ETHICAL

THE PROTOCOL DEVIATIONS HANDBOOK

V 1.0

FOREWORDS

A written protocol is at the heart of every scientific investigation including in the context of clinical trials. Deviations from the directions given in the protocol, whether intentional or unintentional, isolated or systematic, big or small affect the strength of the results and possibly the safety of participants. It is therefore natural that tracking, recording, reporting and remediating to Protocol Deviations is a major concern in clinical development.

This handbook will try to summarize the Protocol Deviation process, list the involved parties, describe the various methods and actions provisioned by regulations, and discuss tools and procedures that may alleviate the burden and improve the outcome of Protocol Deviations management.

We hope that readers will find the handbook useful and practical. Moreover, it is hoped that this piece of work will contribute to add yet another small stone to the construction of a safer world for patients and their families by supporting a better understanding and management of Protocol Deviations.

This Protocol Deviation handbook was compiled by Ethical GmbH, a Swiss eClinical company specialized in Protocol Deviation, Endpoint Adjudication, Safety Data Reconciliation, electronic data capture and other data management software services for clinical research with a cumulative experience of 300 international clinical trials, over 10,000 investigator sites and hundreds of thousands of patients.

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1. Introduction

Clinical development is a complex and highly regulated business. Creating and developing new medicines or medical devices must always be done with the safety and well-being of patients in mind whether they participate as subjects in clinical trials or they use the drug or device already on the market. To achieve the necessary level of oversight and to ensure that scientific, legal and ethical requirements are fully adhered to, numerous processes have emerged over the years and many rules are enforced by health authorities and government agencies.

A written protocol is at the heart of every scientific investigation including in the context of clinical trials. Deviations from the directions given in the protocol, whether intentional or unintentional, isolated or systematic, big or small affect the strength of the results and possibly the safety of participants. It is therefore natural that tracking, recording, reporting and remediating to Protocol Deviations is a major concern in clinical development.

This handbook will try to summarize the Protocol Deviation process, list the involved parties, describe the various methods and actions provisioned by regulations, and discuss tools and procedures that may alleviate the burden and improve the outcome of Protocol Deviations management.

We hope that readers will find the handbook useful and practical. Moreover, it is hoped that this piece of work will contribute to add yet another small stone to the construction of a safer world for patients and their families by supporting a better understanding and management of Protocol Deviations.

2. Definitions

Protocol Deviations are relatively poorly defined in regulations and guidelines and different terms are often used interchangeably throughout publications, SOPs and sponsor-specific references. In addition, while the classification as major or minor is usually accepted, other classifications have been suggested to better capture the impact of deviations. We therefore begin this handbook with a list of definitions borrowed from various sources in an attempt to be as exhaustive as possible and to clarify some important concepts. The terms are listed in alphabetical order.

2.1. Escalation

A Protocol Deviation that needs to be escalated to the Ethics Committee / Institutional Review Board for immediate action.

An escalation issue is generally understood as an issue for which at least one of the following is applicable:

- Presents a notable departure from GCP/GMP
- Presents a notable departure from company and/or trial procedures

- Presents serious risk for reliability and robustness of the data
- Presents serious risk of subject safety and rights
- Impacts multiple trials and/or sites
- Requires immediate escalation to ensure compliance with regulations, guidelines, company standards and local law
- If unaddressed, may compromise the human safety, market authorization or acceptability of the investigational product, data, facilities or systems intended for regulatory submissions
- If unaddressed, regulatory actions appear possible or probable.

2.2. Ethics Committee (EC)

The Ethics Committee is an independent body in a member state of the European Union, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent[1].

2.3. Finding

Any non-conformance to protocol, Good Clinical Practice (GCP)/Good Manufacturing Practice (GMP) and any study procedure that requires consideration, follow up, or escalation. This term covers any possible issue or Protocol Deviation.

2.4. Institutional Review Board (IRB)

Under the US FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research[2].

[1]Directive 2001/20/EC
[2]US FDA: Institutional Review Boards Frequently Asked Questions. Guidance for Institutional Review Boards and Clinical Investiators. January 1998

2.5. EC/IRB Review Process

EC/IRB regularly review all reported deviations and requested exceptions to the study protocol.

2.6. IRB/EC review of Major Protocol Violations

A Protocol Violation report discusses what measures have been put in place to prevent future re-occurrences of the same event. The investigator should also evaluate Protocol Violations for any trends or patterns that would require additional corrective actions or submission of a protocol modification to prevent future Violations. Repeated Violations of a similar nature may be a clear indication that a permanent change (i.e. a modification) to the study procedures is necessary.

For Federal reporting purposes, the IRB will need to determine whether the Protocol Violation constitutes an instance of serious or continuing non-compliance. The investigator will receive an Acknowledgement of Protocol Violation.

Major Protocol Violations that occur in research that involves minimal risk (originally reviewed and approved via expedited review procedures, or determined by the convened IRB to meet expedited review criteria) may be eligible for expedited review.

