Standard Operating Procedure			**51.008**
Handling non-compliance with Good Clinical Practice (GCP) and/or the trial protocol in clinical research sponsored, co-sponsored or hosted by NHS Greater Glasgow and Clyde			
Version	4.0		
Prepared by	Caroline Watson	Signature	Date
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1 SOP Category
NHS GG&C Sponsor R&I

2 Staff Category
- R&I Co-Ordinators
- R&I Director
- R&I Senior Manager
- R&I Research Governance Manager
- R&I Lead Pharmacist Clinical Trials
- R&I Senior Managers
- Pharmacovigilance Managers
- R&I Biorespository team
- R&I Safehaven team
- R&I Innovation team
- R&I Pharmacy team
- R&I Clinical Trial Monitors
- Chief Investigator
- CRF Quality Assurance Lead
- Project Managers
- Clinical Trials Unit (CRUK-CTU) Glasgow staff
- Beatson CRF Head of Trial Co-ordination
- Principal Investigators
- The University of Glasgow Research Governance manager

3 Scope
This SOP applies to all staff engaged in clinical research sponsored, co-sponsored or hosted by NHS Greater Glasgow and Clyde. Principal Investigators may be provided with this SOP for their information, however, it is the responsibility of the CI, Project Managers, Monitors, QA staff and representatives from CRFs to ensure the content of this SOP is included within training provided to Principal Investigators. Under Staff Category individuals are named who have a designated responsibility within the SOP and their role is defined within. Others are named for reference as they are sponsor representatives or NHS employees and need to be aware of the process.

4 Purpose
The purpose of this SOP is to describe the process of reporting, handling and documenting non-compliances in clinical research sponsored by NHS GG&C, co-sponsored by NHS GG&C and The University of Glasgow, or hosted by GG&C. The term Protocol encompasses a Clinical Investigation Plan for Device Trials.

5 Procedures

Non-compliance is defined as "An act, item or result which does not comply with the protocol, standard operating procedures, GCP or Regulatory requirements". A non-compliance may also be as a result of Poor Quality or Fraud in Clinical research as defined in SOP 53.002.

5.1 Reporting Requirements

Any member of staff can report an issue of non-compliance to the Sponsor team or NHS Research Governance.

Any concerns over compliance to GCP, Regulations, Sponsor or Research and Innovation processes or non- compliances relating to the conduct of a study should be discussed with the Research Governance Manager and /or R&I Lead Clinical Trials Pharmacist.

This applies to NHS GG&C research processes supporting research (including R&I departments), and research studies (CTIMP, non-CTIMP and medical device trials) sponsored, co-sponsored and hosted by NHS GG&C.

For clinical research where non compliances are defined as protocol related section 5.4 should be followed.

If issues of non-compliance are highlighted to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist that pertain to a trial hosted within GG&C, then the Sponsor organisation should be notified (via the Principal Investigator (PI) at the site on which the non-compliance occurred or by the Research Governance Manager and/or Lead Clinical Trials Pharmacist).

5.2 Categorising a Non-Compliance

There are a wide variety of issues which can be identified as a non-compliance, each of these issues can be categorised using the criteria detailed below. Non-compliances, suspected to be categorised as 3 or 4 must be immediately escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist. A Sponsor representative may be contacted in the first instance and this should be escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist as appropriate; this can be achieved through e-mail or telephone call. If there is dubiety over which category a non-compliance falls into, err on the side of caution and report the non-compliance which will then be reviewed and categorised by the Research Governance Manager or R&I Lead Clinical Trials Pharmacist.

Category 1:
Issues of non-compliance of an administrative or technical nature are detected that do not compromise patient safety and/or the integrity of the data.

Category 2:
Issues are detected that could affect the conduct of the study but do not constitute a potential serious breach of GCP or the protocol. Category 2 may include issues that have minor impact on patient safety and/or the integrity of the data. However, it is still important to record Category 2 issues as a reasonable volume of the same issue can lead to a Category 3 issue.

Category 3:
Issues are detected that may have a major impact on patient safety and/or integrity of the data. This may include potential serious breaches of GCP and/or the trial protocol.

