

**Corrective and Preventive Action**

**CAPA in Clinical Research**

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**CAPA – More than an Acronym**

CAPAs - corrective and preventive actions - are improvements to an organization's processes taken to eliminate causes of non-conformities or other undesirable situations. CAPA is a concept within (GMP) and numerous ISO business standards; it focuses on the systematic investigation of the root causes of identified problems or risks in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).

Corrective actions are implemented in response to customer complaints, unacceptable levels of product non-conformance, issues identified during an internal audit, or adverse or unstable trends in product and process monitoring such as would be identified by Statistical Process Control (SPC). Preventive actions are implemented in response to the identification of potential sources of non-conformity.

To ensure that corrective and preventive actions are effective, the systematic investigation of the root causes of failure is pivotal. CAPA is part of the overall quality management system (QMS).

**CAPA and Underlying Regulations**

FDA regulations for CAPA for the pharmaceutical company are defined in Code of Federal Regulations (CFR) 21 section 211, as part of the Quality System Regulation. This process identifies reported and potential causes of product SQUIP - Safety, Quality, Integrity, Potency or Purity - performs root cause analysis of deviations, and determines appropriate corrective and preventive actions to eliminate repetition of failure. The program ensures that corrective and preventive actions get implemented through proper management reporting and review. FDA views this as a linkage to the entire quality management process. That is why the FDA makes sure that CAPA audit is done without any deviation at all levels of its inspection in all pharmaceutical companies.

**CAPA in Clinical Research**

The clinical research industry is undergoing a paradigm shift; the regulatory agencies are now looking for a structured investigation of issues that are encountered during a clinical trial. Pharmaceutical, biotechnology, and medical device companies are moving from a focus on detecting and fixing problems to a focus on preventing them, and sponsors and sites are implementing quality management systems to successfully make the switch. Poor CAPA investigations continue to be among the top deficiencies issued to companies within the clinical research industry resulting in warning letters to clinical investigators, institutional review boards, contract research organizations, and sponsors.

Developing a Quality Management System (QMS) within clinical research must begin long before the first patient is enrolled and continue through the completion of the clinical study report and any other relevant submission documents for drug applications. A key component is an effective Corrective and Preventive Action (CAPA) program.

Although there are no current mandatory regulatory requirements to implement a Clinical CAPA process, managing clinical quality using corrective and preventative actions is not new to clinical. The International Conference for Harmonization (ICH) released guidelines for Good Clinical Practice (GCP) as a scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.
CAPA requirements are not specifically stated in Good Clinical Practice (GCP) regulations. However, requirements for a QMS and a subsequent CAPA process in clinical trials are guided by ISO 9000 and ICH GCP 5.1.1.

Quality in the clinical context addresses the benefits and risks of a medical product or procedure while assuring protection of human subjects; therefore, clinical CAPAs should focus on issues that compromise patient safety and/or data integrity. A systematic CAPA approach includes incident identification (routine non-compliance vs. serious non-compliance), investigation of incident causality, development of an action plan based on root cause analysis, action plan verification and validation, action plan implementation, effectiveness checks and closure. CAPA management programs may also include the analysis and tracking of any GCP compliance trends or issues to identify ongoing quality improvement initiatives across clinical trials and development projects.

Developing an effective CAPA program is in the self-interest of sponsors and investigational sites to improve the quality of investigations as it has always been either a requirement or an expectation that the biopharmaceutical industry will perform thorough investigations and implement effective CAPA to ensure subject safety and data integrity during clinical trials.

**CAPA Identification at Investigational Sites**

CAPA needs may be identified as a result of specific non-conformities during the conduct of a clinical study. These may include, but are not limited to:

- Protocol deviations/violations
- Site staff complaints
- Site-internal audit/monitoring findings
- Study specific monitor visits (sponsor/delegate)
- Operational problems identified at the site
- Research participant (subject) complaints

The need to develop a CAPA may be identified through the analysis of data sources. The following is a non-exhaustive list of data sources:

- Protocol deviations/violation trends
- Site-internal monitoring trends
- Site-internal auditing report trends
- External audit/inspection reports (e.g. FDA Form 483)
- External audit/inspection trends
- Trends identified during monitoring and communicated in follow-up letters
- External audit/inspection trends
- Trends identified during monitoring and communicated in follow-up letters
- Human research participant (subject) complaint trends
- Human research participant (subject) complaint trends
- Rate of screening failures
- Number of subject withdrawals
- Number of premature terminations
- Reporting trends of adverse events and unanticipated issues
- Site staff member observations/concerns (e.g. high staff turnover)
- Risk assessment of clinical trial operations and quality systems
- Sponsor communications of study and/or data concerns
- IEC/IRB-identified concerns

Once non-conformity was detected, the need for corrective actions needs to be evaluated. The evaluation and determination of planned corrective action need to be based upon the potential impact on human research participant protection and regulatory requirements.

