

DH07

PHUSE EU Connect 2024

Finding out subject compliance data in clinical trials

Thinking beyond the quality. A shift from data custodian to data detective.

15.11.2024

BIONTECH

Agenda

01. What is subject data compliance and impact of Non-Compliance
02. Role of Statistical Programmer
03. Key Compliance Metrics
04. Data compilation & Outcome presentation
05. Frequency of Compliance Monitoring
06. Conclusion and Future Recommendations

01: What is subject data compliance?



Subject compliance refers to the extent to which participants in a clinical study adhere to the study protocol.



Scheduled Visits: Regular visits allow for monitoring of the participant's health status, the collection of biological samples, and the recording of adverse events.



Adherence to Medication : Participants are expected to take medications as prescribed in terms of dose, frequency, and duration



Dietary and Lifestyle Restrictions: In some studies, participants may need to adhere to specific dietary or lifestyle recommendations.



Completion of Study-related Procedures: Participants must undergo tests, scans, and other assessments as specified in the protocol.

01: Impact of non-compliance

Non-compliance may widen the risk both at scientific and nonscientific level



Operational and Regulatory Impact

- Increased Costs and Resources
- Delays in Study Timelines
- Regulatory and Ethical Implication
- Protocol Amendments

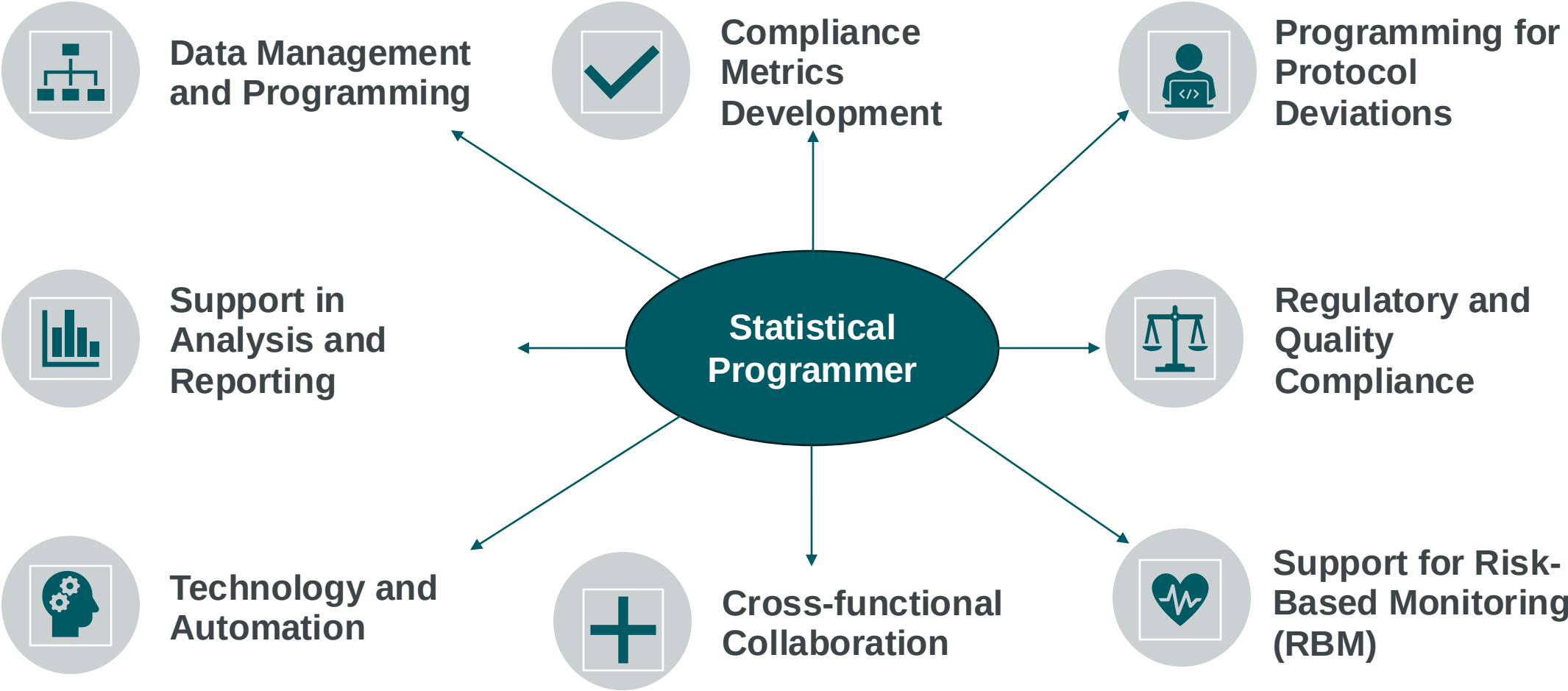


Scientific Impact (Validity and Data Integrity)

- Reduce Statistical Power
- Bias in Study Results
- Data Quality and Integrity
- Increase in Variability
- Impact on Safety and Efficacy Findings

