***Definitions:*
Compliance (in relation to trials)** – Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements (ICH GCP 11.15)

**Deviation/Violation –** Protocol deviation is not defined by either DHHS human subject regulations (45 CFR 46) or FDA human subjects regulations (21 CFR 50). Per NIH, an unplanned excursion from the protocol that is not implemented or intended as a systematic change. May also refer to any other unplanned, instance(s) of protocol noncompliance1. *While some differentiate the two with ‘deviation’ being used for less serious instances of noncompliance, the industry has moved towards the terms being used interchangeably and further qualifying as either ‘minor’ or ‘major’.*

**Serious Noncompliance –** Failure to follow any of the regulations and policies or failure to follow the determinations of the COMIRB and which, in the judgment of either the COMIRB Chair(s) or the convened panel, increases risks to participants, decreases potential benefits, or compromises the integrity of the human research protection program. Research being conducted without prior IRB approval is generally considered serious non-compliance. (COMIRB Policy & Procedures Effective Date December 1, 2020). *Definition may vary depending on the IRB—always refer to the protocol’s IRB of record for current policies and definitions.*

**Continuing Noncompliance –** Pattern of noncompliance that, in the judgment of the panel Chair(s) or convened panel, suggests a likelihood that instances of noncompliance will continue without intervention. Continuing noncompliance also includes failure to respond to a request to resolve an episode of noncompliance within 30 days. (COMIRB Policy & Procedures Effective Date December 1, 2020). *Definition may vary depending on the IRB—always refer to the protocol’s IRB of record for current policies and definitions.*

**Deviation Log –** Comprehensive list of known deviations that occur at the study site. Deviation log may be required to be submitted to the IRB at continuing review per IRB of record’s policy. Documentation of PI review should be evident via signature, email correspondence, etc.

**Unanticipated Problem (UAP) –** Any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others, or indicates the participants or others are at increased risk of harm than was previously known or recognized (COMIRB Policy & Procedures, Effective Date December 1, 2020)

**Note to File (NTF) or Memo to File –U**sed to acknowledge and clarify a discrepancy or error. May include corrective and preventive action. Of note, per the NIDCR Guidelines for Writing Notes to the Study File – NIH Research Toolkit, a NTF should identify a discrepancy or problem in the conduct of the clinical research study, note the root cause of the identified problem, identify the corrective action taken to prevent recurrence of the problem, and document that the corrective action has resolved the problem. The tone of NTF should be forward-looking and not seek to explain an error.

**Root Cause Analysis –** The *underlying* identified issue/problem, which initiated other possible nonconformities. *(DSMC Guidance Document on CAPA Plans)*

**Corrective Action –** Short-term and immediate resolution of any nonconformities found. These actions may include but are not limited to notifications, documentation, reporting, data corrections, etc. Include all personnel affected/working on the study. If the study personnel were instructed to perform specific corrective actions by the Monitor, Sponsor, DSMC, etc., indicate by whom, their title, and date notified. If the corrective plan or action taken fail to correct the root cause, describe why and create an alternative corrective action plan that will be implemented. Be sure to document training on the corrective action plan. *(DSMC Guidance Document on CAPA Plans)*

**Preventative Action –** Long-term, sustainable solution to address root cause(s) and prevent recurrence. This may involve more than one action, including but not limited to training, site commitment, any process changes, etc. Include all personnel affected/working on the study. If the study personnel were instructed to perform specific corrective actions by the Monitor, Sponsor, DSMC, etc., indicate by whom, their title, and date notified. *(DSMC Guidance Document on CAPA Plans)*

***References:***

1 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3487227/>

COMIRB Policy & Procedures, Revised, Effective Date August 18, 2016

DSMC Guidance Document on CAPA Plans

ICH GCP E6 (R2)

***Use the Right Tool for the Job:***

Late entry to source is appropriate:

* Reason for error is self-evident or easily explained by the author of the notation
* One-offs, transcription errors, typos, etc.
* Updated or changed information
* Missed procedure(s), other deviation that does not require potential process changes or examinations to ensure it won’t happen again (.i.e., preventative action is not required)

NTF (include both corrective/preventative action) is required:

* Corrected data, reason for the error and/or author cannot be appropriately reconciled in a late-entry amendment to the source
* When further explanation of the error is needed
* Error(s) occurred across staff, participants, trials, etc. May require further investigation to determine whether process change, root-cause analysis and/or corrective/preventative action is required.

Root Cause Analysis is needed:

* Etiology of the error(s) and, more importantly, an effective way to prevent future occurrences is multifaceted, unclear or unknown

***NTF Do’s and Don’ts***

**DO**

* Escalate correspondence with keywords such as ‘immediate action’, ‘serious/continuing noncompliance’, ‘immediately reportable’, etc. to supervisor
* Escalate correspondence if coming from an unusual source or in an unusual manner from sponsor, CRO and/or IRB
* Be forward-looking; mistakes will happen but focus document on the corrective steps to resolve the error(s) and the preventative action taken to limit repeat occurrences
* Author by the individual, entity or organization responsible for its content; i.e., clinical staff should not document pharmacy action without pharmacy input and joint signature
* Provide both completed and planned corrective/preventative actions
* Provide timelines for completion of all corrective and preventative action
* Provide a method of verification or monitoring the effectiveness of the actions taken
* Specify the scope of applicability of the corrective/preventative action, i.e., whether actions will be implemented at the protocol, department or institutional level.
* Establish consistent department/team process for NTF creation, review, sign-off
* Institute a mechanism for tracking NTFs within the department/team to identify trends
* Update NTF with an appropriate audit trail if needed to correct/update information

**DON’T**

* Include unrealistic or unverifiable preventative actions
* Include more internal information than is relevant; e.g. errors in lab collection should not be attributed to new lab personnel or staff turnover
* Complete without review from relevant staff, including a supervisor/senior staff member
* Remove NTF once completed and ‘filed’; at that point, it becomes part of the study record

***Audit/Inspection Response Do’s & Don’ts (\*\*All NTF Do’s and Don’ts apply\*\*)***

 **DO**

* Think of corrective/preventative action as a concept versus a document
* Respectfully note whether you agree or disagree with the finding/observation (providing supporting documentation as applicable)
* Include commitment from senior leadership and all applicable stakeholders in corrective/preventative action(s)
* Address each observation/finding separately
* Critically complete and document a root cause analysis (but do not submit) focusing on actions within the site’s control
* Internally identify the difference between a true ‘one-off’ error and system/process flaw
* Submit supporting (de-identified as applicable) documentation including; training records, SOPs, study records, etc.)
* Respond in a timely manner; within 7-15 days unless otherwise specified in writing by the auditor/inspector

**DON’T**

* Include the Investigator’s opinion on the usefulness of particular data points or involvement as the Overall PI as justification for not following the protocol as written
* Use staffing or high-enrollment as a root-cause unless you include a commitment from senior leadership as to how that will be addressed
* Shift responsibility for, or minimize the deviation/finding
* Submit without review of another person-preferably at least one senior and one junior reviewer to ensure feasibility of preventative action(s).