TransCelerate BioPharma, Inc.

Protocol Deviation Process Guide

Accelerating the Development of New Medicines

TransCelerate

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1. INTRODUCTION

Clinical study protocols must be conducted according to the International Council for Harmonization (ICH) guidance on Good Clinical Practice (GCP)[1] which, among other things, outlines safeguards for the rights, safety and well-being of the participants. Protocols "should [also] be designed, conducted and analyzed according to sound scientific principles to achieve their objectives; and should be reported appropriately."[2] If conducted as designed, the data produced should be reliable and reproducible supporting clear interpretation of the results all while maintaining vigilance for the protection of the participant. It seems intuitive that deviations to the protocol could negatively impact the participant or the interpretability of the data and should be avoided.

The reality is that, despite best efforts, protocol deviations do happen. However, they do not all have the same level of impact. Examples of *important* protocol deviations, defined as those with the most impact, were issued in ICH E3[3] in 1996 to include in the clinical study report (CSR). A formal definition of important protocol deviations and additional examples were issued in ICH E3 Q&A R1[4] in 2012.

The information presented leverages risk-based approaches from ICH E6 R2 GCP[5] and risk management and issue management[6] concepts from the clinical Quality Management System conceptual framework[7,8] to potentially guide Sponsors, Clinical Research Organization(s) and Investigational Sites in the management of protocol deviations.

1.1 Background

The ICH E3 Q&A R1 defines a protocol deviation as "…any change, divergence, or departure from the study design or procedures defined in the protocol." The Q&A also introduces a definition for important protocol deviations, defining them as "…a subset of protocol deviations that may significantly impact the

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[1] *GCP reference. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&mid=WC0b01ac05800268ad Accessed 13Mar2018.*

[2] *ICH E8 General Considerations for Clinical Trials section 2.2 March 1998.*

[3] *ICH E3 Structure and content of clinical study reports section 10.2 July 1996.*

[4] *ICH E3 Guideline: Structure and content of Clinical Study Reports Questions & Answers (R1) July 2012 question 7. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf.*

[5] *ICH E6 R2 Integrated Addendum to ICH E6 R1 Guidelines for Good Clinical Practice E6 R2 Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf Published November 2016.*

[6] *Callery-D'Amico S, Sam L, Grey T, Greenwood D, TransCelerate's Clinical Quality Management System: Issue Management, Therapeutic Innovation & Regulatory Science 2016 Vol 50 (5) 530-535.*

[7] *Meeker-O'Connel A, Sam L, Bergamo N, Little J, TransCelerate's Clinical Quality Management System: From a Vision to a Conceptual Framework, Therapeutic Innovation & Regulatory Science 2016 Vol 50(4) 397-413.*

[8] *TransCelerate. Quality Management System. Available at: http://www.transceleratebiopharmainc.com/assets/quality-management-system-assets/ Accessed 27Feb2018.*

completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being."

The ICH E3 Q&A R1 also allows for flexibility in the definition based on protocol design. However, anecdotally and in response to a TransCelerate member survey,[9] member companies and Investigational Sites indicate that there is considerable variability regarding interpretation of what is an important protocol deviation which results in inefficiencies in the identification, collection, and reporting of these deviations. Over interpretation could potentially delay the identification of important patient safety information, by increasing the noise in the system. Under interpretation could influence the reliability of the study results and patient safety signals.

Investigational site personnel have expressed frustration with the varied interpretation across different Sponsors of what constitutes an important deviation.[10] Varied and sometimes conflicting instruction limits their ability to identify protocol deviations and establish preventative actions which may result in direct impact to participants. Additionally, this variation may delay reporting to or obscure interpretation of protocol deviations by investigational site institutional review boards (IRBs) or ethics committees (ECs).

Sponsor interpretation may differ from that of the Health Authorities. Agency inspectors have disagreed with the Sponsor's classification of important and non-important protocol deviations. Unfortunately, this is not known until the time of inspection for a specific application, which is well beyond a time point when any contemporaneous adjustment can be made.

Proposed definition refinements and potential approaches have appeared in the published literature.[11,12] However, there has not been a substantial uptake within the clinical research community, presumably as the articles did not contain feedback from the regulators.

ICH E3 Q&A R1 offers guidance on the definition of important protocol deviations and states that Sponsors have flexibility in this activity. The flexibility is welcomed, but the impact of varied interpretation for the same situation leads to tangible impacts. Nuances in protocol design, objectives, and patient population warrant flexibility, but further understanding those different situations will provide clarity and support the core and pragmatic purpose of rapidly identifying situations which would directly impact interpretability of study data or directly impact patients' rights, safety or well-being.

1.2 Toolkit Components

The Protocol Deviation Toolkit is comprised of 3 components: a Protocol Deviation Process Map (Map), this Protocol Deviation Process Guide (Guide), and a Protocol Deviation Assessment Plan (PDAP)

[9] Reference TransCelerate survey results.

[10] Reference TransCelerate supplemental site survey results.

[11] *Mehra M, Kurpanek K, Petrizzo M, Brenner S, McCracken Y, Katz T, Gurian M. The Life Cycle and Management of Protocol Deviations. Therapeutic Innovation & Regulatory Science 2014 Vol 48(6) 762-777.*

[12] *Mohan S, Mehra M, Petrizzo M, Katz T, A Toolkit for the Management of Protocol Deviations, 2016.*

template. The processes shown on the Map and described in this Guide are not linear. They describe a holistic approach to the management of protocol deviation.

The Map illustrates a high-level process flow for Protocol Deviation Management. It includes the following components: PREPARE, IDENTIFY & COLLECT, CONFIRM, REVIEW & ANALYZE, and CLOSE OUT. REPORT and TRAIN are ongoing activities illustrated as horizontal bars.