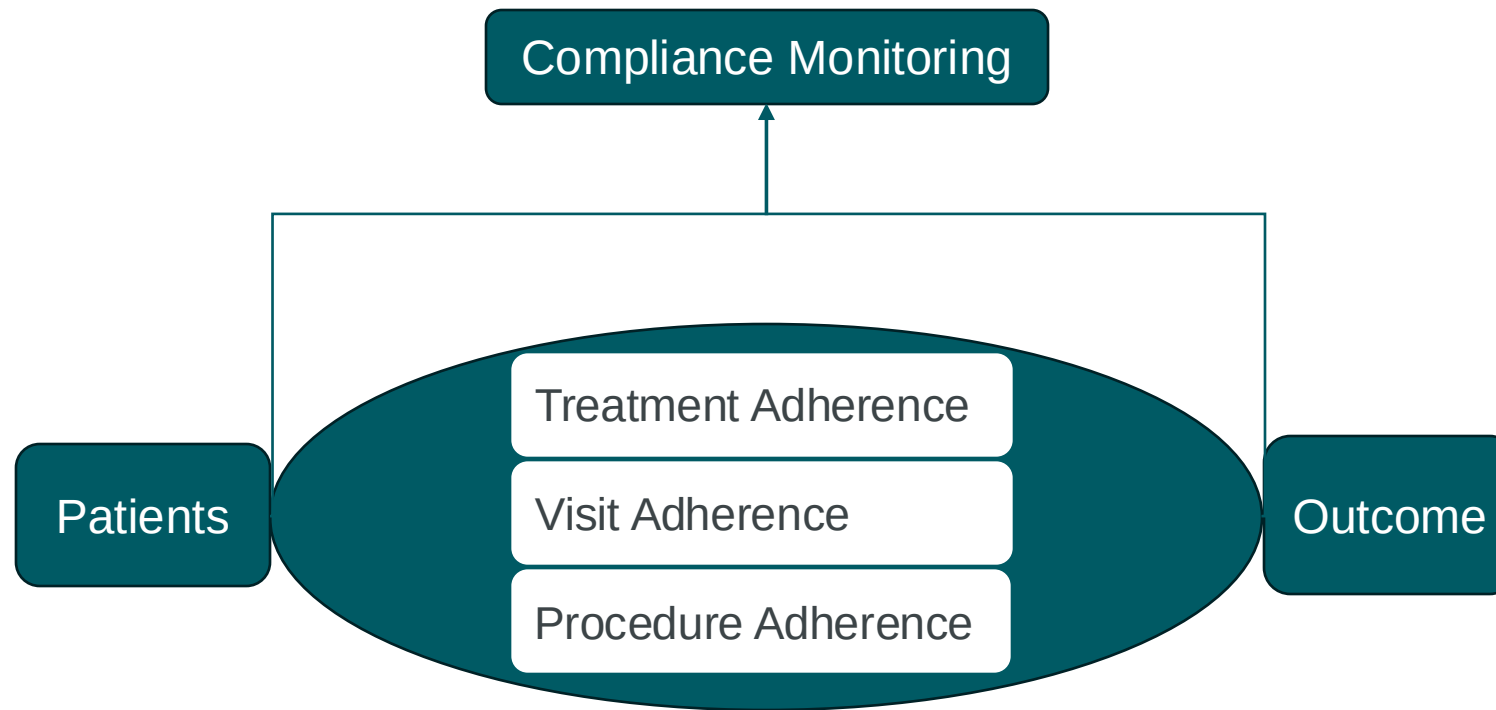
02: Role of Statistical Programmer

Leveraging the advantage of being programmer and broader access to information



03. Metrics of Subject Compliance

Key Metrics for Compliance



Treatment Adherence:

- *Oral/Bolus* (Monitoring pill counts or electronic medication monitors)
- *IV/Infusion Therapy*: Tracking attendance for scheduled treatments

Visit Adherence:

- Percentage of patients attending all required clinic visits.
- Understanding the window of variation (For unscheduled Visit)

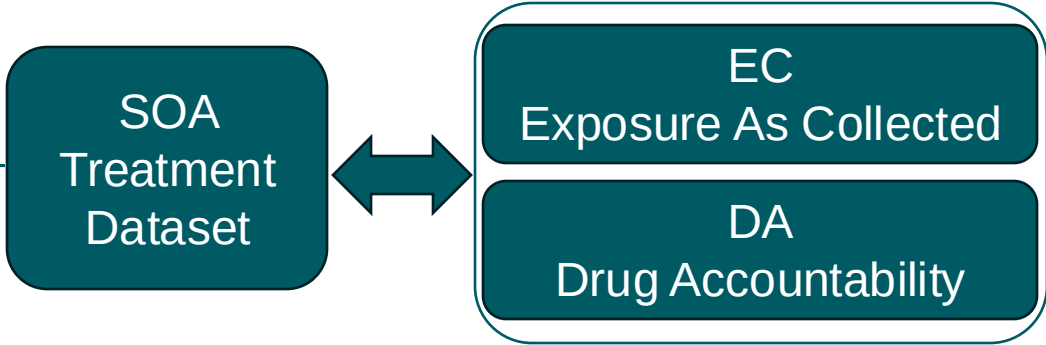
Procedure Adherence:

- Adherence to diagnostic tests, imaging (e.g., CT, MRI), and biopsies.