Preventive actions are not dependent on the occurrence of non-conformity and are initiated to eliminate potential causes of non-conformities, regulatory non-compliance, or potential human research participant quality of research care issues.

Not all noncompliance/deviations require corrective and/or preventive actions.
Root Cause Analysis (RCA)

Root cause analysis is an approach for identifying the underlying causes of why a problem/non-conformity occurred so that the most effective corrective and/or preventive actions can be identified and implemented. Three of the commonly used RCA methods are The 5 Whys, the Failure Mode and Effect Analysis (FMEA) and the Fishbone Diagram.

The 5 Whys: The 5-Why technique is a method of root cause analysis that asks the question "why?" on multiple levels to identify the root of the problem. The 5-Why method may seem simple, but that's where its power lies: instead of overanalyzing a problem, by repeatedly asking the question “Why” the layers of symptoms which can lead to the root cause of a problem can be peeled away.

Very often the ostensible reason for a problem/non-conformity will lead to another question. Although this technique is called “5 Whys,” one may find that one will need to ask the question fewer or more times than five before the issue related to a non-conformity can be found.

Failure Mode and Effect Analysis (FMEA): This method helps to identify and to quantify potential risks of operational processes. It is a systematic approach to identify and to rank all the possible ways in which a process could fail. The step-by-step FMEA technique prioritizes potential risks using a relative rating scale. The risk is a function of three factors: 1) the severity of the effect of a failure/non-conformity; 2) the frequency of occurrence of the failure/non-conformity; 3) the ability to detect or prevent the failure/non-conformity.

By evaluating each failure mode and effect in terms of these three factors, a Risk Priority Number (RPN) is generated. The RPN is used to rank the relative risks associated with a process; the higher the RPN, the higher the relative risk.
Fishbone Diagram: The fishbone diagram (also called Ishikawa diagrams, herringbone diagrams, cause-and-effect diagrams, or Fishikawa) are causal diagrams created by Kaoru Ishikawa (1968) that show the causes of a specific problem/non-conformity. The Fishbone diagram is an efficient method of mapping out the various levels of root cause analysis and takes cause and effect into consideration. The name of the fishbone diagram comes from its characteristic shape, where the head of the fish is the problem being researched, and the bones of the fish are the root causes.

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<th>Glossary</th>
<th>References</th>
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<td><strong>CAPA</strong> (corrective action and preventive action): A systematic approach that includes actions needed to correct (“correction”), avoid re-occurrence (corrective action), and eliminate the cause of potential non-conforming product or process and other quality problems (preventive action).</td>
<td>Code of Federal Regulations (CFR) 21 section 211 <a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=211">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=211</a></td>
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<td><strong>Correction</strong>: Action to eliminate the causes of a detected non-conformity. Corrections are typically one-time fixes. A correction is an immediate solution such as repair and rework. Also known as remedial or containment action.</td>
<td>International Conference for Harmonization (ICH) released guidelines for Good Clinical Practice (GCP) <a href="http://ichgcp.net/">http://ichgcp.net/</a></td>
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<td><strong>Corrective action</strong>: Action to eliminate the causes of a detected non-conformity or other undesirable situation. The corrective action should eliminate the reoccurrence of the issue.</td>
<td>International Conference for Harmonization (ICH) released guideline for Pharmaceutical Quality System (Q10) <a href="http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf">http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf</a></td>
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<td><strong>Effectiveness</strong>: The degree to which a planned effect is achieved. Planned activities are effective if these activities are realized. Similarly, planned results are effective if these results are actually achieved. For example, an effective process is one that realizes planned activities and achieves planned results.</td>
<td>ISO 9000 – Quality Management <a href="http://www.iso.org/iso/iso_9000">http://www.iso.org/iso/iso_9000</a></td>
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<td><strong>Preventive action</strong>: Action to eliminate the cause of a potential non-conformity or undesirable potential situation. The preventive action should prevent the occurrence of the potential issues.</td>
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<td><strong>Quality Management System (QMS)</strong>: Management system to direct and control an organization with regard to quality.</td>
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<td><strong>Root cause analysis (RCA)</strong>: analysis necessary to determine the original or true cause of a system, product or process non-conformity. This effort extends beyond the effects of a problem to discover its most fundamental cause.</td>
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<td><strong>Trend</strong>: A sequence or pattern of data. Analysis of a trend is performed to detect a special cause amidst the random variation of data.</td>
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