

# Standard Operating Procedure



## Protocol Deviations, Non-Compliance and Serious Breaches Clinical Trials

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It is the responsibility of all users of this SOP to ensure that the correct version is being used. The definitive versions of Noclor SOPs are available from the Noclor website <https://www.noclor.nhs.uk/training-resources> either by checking the document library or by carrying out a specific document search

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## Version History

SOP Reference ID	Effective Date	Reason for Change
SOP CA006 Version 1.0	14/04/2009	
SOP CA006 Version 2.0	18/11/2011	Administrative change from Camden PCT to CNWL NHS Foundation Trust (Camden Provider Services). Minor revisions/clarifications to procedures.
Noclor/Spon/S10/01	01/03/2016	Newly created Noclor SOP (applicable to all Noclor partner NHS Trusts). New numbering system adopted so this SOP has been assigned first version. New SOP format and revised procedures to include recording and reporting of protocol deviations, violations and non-compliance.

## Authorship and Authorisation

Author Job Title:	Noclor Sponsor Representative		
Reviewed by:	Noclor Senior Management Group	Date:	10 <sup>th</sup> February 2016
Authorised by:	Lynis Lewis, Noclor Service Director		
	Signature:	Signed copy held by Noclor	Date: 15 <sup>th</sup> February 2016

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## 1. Purpose

Clinical trials should be managed and conducted in accordance with the approved protocol, sponsor Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the relevant regulations (as applicable). Departures from the protocol and procedures can usually be categorised according to seriousness and type of departure into protocol deviations, minor or major violations and serious breaches.

Directive 2005/28/EC as implemented in the UK by SI 2006/1928, amending the Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031), requires Sponsors to notify the MHRA in writing of any serious breach of GCP or trial protocol in connection with a Clinical Trial of Investigational Medicinal Products (CTIMP), within 7 days of becoming aware of such a breach. Failure to comply with Sponsor responsibilities for reporting serious breaches is a criminal offence.

This Standard Operating Procedure (SOP) describes the procedures for recording and reporting protocol deviations, protocol violations, non-compliances and serious breaches in clinical trials sponsored by a Noclor Partner NHS Trust.

## 2. Scope

This SOP should be followed by Chief Investigators (CIs) that are responsible for setting up and managing clinical trials (CTIMPs and non-CTIMPs) to ensure that all departures from the protocol, procedures and GCP are recorded and reported in accordance with this sponsor procedures and regulatory requirements (where relevant).

*This SOP does not cover 'all other research' which falls within the scope of the Research Governance Framework for Health and Social Care (2nd Edition) that is sponsored by a Noclor Partner NHS Trust. CIs of non-clinical trial research should refer to the SOP Research Management and Monitoring (Sponsored Research) Noclor/Spon/S06/0X for information on how deviations, incidents and non-compliance for non-clinical trials should be recorded and reported.*

## 3. Abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File

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## 4. Procedure and Responsible Personnel

The clinical trial protocol (and supporting trial procedures where relevant) should document the procedures for Investigators to follow for recording and reporting of departures from protocol, trial and sponsor procedures/GCP and serious breaches. For CTIMPs, Principal investigators (PIs) should be trained in the procedures at the Site Initiation Visit (SIV).

Monitoring systems and quality control checks should be implemented within a clinical trial to identify any departures from the protocol/procedures (these systems and checks should be documented in the trial-specific monitoring plan). Mechanisms should be put in place (as part of the clinical trial data management plan) to take in to account any protocol deviations and non-compliances in the end of study report.

The Chief Investigator (CI) is responsible for the overall management of deviations/non-compliances within their clinical trial and escalating to sponsor according to this SOP where instructed. The ultimate assessment of the seriousness of a violation/non-compliance will be made by the sponsor (in discussion with the CI).