Key Compliance Metrics (Continued...)

Treatment Adherence

Schedule of Assessments						
Study Schedule						
Schedule of Events	Screening	Cycle 1	Cycles 2-17	Cycle 18-35	EOT	Post Treatment
Cycle Day	Up to Day -28	Day 1	Day 1	Day 1	At Discontinuation	PD/Survival FU
Visit Number	V1	V2	V3 to V18	V19 to V35		Every 4 months
Visit Window (Days)		±3	±3	±3	1-30	±14
Vital Signs/Weight	x	x	x	x	x	
Study Drug Administration See (Note)		x	x	x		



Components that contribute to evaluation of Treatment Adherence score.

- ➔ Dosing visit
- ➔ Dose accountability
- ➔ Dose Delay/Drop or Reduce
- ➔ Infuse Duration

TREATMENT PLAN AND TIMING OF PROCEDURES

Study Interventions

Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Sourcing
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SOA: Schedule of Assessment

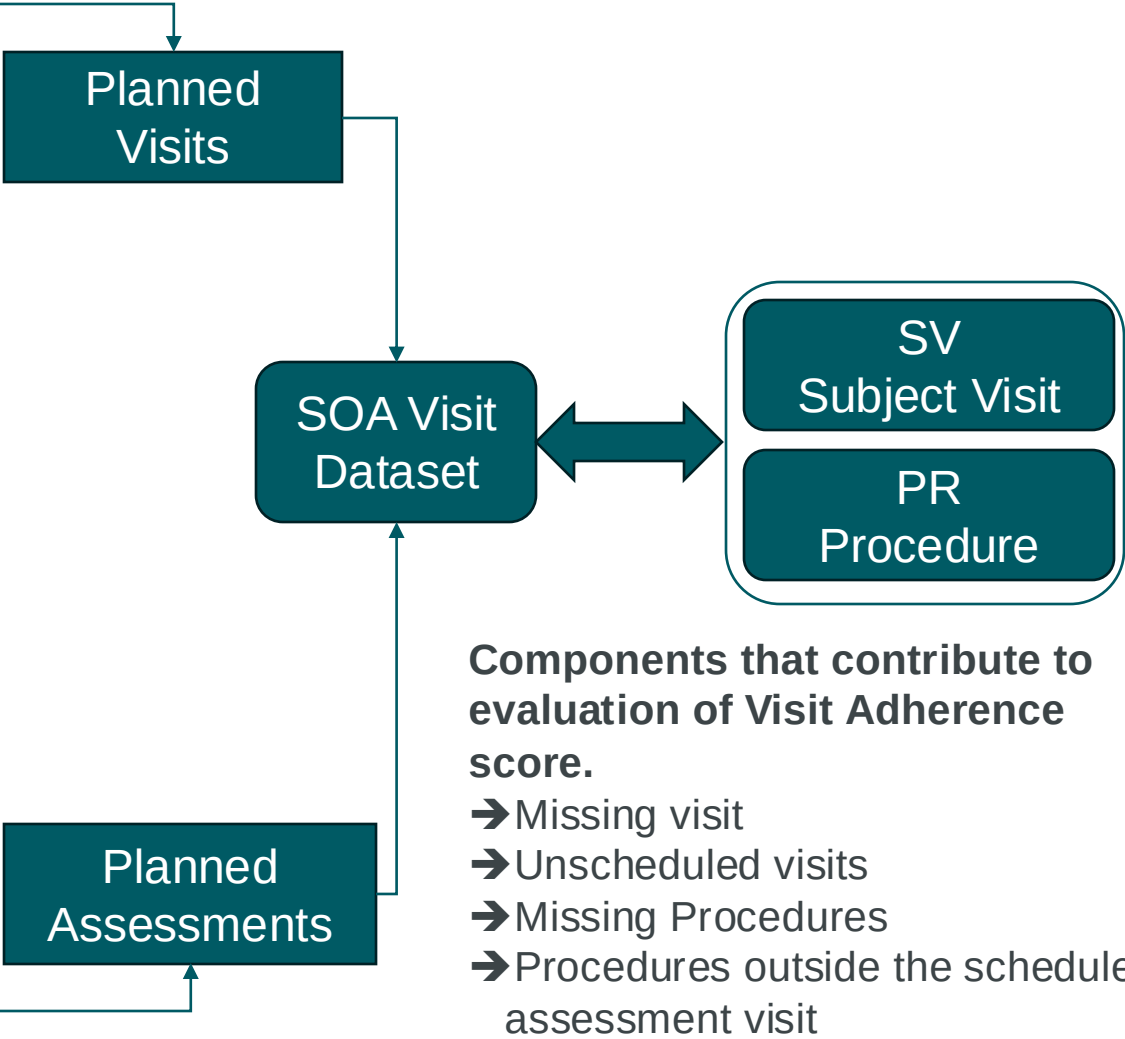
Key Compliance Metrics (Continued...)

