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Finding out Subject Compliance data in clinical trials.

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ABSTRACT

Compliance in clinical trials is often overlooked, leading to underestimated impacts of patient noncompliance. Improved analysis of patient adherence during drug testing could enhance trial conduct. Subjects are typically required to adhere to protocol visits, complete forms between visits, and report side effects. These activities gauge subject adherence, crucial for trial reports. However, missing data from incomplete visits hinders accurate safety and efficacy assessments, potentially compromising participant compliance. To address this issue, it's imperative to monitor and assess subject data compliance with the study protocol throughout the trial. Our presentation will delve into various methodologies for ongoing study assessment, including monitoring compliance with procedures such as CT scans, bone scans, and Patient-Reported Outcomes (PROs). By discussing these strategies, we aim to underscore the significance of compliance monitoring in upholding the integrity and reliability of clinical trial outcomes, ensuring that findings accurately reflect the effects of the tested interventions.

INTRODUCTION

What is Subject compliance:

Participant compliance (also known as adherence) refers to the degree to which participants in a clinical study adhere to the study protocol, including the prescribed treatment regimen, scheduled visits, and other study-related activities. It can encompass various aspects such as taking medications as directed, attending follow-up visits, completing study questionnaires, and following lifestyle or behavioral guidelines provided by the research team. Subject compliance plays a critical role in the success of clinical trials as it directly impacts the accuracy, reliability, and validity of study results.
Key Aspects of Subject Compliance [1]:

- Medication Adherence: Taking the correct dose of a prescribed drug at the specified times and under the conditions required by the study.
- Follow-Up Visits: Attending all scheduled clinical visits for monitoring, tests, and assessments as specified in the protocol.
- Procedural Adherence: Following non-medication-related instructions, such as participating in specific exercises, avoiding prohibited foods, or adhering to lifestyle changes outlined by the study.

- Reporting and Monitoring: Subjects are expected to accurately report any side effects, symptoms, or other relevant health information throughout the study. This may include completing diaries or questionnaires or using wearable devices to track health data.

Implication of subject Non-compliance:

Subject non-compliance in clinical studies can have serious implications on the quality, reliability, and interpretation of trial outcomes. It affects the overall success of the study, compromises patient safety, and can even result in the failure of the trial. The following are detailed breakdown of the impact of subject non-compliance:

- Reduced Data Accuracy and Reliability
- Bias in Study Outcomes
- Decreased Statistical Power
- Invalid or Inconclusive Results
- Regulatory and Ethical Consequences
- Increased Cost and Duration
- Impact on Patient Outcomes
- Hindrance to Drug Development and Approval

ROLE OF STATISTICAL PROGRAMMER:

The review of subject compliance in clinical trials is a multidisciplinary effort involving various functional groups, from clinical operations and principal investigators to data management, biostatistics, and regulatory affairs. We, a statistical programming team, are also a crucial part of this effort. The role of a statistical programmer in ensuring subject compliance in clinical studies is multifaceted and integral to the overall process of monitoring, analyzing, and reporting compliance-related data. Our work helps ensure the accuracy and integrity of the trial data, which in turn impacts the evaluation of treatment efficacy and safety. Below are key aspects of a statistical programmer's role concerning subject compliance:

- Data Management and Programming
- Compliance Metrics Development
- Programming for Protocol Deviations
- Support in Analysis and Reporting
- Support for Risk-Based Monitoring (RBM)
- Regulatory and Quality Compliance
- Technology and Automation
- Cross-functional Collaboration

MATRICS OF PARTICIPANTS COMPLIANCE

Treatment Adherence

Treatment Adherence refers to how well participants follow the prescribed treatment regimen, including the correct dosage, timing, and frequency. The EX (Exposure), EC (Exposure as Collected), and DA (Drug Accountability) datasets are used to capture various aspects of treatment administration, collection, and accountability. Treatment compliance can be analyzed by utilizing these datasets in a structured way.