Additionally, there are three feedback loops:

- **PDAP Feedback Loop** highlights areas which may contribute to updates and maintenance of the PDAP.
- **Inputs Feedback Loop** highlights areas which may contribute to updates and maintenance of the Protocol level inputs (e.g., Protocol, SAP, RACT). Additionally, feedback may influence Intermediate or Organizational level inputs.
- **Analysis Feedback Loop** highlights areas which may contribute to periodic reviews.

The Guide describes each component of the Map in detail. For ease in reading, REPORT and TRAIN are each discussed in single sections in this document. The Guide also contains a Decision Tree. See Figure 1 below.

The PDAP template is provided to document the approaches used to facilitate consistency within or across clinical studies. Although designed to be used together, users can choose to apply any or all of the toolkit components.

Several examples are provided within this toolkit. All are intended to illustrate context and serve as example only. Lists of examples are not intended to be all-inclusive, exhaustive, or mandatory.

1.3 Where Do the Risk-based Approaches Fit In?

Risk-based approaches apply throughout the toolkit.

- Definitions: The risk-based approach from ICH E6 R2 has been added to the definition of important protocol deviations.
- PREPARE: Program and Protocol level risk assessment classification tools (RACT), or other risk assessment tools may be leveraged when developing the PDAP.
- Classify: Protocol deviations classified as important should align with key or critical study data points or processes.
- ANALYZE: Application of a risk-based monitoring methodology may also identify trends not previously outlined in the PDAP.

2. Definitions

2.1 What is a Protocol Deviation?

As noted previously, the ICH E3 Q&A R1 defines a protocol deviation as "…any change, divergence, or departure from the study design or procedures defined in the protocol." The current definition is often over interpreted leading to inclusion of a wide scope of items being reported. For this reason, we recommend adding the following clarifying points:

1) An event occurred – to avoid theoretical situations;
2) The event is related to the protocol or documents referenced in the protocol (e.g., laboratory manual)
3) The event is independent of fault, blame or circumstance – to ensure an objective approach to identification. (e.g. sample tube broke in route to central laboratory, participant refused a procedure)

Events, issues or situations which are not protocol deviations may require some action or follow-up, and companies should have other tools and processes which can be applied. However, these and other similar issues should not be included in any analysis of protocol deviations. This will reduce noise which could delay identification of trends or dilute the impact of true protocol deviations.

Examples of situations which are not protocol deviations under the definition proposed above include:

- Principal Investigator not available during an on-site monitoring visit;
- Participant's name misspelled within a source document;
- CRA delayed in his/her own training;
- Contract not signed.

2.2 Defining Important and Non-important Protocol Deviations

As described in ICH E3 Q&A R1:

> "A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.
>
> *Important protocol deviations* are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial."

Incorporating the risk-based approaches from ICH E6 R2, we propose clarifying the definition of important protocol deviations to focus on key or critical study data. The updated definition would then become:

> *"Important protocol deviations* are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of **key** study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial."

ICH E3 Q&A R1 indicates that Sponsors have some flexibility in determining what is an important protocol deviation, stating 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." Building on this guidance we suggest the following interpretations:

- The terms "protocol deviation" and "protocol violation" may have different meanings and should not be used interchangeably. Protocol violations should be reserved for situations involving application of specific country/regional laws or regulations;
- "Significant" in the context of protocol deviations is not a statistical term;
- "Important", "major", "critical" and "significant" are synonyms when referring to important protocol deviations. Moving forward, the use of "important" is proposed as a common terminology to classify important protocol deviations.

The concepts of key or critical study data and processes are not new. They have been outlined in multiple publications[13] and industry conferences, and are a key component of risk-based approaches to clinical study management[14]. We believe the same risk-based principles are applicable to defining important protocol deviations in individual clinical studies and should be included in the terminology surrounding important protocol deviations.

- "Key" or "critical" study data and processes may include, but are not be limited to:
  - Data and processes related to the primary and key secondary endpoints of the clinical study;
  - Activities critical to ensure participant safety;
  - Processes that support participant privacy and ethical treatment;
  - Processes that underpin data quality.

There is no formal definition of a non-important protocol deviation in ICH. It follows that if a protocol deviation that does not meet the criteria of important it is non-important.

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[13] *TransCelerate: Risk based monitoring assets* Available at: http://www.transceleratebiopharmainc.com/assets/rbm-assets/ Accessed 27Feb2018.

[14] *TransCelerate Risk-based monitoring methodology position paper.* Available at: http://www.transceleratebiopharmainc.com/wp-content/uploads/2016/01/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf.pdf Accessed 27Feb2018.

2.3 Decision Tree

To aid stakeholders in decision making, a proposed decision tree (Figure 1) and table of examples (Appendix 1) are offered as a guide in the identification and classification of important and non-important protocol deviations. In addition to importance classification, the table also includes analysis categories. It contains the 4 categories outlined in the ICH E3 Guideline, as well as 3 additional recommended categories.

1. **Is it a protocol deviation?**

   Did it occur?

   AND

   Is it related to a data point or process in the protocol or documents referenced in the protocol?

   Answer YES to <u>both</u> questions:

   Identify as a protocol deviation. Continue to Classification questions.

   Otherwise:

   Not a protocol deviation, but still may be an issue or event which needs to be addressed. Ensure appropriate action(s) are taken with corresponding documentation.

2. **Protocol Deviation Classification**

   Could the protocol deviation impact the completeness, accuracy, and/or reliability of key or critical protocol-identified data or processes?
   - Example: The primary and/or key secondary endpoint results cannot be fully assessed;
   - Example: The primary and/or secondary endpoint result is inaccurate;
   - Example: At least one participant's data collection or result was affected.

   OR

   Could the protocol deviation impact the participant's rights, safety or well-being?
   - Example: A participant was not consented;
   - Example: A critical protocol-required safety procedure was not completed.

   Answer YES to <u>either</u> question:

   Classify as an important protocol deviation.

   Otherwise:

   Classify as a non-important protocol deviation.