Category 4:
Issues are detected that have a significant/critical and/or immediate impact on patient safety and/or integrity of the data. This may include life threatening patient safety issues and potential serious breaches of GCP and/or the trial protocol.

Non-compliances relating to research system/process failures, failures to comply with GCP, Regulations, Sponsor SOPs, eligibility; pharmacovigilance processes or GDPR issues must be escalated to the Research Governance Manager as suspected Category 3 or above. GDPR issues should also be reported to Information Governance within the NHS and when appropriate logged on DATIX.

Protocol deviations relating to consent; eligibility; pharmacovigilance processes; data issues relating to primary or secondary endpoints must also be escalated to the Research Governance Manager.

All protocol deviations relating to IMP prescribing, dispensing, administration or accountability must be escalated with the Sponsor Pharmacist and/or the Sponsor Pharmacy Technician for the trial. Any that are suspected to be Category 3 must be escalated to the R&I Lead Pharmacist. Non-compliances relating to laboratories must be escalated to the R&I Lead Pharmacist.

All non-compliances and protocol deviations relating to laboratory issues suspected to be category 3 & 4 must be escalated to the R&I Lead Clinical Trials Pharmacist. Category 1 and 2 laboratory issues should be discussed with the R&I Coordinator, Project PM and R&I Lead Clinical Trials Pharmacist as appropriate.

All escalated suspected category 3 & 4 non-compliances will be logged on the non-compliance log and if the issue is re-classified at a lower category this will be documented on the non-compliance log.

Discussions relating to non-compliances and process can occur at any point with the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist as described above. However, if a non-compliance has occurred and it is suspected of being a Category 3 or 4 or meets any of the criteria above it must be escalated immediately.

5.3 Identifying Non-Compliances

Non-compliances can be identified by anyone involved with research, such as, but not limited to, Sponsor, Site staff, Vendors, Laboratories, R&I Departments or Data Centres. In the event a non-compliance is identified by any member of staff, this must then be documented. All protocol deviations are non-compliances but not all non-compliances are protocol deviations.

5.3.1 NHS GGC Sponsored/Co-Sponsored Research

If suspected Category 1 or 2 the individual will notify the project manager, trial monitor or Sponsor representatives directly and the issue must be logged in the local site file and discussed with the trial monitor and or Project manager. If related to monitoring or audit this can be in the form of a monitoring or audit report. Processes for the handling and oversight of protocol deviations are discussed in more detail in section 5.4. Category 1 and 2 non-compliances that are not defined as protocol deviations should also be presented to the trial management team by Project managers and or monitors if any concerns or trends are identified.

The ability to determine trends in inaccurate data or increased amounts of missing data is likely to be identified by the data centre. The Sponsor requests through contractual agreements that the data centre provides this information to monitors and Trial Management Groups. It is the monitor's responsibility to request reports from the data centre relating to key trial data.

Suspected Category 3 or 4 non–compliances will be escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist as appropriate, and will be logged on the non-compliance log within Q-Pulse.

5.3.2 Hosted Research

If issues of non-compliance are highlighted that pertain to research hosted within GG&C, then the Sponsor organisation must be notified as detailed in section 5.1. The Sponsor processes must be followed as detailed in the relevant section(s) of the Investigator Site File. Any suspected Category 3 or above must also be reported to the NHS GG&C Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist. These will be logged on the NHS GG&C non-compliance log within Q-Pulse. Section 5.4.4 describes in detail the requirements of the hosted activity managed within clinical research facilities in Glasgow for the trial team.

5.4 Protocol Deviations

5.4.1 Non-Compliances relating to the Protocol for Non-Cancer Trials

Protocol deviations are specific non-compliances relating to activity that deviates or violates the processes defined and approved within research protocols. A Protocol deviation is an unintended departure from the protocol which has been identified retrospectively. A protocol violation is an upfront decision to deviate from the protocol.

If defined as category 1 or category 2 this will be recorded on the protocol deviation log (Form 51.008C) by the site, this log must be signed by the PI and sent to the monitoring inbox and project managers for review on a Quarterly basis. The monitors (CTMs) will review the log quarterly to ensure the defined category is correct and that no suspected category 3 or category 4 deviations have been listed in error as lower categories.