Adherence to the schedule of visits and procedures

Schedule of Assessments						
Study Schedule						
Schedule of Events	Screening	Cycle 1	Cycles 2-17	Cycle 18-35	EOT	Post Treatment
Cycle Day	Up to Day -28	Day 1	Day 1	Day 1	At Discontinuation	PD/Survival FU
Visit Number	V1	V2	V3 to V18	V19 to V35		Every 4 months
Visit Window (Days)		±3	±3	±3	1-30	±14
Vital Signs/Weight	x	x	x	x	x	
Physical Examination	x	x	x	x	x	
ECOG Performance Status	x	x	x	x	x	
12-lead ECG	x	x	x	x	x	
CBC with differential	x	x	x	x	x	
Comprehensive Serum Chemistry Panel	x	x	x	x	x	
Coagulation Parameters	x				x	
Urinalysis	x				x	
Thyroid Function	x	x			x	
Tumor Imaging ^Y	x	x			x	
Survival assessment						x

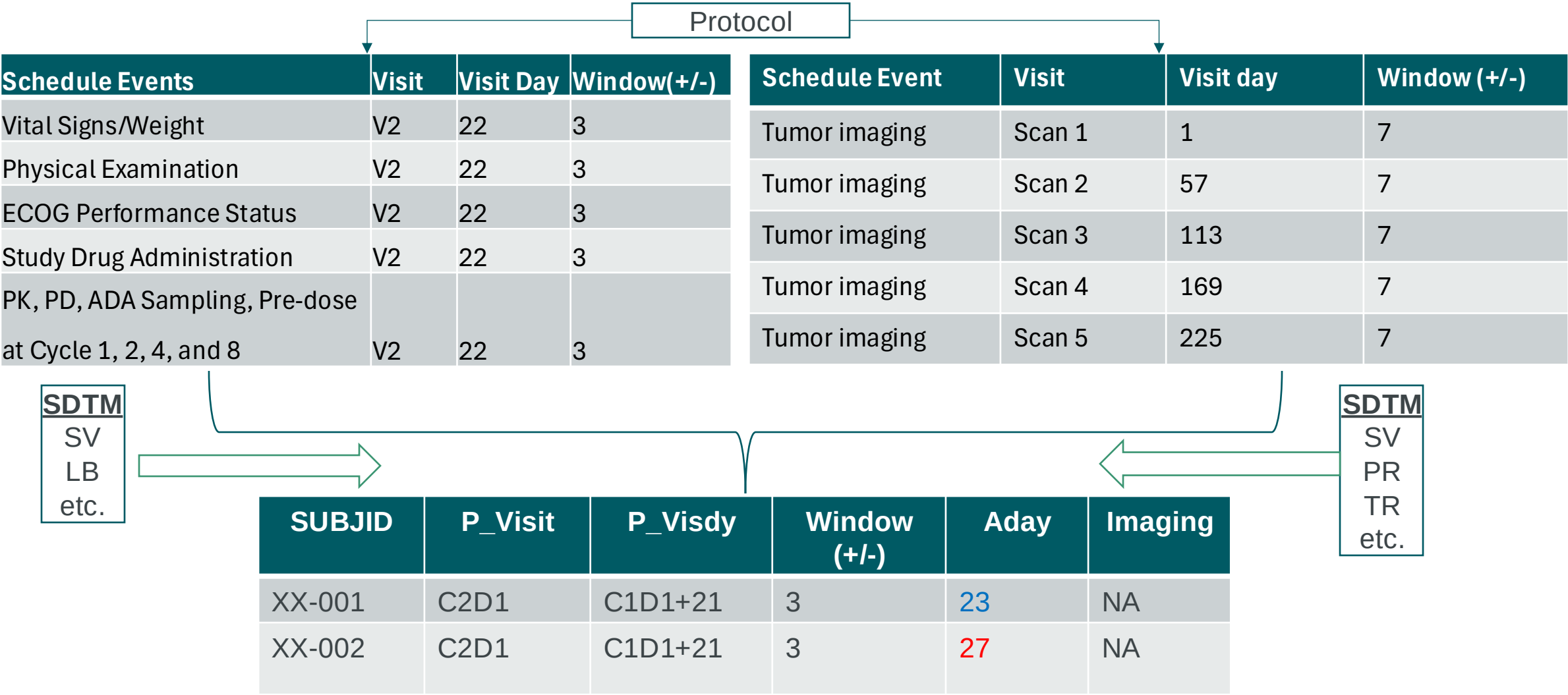
Y. Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to C1D1; and while on study, at week 8 (±1 week) from C1D1, then every 9 weeks (±1 week) from the most recent scan for the first year, and every four months (±2 weeks) in second year. The same imaging technique should be used for an individual patient throughout the study

SOA: Schedule of Assessment



Key Compliance Metrics (Continued...)