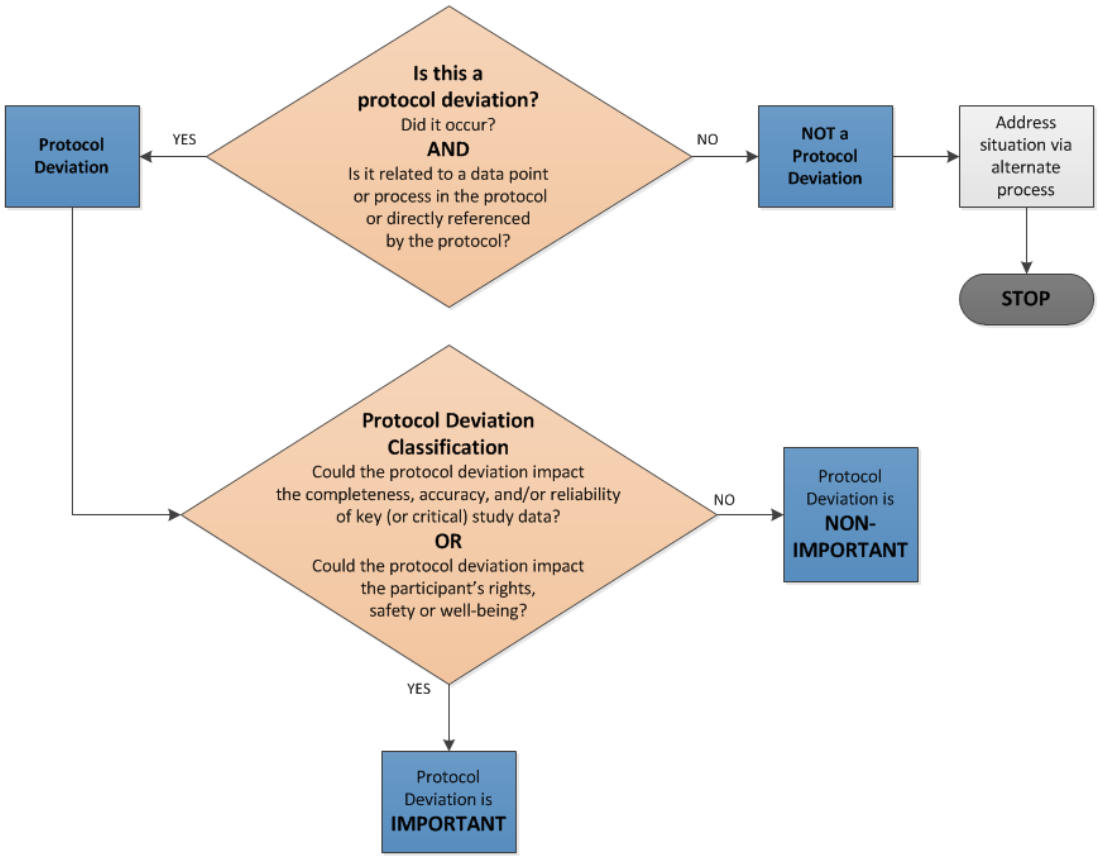

Figure 1 Protocol Deviation Decision Tree

The classification of a non-important deviation can change to important in some situations. Most commonly, meeting a pre-determined threshold or the outcome of a periodic trend analysis could trigger this reclassification. Conversely, protocol deviations classified as important may be reclassified to non-important. When either occurs, we recommend the study team determine if retrospective reclassification is appropriate. Decisions related to reclassification should be documented.

The value of a decision tree is consistent application of critical thinking within a company or organization, and potentially across the industry. As the external paradigm in a specific therapeutic area or indication changes and as new data becomes available for the study intervention being evaluated, a best practice to maintain consistency within a company is to have periodic reviews within a therapeutic area or indication area. Observations from ongoing clinical studies may also feedback into these periodic reviews. The outcome of these periodic reviews may result in updates to the definition of important or non-important protocol deviations.

Additional examples of important and non-important protocol deviations and not a protocol deviation are included in Appendix 1.

A protocol specific plan documenting the management of protocol deviations is a best practice to support consistency within a study, across a program, and within a company or organization. The PREPARE section of this document describes this approach in further detail.

2.4 Where Do GCP Compliance Issues Fit In?

Because clinical studies are conducted according to ICH GCP, and protocols make direct reference to GCP, some have assumed that all GCP compliance issues are also protocol deviations, thus inflating the volume of events. For example, a missing signature on the Delegation of Authority log needs to be addressed - perhaps as an action item if not completed during the CRA visit. In most cases, this granular procedure is not written in the protocol and thus this is not a PD.

To reduce the noise generated by this volume of events, we propose to address GCP issues outside the protocol deviation process unless they meet the classification of important as outlined via the Protocol Deviation Decision Tree (Figure 1). This will leverage the use of risk-based and issue management approaches, to identify the subset of GCP issues that are important protocol deviations.

Examples of GCP compliance issues which may also be important protocol deviations include:

- Study participant received expired investigational product
- Key or critical study procedures performed by study site staff without the appropriate qualifications or training.

Some GCP compliance issues may also qualify for expedited reporting to Regulatory Authorities depending on local regulatory requirements e.g. serious breaches. Each company should follow their escalation and assessment paths for decision making and reporting to relevant authorities.

2.5 The Protocol

The protocol and documents referenced in the protocol are the primary source when determining whether something is or is not a protocol deviation. Therefore, a best practice is to conduct risk assessment reviews and define protocol deviation classification approaches prior to finalization of the protocol. This allows changes to be made to the protocol to mitigate the occurrence of protocol deviations. The following guiding principles from the TransCelerate Common Protocol Template (CPT), which was informed by feedback from regulators and other stakeholders[15] and additional best practices can be applied to any protocol.

- Be streamlined;
- Be consistent:
    - Avoid text referring to the Informed Consent Form (ICF);

[15] TransCelerate Common Protocol Template Available at: http://www.transceleratebiopharmainc.com/assets/common-protocol-template/ Accessed 13 Mar 2018.