Any actual or suspected category 3 and 4 deviations noted on Form 51.008C will be immediately escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist and then reported using Form 51.008A, reviewed and signed by the PI. Form 51.008B will be completed by the monitor or Project Manager and sent to NHS Research Governance and/or R&I Lead Clinical Trials Pharmacist as appropriate for logging and review, the CI should also be notified. Flowchart 1 describes the process that should be followed when reporting deviations. Those escalated but already captured on Form 51.008C will still be retained on Form 51.008C also.

If a site is not engaging with completion of protocol deviation forms or implementing CAPA, i.e. not responding to requests for information in a timely manner, the issue should be firstly escalated to the CI for them to resolve with the local PI. If this does not result in successful completion of the forms or implementing a CAPA, the issue should then be reported to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist who will make contact with the site team directly in order to support the resolution of the issue. If the issue is not resolved the Lead Clinical Trials Pharmacist or Research Governance Manager will decide whether the lack of engagement should be captured on a file note or escalated to the local Research Governance team, GHSPRAG or MHRA depending on the nature of the issue.

5.4.1.1 Protocol deviations identified by monitors (CTIMPS)

Non-compliances identified during monitoring as protocol deviations will be categorised by the Monitors. Those deviations Categorised as 1 or 2 will require the site to complete the protocol deviation log, Form 51.008C, as instructed by the Monitor. A summary of the non-compliance as captured on Form 51.008C will be forwarded to the Project Manager, Statistician and CI as part of the trial management meetings by the monitor on a quarterly basis. For any deviations deemed as category 3 or 4, the Monitor will immediately escalate to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist and ask the site to complete Form 51.008A including review by the PI. Form 51.008B will then be completed by the Monitor. Forms 51.008A and 51.008B are then forwarded to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist as appropriate. These forms require review and sign off by the CI, local PI and statistician. The CI and PI must review the impact of the deviation on safety of the research participants and the statistician for impact on the quality of the data and impact on endpoints.

NOTE- For trials managed by the CRUK CTU Glasgow the CTU SOPs will be followed and are aligned to the forms within this SOP.

5.4.1.2 Protocol deviations identified through data handling (data management centres and data safehavens) for all NHS GG&C Sponsored and co-sponsored CTIMPs)

Irregularities in data will be captured through the data query process. When NHS GG&C outsources this activity to data management centres contracts and agreements will ensure that the data management centre updates the Sponsor of potential protocol deviations they have identified, during the Trial Management meetings or earlier if the deviation impacts patient safety or quality of the trial.

In this event, upon notification from the relevant Data Management Centre or Safehaven, deviations relating to data will be categorised by Monitors acting on behalf of the Sponsor. If deemed to be Category 1 or 2, the protocol deviation log will be used (Form 51.008C). Any issue deemed as category 3 or 4 must be escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist immediately and reported on the Sponsor deviation form (Form 51.008A) by the Project Manager with the assistance from the site. Form 51.008B will then be completed by the Monitor, the CI should also be notified. These forms require review and sign off by the CI, local PI and statistician. The CI and PI must review the impact of the deviation on safety of the research participants and the statistician for impact on the quality of the data and impact on endpoints.

Any issue deemed as category 3 or 4 must be escalated to the NHS Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist immediately. The CI should also be notified.

NOTE- For trials managed by the CRUK CTU Glasgow the CTU SOPs will be followed and are aligned to the forms within this SOP.