2.7. IRB/EC review of Minor Protocol Violations

A Protocol Violation report discusses what measures have been put in place to prevent future re-occurrences of the same event. The investigator should also evaluate Protocol Violations for any trends or patterns that would require additional corrective actions or submission of a protocol modification to prevent future Violations. Repeated Violations of a similar nature may be a clear indication that a permanent change (i.e. a modification) to the study procedures is necessary.

2.8. IRB/EC review of Protocol Exceptions

Investigators requesting a Protocol Exception must submit a Protocol Exception request to the IRB office with any supporting documentation. The Protocol Exception is processed within the IRB office. The submission is pre-reviewed for completeness and determines the level of review required.

The IRB/EC usually review the Protocol Exceptions via expedited review procedures and document their determination. Once a determination is made by the IRB/EC, the investigator will receive a notification of determination from the IRB/EC.

2.9. Management and Reporting of Protocol or GCP Deviations and Serious Breaches

If a Deviation from the protocol or GCP occurs during a trial, the PI must be notified and it must be recorded on the 'Protocol Deviation Log'. The 'Protocol Deviation Log' should be kept in the Investigator Site File (ISF) and be made available for regular review during monitoring/audits by members of the trial management team.

Members of the trial management team will review the 'Protocol Deviation Log' regularly and:

(a) decide whether Deviations need to be investigated further
(b) ensure that the relevant information has been obtained and recorded
(c) ensure appropriate remedial action has been taken and documented
(d) ensure serious breaches have been reported and the Sponsor informed

If the Deviation is classified by the PI as a 'serious breach' according to the definition above, the PI should complete a 'Notification of Serious Breach of Trial Protocol or GCP' form in addition to recording the Deviation on the 'Protocol Deviation Log'. The notification form must be signed by the PI or other medically qualified person who is fully aware of the trial protocol and authorized to do so by the PI.

2.10. Planned Changes to Research Protocol

The most common planned changes to research protocols are made through submission of changes such as an increase in subject number, changes in investigators or key personnel, a change to the funding source, changes in procedures and revised consent documents. These all involve an amendment to the protocol and are not Protocol Deviations themselves (although they may result from a Protocol Deviation).

In the case of Deviations which are planned exceptions to the protocol, such Deviations should be reviewed and approved by the IRB, the sponsor, and by the FDA for medical devices, prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.150(a)(4)).

2.11. Principal Investigator

A Principal Investigator (PI) is the individual in a given hospital or medical center responsible for the preparation, conduct, and administration of a research study, grant, cooperative agreement, training, public service project, contract, or other sponsored project.

2.12. Privacy Incident

The attempted or successful unauthorized access, receipt of, use, disclosure, modification, loss or destruction of Personal Information. Privacy Incident examples can include (but are not limited to): a study site (or study partners) sent Sponsor identifiable information about participants (e. g., study subjects), Sponsor received a copy of study data from another sponsor's study, study files/records were lost by courier in transit to sponsor or interference/hacking of electronic systems containing Personal Information.

2.13. Protocol

Trial protocols are documents that describe the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials. Trial protocols provide the background and rationale for conducting a study, highlighting specific research questions that are addressed, and taking into consideration ethical issues. Trial protocols must meet a standard that adheres to the principles of Good Clinical Practice, and are used to obtain ethics approval by local Ethics Committees or Institutional Review Boards[3].

2.14. Protocol Deviation

A Protocol Deviation is any change, divergence, or departure from the study design or procedures defined in the approved protocol, consent document, recruitment process, or study materials (e.g. questionnaires) originally approved by the IRB or Ethics Committee (see Table 1 for examples of Protocol Deviations). Protocol Deviation is a general term and includes, Protocol exceptions, changes made to avoid immediate harm to subjects, and Protocol Violations. [4,5] Protocol Deviations can be either major or minor.

Protocol Deviations may include unplanned instances of protocol noncompliance. For example, situations in which the clinical investigator failed to perform tests or examinations as required by the protocol or failures on the part of subjects to complete scheduled visits as required by the protocol, would be considered Protocol Deviations.

Repeated failure by an investigator to report Protocol Deviations may be viewed as non-compliance with the US federal regulations and other international regulations.

[3]Cipriani A, Barbui C. What is a clinical trial protocol? Epidemiol Psichiatr Soc. 2010 Apr-Jun;19(2):116-7. PMID: 20815294.
[4]45 CFR §46.103 (b) (4) (iii)
[5]21 CFR §56.108 (a) (4)

2.14.1. Major Protocol Deviation

An accidental or unintentional change to, or non-compliance with the IRB-approved procedures (e.g., the protocol, informed consent document, recruitment process or study materials) without prior sponsor and IRB/EC approval. Major Protocol Deviations generally do:

a) Increase risk and/or decrease the benefit to the participants;
b) Affect the subject's rights, safety or welfare and/or the integrity of the research data.