  - Avoid text referring to specific case report form or other study related forms;
- Consider leveraging CPT content when possible to ease interpretation by multiple stakeholders;
- Minimize unnecessary details and allow for the Investigator's judgement, when possible;
- Allow realistic visit windows, focusing on the time points which align to the Statistical Analysis Plan (SAP);
- Align protocol procedures with the standard of care (SOC) when possible. Differences from SOC should be clearly identified and support the objective(s) of the protocol.

3. PREPARE

3.1 Overview of the PDAP

The PDAP utilizes an issue management approach from the TransCelerate Quality Management System to support consistent identification, classification and categorization of protocol deviations for each clinical study (Figure 2). Once created, it supports continued and consistent responses to the question "What is an important protocol deviation?" The PDAP also documents thresholds for when non-important protocol deviations may become important.

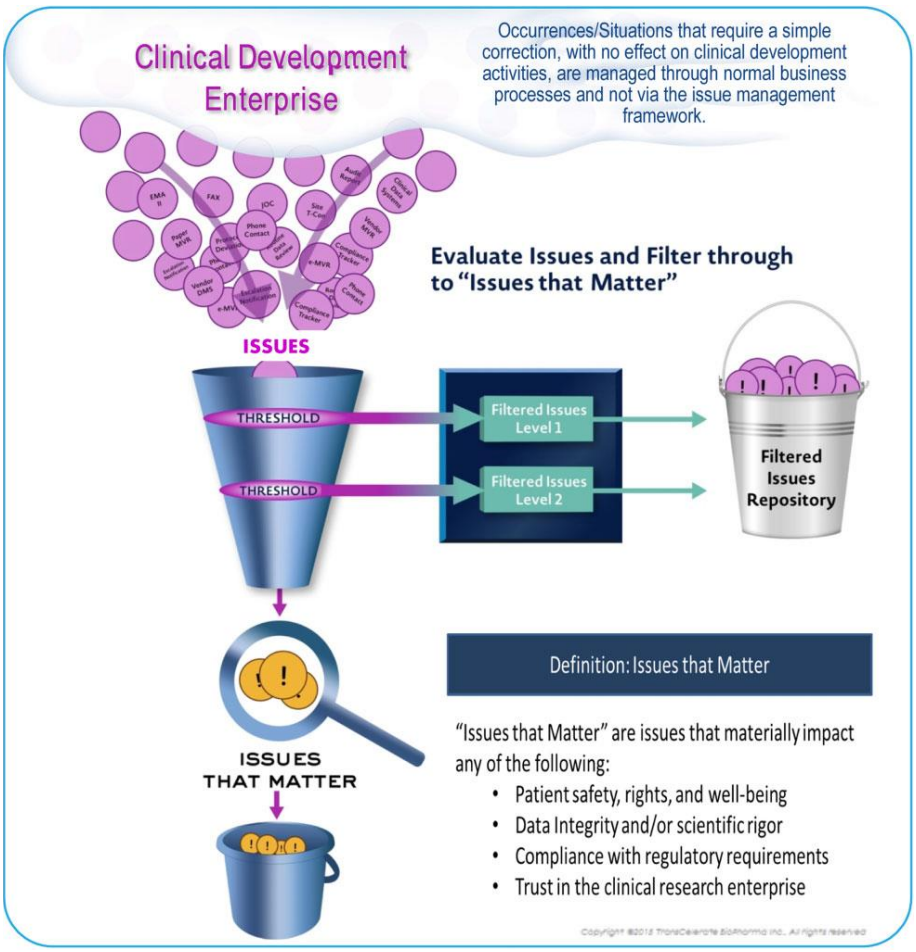

Figure 2 Issue Management Illustration

As illustrated in Figure 3, the PDAP may be created as a stand-alone document or incorporated into existing Integrated Quality and Risk Management Plans (IQRMPs). Whatever the form, we recommend that it is created in conjunction with protocol development and maintained as a living document until the last study data has been reviewed. As a living document, suitable version control measures should be utilized.

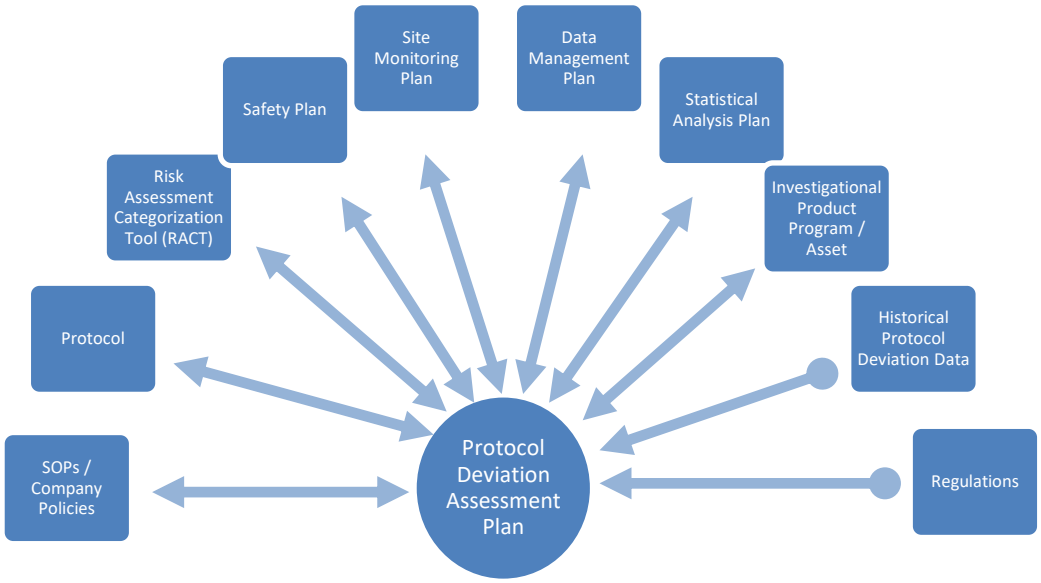

Figure 3 Relationship among Protocol Deviation Assessment Plan (PDAP), other Integrated Quality and Risk Management Plans (IQRMPs) and other protocol documents

3.2 Creating the PDAP: Organizational, Intermediate, and Protocol Level Inputs

The first step is to define and prospectively identify important protocol deviations which may occur for the clinical study. Inputs for these definitions may come from organizational, intermediate and protocol level components as illustrated in Figure 4. It is anticipated that the Protocol Deviation Decision Tree (Figure 1) will have been used when defining inputs to the PDAP.