5.4.1.3 Protocol deviations identified by Site, Project Management or Pharmacy

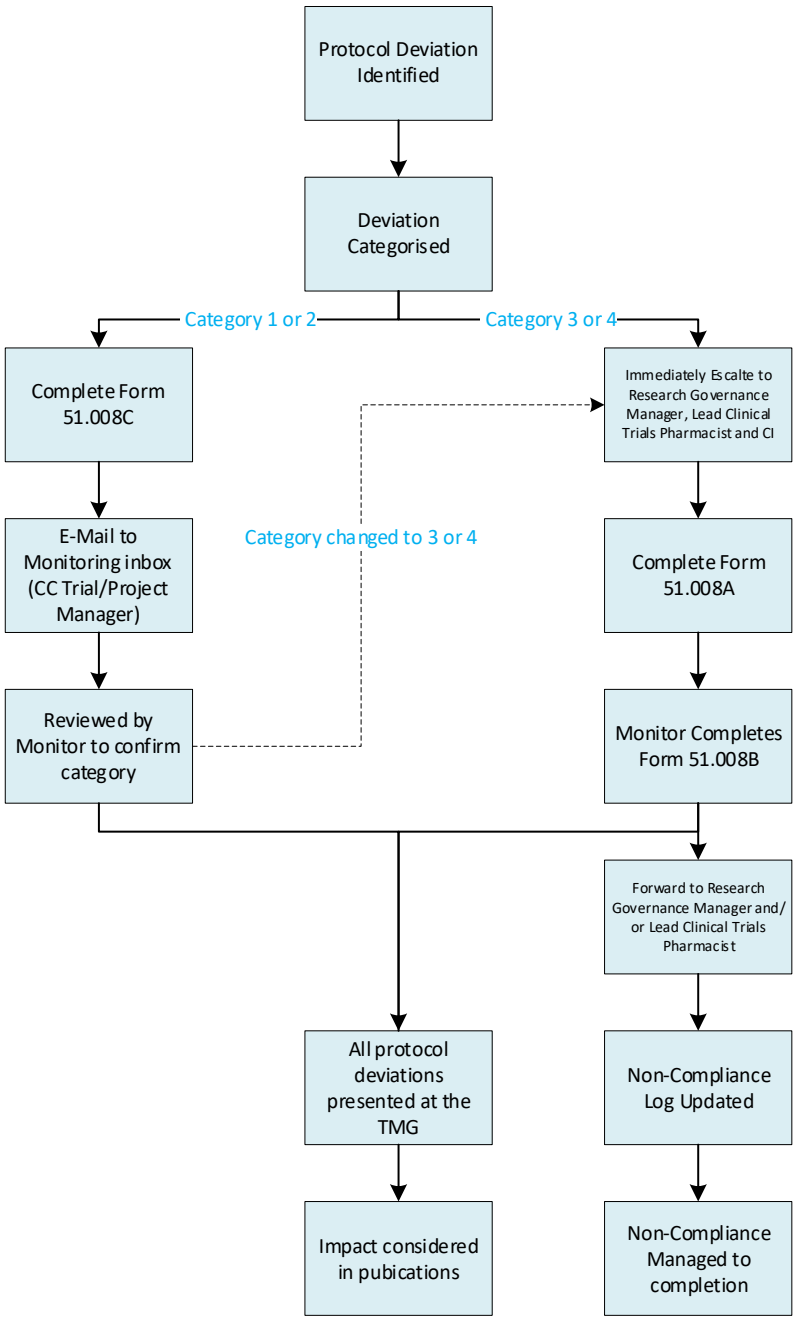
Deviations in complying with the protocol can be identified through other sources. The category of the deviation will be determined by the Monitor, Research Governance Manager or R&I Lead Clinical Trials Pharmacist as appropriate. The site protocol deviation log should be used for category 1 and 2 deviations (Form 51.008C), as instructed by the Monitor, Research Governance Manager or R&I Lead Clinical Trials Pharmacist. If a category 3 or 4 deviation occurs these must be escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist immediately. The Project Manager will be responsible for the completion of Form 51.008A with the assistance of the site. Form 51.008B will be completed by the monitor or a Sponsor representative.

Any issue deemed as category 3 or 4 must be escalated to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist immediately. The CI should also be notified.

Protocol waivers are not permitted within trials sponsored or co-sponsored by NHS Greater Glasgow and Clyde.

All protocol deviations will be provided to the statistician for the trial by the Monitor or Project manager on a regular basis. It is the responsibility of the statistician to assess the potential impact of deviations individually and as a whole for impact on the outcome of the trial.

NOTE- For trials managed by the CRUK CTU Glasgow the CTU SOPs will be followed and are aligned to the forms within this SOP.