Steps to calculate Treatment Adherence:

1. Identify the Treatment Regimen and Frequency from Schedule of Assessment (SOA) table from the protocol:
   Create SOA parent dataset with protocol expected schedules, including -
   - The planned treatment frequency (e.g., daily, weekly, etc.).
   - The planned dose for each administration.
   - Any treatment windows or allowed deviations in the timing of treatment (e.g., taking the dose within a certain number of days).
2. Create a subject level matrix dataset by extracting data from the EX, EC, and DA Datasets along with dosing visit.
   - EX (Exposure):
     - Treatment Name
     - Dose administered
     - Start date of administration
     - End date of administration (if relevant)
   - EC (Exposure as Collected):
     - Planned dose
     - Actual dose taken, as reported by the participant
     - Start date of administration
     - End date of administration (if relevant)
   - DA (Drug Accountability):
     - Treatment Name
     - Amount of drug dispensed
     - Amount of drug returned
     - Date of drug accountability visit or assessment
3. Comparison of the collected data with SOA:
   Combine Subject level matrix dataset with SOA dataset to calculate the Treatment adherence score by comparing actual dose parameter such as dosing visit, dose accountability, dose delay, drop or reduce with corresponding planned visit and planned dose from SOA. When a subject dosing information is aligned with SOA data, the adherence score would be 1 else 0. Hence record the outcome as 0 or 1.

Visit Adherence:

Visit Adherence refers to how well participants adhere to the scheduled visits according to the study protocol. Protocol SOA outlines the planned visits along with the expected timing and clinical assessments in a structured table. To calculate visit adherence, we compare the scheduled visits from SOA to the actual visits recorded in the data.

Steps to calculate the visit adherence score:

1. Create SOA dataset – Extract information from Protocol SOA into a dataset. The key variables are as follows – Schedule events, Visit, Visit Day and Window(+/-).
2. Subject visits dataset – Create SV dataset consolidating information about the timing of subject visits (scheduled and unscheduled) from EDC data as well as external data. The key variables are Visit, start date, End date, Visit day.
3. Combine the SOA dataset with Subject visit data to calculate the adherence score. For each subject, compare the actual visit dates from the subject visit data with the planned visit dates and visit windows. If the actual visit occurred within the defined visit window, the visit is considered compliant, and the score would be 1. For each missed or out of the window visit, the score would be 0.

Procedure Adherence:

Procedure adherence can be measured by comparing the actual procedures performed (e.g., lab tests, imaging, biopsies) as recorded in the collected data with the planned procedures as outlined in the SOA. Procedure compliance refers to whether the planned procedures were performed according to the study protocol and within the expected time windows.

Steps to calculate the procedure adherence score:

Two main sources of data will be compared in this process.

- Collected Procedure data – The dataset typically contains details about type of procedure, start date, actual visit, visit day per subject.
- SOA dataset

Combine the SOA dataset with Subject procedure data to calculate the adherence score. Based on the comparison of planned and actual data the score will be assigned – 1 for Adherence and 0 for missing or out of window assessments.

OUTCOME PRESENTATION

Summary statistics for the compliance metrics datasets can be presented in a table format, presenting percentage of compliance for each metrics group by time of assessments (i.e., Scheduled Visits). The value of compliance may vary between 0 to 100%.

Table 1: Compliance Table by visit

Label	Treatment (%)	Visit (%)	Procedure (%)	Overall (%)
Visit 1	80	100	80	70
Visit 2	80	80	70	50
Visit 3	70	90	100	60
Visit 4	xx	xx	xx	xx
Visit 5	xx	xx	xx	xx
Visit n	xx	xx	xx	xx
EOT/EOS	xx	xx	xx	xx

Table 2: Compliance Table by Visit and Subgroups

Subgroup table, to represent variation of compliance among different subgroups and its cumulative impact.