2.14.2. Minor Protocol Deviation

A minor or administrative departure from the IRB/EC-approved protocol procedures (e.g., the protocol, informed consent document, recruitment process or study materials) that was made without prior sponsor and IRB approval. It is an accidental or unintentional change to or non-compliance with the research protocol that does not:

a) Increase the risk or decrease the benefit to the patient;
b) Significantly affects the subject's rights, safety or welfare and/or the integrity of the research data.

2.14.3. Potential Major Protocol Deviation

Any Protocol Deviation that is not classified/referenced on the predefined Protocol Deviation criteria list but has the potential to impact subjects' rights, safety or well-being, or the integrity and/or results of the clinical study. Potential Major Deviations require prompt review, confirmation of whether they are major or minor, and a documented decision by the study team.

2.14.4. Escalation

A special group of PDs require escalation to Health Authorities for further scrutiny and potential action. These are typically PDs affecting more than one site and/or more than one study (also see Escalation above).

2.15. Protocol Deviation Form

The form(s) used by the Protocol Deviation Review Committee members to perform and record their assessment. The forms can be processed as paper or, as online fillable forms using Electronic Data Capture (EDC).

2.16. Protocol Deviation List

A list of all Protocol Deviations, whether major or minor that have been discovered by any of the parties involved in a Clinical Trial (site staff, Principal Investigator, Monitor…)

2.17. Protocol Deviation Review Charter

The Protocol Deviation Review Charter is the fundamental document describing the Protocol Deviation Review Standard Operating Procedures applicable to a specific Clinical Trial.

2.18. Protocol Deviation Review Committee (PDRC)

The group of persons in charge of assessment of Protocol Deviations. The Protocol Deviation Review Committee is usually composed of independent expert clinicians that operate independently and are blinded to the clinical trial operations.

2.19. Protocol Deviation Review Committee Chairperson

The person who presides the Protocol Deviation Review Committee and ensures the respect of procedures. The Protocol Deviation Review Committee Chairperson is often requested to resolve disagreement situations.

2.20. Protocol Deviation Review

The procedure by which findings identified as potential Protocol Deviations or Violations are submitted to a panel of independent experts (The Protocol Deviation Review Committee) to be assessed in a blinded way. Protocol Deviation Review is used in clinical trials to manage subjective evaluations of Protocol Deviations.

2.21. Protocol Deviation Review Workflow

The procedure, as described in the Protocol Deviation Review Charter, by which the Protocol Deviation Review is made. It is usually defined by stating:

- How many coincident judgments are needed for a valid assessment
- How PDRC members judgments are reported in the final assessment
- What happens in case of disagreements
- What happens in case of re-submission following changes in the finding information

2.22. Protocol Deviation Status

A Protocol Deviation may be in one of the following statuses within the process of review: not reviewed, in review or reviewed.

2.23. Protocol Exception

A temporary Protocol Deviation that is pre-approved by the sponsor and the IRB prior to its implementation. Protocol exceptions are generally for a single subject (e.g., the patient/subject is allergic to one of the medications provided as supportive care) or, occasionally, a small group of subjects. The Protocol Exception is usually evaluated by both the sponsor and the IRB/EC in order to determine that it does not increase the risk to the subject (s), or jeopardize the integrity of the research data. Documentation of sponsor (or Health Authorities) pre-approval and IRB/EC approval of the exception should be maintained in the study file.

Protocol exceptions must be submitted to IRB/EC and granted approval prior to subject enrolment and implementation, except where necessary to eliminate apparent immediate hazards to the Human Subjects[6,7,8].

The investigator has ultimate responsibility for obtaining prior IRB/EC approval for Protocol exceptions. Repeated failure to obtain prospective IRB/EC approval for Protocol exceptions may be viewed as non-compliance with the health regulations and more generally with the guidelines that govern ethical conduct of research.

An example of Protocol Exception would be the enrolment of a research subject who fails to meet all of the protocol eligibility criteria (e.g., the subject may have been evaluated for all other parameters, and it was determined that not meeting this inclusion criteria or laboratory screening value would not cause harm to the subject or alter the validity of the study).

[6]DHHS 45 CFR §46.103(b)(4)
[7]FDA 21 CFR §56.108(a)(4)
[8]ICH 3.3.7

2.24. Protocol Violation

A Protocol Violation is a subset of Protocol Deviation[9]. It is any planned or intended change or Deviation from the IRB approved study protocol, consent document, recruitment process, or study materials that were not approved by the IRB prior to implementation. Generally, Protocol Violations occur after the subject is enrolled in the research. However, some Protocol Violations, such as Deviations from the approved consent process, can occur before the subject is enrolled in the research. Protocol Violations may be either major Protocol Violations or minor Protocol Violations, based on their relative severity. Examples of protocol violations may include the following[10]:

- Inadequate or delinquent informed consent
- Inclusion/exclusion criteria not met
- Unreported serious adverse events
- Improper breaking of the blind
- Use of prohibited medication
- Incorrect or missing tests
- Mishandled samples
- Multiple visits missed or outside permissible windows
- Materially inadequate record keeping
- Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
- Subject repeated non-compliance with study requirements

2.24.1. Major Protocol Violation

A major Protocol Violation is a Deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. All major Protocol Violations must be reported by the investigator to the IRB within five (5) working days of learning of the Violation.