- **Organizational level**: defines an important protocol deviation consistently for all protocols conducted by the organization. The situations addressed are usually based on regulations and described in standard operating procedures (SOPs) or corporate policies;
- **Intermediate level**: defines important protocol deviations consistently across a department or group within an organization. Depending on company structure, these inputs may include:
  - Therapy area: Ensuring consistency across all indications and all interventions;
  - Indication: Ensuring consistency within an indication for all interventions;
  - Asset or Intervention: Ensuring consistency across all protocols involving the same medicinal compound, asset, investigational product or delivery system;
  - Program: Ensuring consistency across multiple protocols intended to complement each other (could be based by indication or by asset/investigational product);
- **Protocol level:** defines an important protocol deviation specifically for the clinical study. These inputs should not duplicate or contradict any Organizational or Intermediate level inputs.

To support consistency, it is recommended that Organizational and Intermediate level definitions of importance are used whenever possible, and protocol level definitions are only introduced where

necessary. This will reduce variability in classification and categorization and help to support consistency in analysis and reporting.

Teams who use a program level or protocol level RACT or other risk assessment methodology may find these tools useful to identify potential situations which would be considered important protocol deviations.

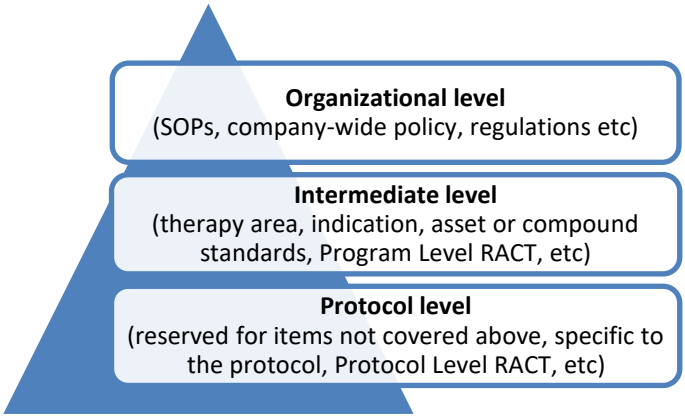

Figure 4 PDAP Levels: Organizational, Intermediate, Protocol

The PDAP should describe those protocol deviations which will be classified as important. A pragmatic approach should be applied when considering inclusion of non-important protocol deviations. Most commonly, non-important protocol deviations should be included if being evaluated for meeting a threshold or commonly misclassified. As illustrated in the template, the PDAP should outline the following elements:

- Guidance for consistent classification and categorization of protocol deviations;
- Process(es) for identifying protocol deviations;
- Thresholds at which non-important protocol deviations may become important. When setting thresholds for upgrading a non-important deviation to important, the key or critical protocol-identified data points or processes should be taken into account;
- Primary study team role responsible for identifying protocol deviation.

Additionally, the below topics related to protocol deviations may be included in the PDAP, or other clinical study plans.

- Frequency of data reviews or trend analyses;
- Feedback and/or escalation pathways;
- Type and extent of reconciliation to be performed (e.g., between protocol deviation collection tool and the clinical database);
- Documentation, approval, and archiving requirements.

3.3 Maintenance and Use of the PDAP

The PDAP is a living document and as such is intended to be reviewed and potentially updated, using suitable version control measures, throughout the study. It is anticipated that the PDAP will remain a living document until the last study data has been reviewed. The Map illustrates many of these input sources via PDAP Feedback Loop. Updates may result from:

- Periodic reviews of non-important protocol deviations which result in reclassification of a protocol deviation to important;
- Adjustments to thresholds for reclassification based on analyses and new information availability;
- Corrective and Preventative Actions (CAPA) from internal audits or Health Authority inspections;
- New risks or important protocol deviations which occurred during the clinical study;
- Protocol amendments.

It is anticipated that the PDAP would be used by study team members during the conduct of the clinical study. In addition to the PDAP, team members may also find value in using the Protocol Deviation Decision Tree (Figure 1) to aid in evaluating issues, events or situations which arise during the conduct of the clinical study.

4. TRAIN

Once the PDAP is created, training should be provided to the relevant study team members. Each team member should be aware of the role they are expected to play in reducing the occurrence of protocol deviations, and in accurately identifying, collecting, classifying, categorizing, analyzing and reporting.

As a best practice, we recommend the following training approaches:

- Train study site personnel on the protocol, not on the PDAP;
- Train study team (including CRAs, CRO, vendor, etc.) on the protocol and the PDAP.

The study team (including CRAs, CRO, vendor, etc.) should also be trained on the protocol amendments and any corresponding updates to the PDAP. These changes may include: identification methods, new important protocol deviation identified, etc.

For ease in reading, the following retraining and feedback components relate to topics described later in this document.

- IDENTIFY: A best practice is to have the individual who identifies the protocol deviation propose a classification and categorization. If this initial assessment is altered during the CONFIRM stage, the identifier should receive feedback explaining the rationale for the alteration so they can correctly apply the approach in the future. If the feedback is not correctly applied, the individual may need to be retrained on the protocol, the PDAP or other processes.
- & ANALYZE: Protocol deviations or other issues identified may lead to an action of retraining study site personnel on the protocol.

