Clinical Oversight: Be VERY Sure
Recently, U.S. Food and Drug Administration (FDA) issued Warning Letters to pharmaceutical companies and their outsourcing partners have resulted to focus on clinical oversight. The letters have galvanized sponsors to take a close look at their ability to withstand such regulatory scrutiny internally, and to develop proactively their internal capabilities and infrastructure to better manage their outsourced clinical development programs. This white paper focuses on clinical oversight in regulatory perspective and recommendations to build quality risk management into the clinical trials process.

In the past two decades, the number and complexity of clinical trials have grown dramatically. These changes create new challenges in clinical trial oversight. Thus, effective clinical oversight is critical to the protection of human subjects and the conduct of high-quality studies. FDA is considering the need for additional guidance describing overarching quality risk management approaches to clinical trial oversight to ensure adequate protection of human subjects, quality, data integrity and compliance with applicable regulations.

Quick background

Clinical oversight is a methodology intended to assist sponsors of clinical investigations in developing strategies and plans for investigational studies of medical products, including human drug, biological products and medical devices to ensure human subject protection, data integrity and regulatory compliance.

It focuses on proactive risk management in clinical research and helps in completing clinical trials successfully within the timelines and budget. Applying Quality Risk Management (QRM) principles to clinical research from the early stages of drug development can expedite the process of bringing quality drugs from bench to market, addressing regulatory challenges and patient safety.

Quality risk management guidelines were established for GMP and medical devices. However, there were no guidelines available on handling of risk in clinical trials. The aim of clinical oversight methodology is to provide guidance on handling of risk in clinical trials. It is a holistic approach to clinical quality management that incorporates risk management principles of ICH Q8 and ICH Q9. It helps in identifying critical activities and potential risks involved in clinical trial conduct, which reduce or eliminate the risks and minimize the likelihood of errors and prevent their reoccurrence.

Prospective Approach

Clinical oversight is a systematic process put in place to identify, assess, control, communicate and review the risks associated with the clinical trial during its lifecycle. Effective clinical quality oversight implementation helps in identifying potential risks, root causes, assessing possible consequences and their prevention. Also, helps in developing proactive risk management plans.

QA and Clinical Project Managers will play important role in clinical oversight. Clinical Project Manager (CPM) is responsible for developing project plans, which should include the budget, timeline, team performance, Gantt charts, resource plans, communication plans, risk logs and deliverables. Whereas, QA is responsible for preparing project specific QA plan, which include Audit objectives, audit scope, number of centers/sites, facilitating regulatory inspections, handling of suspected scientific misconduct/emerging project issues, CAPA and risk management plans. The use of both quality plans and oversight plans facilitates a proactive approach between sponsor and vendors to discuss and define expectations at the engagement (contractual) stage, set them at the kickoff stage, and manage them throughout the entire program.
Clinical quality oversight should be appropriately defined in the organization’s quality management system. Executive Management should be involved in the identification and implementation of clinical quality oversight principles within the organization. Designated project specific QA team is responsible ensuring clinical oversight activities. Project Managers are responsible for developing project specific risk management plans prior to start of trial in association with concerned project stakeholders and the same should be reviewed and approved by QA and Sponsor. The clinical quality oversight process should be reviewed at regular intervals as part of the quality systems review (along with Customer feedback, complaints, deviations, violations etc.).

Risk Management (RM) is the process of measuring or assessing risk and developing strategies to manage it. All risks can never be fully avoided or mitigated simply because of financial and practical limitations. In other words, organization has to accept level of residual risks. In ideal RM, a prioritization process followed whereby risk with the greatest loss and the greatest probability of occurring are handled first. Risks with lower probability of occurrence and lower loss are handled later applying clinical risk management. The steps involved in risk based quality management process are shown below (see Figure 1):

**Risk based quality management process in Clinical trials**

- **Initiate**
  - Information on systems and project

- **Risk identification and assessment**
  - What may go wrong? Chance of occurrence? What would be in particular the impact on trial subjects rights/well being/safety and/or on the reliability of the trial results?