Flowchart 1: Process for reporting a protocol deviation for Sponsored and co-Sponsored CTIMPs

5.4.2 Protocol Non-Compliances highlighted by or to CRUK-CTU Glasgow

For trials sponsored or co-sponsored by NHS GG&C and co-ordinated by the Cancer Research UK Clinical Trials Unit (CRUK-CTU Glasgow) staff within the unit will take responsibility for completing a CRUK-CTU Glasgow protocol deviation form, described within their local SOPs. Protocol deviations that are suspected to be category 3 or above will be escalated immediately to the Sponsor representative and the Research Governance Manager and R&I Lead Clinical Trials Pharmacist. All protocol deviations will be provided to the statistician and the CI for the trial.

For trials managed by the CRUK CTU Glasgow the CTU SOPs will be followed for sections 5.4.1.2 and 5.4.1.3 and are aligned to the forms within this SOP.

Category 1 and 2 non-compliance process are covered within the CRUK-CTU Glasgow SOPs and are aligned with this SOP.
Any non-compliances labelled as category 3 or above within CRUK –CTU Glasgow will be escalated to the Research Governance Manager and/or R&I Lead Clinical Trial Pharmacist. Information will be assessed by the NHS Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist and when appropriate the QA Officer from CRUK-CTU Glasgow in order to establish the severity of the issue in order that potential serious breaches of GCP can be identified and reported to the MHRA and Ethics.

5.4.3 Non-compliances highlighted by Laboratories and/or sample handling, transport and storage processes

The CI and Project Manager responsible for engaging with laboratories and biobanks (and other organisations involved the processing and handling of samples) involved in research will ensure any non-compliance or deviations in these processes are captured, documented and reported to the Sponsor. Any deviations must following the processes described for use of Forms 51.008A, B & C. Categorisation of the non-compliance will be made by the R&I Lead Clinical Trial Pharmacist or representative.

Note- This section also refers to process required for trials managed by CRUK – CTU Glasgow involving Laboratories, sample handling, transport and storage.

5.4.4 Non-compliances that arise within the Glasgow CTU and CRUK CTU Glasgow site

If a non-compliance arises from research services provided by the GCTU and the CRUK CTU Glasgow, this should be reported by the CTU, (in which the non-compliance occurred), to the appropriate Sponsor, as described in contracts or service level agreements. They will also be escalated to the CRUK-CTU Glasgow GCP Compliance Committee or Glasgow CRF, where appropriate.

For trials sponsored or co-sponsored by NHS GG&C the non-compliance should be reported to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist.

5.4.5 Non-compliances that arise by contracted services (vendors)

For non-compliances that arise for trials sponsored or co-sponsored by NHS GG&C, from research services provided by an external vendor, the contract with the vendor will state that non-compliances will be reported to the Sponsor. The Sponsor representative will then escalate them to the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist.

5.5 Managing Non-compliances

Non-compliances which have been categorised as 3 or 4 will be logged on the Non-ompliance Log within Q-Pulse and given a unique identification number. The root cause and Corrective and Preventative Actions (CAPA) will be established by the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist as appropriate.

Audit trails for each escalated non-compliance or escalated protocol deviation will be retained on an NHS server by the Research Governance Manager and/or R&I Lead Clinical Trials Pharmacist when dealing with the non-compliance.

The Research Governance Manager will report all non-compliances to GHSPRAG until the non-compliance has been resolved and closed off on the log. It is the responsibility of all involved in research to respond to requests and CAPA related to non-compliances in a timely manner and to keep the R&I Lead Clinical Trials Pharmacist or Research Governance Manager up to date on progress of completion.

5.6 Reporting

5.6.1 Reporting to Ethics and MHRA

For non-compliances that result in a potential serious breach of GCP or the protocol will be reported to the MHRA and Ethics by the Research Governance Manager or R&I Lead Clinical Trials Pharmacist, as appropriate in accordance to SOP 51.009. For research that is not defined as a CTIMP only Ethics will be notified.