Example (Visit Adherence)



04. Data compilation & outcome presentation

Outcome representation (Continued..)

Data compilation and Metrics score

Metrics 1: (Reference/Baseline range= 80%, i.e., $\geq 80\%$ = **1** and $< 80\%$ = **0**)

Components		Results	Score (0-1) Weight	Metrics Score	Metrics Outcome
Subject completed visit (Y/N)	⇒	Y	⇒ 0	1-Sum(score1 + score n) / count(Component) 1-(0.75/4)= 81%	⇒ 1
Delay/Interruption in Infusion(Y/N)	⇒	Y	⇒ 0.25		
At least 3 Hours gap before dosing (Y/N)	⇒	N	⇒ 0.5		
Dose reduced or dropped (Y/N)	⇒	N	⇒ 0		
More than 30% pills returned (Y/N)	⇒	NA	⇒ 0		
Outcome: 0= Non-compliant 1= Compliant					

Outcome representation (Continued...)

Datasets/Tables

Key Metrics Data (One record per subject and planned timepoint)

Subject	Label	Treatment	Visit	Procedure	Overall
XX-001	Visit 1	1	1	1	1
XX-002	Visit 1	1	1	1	1
XX-003	Visit 1	1	1	1	1
XX-004	Visit 1	1	1	1	1
XX-005	Visit 1	1	1	1	1
XX-006	Visit 1	0	1	1	0
XX-007	Visit 1	1	1	1	1
XX-008	Visit 1	1	1	0	0
XX-009	Visit 1	1	1	1	1
XX-010	Visit 1	0	1	0	0

Compliance Table (One Record per planned timepoint)

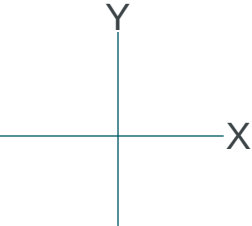
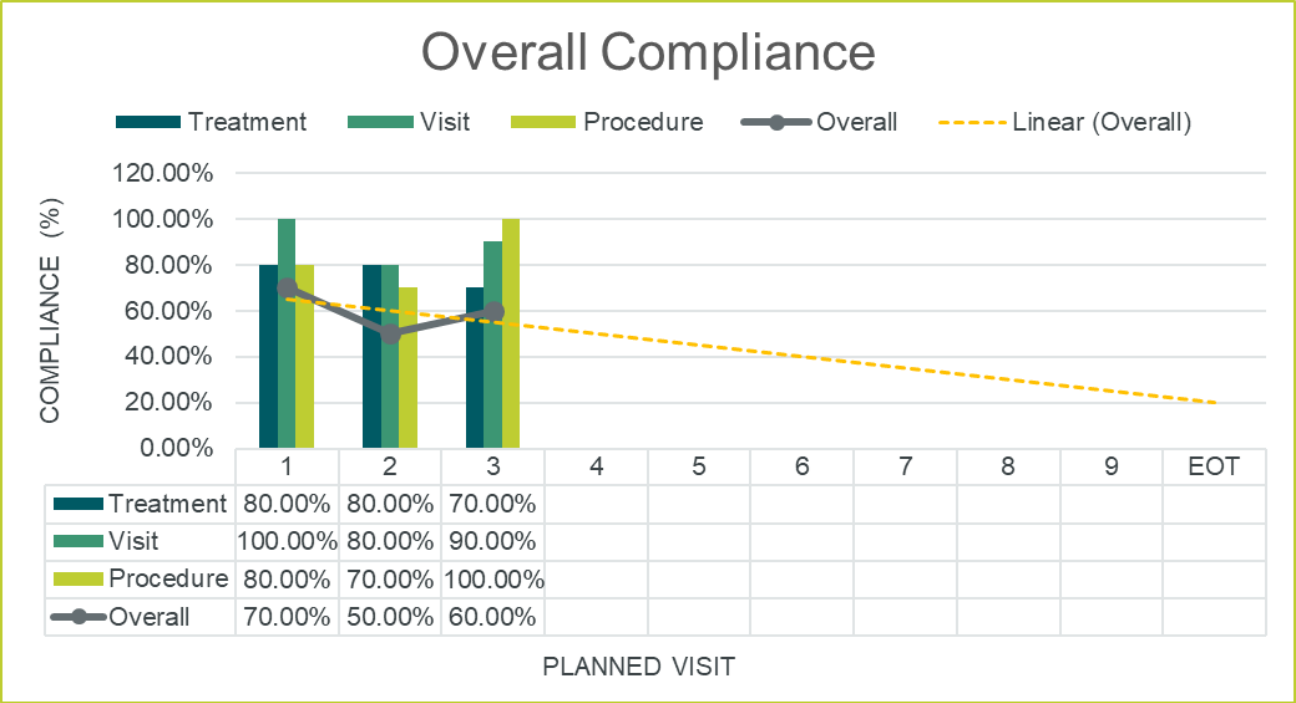
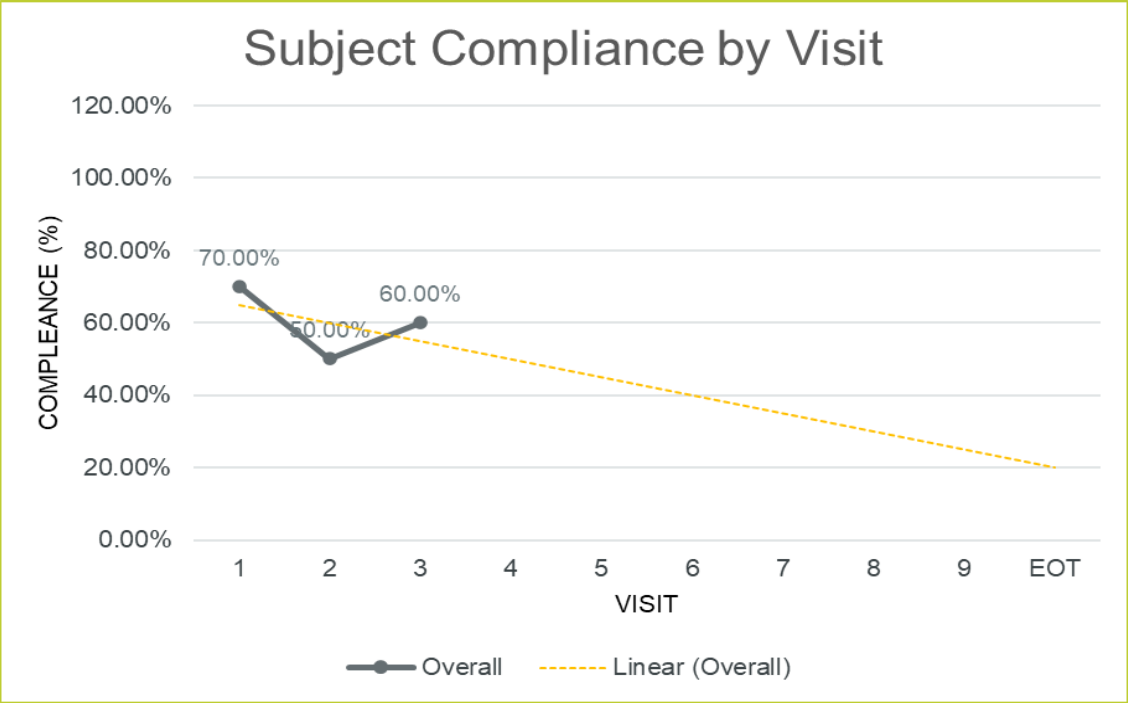
Label	Treatment (%)	Visit (%)	Procedure (%)	Overall (%)
Visit 1	80	100	80	70
Visit 2	80	80	70	50
Visit 3	70	90	100	60
Visit 4	xx	xx	xx	xx
Visit 5	xx	xx	xx	xx
Visit 6	xx	xx	xx	xx
Visit 7	xx	xx	xx	xx
Visit 8	xx	xx	xx	xx
Visit 9	xx	xx	xx	xx
EOT/EOS	xx	xx	xx	xx