Label	Sub Group	Treatment (%)	Visit (%)	Procedure (%)	Overall (%)
Visit 1	Male (n = 5)	100.0%	100.0%	100.0%	100.0%
Visit 1	Female (n = 5)	60.0%	100.0%	60.0%	40.0%
Visit 1	Site - S001 (n = 4)	75.0%	100.0%	75.0%	50.0%
Visit 1	Site - S002 (n = 4)	100.0%	100.0%	100.0%	100.0%
Visit 1	Site - S003 (n = 2)	50.0%	100.0%	50.0%	50.0%
Visit 1	Age <50 (n = 5)	80.0%	100.0%	80.0%	60.0%
Visit 1	Age >=50 (n = 5)	80.0%	100.0%	80.0%	80.0%
Visit 2	Male (n = 5)	80.0%	80.0%	100.0%	60.0%
Visit 2	Female (n = 5)	60.0%	100.0%	100.0%	60.0%
Visit 2	Site - S001 (n = 4)	50.0%	100.0%	100.0%	50.0%
Visit 2	Site - S002 (n = 4)	100.0%	100.0%	100.0%	100.0%
Visit 2	Site - S003 (n = 2)	50.0%	50.0%	100.0%	0.0%
Visit 2	Age <50 (n = 5)	60.0%	80.0%	100.0%	40.0%
Visit 2	Age >=50 (n = 5)	80.0%	100.0%	100.0%	80.0%

Descriptive statistics (Histogram/ Mix diagram)

Figure 1: Line plot to represent compliance variability across different visits. The trend line is the regression probability of the percentage compliance from previous records.

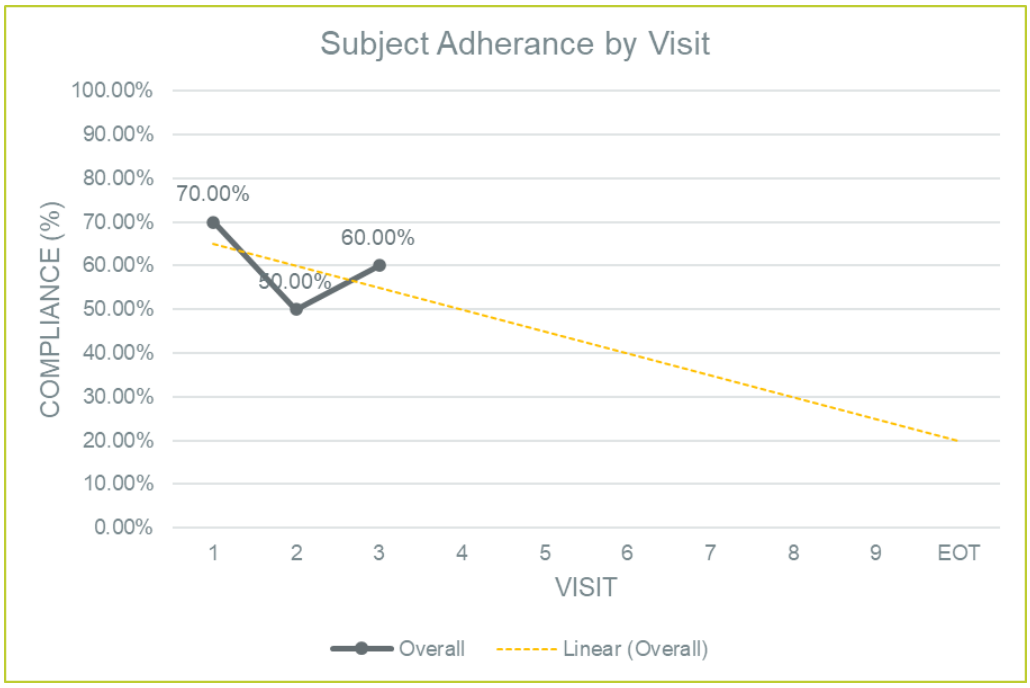


Figure 2: Mixed Plot, to represent variability of compliance across visit combined with the key metrics that contributed to overall compliance.