	Procedure	Responsible Personnel
4.1	<p><b>Protocol Deviations</b></p> <p>Unintended (non-serious) departures from the approved protocol would be considered 'protocol deviations'; they are usually identified retrospectively through monitoring and data validation of CRFs.</p> <p><i>An example of a protocol deviation could be: a study visit date being outside the window defined in the protocol.</i></p> <p>4.1.1 Protocol deviations do not require routine reporting to the sponsor, they should be recorded on the protocol deviations, violations &amp; non-compliance to GCP log Noclor/Spon/T04/01 as <u>Category 1</u> and retained at site in the Investigator Site File (ISF)</p> <p>4.1.2 The log should be provided to the CI/sponsor on request for monitoring/audit purposes</p> <p>4.1.3 The Chief Investigator and study oversight groups should continually monitor protocol deviations to establish whether an amendment to the protocol or further training is required to prevent escalation into more serious violations or breaches. It is the responsibility of the CI/ PI to train the research team (as delegated) on the trial protocol to avoid repeat deviations.</p>	Chief Investigator(CI)/ Principal Investigator (PI)

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<p>4.2</p>	<p><b>Protocol Violations/ Non-Compliance</b></p> <p>A <u>minor protocol violation or non-compliance</u> is any deviation from the protocol, study or sponsor procedures that is not approved by the sponsor/REC/MHRA prior to its implementation that does not impact on the subjects' safety or compromise the integrity of study data. However if left unreported could lead to more major violations /non-compliance issues further down the line.</p> <p><i>An example of a minor violation could be: missing original signed consent forms (only photocopies present in ISF)</i></p> <p>A <u>major protocol violation or non-compliance</u> is one that may impact on the participant safety or affects the integrity of the study data.</p> <p><i>Examples of major violations are :</i></p> <ul style="list-style-type: none"><li>○ <i>Failure to obtain informed consent (no evidence)</i></li><li>○ <i>No evidence of medical assessment of eligibility of participant in being enrolled in a CTIMPs</i></li><li>○ <i>Subject does not meet the eligibility criteria for the study (protocol waivers are not acceptable)</i></li><li>○ <i>Failure to report SAEs in line with the protocol and sponsor SOPs</i></li></ul> <p><b>Recording and Reporting Protocol Violations /Non-Compliances</b></p> <p>4.2.1 Protocol Violations /Non-Compliances should be recorded on the protocol deviations, violations &amp; non-compliance to GCP log Noclor/Spon/T04/01 as <u>Category 2</u> (protocol violation) or <u>Category 3</u> (non-compliance to GCP, sponsor procedures etc)</p> <p>4.2.2 Reported to sponsor (copied to CI) within 24 hours of becoming aware of the violation/non-compliance using the Non-Compliance Report Form Noclor/Spon/T05/01.</p> <p>4.2.3 The report should be prepared by the person who has identified the violation/noncompliance and signed off by the Investigator (where relevant).</p> <p>4.2.4 The report should be submitted by email (send signed scanned copy of report) to sponsor trial-specific email address and copied to CI for urgent attention referring in the subject of the email as 'Non-Compliance Report'</p> <p>4.2.5 The original report should be retained in the ISF/TMF (as</p>	<p>Chief Investigator(CI)/ Principal Investigator (PI)</p>
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	<p>relevant)</p> <p>4.2.6 The report should include details of Corrective and Preventative actions (CAPA) as relevant to the event.</p> <p>4.2.7 No patient identifiable information should be included in the report.</p>	
4.3	<p><b>Confirmation of Receipt</b></p> <p>Noclor Sponsor Representative will assign a unique sponsor reference to the report and confirm receipt (by email). This confirmation should be retained with the report in the ISF/TMF (as relevant). The unique sponsor reference should be used in all future correspondence regarding the reported non-compliance.</p>	Noclor Sponsor Representative
4.4	<p>Non-compliance reports received will undergo prompt initial assessment by Noclor/CI to confirm that the violation does not constitute:</p> <ul style="list-style-type: none"> <li>▪ an Urgent Safety Measure (USM) -a measure has been implemented without prior authorisation by the REC (and MHRA where applicable) in order to protect clinical trial participants from any immediate hazard to their health and safety. Refer to Noclor/Spon/S08/0X</li> <li>▪ a <u>serious breach</u> which would require further investigation and escalated reporting. <b>See 4.6</b></li> </ul>	Noclor Sponsor Representative/Chief Investigator (CI)
4.5	<p>For violations/non-compliances reported and <u>determined as not</u> being a serious breach or USM</p> <p>4.5.1 the sponsor (in communication with CI and where required with site also) will complete the 'For sponsor use only' section of the Non-Compliance Report Form Noclor/Spon/T05/01</p> <p>4.5.2 Where appropriate the non-compliance may trigger a 'for cause' on-site monitoring visit or audit</p> <p>4.5.3 The non-compliance will be reported by the Noclor Sponsor Representative to other parties as relevant (for example escalated to the host site R&amp;D department to facilitate compliance)</p> <p>4.5.4 The CI will ensure that appropriate corrective and preventative actions (CAPA) are taken (and evidenced) and communicate with sponsor when the 'status' of event is considered closed where relevant.</p>	Noclor Sponsor Representative/Chief Investigator (CI)

