue has been discussed with the Lead Investigator or PaCCSC Coordinating Centre and it has been agreed that the participant can proceed;
- A protocol visit date deviation outside the study visit window, or not conducted;
- Isolated incident of a missed or incomplete study procedure (e.g. laboratory test or completion of a questionnaire);
- Isolated incident of a missed or incomplete study evaluation (e.g. exam).

### 2. Protocol violation

A protocol violation is **any** departure from the approved protocol, trial documents, or any other information relating to the conduct of the study which may affect the safety of trial participants or the study outcomes.

Any violations that may impact on the participants' safety or affect the integrity of the study data must be reported to the Sponsor and the approving 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/violations to the PaCCSC Coordinating Centre as soon as the deviation/violation is identified using the Protocol Deviation/Violation Report Form.
  - In addition, if these are deemed a potential serious breach or an urgent safety measure, the Principal Investigator is to report the deviations/violations to the approving HREC.

The PaCCSC National Project Officer is responsible for:

- Logging all violations on a Protocol Deviation/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 study database may also be required.

The Lead Investigator, 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 is likely to have a significant impact on 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/violation has been identified, it is important that the site notifies the PaCCSC Coordinating Centre of what corrective and preventative actions they have taken so that a formal plan of corrective and preventative actions can be devised. The site uses the Protocol Deviation/Violation Report Form to report self-identified issues (Template 7).

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

#### 4.1 Deviations

**Recording:** Deviations are recorded in the Case Report Form (CRF) (*refer* SOP 5.23.2 CRF Completion), study File Notes (*refer* SOP 4.9.2 File Notes), as a notation in the database, and/or an email discussion.

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



## 4.2 Violations

**Recording:** Violations are recorded in the Case Report Form (CRF), protocol Deviations/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 3 calendar days of staff becoming aware of that violation. Violations, if identified by the site, are to be reported to PaCCSC using the protocol Deviations/Violations Report Form for further assessment and onward reporting if required.

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

- If the violation is determined to be a potential safety concern this must be reported to the competent authority and HREC within regulatory timelines.
- If the violation is identified by PaCCSC Coordinating Centre during remote or on-site monitoring, the violation is to be recorded within the corrective action sheet (if appropriate) and a completion of a Protocol Violation Form and then logged into the Protocol Deviation/Violation Log. The Lead investigator is notified of the violation via email of the Protocol Deviation/Violation Form. The Lead Investigator may then form a sub-committee based on the seriousness of the violation.
- A violation may constitute a triggered 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 maybe required by PaCCSC Coordinating Centre in line with current regulations.

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

## 4.3 Assessment by PaCCSC

PaCCSC 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 Trials Management Committee;
- The study Lead Investigator, unless the Lead Investigator 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 National Manager and/or 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 (the Protocol Deviation/Violation Form can also be used for this) 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. further site or Principal Investigator training, removal 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 PaCCSC committees:

- Trial Management Committee;
- Scientific Committee;
- Management Advisory Board;
- 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).

The issues resulting from the considerations of violations will also form an agenda item for Site Coordinator Teleconferences or meetings.

##### **Externally:**

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

The breach 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 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).



### **Other related SOPs**

- 4.2.4 Delegation of Duties
- 4.9.2 File Notes
- 5.18 Monitoring
- 5.23.2 CRF Completion
- 6.12 Ethical Approval
- 8.0 Essential Documents

### **Other 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](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)

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<b>History</b>			
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)

<b>Approval</b>		
Version	Approval Name	Approval Signature
1.2	David Currow	