EOT: End of treatment EOS: End of study

Outcome:
0= Non-compliant
1= Compliant

Outcome representation (Continued...)

Descriptive statistics

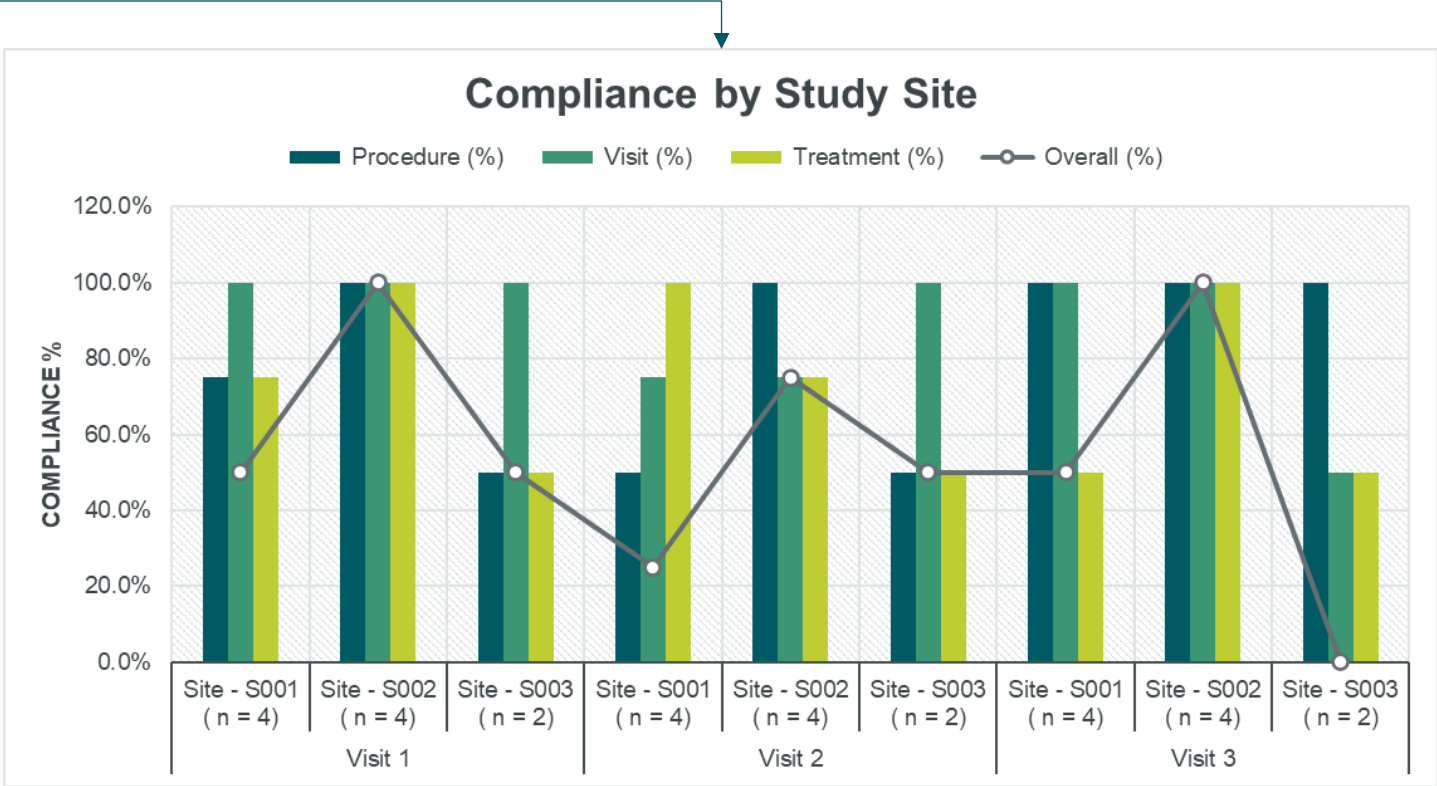


EOT: End of treatment EOS: End of study

Outcome representation (Continued..)

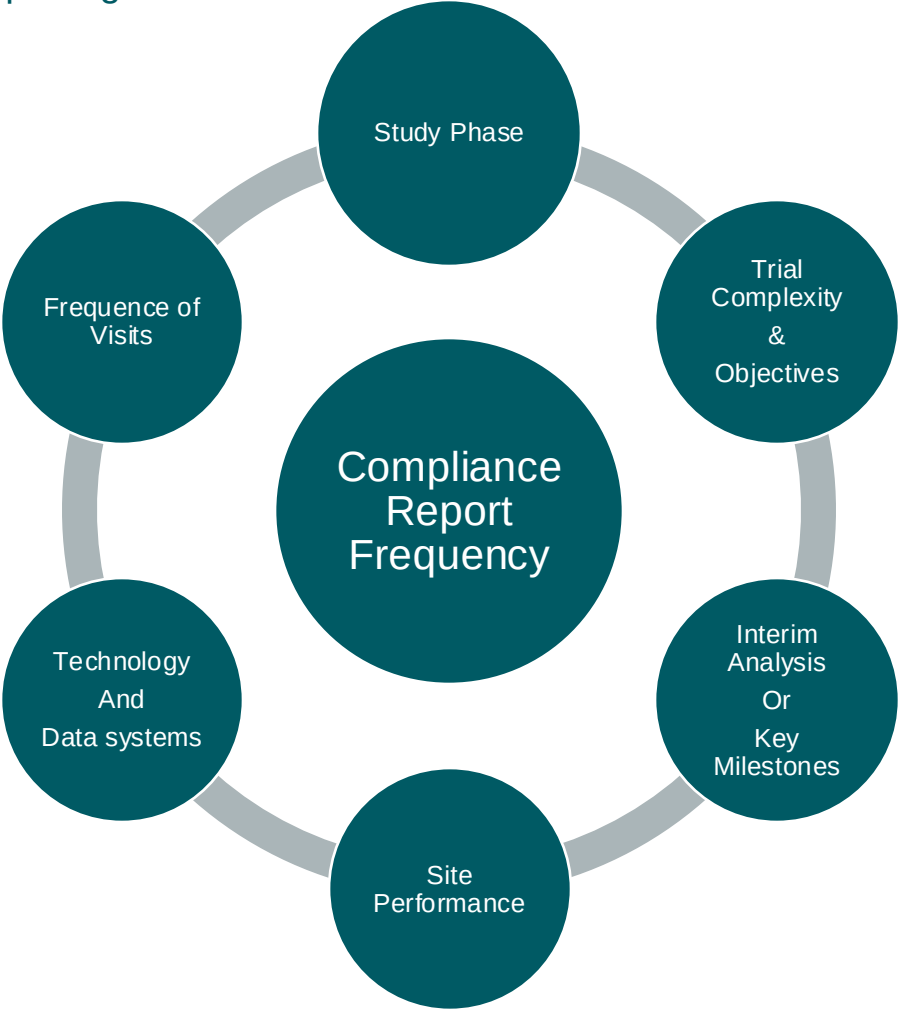
Diving deep to understand the variability among subgroups

Label	Subgroup	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%



05: Frequency of Compliance Reporting?