Reporting to Glasgow Health Science Partnership (GHSP RAG) Regulatory Approval Group and Glasgow Health Science Partnership Delivery Board. A report on all non-compliances will be provided by the Research Governance Manager to GHSP RAG members as part of the GHSP RAG meetings. The Chair of GHSP RAG will be responsible for reporting non-compliances to the GHSP Delivery Board.

5.6.2 Reporting research non-compliances to local Clinical Governance

Within NHS GGC as participating site, any non-compliances that result in potential patient safety issues will be reported through the NHS GGC Clinical Governance reporting system, DATIX. It is the responsibility of the trial team to report the incident on DATIX. NHS GG&C Site errors and "near misses" leading to non-compliance issues should be reported on DATIX by the appropriate department. The Research Governance Manager or R&I Lead Clinical Trials Pharmacist will inform the investigator/trial team if the incident needs to be reported on DATIX, if not already done. For sites external to NHS GGC that are participating in NHS GGC Sponsored or Co-Sponsored trials the Research Governance Manager or R&I Lead Clinical Trials Pharmacist will advise the investigator/trial team if the incident needs to be reported vial their local clinical governance system/process.

The R&I Director will report non-compliances to the NHS Board.

Examples of non-compliances that should be reported on DATIX (or equivalent) include, patient consenting to multiple trials with trial Investigators and Sponsors unaware of other trial; wrong dose of IMP given which leads to potential patient safety issue; patients on trials who are ineligible for the trial (do not meet inclusion/exclusion criteria) and data protection non-compliance issues.

Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS) may be reported through DATIX (or equivalent) in addition to being reported via the Pharmacovigilance Reporting system which is a regulatory requirement. These are not considered a non-compliance as such unless the SAE or SUSAR resulted from a breach of GCP or a breach of the protocol.

5.7 Publication

It is the responsibility of the CI and Trial management team to ensure when reports and publications are released that non-compliances and protocol deviations have been considered during the analysis. It is the responsibility of the CI to ensure this consideration is documented within the Trial Master File.

5.8 Temporary Halt or Early Termination of Clinical Trial

In certain circumstances, e.g. following a series of non-compliances deemed to be of a serious nature it may be required to temporarily halt or terminate early a clinical trial of investigational medicinal products, this process is defined in SOP 53.003.

6 Referenced documents

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)

7 Related documents

- SOP 53.001 – Notification of urgent safety measures for clinical trials of investigational medicinal products.
- SOP 53.002 – The handling of poor quality and fraud in clinical research
- SOP 53.003 – Temporary halt or early termination of clinical trials of investigational medicinal products
- SOP 51.009 – Notification of serious breaches of Good Clinical Practice or the trial protocol for clinical trials of investigational medicinal products.
- Form 51.004A – Risk Assessment Tool
- Form 51.008A - Protocol Deviation Reporting Form
- Form 51.008B - Protocol Deviation Reporting Form (part 2)
- Form 51.008C – Protocol Deviation Log
- GUI 51.008A – Managing Non-Compliance in Q-Pulse
- GUI 51.008B – Protocol Deviations Guidance

8 Document History

Version	Date	Description
1.0	14/07/2009	Release of Version 1
2.0	06/11/2013	Section 4.1.1 who to report GCP issues Section 4.2 The grading is not done by GBRAG but by Governance Manager and reported to GBRAG Section 4.2.2 The Handling of the issues is dealt with by Governance Manager and SOP needs to reflect this Addition of form 51.008 A
2.1	19/01/2015	Section 2 and 3 addition of research investigator Section 5 clarification of procedures Section 5.1.2 clarification of reporting procedures and storage of forms Section 5.2 clarification of sponsor procedures Section 5.2.1 new section Explanation of issues numbering
3.0	14/07/2016	Renumbered and change of author Section 5 amended to clarify process and include process flow chart Amendment of FORM 51.008A Addition of FORM 51.008 B
3.1	20/12/2018	More defined process for handing and categorizing protocol deviations
4.0	19/04/2022	Restructure and review of whole document and introduction of use of Q-Pulse. Updated to include publication and responsibility of statisticians. Updated to include protocol deviation recording process implemented under process development during COVID 19 pandemic