No matter who discovers a major Protocol Violation (e.g., sponsor or their agent during a monitoring visit), the investigator is responsible for reporting it to the IRB.

2.24.2. Minor Protocol Violation

A minor Protocol Violation is one that does not impact s
ubject safety, compromise the integrity of the study data, or affect the subject's willingness to participate in the study. No matter who discovers a minor Protocol Violation (e.g., sponsor or their agent during a monitoring visit), the investigator is responsible for reporting it to the IRB.

All minor Protocol Violations do not require prompt reporting and should be reported by the investigator to the IRB within ten (10) working days (or no later than at the time of continuing review) of learning of the Violation.

[9]Bhatt A. Protocol deviation and violation. Perspect Clin Res 2012;3:117.
[10]Norman M. Goldfarb Journal of Clinical Research Best Practices Nov 2005

2.25. Risk Management Plan

Protocol Deviations carry risks to clinical trials. Risk management comprises of a series of activities or processes that are undertaken throughout the life cycle of a clinical trial to identify, evaluate, monitor, control, prevent, mitigate, communicate and review, any factor (or process) that threatens the quality of the trial. This pertains to risks undertaken by participants as well as all other steps related to the trial especially the quality, reliability and integrity of the trial data. Risk management should start at the beginning of the trial (at the time of protocol design) so that risk mitigation can be a part of the protocol and other essential documents and processes. Risks are defined as the combination of probability of occurrence of harm and the severity of that harm.

The ICH Q9[11] document on Risk Management outlines the basic principles and process of risk management as applicable to the pharmaceutical industry. These principles and practices apply to all clinical trials. These processes help facilitate a robust clinical trial with a focus on quality and participant safety.

2.26. Serious Breach

A serious breach is a Deviation from the trial protocol or GCP which is likely to affect to a significant degree:

a) The safety or physical or mental integrity of the subjects of the trial; or
b) The scientific value of the trial

The Sponsor has delegated the responsibility of identifying and assessing serious breaches occurring during the day to day running of the clinical trial to the Principal Investigator (PI).

2.27. Significant Quality Issue

A non-conformance issue, quality finding or regulatory compliance issue with immediate or future potential to affect the safety, effectiveness, performance, supply or compliance with specifications or regulatory requirements. The issue may have significant impact on product supply in the market/clinical trials, patient safety, patient rights, data integrity and/or compliance status of the company. This includes the discovery of regulatory compliance issue, significant regulatory authority inspection, critical audit observations and fraud and misconduct.

2.28. Unplanned Changes to Research Protocol

This category includes unplanned changes to a clinical protocol that are not approved by the IRB. Such unplanned changes are either Protocol Deviations or Protocol Violations. These unplanned changes may include changes to the IRB-approved research protocol, Good Clinical Practice (GCP) guidelines or regulatory standards.

[11] ICH Harmonised Tripartite Guideline, Quality Risk Management, Q9

3. Scope of the Protocol Deviations Procedure

The procedure for identifying, recording, documenting and reporting Protocol Deviations during clinical trials and that of remediation and prevention encompass a large array of departments within a Sponsor or CRO organization as well as numerous external parties such as the investigational site PI and other personnel, the IRB/EC, suppliers of external services and finally the health authorities.

In this chapter we will review the roles and responsibilities of each of these parties.

3.1. Roles and Responsibilities

There are numerous players in the process and all have an important role to play.

3.1.1. Sponsor / CRO

Within the sponsor or CRO organization, there are several departments involved in the management of Protocol Deviations.

Monitors

The monitors are in the first line of the identification and reporting process for Protocol Deviations. It is important that all field based personnel is familiar with the study protocol, the procedures and the requirements as well as any company-wide standards that need to be adhered to across all studies conducted by the organization.

Medical

Medical teams are involved in the review of all or part of the reported potential Protocol Deviations and help to determine whether the reporting is accurate and to classify the Deviation.

Data Management

Many Deviations can be identified by comparing data elements within the clinical database. Data management can run regular checks to identify PDs which will be further discussed by the clinical team for classification.

Safety

Protocol Deviations may result in adverse events or otherwise impact the safety of the subjects. Safety must always be associated to the review of PDs.

Compliance

Some Protocol Deviations may be related to non-compliance with local rules and regulations or with GCP/GMP rules. If the sponsor has a dedicated compliance group, they should be consulted as well.

Legal

The Legal department may be consulted if Protocol Deviations constitute a breach of legal obligations either by law or in reference to the contract between the site and the Sponsor / CRO.

Regulatory

The Regulatory Affairs department must be systematically consulted for possible actions such as communication with Health Authorities.

Quality

Internal Quality departments conducting internal audits may identify Protocol Deviations that were not reported or that were not adequately handled. These can then be added to the list and, if appropriate, CAPA may be initiated.