What can influence the frequency of such reporting



06: Conclusion & Future recommendations

❖ **Summary:**

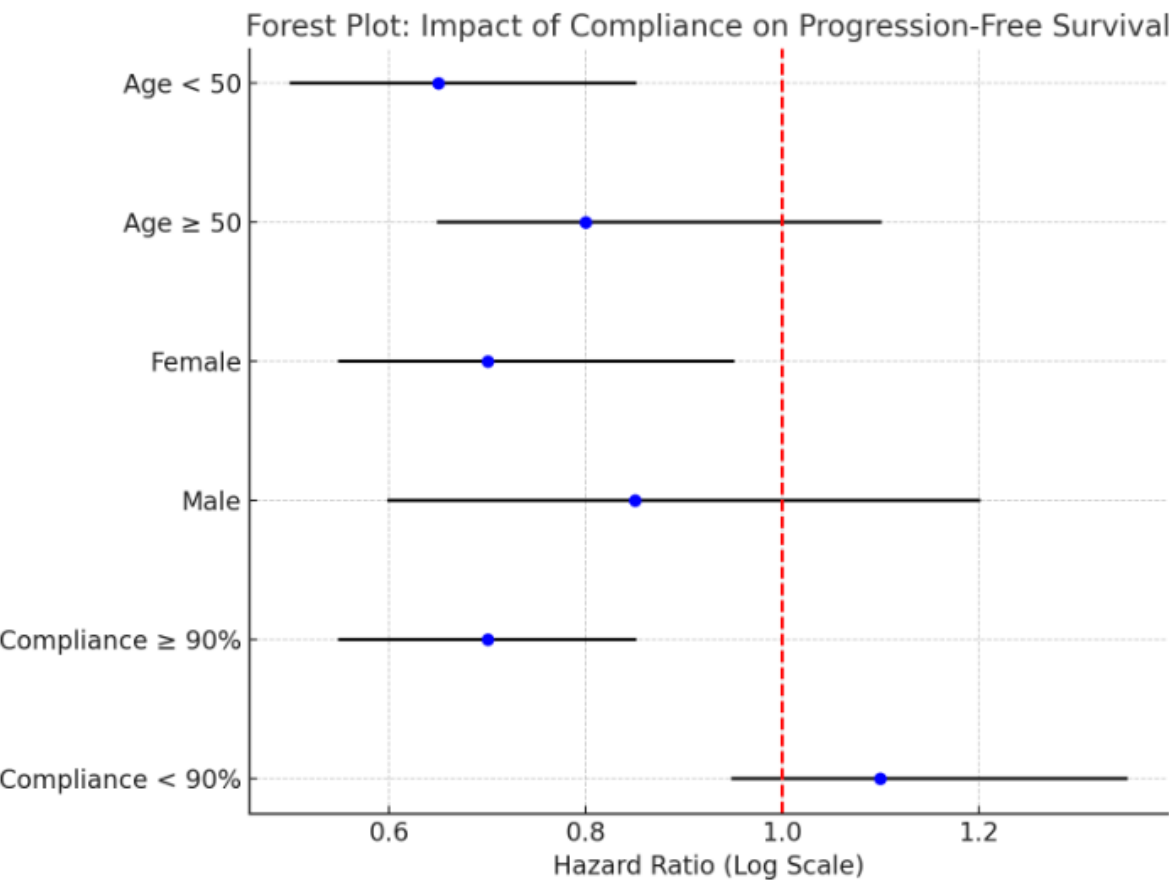
- ❑ Compliance is a critical factor in the success of oncology clinical trials, particularly in Phases II and III, where long-term data is needed for efficacy and safety.
- ❑ An early identification of non-compliance and the trend can be very informative for the study team to take necessary actions on the go (i.e., introducing supplementary tracking tools or interventions such as E-Diaries, wearables, reminder system, patient education etc.).

❖ **Recommendations for future studies:**

- ❑ In case of adaptive study design, a robust compliance tracking system will help Bio-Stat to foresee the impact and plan corresponding actions.
- ❑ Having internal data from multiple historical studies could help adding inputs to protocol to ensure better Compliance.

Future Thoughts

To explain variability in the primary or secondary endpoints.



Subgroup	HR (95% CI)
Age < 50	0.65 (0.50, 0.85)
Age ≥ 50	0.80 (0.65, 1.10)
Female	0.70 (0.55, 0.95)
Male	0.85 (0.60, 1.20)
Compliance ≥ 90%	0.70 (0.55, 0.85)
Compliance < 90%	1.10 (0.95, 1.35)

Thank You.

Questions?

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