- **Review**
  - Results and new information (e.g. new pre-clinical data, new safety data, updated investigator brochure, protocol amendment) and ongoing review (e.g. Data Monitoring committee meeting output, Audit report concerns)

- **Risk control**
  - Decision made to reduce and/or accept risks
  - Where risks are to be mitigated, the methodology adapted to conventional GCP should be defined (e.g. intensive, regular or reduced on-site monitoring and/or central monitoring, targeted SDV on primary endpoint variable etc)

- **Implementation**
  - putting in place the actions identified, particularly for high risks, but conversely there may be implication on low risks.

- **Risk Communication**
  - Documentation Of Process (e.g. Risk Management measures) with reviews of the measures as necessary communication to all stakeholders/decision makers.
Clinical oversight process

Clinical oversight starts from protocol development stage to IND/NDA submission to Regulatory authorities. The basic idea of clinical oversight is identification of the risks on a continuous basis for all risk-bearing activities throughout the design, conduct and evaluation of clinical trials based on existing and ongoing or emerging information about the investigational product(s).

Applying risk based quality management approaches to clinical trials can facilitate better and more informed decision making and make the most use of the available resources. It should be appropriately documented and integrated within existing quality systems. It is the responsibility of all involved parties to contribute to the delivery of an effective risk-based quality management system.

Implementation of Clinical Oversight in clinical trials will result in successful completion of clinical trials. Prior to start up of any clinical trial activities, concerned project manager and QA should facilitate Quality Risk Management meeting with concerned stakeholders to identify potential risks, search for and locate risks before they become problems. Make sure risks are broken down to sufficient degree and potential root causes are identified. Clinical oversight team responsibilities will includes QMS compliance, Audit & GCP Compliance, Centralized remote monitoring, Vendor Management, TMF building & Document management, Clinical Trial Disclosure (see Figure 2). Failure to adhere to the above mentioned processes would lead to warning letters from the Regulatory bodies (see Figure 4).

Figure: 2 Overview of Clinical Oversight

Clinical oversight team should establish the clinical oversight plan before start of the clinical trial. This plan should cover the oversight of following critical activities as mentioned below (see Figure 3):
## Figure 3: Clinical oversight activities

<table>
<thead>
<tr>
<th>Clinical oversight activities</th>
<th>Description</th>
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| **Patient recruitment and site performance:** | - Screen Failure Rates and Reasons  
- Enrollment Trending (High and Low)  
- Patient Drop-out rates/Study Discontinuation |
| **Data management:** | - Data Entry Cycle Times  
- Electronic data capture  
- DCF resolution  
- Data quality  
- Quantity of data |
| **Monitoring/centralized monitoring:** | - Monitoring Approaches (e.g., timing, intensity, activities, documentation)  
- Communication of Monitoring Results  
- Monitoring issues and management of Noncompliance  
- Monitoring Plan Amendments  
- Data that support primary and secondary endpoints  
- critical study endpoints  
- protocol-required safety assessments  
- evaluating, documenting, and reporting serious adverse events  
- unanticipated adverse device effects  
- subject deaths  
- withdrawals, especially when a withdrawal may be related to an adverse event  
- Adherence to protocol eligibility criteria |
| **Safety:** | - AE reporting  
- Out of Range Values and Panic Alert Trends  
- SAE outlier/distribution analysis  
- SAE trending and associating aging  
- Protocol specific critical variables  
- evaluating, documenting, and reporting serious adverse events |
| **Investigational product accountability:** | - Accountability and administration of the investigational product (e.g., ensuring the integrity of randomization at the site level, where appropriate) |
| **Quality/Compliance:** | - Protocol Deviations  
- Overdue Action Items  
- Query Response Times  
- CRA Visit Response Times  
- On-site/Off-site Visit Compliance  
- Query Incidence Rates (field, site, study level)  
- Lost to Follow-up Occurrences  
- Protocol specific critical variables |
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Vendor Management & Oversight:
- Issue management with vendors like CRO/SMO, central laboratory, IP shipment.
- Focus on core clinical trial activities like monitoring, quality data generation and timeline management

TMF Building, Standardization & Management:
- Ensure Standardized documentation processes and offers support in document management in their existing system
- Ensure documentation processes, smooth tracking, retrieval of documents and exchange of information
- Saves sponsor’s valuable time but also reduces the administrative overhead associated with TMF building & management during clinical trials and throughout development cycle

Clinical Trial Disclosure (CTD) Services:
- Ensure clinical trial disclosure (clinical trial registration and results publishing) as per the regulatory requirements
- Ensure Compliance writing, review, editing, harmonization and postings of clinical trial information intended for publication on ClinicalTrials.gov or other international clinical trial registries. This includes but not limited to protocol, registration, clinical study reports, result disclosures, ICH/E3 results summaries, citations, SAS/XML programming etc.