3.1.2. Principal Investigator / site personnel

If a Deviation from the protocol or GCP occurs during a trial, the PI must be notified and it must be recorded on a 'Protocol Deviation Tracking Log'. The 'Protocol Deviation Tracking Log' should be kept in the Investigator Site File (ISF) and be made available for regular review during monitoring/audits by members of the trial management team. Protocol Deviations should also be recorded in the Case Report Form (CRF) for the trial.

Members of the trial management team will review the 'Protocol Deviation Tracking Log' regularly and:

a) Decide whether Deviations need to be investigated further
b) Ensure that the relevant information has been obtained and recorded
c) Ensure appropriate remedial action has been taken and documented
d) Ensure serious breaches have been reported and the Sponsor informed

If the Deviation is classified by the PI as a 'serious breach' according to the definition above, the PI should complete a 'Notification of Serious Breach of Trial Protocol or GCP' form in addition to recording the Deviation in the CRF and on the 'Protocol Deviation Tracking Log'.

The notification form must be signed by the PI or other medically qualified person who is fully aware of the trial protocol and authorized to do so by the PI.

The Sponsor along with the trial management team will investigate reports of potential serious breaches and fully document any action taken. If evidence is obtained that a serious breach has occurred, the Sponsor will report the serious breach in accordance with the applicable regulatory requirements[12].

3.1.3. IRB/EC[13]

Institutional Review Boards or Ethics Committees follow ICH guidelines and have internal procedures guiding the management of Protocol Deviations reported to them or discovered during audits and inspections.

Federal regulations and institutional policy require the IRB to review and approve proposed changes to research projects before initiation of these changes, except when changes are "necessary to eliminate apparent immediate hazards to the subject"[14]. Most proposed changes are reviewed through submission of amendments. Any changes that are made to eliminate apparent immediate hazards to a participant should be reported as soon as possible after they occur as a Protocol Deviation. Deviations range in seriousness according to how the changes may impact participant safety, the degree of noncompliance with federal and state regulations, and the degree of foreknowledge of the event. Deviations must be reported to the IRB with a description of the Deviation, its impact on participant safety (if any) and a description of how similar events will be avoided in the future. Once reported, the IRB can make a decision regarding an appropriate response or remedial action. Note that repeated Deviations of the same type may be an indication that an amendment is needed to permanently change the project.

3.1.4. Health Authorities

Health Authorities may be informed of certain types of Protocol Deviations or may discover these during Audits and Inspections. The FDA has listed verification of protocol violation documentation as an evaluation criteria during the inspection conducted at investigational sites after marketing application.

Similarly the European Medicines Agency (EMA) has highlighted the importance of reporting violations and inclusion in the Clinical Study Report.

What needs to be reported to the European Medicines Agency[15]?

- Any serious breach of:
    - The Regulation (EU) No 536/2014.
    - The version of the protocol applicable at the time of the breach.

[12]HARP-2 Management and Reporting of Protocol or GCP Deviations/Serious Breaches_v1.0 Final_03/09/2010
[13]ICH GCP 3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)
[14]45 CFR 46.108(a)(3)(iii)
[15]EMA/430909/2016, Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

- For the purposes of this Regulation, a “serious breach” is a breach which is likely to affect to a significant degree:
    - The safety and rights of a subject.
    - The reliability and robustness of the data generated in the clinical trial.

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors.

Serious breaches are notified through the EU CT system.

3.2. Actions following the reporting of a Protocol Deviation

Following the discovery and reporting of a Protocol Deviation by the site personnel, a number of actions may follow depending on the nature, frequency and importance of the Deviation.

3.2.1. Collection/documentation of PDs

The PI must inform the Sponsor as soon as a Deviation is reported. Alternatively, Protocol Deviations may be discovered during monitoring, by data comparison or by medical review. All PDs must be reviewed by the clinical team to assess their nature (Minor, Major, Escalation, etc.) and documented in the Trial Master File (TMF).

3.2.2. Evaluation of Protocol Deviations

Once reported, a Protocol Deviation must be evaluated to determine whether it is actually a PD or not and, if yes, if it is Minor, Major or requires escalation to Health Authorities. This is sometimes rendered difficult by the varying sources of PD identification and can be a lengthy and imprecise exercise. Efforts are made by technology companies to develop specific software tools to assist with the process.

By the Sponsor

The Sponsor’s clinical team must have a process (SOP) in place for the regular review and evaluation of PDs. This is typically conducted on a monthly basis during the trial and requires the participation of all concerned parties. The results of the evaluation are to be recorded and filed in the Trial Master File (TMF). The lack of dedicated software tools often makes this a tedious process with imperfect results exposing Sponsors to regulatory findings and sanctions.

By an Independent Committee

Occasionally, in complex or unclear situations, Protocol Deviations may need

to be adjudicated by an independent committee of experts. This usually requires the use of a dedicated software platform to record the committee's decisions. Independent reviewers can then decide if a Deviation actually occurred and classify it according to the set rules.