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	<p>4.5.5 Noclor will retain a central file and an electronic log (on the Noclor IMS system) of all non-compliances reported across all clinical trials sponsored by a Noclor partner (and clinical trials hosted but not sponsored by a Noclor partner where non-compliances have been flagged up to Noclor). This information will be used to identify any trends in non-compliance [for example the information gathered may lead to termination of an investigator site; assist in identifying training needs or inform feasibility assessments/selection of sites/PIs in future studies etc).</p> <p>4.5.6 The IMS system will be used to track status of CAPA plans and report non-compliance as required</p> <p>4.5.7 the CI will circulate non-compliance reports as required to the relevant parties involved in study oversight through agreed mechanisms (as documented in Charters/ToR)</p> <p>4.5.8 the CI will retain all information pertaining to deviations/violations/non-compliances in the TMF</p> <p>4.5.9 the CI will take into account any non-compliances in the end of study report</p>	
4.6	<p><b>Serious Breaches</b></p> <p>A 'serious breach' is defined as a breach likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial</p> <p>Making a judgment on whether a potential breach or non-compliance (or persistent non-compliance) is 'serious' and requires reporting is the responsibility of the Noclor Sponsor Representative. If Noclor fails to discharge the sponsor's responsibilities for CTIMPs in reporting serious breaches within the regulatory timeframes it is a criminal offence.</p> <p>4.6.1 When Noclor have received notification (from whatever source<sup>1</sup>) that a potential serious breach may have occurred the clock starts (Day 1 = day made first aware of potential serious breach).</p>	Noclor Sponsor Representative/Chief Investigator (CI)

<sup>1</sup> The identification of potential serious breaches may come from various sources. Sources are listed here (the list is not exhaustive) : on further investigation of a reported non-compliance/protocol violation; through report/investigation into fraud or misconduct; via a formal complaint or reported incident; flagged by monitoring (review of monitor reports) or central sponsor oversight activities; flagged up at audit notified by external personnel (for example by host site R&D or members of the public); through TSC /IDMC; via central review of meeting minutes and email correspondence; analysis of samples/data.

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If the Noclor Sponsor Representative is not the person to have identified the potential serious breach then they should be the first person that is notified at Noclor. If other members of Noclor staff are notified in the first instance they should ensure escalation directly to the relevant Noclor Sponsor Representative or if in any doubt the Noclor Service Director (*this should be imbedded in their daily working practice at Noclor rather than requiring all members of staff to train specifically in this SOP*).

- 4.6.2 If the evidence is clear that a serious breach has occurred the Noclor Sponsor Representative will notify the REC and MHRA (for CTIMPs) within the 7 calendar days of becoming aware of the breach, and investigate and take action simultaneously (or after notification).
- 4.6.3 In situations where a potential serious breach has occurred but the evidence is not clear, a degree of immediate initial investigation may be required by Noclor Sponsor Representative prior to notification (notification still needs to be within the 7 calendar days timeframe) to confirm that a reportable breach has occurred. For CTIMPs, the Noclor Sponsor Representative may seek clarification from the MHRA on a potential serious breach by contacting the MHRA Clinical Trial Helpline directly.
- 4.6.4 Noclor Sponsor Representative will report serious breaches (for CTIMPs and non-CTIMPs) using the MHRA Template Serious Breach Notification Form (see [MHRA website](#) for up to date guidance on serious breaches and current report template). The report should detail the nature of the event, the impact of the event and any corrective and preventative actions taken (or planned).
- 4.6.5 For CTIMPs, the MHRA will assign the reported serious breach a unique GCP identifier reference. The serious breach may trigger an MHRA inspection if they suspect the law has been broken.
- 4.6.6 Follow-up reports/updates may be required after the initial report (using the same report template form) which should be clearly identified as a follow-up report and will include the unique GCP identifier (for CTIMPs)
- 4.6.7 The serious breach will trigger a for-cause site monitoring visit or audit (as part of the CAPA)
- 4.6.8 Where appropriate the non-compliance will be reported