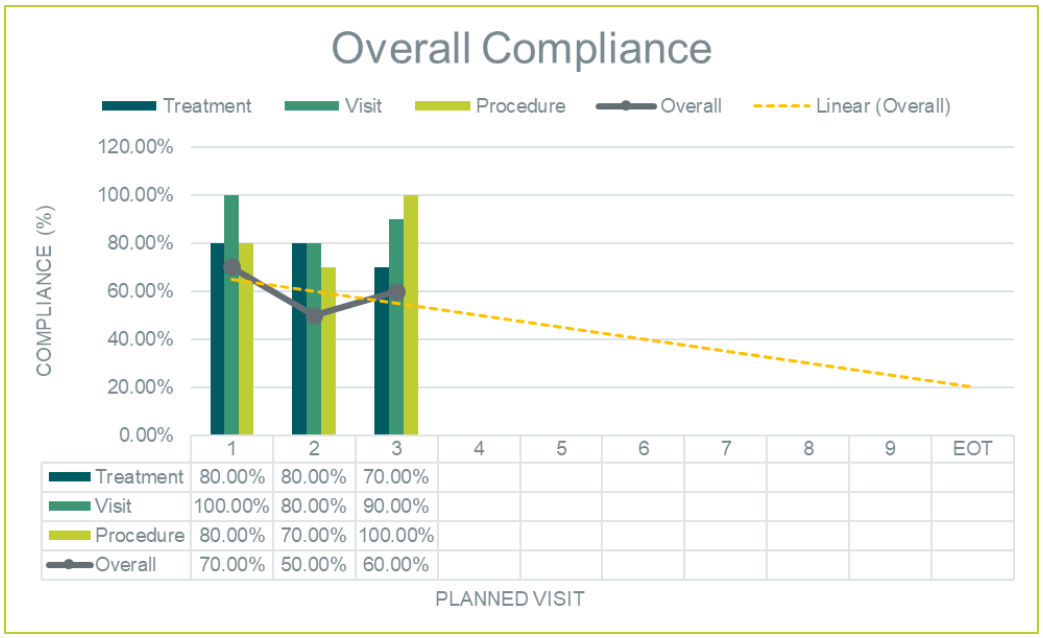
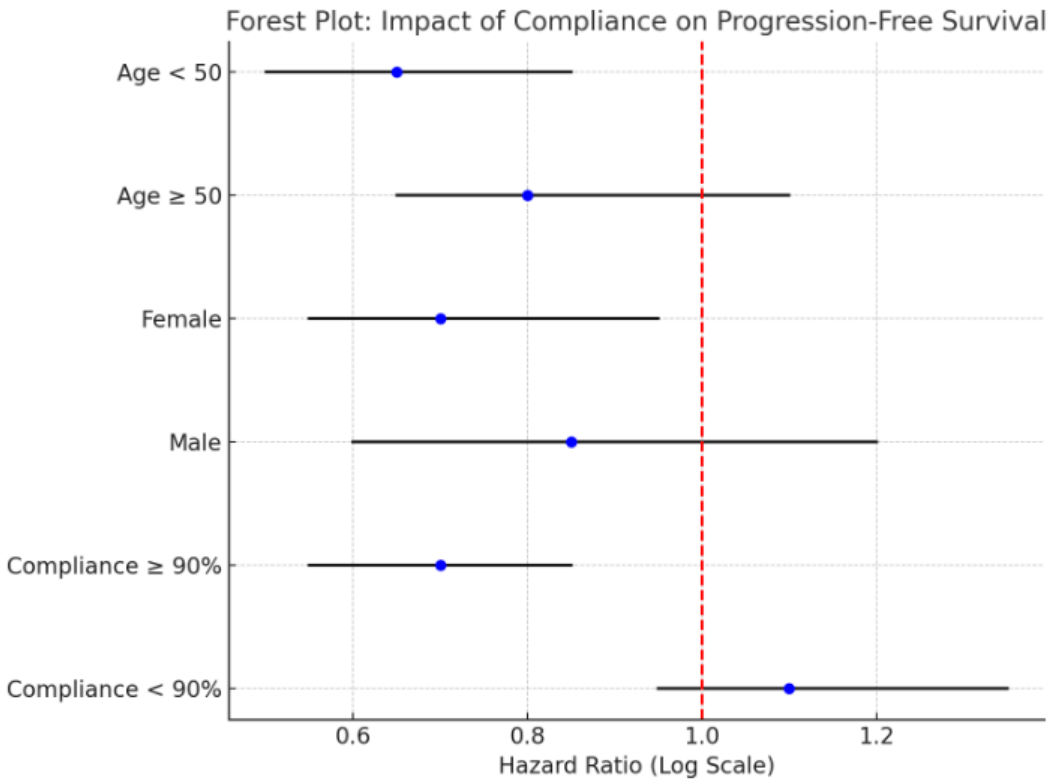


Figure 3: Forest plot, Impact of compliance on Endpoint measurement combined with subgroups (i.e., PFS).