5. IDENTIFY & COLLECT

5.1 IDENTIFY

Protocol deviations can be identified via programmatic or manual processes. Programmatic identification is based on data captured in a database which can be programmed and identified by an electronic/computerized process. Manual identification relies on human interpretation. In both cases, a well-defined PDAP is essential for intracompany consistency and timely identification of protocol deviations. The PDAP should include the method of identification for potential important protocol deviations. This will help ensure there is alignment of efforts and that team members focus on items which cannot be identified via the alternate approach.

Manual identification approaches can vary but should focus on information not captured in an electronic data capture system. On-site identification is commonly the result of the CRA's review of source data and processes, or interaction with study site personnel. Sometimes a question posed by the site staff can lead to the discovery of a protocol deviation. Off-site or central review is another manual approach which is comprised of individual or team review of data listings, statistical tables, trend analyses or other data reports. Using these data tools, individual study team members or a collection of study team members decide on whether something is or is not a protocol deviation.

As a best practice, the identification of potential protocol deviations should rely on programming and reports whenever possible. The identification of those elements which are not programmable through a data source should be a primary focus for CRAs during on-site visits.

Application of risk-based monitoring methodology may not identify all protocol deviations. However, it should identify important protocol deviations. During risk assessment activities, the study team should identify the critical data and processes that would matter most in the clinical study. Armed with this prioritized information, the study team can focus identification activities on the protocol deviations with the greatest impact on participant safety and the reliability of study data.

A subset of protocol deviations may qualify for expedited reporting to Regulatory Authorities depending on local regulatory requirements e.g. serious breaches. These cases should still be processed with other protocol deviations, but each company should follow their escalation and assessment paths for decision making and reporting to relevant authorities.

If important protocol deviations are identified during the conduct of the clinical study which are not included in the PDAP, the study team should consider re-visiting or updating the PDAP.

5.2 Classify and Categorize

Each protocol deviation is to be classified and categorized upon identification. Classify is defined as the determination of the protocol deviation as being important or non-important. Categorize is defined as the type of protocol deviation (e.g., inclusion/exclusion).

6. CONFIRM

Protocol deviation classification and categorization should be confirmed. It is recommended that a study team member (or group of study team members), other than the identifier, perform this review. This confirmation will determine the pathway illustrated on the Map the protocol deviation will follow.

Feedback and possible retraining should be provided to the identifier if the protocol deviation is misclassified, miscategorized, or otherwise erroneously reported.

6.1 Important Protocol Deviation Pathway

Based on collection method (programmatic and/or manual) important protocol deviations should be reconciled and all discrepancies should be addressed. Examples of reconciliation include:

- Removal of duplicate protocol deviations (e.g., those that were identified via both programmatic and manual methods);
- Consistency between data point(s) and protocol deviation (e.g., data point in the clinical data base contained a transcription error – once corrected no protocol deviation existed).

6.2 Non-important Protocol Deviation Pathway

For non-important protocol deviations, periodic aggregate reviews should be completed to identify trends or systemic errors which may meet a threshold to upgrade the classification to important.

6.3 Store

Protocol deviations, including the classification and categorization and any associated data points, should be stored in a validated repository or system to support review and reporting (e.g., Clinical Trial Management System [CTMS], Electronic Data Capture [EDC], Trial Master File [TMF] or a custom system).

The storage approach should consider the following key elements:

- Both important and non-important protocol deviations can be retrieved or regenerated for varied reporting needs, during the clinical study and at closeout;
- Non-important protocol deviations can be retrieved or regenerated for trending analysis during the clinical study.

PDAP and any other supporting documents should be stored with other protocol related decision-making records.

- Documentation, including definitions of important protocol deviations and version control elements, is available for reference during and after the clinical study;
- Documentation of decision making is available during and after the clinical study.

7. REVIEW & ANALYZE

Study teams typically conduct periodic reviews, monitor clinical study data and conduct analyses on an ongoing basis during the conduct of the clinical study. The department/functional area involved and approach to the data vary based on organizational structure. These activities are typically focused on safety and efficacy elements at the individual participant level data, across study sites, countries and the protocol as a whole.

Existing approaches may be leveraged to identify protocol deviations not previously noted on the PDAP and to assess whether the frequency or volume of non-important protocol deviations should trigger a reclassification to important. If existing data reviews and analyses cannot be leveraged, additional efforts should be considered.

Other actions which may be triggered by the analyses include:

- Illustrated as Inputs Feedback Loop on the Map
    - Escalating some protocol level deviations for consideration at the intermediate or organizational levels
    - Amending the protocol or other protocol related documents to mitigate future protocol deviations
- Illustrated as PDAP Feedback Loop on Map
    - Updating the PDAP or other documents and processes within the clinical study
    - Updating the PDAP to reflect reclassification of a protocol deviation
    - Retraining Investigational Sites on the protocol or associated references;
    - Retraining study team personnel on the protocol, PDAP, or other clinical study documents;
    - Assessing if any new programmatic checks are required
- Illustrated as Analysis Feedback Loop on the Map
    - Updating RBM activities
    - Updating existing periodic review edit checks
    - New safety signals identified which influence periodic reviews.

In this ANALYZE phase, an assessment should be made to determine the impact of the protocol deviation on the data sets and populations included in the SAP. These decisions are commonly made in a structured study team meeting led by the statistician. Important protocol deviations may be one of several factors used to determine which participants are excluded from the “per protocol” analysis study population, and may affect individual data points used in statistical analysis.

Each company should determine when to finalize their PD process (close out the living PDAP or other documents used). We recommend that finalization occur after the last study data has been reviewed.

8. REPORT

8.1 Expedited Reporting

Throughout the clinical study, GCP compliance issues or some protocol deviations may qualify for expedited reporting to Regulatory Authorities depending on local regulatory requirements (e.g. serious breaches). Each company should follow their escalation and assessment paths for decision making and reporting to relevant authorities.

8.2 Periodic Reporting per Local Requirements

Depending on local regulatory requirements, periodic reporting during the conduct of the clinical study may be required. Requestors of these reports may include: central IRB, local IRBs, EC, and Health Authorities. Requirements for timing differ and may include reporting of both important and non-important protocol deviations.