By the IRB/EC[16]

When an IRB or EC is notified about a Protocol Deviation, a set of rules is to be followed depending on the nature of the deviation:

Emergency deviations are those occurring in an emergency situation, such as when a departure from the protocol is required immediately to protect the life or physical well-being of a participant. In such cases there is no time to prospectively seek the approval of the IRB. The sponsor and the IRB must be notified as soon as possible, but not later than 5 days after the emergency situation occurred (21 CFR 812.150(a)(4)). The PI must submit a report to the IRB. Deviations of this nature are always considered to be unanticipated problems involving risks to subjects or others.

Major, non-emergent deviations require approval by the IRB before they occur. Major, non-emergent deviations are planned deviations that are non-emergent and represent a major change in the approved protocol. These deviations are changes that the IRB must approve before the proposed change is implemented (via submission of a Further Study Action for Change in Research). Examples include exceptions to eligibility criteria, exceptions to the form and manner of obtaining informed consent, and exceptions to the schedule of administration of an investigational product.

If a planned major, non-emergent deviation occurs without prior IRB approval, the event is non-compliance which must be reported promptly to the IRB. A PI's failure to report promptly any major, non-emergent deviation for which the PI did not obtain prior approval is itself an incident of non-compliance.

Minor or administrative protocol deviations require reporting to the IRB at continuing review. Minor or administrative deviations are those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." If a protocol deviation occurs which meets this definition, the deviation should be reported to the IRB at the time the continuing review. Examples of minor or administrative deviations include: follow up visits occurring outside the protocol required time frame because of the participant's schedule, or blood samples being obtained at times close to but not precisely at the time points specified in the protocol.

[16] 21 CFR 56.108

For Federal reporting purposes, the IRB will need to determine whether the protocol deviation constitutes an instance of serious or continuing non-compliance. If the protocol deviation is an event involving a change in the protocol to eliminate immediate hazard or harm to subjects, the IRB should ensure that the event was reported in the required 10-day period. Also, the IRB should make certain that the event was reported in the required 10-day period. Also, the IRB should make certain that the investigator implemented appropriate measures to alleviate or eliminate the harm to current and future subjects in the research.

By Health Authorities

Health Authorities may be notified of Protocol Deviations or discover these during Audits and Inspections. The most significant deviations found during various inspections include:

- Enrollment of ineligible subjects
- Violation of protocol affecting safety
- Extensive data corrections and questionable changes
- Inadequate oversight of study personnel
- Inappropriate delegation of authority
- Poor oversight of satellite sites
- No informed consent
- Failure to communicate with IRB
- Falsification

Consequently, the HA may take regulatory actions. For example the FDA may issue a Form FDA-483 “Inspectional Observations” if unreported deviations are discovered during an Audit.

3.2.3. Corrective And Preventive Actions (CAPA)

The Investigational Site and/or the Sponsor may need to initiate a series of actions to correct the effects of the PD and prevent any further repeats. These are called CAPA and are typically recorded in a dedicated quality software or ledger as part of the Quality System.

3.2.4. Warning Letters

Health Authorities may issue warning letters to the Sponsor or CRO if they feel that the oversight of the study was insufficient. There have been cases of warning letters even to the PI. Failing to react immediately to a warning letter exposes the recipient to severe regulatory actions that may have serious consequences both financial and legal.

3.2.5. Potential consequences of PDs

Over-interpretation of the PD definition may lead to the inclusion of situations which are not PDs, such as theoretical situations. The addition of these extraneous situations could potentially delay identification of important patient safety information by increasing noise in the system. Under-interpretation may exclude situations based on fault or other reasons and could decrease the reliability of study results related to both effectiveness and safety. This range of interpretation contributes to varied and sometimes conflicting instruction to sites. This limits their ability to identify PDs and establish preventative actions which may result in direct impact to participants[17].

3.2.6. Tools for the collection, classification and documentation of PDs

Surprisingly, there are very few tools available that are dedicated to the systematic collection and recording of PDs. In the majority of cases these are listed in ledgers, spreadsheets or other tables. Because the original reporting can come from various sources such as the Clinical Trials Management System (CTMS), data management reports, site or IRB/EC reports, PDs are regrouped manually for review by the Sponsor team or the IRB/EC. Managing PDs can therefore be a substantial administrative burden for the clinical research team that can greatly benefit from a specialized tool for the ongoing support and recording of all operations associated with PD assessment and management.

Only recently have dedicated tools such as eDeviation® emerged and their use can greatly facilitate the work of clinical research teams.

3.2.7. Avoiding Common Deviations

Some of the most common deviations reported at the investigational sites are use of unstamped or wrong version of consent or HIPAA document, use of unapproved recruitment strategies, and missed study procedures. The following can help avoid some of these common errors:

- A strong quality management program including regular review of regulatory binder, consent documents and source documents.
- Good communication between all the members of the research team helps to reduce deviations. Some research teams find regular research meetings helpful.
- Training or in-service on protocol or study procedures for relevant staff.
- All relevant research team members should be updated on changes to the protocol and should have access to CPHS approved current documents, e.g. correct version of the consent documents and HIPAA documents.