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further by the Noclor Sponsor Representative (for example to the relevant host site R&D department)

4.6.9 Noclor Sponsor Representative and the CI should ensure that all corrective and preventative actions are appropriate and have been taken (and the breach is closed)

4.6.10 The CI should notifying the relevant study oversight committees and investigator sites of the reported serious breach (providing instruction on any corrective and/or preventative action that has/should be implemented)

4.6.11 The CI must retain copies of serious breach reports and all correspondence relating to a serious breach in the Trial Master File (TMF)

4.6.12 The CI must take into account non-compliance /serious breaches in the end of study report

4.6.13 The Noclor Sponsor Representative will retain a central record of all serious breaches across all sponsored clinical trials using the Noclor IMS system

This system will be used to track and report (internally) serious breaches as required (and will include details of any serious breaches reported to Noclor that relate to Noclor NHS Partner Trust hosted /externally sponsored clinical trials)

## 5. Deviation from SOP

Noclor Sponsor SOPs define working methods which should be adhered to. However, occasionally for specific projects it may be necessary to deviate from the Sponsor SOP.

Formal written explanations/justifications of such deviations must be approved by Noclor Sponsor Representative prior to implementation (or they will be considered a non-compliance to sponsor procedures requiring reporting according to SOP Noclor/Spon/S10/0X).

The deviation from Sponsor SOP should be recorded on the SOP Deviation Form (Noclor/Inter/T12/0X) and sent to the Sponsor Representative for review. A copy of the completed and signed form should be filed with the TMF.

## 6. SOP Storage and Archive

The details of this SOP should be included on the study specific document inventory log (Noclor/Spon/T07/0X).

The Chief Investigator (CI) is responsible for retaining and archiving controlled copies of Sponsor SOPs (and the associated training records) that have been worked to for the duration of a trial in the Trial Master File (TMF).

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## 7. Associated Documents

Document Reference ID	Document Type	Document Title
Noclor/Spon/S08/0X	SOP	Urgent Safety Measures (Clinical Trials)
Noclor/Spon/T04/01	Template	Protocol Deviations, Violations & Non-Compliance to GCP Log
Noclor/Spon/T05/01	Template	Non-Compliance Report Form

## 8. Appendices

UNCONTROLLED DOCUMENT WHEN PH

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## 9. Confirmation of Training

This SOP will be provided to the Chief Investigator (CI) and he/she will have the opportunity to ask specific questions to the author of the SOP.

The CI must e-sign the confirmation of self-training below prior to the study commencing.

The CI is responsible for ensuring that members of his/her study team are trained in the sponsor procedures (SOPs) that are relevant to their specific roles and responsibilities on the study.

I,

confirm that I have read and understood the content of this SOP and will work according to it.

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Controlled copies of Sponsor SOPs should be filed in the relevant section of the Trial Master File (TMF). If this SOP replaces a previous version, the previous version should be retained in the TMF and marked through as superseded.

The SOP details should be added to the document inventory log (Noclor/Spon/T07/0X).

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## 10. SOP Training Log

All members of the co-ordinating trial team concerned by this SOP (according to the role and responsibilities they are being delegated by the CI and as they appear on the co-ordinating trial team delegation log) should sign the SOP training log.

	Full Name	By signing below I confirm that I understand and agree to work to this SOP	
		Signature	Date

This training log should be filed in the relevant section of the TMF.