8.3 Reporting in the Clinical Study Report

Guidance for discussing important protocol deviations in the CSR is addressed in ICH E3. The below components apply for both interim and final CSRs.

- Section 10.2 of the CSR should include a high-level, study-specific summary of important protocol deviations that occurred for the clinical study.
    - Important protocol deviations may be summarized by category. The PDAP template contains the 4 ICH categories plus 3 additional recommended categories.
    - CSR section 10.2 may also refer to the number of participants whose important protocol deviation(s) resulted in exclusion of any/all of their data from any/all analyses.

The impact of important protocol deviations on participant safety or interpretation of study results should also be included. The impact may be by participant level, investigational site level or overall.

GCP issues are usually described in a separate section of the CSR. However, Section 10.2 may include a reference to those participants whose important protocol deviations resulted from a GCP issue(s).

A by-subject listing of important protocol deviations should be included in Section 16 of the CSR.

9. CLOSE OUT

9.1 Beyond the CSR

As reviewed in the REPORT section, important protocol deviations are summarized and included in the CSR and archived. In addition to the final CSR, completing the following tasks is also a best practice:

- Archive non-important protocol deviations in a validated repository or system to support review and reporting (e.g., Clinical Trial Management System [CTMS], Electronic Data Capture [EDC], Trial Master File [TMF] or a custom system) and in supporting PD data sets (e.g. SDTM).
- Conduct a “lessons learned” session.
- Share protocol level important protocol deviations for consideration at intermediate or organizational level (Inputs Feedback Loop on Map).
- Complete any outstanding documentation or archival activity.

Appendices

Appendix 1 Protocol Deviation Classification and Categorization Examples

The table below offers examples of protocol deviation classification and categorization to guide stakeholders in defining important and non-important protocol deviations including ICH E3 Guideline examples. Consistent application of definitions across all levels addresses the problem statements identified in the INTRODUCTION. It supports study teams in consistent rapid identification and processing of protocol deviations and study sites in self-identification of protocol deviations and the development of preventative action plans. This list is not intended to be all-inclusive or exhaustive.

Protocol deviation category	Important protocol deviation examples	Non-important protocol deviation examples	Not a protocol deviation
Informed Consent	• Clinical study procedures conducted prior to signing initial informed consent • Initial consent not signed/dated per local regulatory guidelines • 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	• Participants who entered the clinical study even though they did not satisfy the entry criteria		
Study Intervention	• Participants who received the wrong treatment or incorrect dose	• Participant dispensed study medication which underwent a temperature excursion and was not taken, or was	• Investigational product underwent a temperature excursion

Protocol deviation category	Important protocol deviation examples	Non-important protocol deviation examples	Not a protocol deviation
	• Participant received the 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 dispensed and took study medication which underwent a temperature excursion and was deemed unacceptable for use.	taken but deemed acceptable prior to use. • Stratification error/missed stratification	but was never dispensed to a participant. NOTE: May be considered a GCP issue for resolution outside of protocol deviation 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 who received an excluded concomitant treatment • Participant took an excluded medication during the clinical study. (does not apply to inclusion/exclusion medications).	Note: Instructional text for windows of analysis in the protocol may result in non-important deviations • Example: participant who took a specific class of medication within X days of a specific procedure is considered important, otherwise taking the medication is considered non-important; • Example: participant who took a single dose of a class of medication is considered non-important.	

Protocol deviation category	Important protocol deviation examples	Non-important protocol deviation examples	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 is not a protocol deviation. **Note**: In general, training is not a protocol deviation. It is an issue that does need corrective action and appropriate follow-up.

Protocol deviation category	Important protocol deviation examples	Non-important protocol deviation examples	Not a protocol deviation
Safety Reporting	• Serious Adverse Events (SAEs) not reported within the expected turn-around-time per regulatory reporting requirements (i.e., 24 hours from awareness); • Events of Special Interest (e.g., potential drug induced liver injury [DILI], Hy's Law, major adverse cardiac event) not reported within the expected turn-around-time per protocol reporting requirements; • Pregnancy not reported within the expected turn-around-time per regulatory reporting requirements (i.e., 24 hours from awareness).	• 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 actually were not.
Discontinuation	• Participants who developed withdrawal criteria during the clinical study but were not withdrawn. • Participant who developed withdrawal criteria for study treatment but was not withdrawn from study treatment.		

Appendix 2 Glossary

Word choice influences comprehension and understanding. The below glossary has been assembled to highlight the preferred term used in across the Protocol Deviation Toolkit and corresponding common industry vernacular. Additionally, definitions are supplied for some words or phrases to provide context or intent.

Preferred Term	Definition	Equivalent Terms / Examples
* Common Protocol Template (CPT) term		
Analysis	Generically referring to any assessment of clinical study data for trends, outliers or patterns to support the identification of protocol deviations. Generally, more robust methodology compared to data review and commonly includes more computer-generated outputs based on aggregated data. Note: the Statistical Analysis Plan (SAP) is a separate distinct document. Analyses outlined in the SAP are focused on the safety and/or efficacy evaluations but may identify protocol deviations as a consequence.	Note regarding the Map: Ongoing Analysis are structured reviews of PDs with a holistic view (e.g. aggregate review for trends, blinded data reviews, review of per protocol population criteria)
Best practice	Already being done and considered a better approach (not a future state, but current).	
Categorize / Categorization	Type of protocol deviation	Examples: Informed Consent Safety Reporting Inclusion/Exclusion Study Intervention* Prohibited Concomitant Medication Trial Procedures* Discontinuation