[17]Galuchie, L., Stewart, C. & Meloni, F. Protocol Deviations: A Holistic Approach from Defining to Reporting. Ther Innov Regul Sci (2021). https://doi.org/10.1007/s43441-021-00269-w
[18]Guidance on Protocol Deviations, UTHSC-T

3.3. Clinical Study Report

Important Protocol Deviations must be described in the Clinical Study Report (CSR)[19]. In addition to a brief description of the study design and critical methodological information, the CSR synopsis should provide efficacy and safety results, as well as other critical information, including data on the study population, disposition of subjects, important protocol deviations, and treatment compliance.

The ICH E3 guidance provides examples of the types of deviations that are generally considered important protocol deviations and that should be described in section 10.2 of the CSR and included in the listing in Appendix 16.2.2. The definition of important protocol deviations for a particular trial is determined in part by study design, the critical procedures, study data, subject protections described in the protocol, and the planned analyses of study data. In keeping with the flexibility of the guidance, sponsors can amend or add to the examples of important deviations provided in ICH E3 in consideration of a trial's requirements. Substantial additions or changes should be clearly described for the reviewer.

3.4. New Proposal for Classification of Protocol Deviation

Other classifications have been suggested for Protocol Deviations based on their severity or nature.

For example, a new method has recently been proposed[20]. The authors consider that the earlier system of classification of deviation does not fully take into consideration the impact of the deviations. They have focused on the impact, both on subject safety and quality of data, since these are two most important aspects of clinical trials and have classified deviations in five grades as follows:

- Grade 1: No impact on data quality or patient safety
- Grade 2: Minor impact on data quality
- Grade 3: Minor impact on patient safety
- Grade 4: Major impact on data quality or patient safety
- Grade 5: Leading to patient/(s) death.

Another type of classification has been used by the U.S. Department of Health & Human Services[21]

- Intentional Protocol Deviations
- Protocol deviations that are identified before they occur, but cannot be prevented

[19]Guidance for Industry E3 Structure and Content of Clinical Study Reports Questions and Answers (R1)
[20]Ravindra Bhaskar Ghooi, Neelambari Bhosale, Reena Wadhwani, Pathik Divate, and Uma Divate, Assessment and classification of protocol deviations, Perspect Clin Res. 2016 Jul-Sep; 7(3): 132–136. doi: 10.4103/2229-3485.184817: 10.4103/2229-3485.184817
[21]Secretary's Advisory Committee on Human Research Protections (SACHRP) recommendations

- Protocol deviations that are discovered after they occur
- Protocol deviations to eliminate apparent immediate hazards and IRB-approved changes in research
- Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4)
- IRB approved changes in research under 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4):

ETHICAL

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4. APPENDIX

Table 1: Examples of Protocol Deviations[22]

Category	Protocol Deviation classification examples		
	Important	**Non-important**	**Not a Protocol Deviation**
Informed consent	• Clinical study procedures conducted prior to obtaining initial informed consent • New clinical study procedures performed before participant was re-consented • Re-consent containing updated risk language or important safety information not signed	• If required by local regulation or IRB/EC, participant did not initial all pages	• Administrative items such as: participant did not use requested date format, participant did not sign on requested line, etc
Inclusion/exclusion	• Participant entered the clinical study without satisfying entry criteria		
Study intervention	• Participant received wrong study treatment • Participant received the incorrect dose unit, route of administration, and/or inaccurate frequency of administration or expired product • Participant was non-compliant with study medication/treatment (e.g., above or below Protocol-specified threshold, overdose) • Participant received and took study medication which underwent a temperature excursion and was deemed unacceptable for use	• Participant was dispensed study medication which underwent a temperature excursion and was not taken or was taken but deemed acceptable prior to use • Stratification error/missed stratification	• Investigational product underwent a temperature excursion but was never dispensed to a participant • NOTE: May be considered a GCP issue for resolution outside of PD process • Investigational product had a temperature excursion which was determined to be within acceptable range before it was provided to a participant
Prohibited concomitant medication	• Participant took an excluded concomitant medication during the clinical study • Participant took a specific class of medication within X days before a specific procedure [outside the window, taking the medication may be considered non-important]	• Instructional text for windows of analysis in the protocol may result in non-important Deviations • Participant took a single dose of a class of medication [repeated use may be considered important]	

[22]From: Galuchie, L., Stewart, C. & Meloni, F. Protocol Deviations: A Holistic Approach from Defining to Reporting. Ther Innov Regul Sci (2021). https://doi.org/10.1007/s43441-021-00269-w

