Guideline number	**51.008C**	Version	**1.0**
Title	**Guidance on Types of Non-Compliance and Associated Documentation**		

The purpose of the following guidance document is to offer clarification on how to choose the appropriate process to capture and resolve the variety of issues that may occur when conducting activities associated with Clinical Research. The contents outlined within this Guidance document will be added to future iterations of the relevant documents, e.g. SOP 51.008, Form 51.016M, etc.

Not all instances will be as a result of a Non-Compliance, some are in place simply to offer additional clarity on activity that has taken place.

In certain scenarios, more than one may apply.

An overview of the different types of Non-Compliances and their relationships to each other is shown below in Figure 1. This also shows that file notes are additional documents not solely used in Non-Compliances but may be used to provide additional clarity regarding a Non-Compliance.

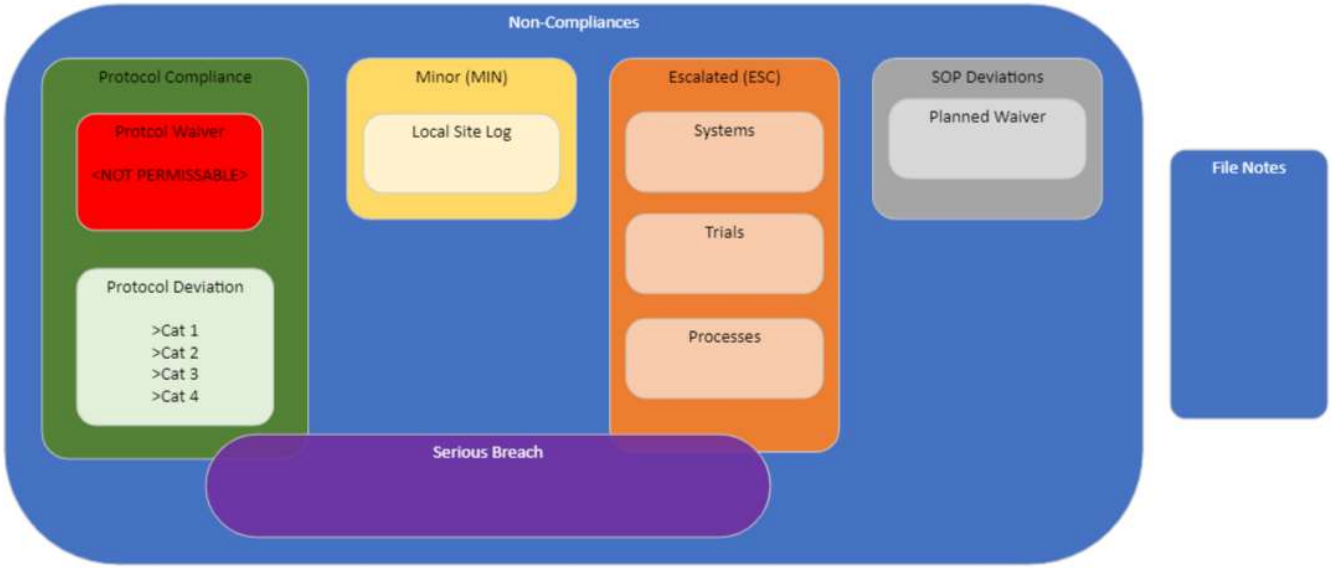

Figure 1 – Non Compliances and File notes

1. SOP Deviation (SOP 01.007)

This is when a planned deviation takes place from that which is detailed within an SOP in the R&I QMS. As standard, all SOPs must be complied with at all times, on occasion in exceptional circumstances it may not be possible to comply. In this event SOP 01.007 may be utilised to seek permission to deviate from an SOP. Any unplanned SOP deviations or exceptions that are discovered – only after the deviation or exception has occurred – must be documented retrospectively. Form 01.007A – Standard Operating Procedures Exception Form can be used for this purpose also. Recurring SOP deviations or exceptions should be flagged to the SOP author for review as the SOP may no longer be fit for purpose. The Form must be completed by the relevant individual wishing to deviate from process or that has identified the deviation and must be signed by the R&I director and stored within Q-Pulse, all forms will be sent to the R&I QA Manager for storage in Q-Pulse and will form part of standard reviews by the R&I QA Manager to identify potential trends.

You may not knowingly deviate from the process outlined within an SOP without initial permission.