FREQUENCIES OF COMPLIANCE REPORTING

The frequency of compliance reporting is a dynamic process requiring close coordination across departments.

Initial Setup and Planning

Engagement with Stakeholders: Start by consulting key stakeholders from biostatistics, safety, clinical operations, and other relevant departments. The goal is to define clear objectives, and timelines.

Defining Objectives: Establish what needs to be monitored (e.g., patient safety, data quality, adherence to protocols, regulatory requirements).

Deciding When to Initiate the 1st Compliance Report

Study Milestones: Typically, the first compliance report is generated at a significant project milestone, such as after the first patient is enrolled, the first data lock, or the end of the first study phase.

Data Availability: Ensure that enough data has been collected for meaningful analysis before issuing the first report.

Initial Risk Review: Early risk assessments (based on data from the first few days/weeks/months of a clinical trial) may trigger the need for earlier reporting if high risks are identified.

Determining Frequency of Subsequent Reports

Regular Monitoring: For ongoing studies, compliance reports are often generated at regular intervals (e.g., monthly, quarterly) based on the study's complexity and regulatory requirements.

Adaptive Frequency: Reporting frequency may change based on the progression of the study, emerging risks, or feedback from stakeholders. A complex study with multiple variables might require more frequent updates at certain stages.

Here are the key factors to consider: [2, 5]

- **Study Phase**: Early-phase trials require more frequent reporting (e.g., weekly), while later phases may allow for bi-weekly/monthly reports.
- **Frequency of Imaging Visits**: Shorter intervals between CT scans (e.g., 2-4 weeks) require more frequent reporting (e.g., weekly or bi-weekly).
- **Impact on Treatment Decisions**: If scans guide treatment decisions, real-time or daily reports may be needed to avoid delays in critical decisions.
- **Patient Safety and Disease Monitoring**: For aggressive cancers or safety-critical time points, frequent reporting ensures timely imaging.
- **Trial Design and Complexity**: Adaptive or multicenter trials may require more frequent or site-specific reports.
- **Technology and Data Systems**: Real-time data systems allow for daily or near-real-time reporting; manual systems may result in less frequent reports.
- **Participant Population**: Elderly or vulnerable populations may require more frequent monitoring (e.g., weekly) due to higher risk of non-compliance.
- **Site Performance**: Sites with logistical challenges may need site-specific reports generated bi-weekly or weekly.
- **Interim Analysis or Key Milestones**: Generate reports before interim analysis or key milestones to ensure complete imaging data is available for review.

Cross-functional Communication

Regular meetings with biostats, safety, clinical operations, and other involved teams ensure that all parties are aligned on reporting needs, frequency, and content.

Continuous feedback loops should be built in, as initial reporting decisions may need to evolve over time.

CONCLUSION:

Compliance plays a pivotal role in the success of oncology clinical trials, particularly during Phases II and III, where consistent and accurate long-term data is essential for determining both efficacy and safety. Non-compliance can significantly impact study outcomes, delay results, and potentially compromise patient safety. Therefore, developing effective strategies to monitor and improve compliance is crucial for ensuring reliable trial results and overall study success.

Future Recommendations:

1. **Implementation of Advanced Tracking Systems:** Future trials should integrate advanced compliance tracking systems, such as real-time electronic diaries (E-Diaries), wearable devices, and automated reminders, to monitor patient adherence in a timely manner. These tools can assist in identifying non-compliance early and prompt the study team to take corrective actions.
2. **Patient-Centered Interventions:** Tailored interventions, including patient education programs, can help improve understanding and motivation, ensuring better adherence to study protocols. Ongoing education can also reinforce the importance of compliance for study success and patient safety.
3. **Adaptive Designs with Predictive Analytics:** In studies with adaptive designs, leveraging predictive analytics can help anticipate non-compliance patterns. Integrating these analytics within compliance tracking tools will allow for proactive measures to mitigate risks and ensure more accurate trial outcomes.
4. **Collaboration Between Bio-Stat and Clinical Teams:** For optimal results, a close collaboration between biostatistics teams and clinical trial operations is necessary. This will allow for real-time adjustments and foresight on compliance-related impacts, ensuring efficient study execution and high data quality.

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