Category	Protocol Deviation classification examples		
	Important	**Non-important**	**Not a Protocol Deviation**
Trial procedures	• Missed safety or efficacy assessments related to primary or key secondary endpoints • Key safety or efficacy endpoint data collected on equipment which was not properly calibrated at Protocol defined time points • Specific personnel for key or critical protocol specific procedures did not complete specific training (e.g., in a neuroscience therapy area, the rater was not trained on how to assess a key study endpoint)	• Procedures not directly related to participant safety (e.g., outcomes research) • Repeat efficacy measures not performed after predefined endpoints • Missed procedures that have no impact on reliability of study results (e.g., exploratory analysis) • Missed laboratory measurements that are not part of key or critical safety or efficacy endpoints • Non-critical procedures performed out of a specified window • Failure to calibrate equipment relating to non-key safety or efficacy endpoints, at protocol defined time points	• Anticipated quantity of lab collection kits not on-site • Not calibrating a piece of equipment on a day it was not used to obtain participant data • Training of CRAs or other sponsor personnel • Note: In general, training is not a PD. It is an issue that does need corrective action and appropriate follow-up
Safety reporting	• Serious Adverse Events (SAEs) or Pregnancy not reported within required reporting timeframe (e.g. 24 h from awareness) • Events of Special Interest (e.g., potential drug induced liver injury [DILI], Hy's Law, major adverse cardiac event) not reported within protocol specified timeframe	• Non-serious AEs (NSAEs) not reported within predefined protocol timelines	• Site appropriately reported an SAE. Later, the sponsor data management team asked for the SAE to be split and recorded as multiple events. The time stamp of the new data entry made it appear that the site was delayed, but they were not
Discontinuation	• Participant developed withdrawal criteria during the clinical study but was not withdrawn • Participant developed withdrawal criteria for study treatment but was not withdrawn from study treatment		

Table 2: Impact and Likelihood Risk scoring

Impact Scoring Reference

Impact Score	Description	Risk area: Regulatory / Compliance		Risk area: Operational
5	**Extreme**	Risk of regulatory actions including Fines and Penalties; Prosecution / regulatory supervision; FDA Application Integrity Policy.	AND / OR	Major impact on direction of business and ability to meet multiple R&D and/ or corporate objectives.
4	**Serious**	Significant impact on patient safety and data integrity; systemic impact across the organization; remediation efforts unlikely to fully address consequences. Risk of denial of or loss of regulatory approval or Warning Letter.	AND / OR	Major impact on important R&D or corporate business objectives.
3	**Moderate**	Minimal impact on data integrity and patient safety; non-compliance but no long-term implications, isolated impact within organization; Data are still fit-for-purpose with minor remediation efforts. Potential for regulatory findings and actions (e.g.Form FDA 483).	AND / OR	Noticeable impact but business objective still on course.
2	**Minimal**	Minor or technical breach of regulatory requirements with no to limited impact on data integrity or patient safety; Data are still fit-for-purpose. Minimal risk of regulatory findings or enforcement action.	AND / OR	Minor importance to business objectives.
1	**Negligeable**	No impact on patient safety or data integrity; Deviations from best practice with no regulatory Violation; Data are still fit-for-purpose. Negligible risk of regulatory action.	AND / OR	No impact on achieving objectives.

Likelihood Scoring Reference

Score	Description	Range 1 (Quantitative)	Range 2 (Qualitative)	Range 3 (Chronological)
5	**Highly Likely**	>25% probability that the event will occur in the next year.	Almost certain to occur within the next 18 months.	One or more occurrences a week on average.
4	**Likely**	10-25% probability that the event will occur in the next year.	Likely to occur within next 18 months.	One occurrence per month on average.
3	**Moderate**	1-<10% probability that the event will occur in the next year.	May occur within next 18 months.	One occurrence every 6 months - 1 year on average.
2	**Low**	0.1 - <1 % probability that the event will occur in the next year.	Not likely to occur within the next 18 months.	One occurrence every 1 - 3 years on average.
1	**Remote**	<0.1 % probability that the event will occur in the next year.	Not likely to occur within the next 18 months.	One occurrence in greater than 3 years on average.

Table 3: Example of Protocol Deviation Tracking Log[23]

Protocol ID/Number:					Site Name/Number:				
Protocol Title (Abbreviated):									
Principal Investigator:					Page number [1]:				
Ref No.	Subject ID	Date of Deviation	Date Identi-fied	Deviation Description	Dev. Type [2]	Resulted in Adverse Event?	Did Subject Continue in Study?	Meets IRB Reporting Req. (Yes/No)	IRB Reporting Date
1									
2									
3									
4									
5									
6									
7									

Investigator Signature: _____ Date

[23]Source: National Center for Complementary and Integrative Health (NIH)
https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjF3eXJr9XwAhUSAmMBHRsiBiYQFjAAegQIBRAD&url=https%3A%2F%2Ffiles.nccih.nih.gov%2Fs3fs-public%2F-CR-Toolbox%2FProtocol_Deviation_Tracking_Log_ver2_07-17-2015.docx&usg=AOvVaw0EVDpB8I8BxltR5SaDFEuP