2. File Note (Form 51.016M)

A file note is intended to capture details of events that are not immediately apparent to those reviewing the TMF/ISF. A file note cannot be used in place of any of the other processes detailed within this guidance document, but may be used in conjunction with them to provide further clarity. A file note does not cover any form of Protocol Deviation, waiver or breach. For NHSGGC Sponsored /Co-Sponsored trials and studies, a Sponsor representative must sign this document for inclusion in the TMF.

If an existing process exists to document and record decisions or outcomes, a file note cannot be used to replace this as that in turn will result in deviation from SOPs as discussed under point 1, for example file notes should not be used to capture any risks or decision making associated with the conduct of the trial, in this instance the risk assessment should be revisited as per SOP 51.004.

3. Protocol Waiver (SOP 51.008)

A Protocol Waiver is a prospective and planned deviation from an approved protocol for a trial. This is in contradiction to Regulation 29 of SI 2004/1031 and are not permissible. If it is known that the contents of a protocol are not appropriate and cannot be followed then an amendment is required.

n.b. the only course of action is to either follow the protocol as written or submit an amendment to the REC and when appropriate the MHRA.

In the event it is identified that the protocol may not be possible to be followed and this is to be ongoing, this must be identified and recorded as a risk by revisiting the risk assessment. The risks associated if the amendment was not implemented must be documented by the Sponsor R&I Co-Ordinator & relevant team members.

4. Protocol Deviation* (SOP 51.008)

A Protocol Deviation is when the contents of a protocol have not been followed and this has been identified at a later date. It is not permissible to knowingly do so, but in the event the deviation takes place it must be recorded and appropriate actions taken to avoid future occurrence and assess impact to the trial and participants. The degree of seriousness of Protocol Deviations may vary from Category 1 to 4.

Category 1 & 2

Category 1 and 2 deviations must be captured as line listings at site level and presented to the CI and TMG as cumulative lists.

Category 3 & 4

Category 3 & 4 are regarded as more serious due to potential to impact patient safety and/or the integrity of the trial data. Category 3 & 4 Protocol Deviations must be captured on Forms 51.008A & B. The process outlined in these forms covers the CAPA methodology addressing corrective action, root cause & preventative action while assessing impact on patient safety/and or data. If multiple category 1 and 2 occur the CI and TMG should consider whether this should be reported as a category 3 or 4 Non-Compliance due to the number of incidences. Category3 & 4 Non-Compliances may result in the CI being requested to consider a substantial protocol amendment or review trial viability. This will be considered as part of the actions to resolve any Non-Compliance as part of the resulting CAPA.

5. Serious Breach* (SOP 51.009)

A serious breach, as defined in Regulation 29A of SI 2004/1031 is (A) a breach of either the protocol or the principles of GCP which are (B) likely to effect to a serious degree the safety, physical or mental integrity of subjects on the trial or the scientific value of the trial. Both requirements, A and B, must be met to constitute a serious breach.

A – Must meet this criteria to be defined as a breach

B – Must meet this criteria to be defined as serious

If the protocol or principles of GCP are breached but there is no impact to patient or scientific value of the trial then it will be not classed as a Serious Breach, despite the breach of protocol and GCP occurring and will be managed as a Non-Compliance. This may be recorded as a Protocol Deviation or a Non-Compliance before the serious breach is identified. If derived from a Protocol Deviation this record must be retained but contain reference to the Serious Breach reported and the record closed. If derived from an Escalated Non-Compliance this record will be upgraded to a Serious Breach and the original reference retained.

6. Escalated Non-Compliance (SOP 51.008)*

A Non-Compliance, is a failure of a person or organisation to act in accordance with the law, GCP Regulations or policy. If deemed as Category 3 or 4 it will be raised as an escalated Non-Compliance and will be recorded on Q-Pulse (refer to SOP 51.008). This is used to capture all other forms of Non-Compliance e.g., breach of GCP, Protocol Deviations and other processes not detailed above.

For example:

- An unplanned non adherence to SOPs
- A non-serious breach
- System level issues

Although Protocol Deviations are a form of Non-Compliance, they are managed through their own process. Therefore it is not required to raise an escalated Non-Compliance if already captured as a Protocol Deviation.

If an escalated Non-Compliances is deemed Category 1 or 2 this will be recorded on a log at site in the ISF.

n.b. all titles listed above denoted with * make use of the CAPA workflow to investigate and resolve the issues to varying degrees depending on severity.

7. Sponsor Non-Compliances and CRFs/Stakeholders

R&I as Sponsor work in conjunction with a number of different constituent parts as shown in Figure 2, each will have their own process for the recording and management of Non-Compliances.