Preferred Term	Definition	Equivalent Terms / Examples
Classify / Classification	Determination of the protocol deviation as being important or non-important protocol deviation	
Clinical study*	A research study involving human volunteers (also called participants) that is intended to add to medical knowledge.[16] Generically referring to the all aspects of the investigational clinical study including stakeholders (Sponsor, CRO, Investigational Site, IRB/EC, etc), documents (protocol, associated documents, contracts, etc.) and processes (GCPs, SOPs, etc.). Term is not part of the Protocol Deviation Assessment Plan hierarchy.	Study Trial
Critical	Used to describe study data or processes which are the most important to the conduct of the protocol. They typically correspond to the primary or secondary endpoints of the protocol. Aligned with how these references are used externally. See RBM references[13] for more detail.	Key
Data review	Generically referring to any process to review data generated from the clinical study. Commonly includes human interpretation of non-aggregated data. There are multiple frequencies at which this review may occur. Ad Hoc – Triggered by an event Periodic – Recurring Scheduled – Planned	Note regarding the Map: Periodic Reviews are routine reviews of protocol deviations (important and/or non-important) for clinical or operational purposes (e.g. to identify safety signals, to identify follow-up actions for sites, to correct the PD record)

Preferred Term	Definition	Equivalent Terms / Examples
Important	Term used to classify protocol deviations.	Major Critical Significant
Intermediate Level	Middle level of the Protocol Deviation Assessment Plan hierarchy. Outlines definition of important (and optionally non-important) protocol deviations for a subset of studies within an organization. Does not duplicate or contradict with Organizational Level.	Examples of Intermediate Level sources: • Therapy area - ensuring consistency across all indications and all interventions. • Indication - ensuring consistency within an indication for all interventions. • Asset or Intervention – ensuring consistency across all protocols involving the same medicinal compound, asset or investigational product. • Program – ensuring consistency across multiple protocols which are intended to complement each other (could be based by indication or by asset/compound).
Investigator[16]	A researcher involved in a clinical study.	Principal investigator Site or Study Principal investigator
Key	Used to describe study data or processes which are the most important to the conduct of the protocol. They typically correspond to the primary or secondary endpoints of the protocol. Aligned with how these references are used externally. See RBM references[13] for more detail.	Critical

[16] Clinical Trials Glossary: https://clinicaltrials.gov/ct2/about-studies/glossary.

Preferred Term	Definition	Equivalent Terms / Examples
Manual identification	Method of protocol deviation identification which is initially made by a human or based on human assessment or interpretation of data.	Site Monitoring Medical Monitoring Data Review Clinical Data Review
Non-Important	Term used to classify protocol deviations.	Minor
Organizational Level	Highest level of the Protocol Deviation Assessment Plan hierarchy. Outlines definition of important (and optionally non-important) protocol deviations for all clinical studies sponsored by or conducted by the organization. This level is based on company-wide policies and/or SOPs and most commonly focuses on Regulations or ICH Guidelines.	Company Enterprise
Participant*	Human volunteer who participates in a clinical research study.	Subject Patient
Programmatic identification	Anything programmed into a computer and identified via a computer.	Automated checks Edit checks
Protocol	The written description of a clinical study. It includes the study's objectives, design, and methods. It may also include relevant scientific background and statistical information.[16] Used when referring to the document and associated documents (laboratory manual, etc.).	
Protocol Deviation	A protocol deviation is "any change, divergence, or departure from the study design or procedures defined in the protocol". [ICH E3 Q&A R1]	Deviation Protocol violation – only used if applicable to country/regional laws.

Preferred Term	Definition	Equivalent Terms / Examples
Protocol Deviation Assessment Plan (PDAP)	**Template** designed to support and document a consistent approach to protocol deviations for each clinical study. Part of the toolkit	
Protocol Deviation Process Guide (Guide)	**Document** that supports management of protocol deviations including: prepare, identify & collect, confirm, review & analyze, and close out, train and report. Part of the toolkit	
Protocol Deviation Process Map (Map)	**Diagram** that supports management of protocol deviations including: prepare, identify & collect, confirm, review & analyze, and close out, train and report. , Part of the toolkit	
Protocol Level	Lowest level of the Protocol Deviation Assessment Plan hierarchy. Defines important (and optionally non-important) protocol deviations specific to the protocol. Does not duplicate or contradict with Organizational or Intermediate Level.	Study level Trial level
Protocol Violation	Situations involving application of specific country/regional laws or regulations. Not interchangeable with protocol deviation.	
Recommendation	Something that would be beneficial.	Guideline

Preferred Term	Definition	Equivalent Terms / Examples
Report	Study site reporting is not illustrated on Map. Sponsor reporting to external parties included in this toolkit: • Expedited Reporting to Health Authority (HA); • Periodic Reporting to HA or central IRB/EC; • Reporting in CSR (interim or final); • Reporting as part of CTA	
Sponsor	The organization or person who initiates the study and who has authority and control over the study.[16]	Company Enterprise Organization CRO (working on behalf of)
Study intervention*	Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol	Study drug Drug Study medication Study treatment Investigational Product Asset Compound
Study Team	The group of people responsible for the conduct of the clinical study at the Sponsor or CRO. Commonly, includes at least one representative from most functional areas involved throughout the clinical study lifecycle. Note, academic centers or universities may also be the Sponsor of clinical studies.	

Preferred Term	Definition	Equivalent Terms / Examples
Threshold	A value that once reached, is intended to trigger an action (Reference: RBM paper). When a non-important protocol deviation becomes an important protocol deviation.	Occurrence Level Tolerance limit Anomaly Trend
Study Site*	The location where clinical study participants are seen.	Clinical trial site Investigational Site Site

Appendix 3 List of Acronyms

AE	Adverse Event
CAPA	Corrective and Preventative Action
CPT	Common Protocol Template
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTA	Clinical Trial Application
CTMS	Clinical Trial Management System
DILI	Drug Induced Liver Injury
EC	Ethics Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
IP	Investigational Product
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
NSAE	Non-Serious Adverse Event
PD	Protocol Deviation
PDAP	Protocol Deviation Assessment Plan
RACT	Risk Assessment Categorization Tool
RBM	Risk-Based Monitoring
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
TMF	Trial Master File