Figure 4: Violations Leading to Warning Letters:
- Inadequate training of investigators and site staff regarding study responsibilities (requirements of a protocol, supervision, data collection and storage, handling of investigational product, etc.)
- Failure to reporting of SAEs
- Failure to recognize a systemic problem with clinical trial
- Failure to investigate in a comprehensive manner, commensurate with risk
- Insufficient or delayed follow-up/correction of identified deficiencies
- Inadequate vendor oversight (lack of clarity in responsibility/accountability of third parties)
- Inadequate due diligence in mergers/acquisitions
- Poorly designed protocol
- Insufficient training/implementation of new technologies
- Failure to adequately document corrective and preventive actions

Risk identification will be performed using following methods:
- reviewing metrics from prior studies
- brainstorming sessions
- review warning letters and other reports of inspectional findings

Using above risk identification methods, Project Manager will prepare the project specific Risk Management Plan along with the risk mitigation and contingency plans. An Independent clinical oversight team will evaluate the performance of the each clinical trial task using the predefined project specific quality metrics on ongoing basis. If any risks identified during this process, risks will be analyzed and
investigate the root cause. Accordingly appropriate corrective actions will be taken and communicate to all stakeholders.

**Vendor management & oversight**

Both FDA regulations and ICH guidelines on good clinical practice (GCP) mandate sponsor oversight of all clinical research activities where transfer of regulatory obligations has occurred with external parties through contractual obligation. Each company should have the defined standard operating procedures on vendor selection process. During vendor selection, legal compliance of the vendor, financial status, experience, customer complaints, resources and quality of the service should be taken into consideration. Once the vendor is audited that information should be made available to operational team. Sponsors require careful selection and training of qualified individuals to manage the delegated activities (See Figure 5). Vendors are to be audited by QA at least once in year to evaluate their performance.

**Figure 5: Outsourcing activities:**

- Selecting CRO/SMO
- Investigator/Site selection
- Central laboratory services
- Drug accountability and disposition
- Selecting monitors
- EDC vendors
- Study documents translations
- Recordkeeping and record retention
- Investigational New Drug safety reports

**Benefits**

- Increases the clinical data quality and reduce non-conformances, deviations, CAPA, rework, scrap, complaints, etc
- Is an iterative and continuous process where prior risks that became problems are either mitigated or recognized and reviewed in a predictive manner for the future
- Provides a mechanism for risk communication (formalized vehicle/process) and exposure to management
- Provides a framework to better understand processes, what is critical and why
- Helps provide rationale for not spending time on low risk activities, process events, or systems, rather focusing resources and time on the things that are really important
- Can be avoided regulatory surprises and warning letters
- Projects can be completed on time and within budget
- Can overcome vendor hassles
- Ensure adequate protection of human subjects, quality, data integrity and compliance with applicable regulations.
What Next

Clinical Oversight is a proactive approach to identify potential risks, systemic issues early before they become problems and tracks the data over time, which allows for addressing issues. It helps in reducing overall costs by enabling qualified decision making in the planning stage. Quality plans and oversight plans are not the permanent solutions, but they can help in proactively identify the potential risks and its management.

There has been a stronger focus and an increase in sponsor/monitor inspections in recent years, this leads to a significant increase in scrutiny by regulatory agencies. Sponsors should formally address risk management, and those on the leading edge are looking into their internal practices in order to find and close performance gaps through a systematic retrospective analysis of their internal oversight and quality practices. Prospectively, sponsors should develop quality plans and oversight plans for smooth conduct of clinical trials whilst meeting all regulatory obligations. If sponsor do not have such internal clinical oversight capabilities, this task may be outsourced to third party vendors who can oversee all these responsibilities.

References

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3. The Food and Drug Administration’s Oversight of Clinical Trials (Sep 2007)
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5. Primer on Vendor Oversight for Clinical Project Managers_ACRP Monitor_LH_23Jan2012