Depending on the nature of the Non-Compliance, where it originates and the areas of work it impacts it may be appropriate for more than one area to raise a Non-Compliance to address the different areas impacted as shown in Figure 2.

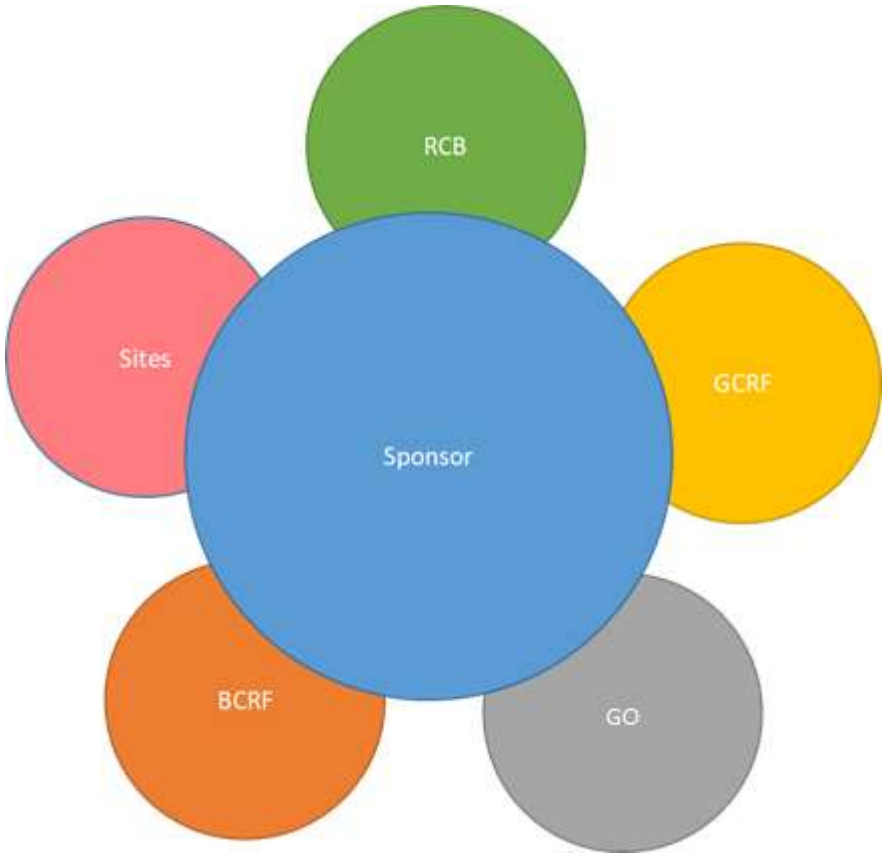

Figure 2 – Sponsor and collaborators

For scenarios when NHSGGC are acting as Sponsor or Co-Sponsor, a Non-Compliance originating in the GCRF or BCRF will be raised and recorded in the GCRF or BCRF following their processes as a participating site. If there is no NHSGGC Sponsor involvement or impact, this may be managed to completion through this process in the same way they resolve Non-Compliances for all of the projects they host for all of the Sponsors they work with. If, however, the nature of the Non-Compliance results in NHSGGC Sponsor involvement, the Non-Compliance will need to be raised through the NHSGGC Sponsor process. The owner of the Non-Compliance within NHSGGC Sponsor team may need the original GCRF or BCRF Non-Compliance to be closed with reference to the new Sponsor number or kept open and managed as part of the NHSGGC Sponsor Non-Compliance to address GCRF or BCRF specific areas while the NHSGGC Sponsor NC address the wider Sponsor level issues. This same principle will be applicable to all sites hosting activity for an NHSGGC Sponsored/Co-Sponsored Trial.

For external sources that are not part of R&I such as GO CTU (Formerly CRUK), RCB or an external vendor, if the issue impacts on NHSGGC as Sponsor it will be appropriate for escalation to NHSGGC Sponsor though Protocol Deviation form or Non-Compliance.

For GO CTU (Formerly CRUK) all internal documentation (Protocol Deviation, file note and Non-Compliance) are signed by the Sponsor representative. For RCB following escalation to NHSGGC as Sponsor the NHSGGC Sponsor SOPs are required to be followed, this does not overwrite RCBs ability to raise and manage their own Non-Compliances. In order to fully address the Sponsors requirements, an escalated Non-Compliance will also need to be raised. The requirement from RCB will be to escalate Non-Compliances to NHSGGC as Sponsor and to engage with the subsequent actions.

Guideline signatories

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Document history

Version	Date	Description
1.0	23/09/2025	First Release

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