

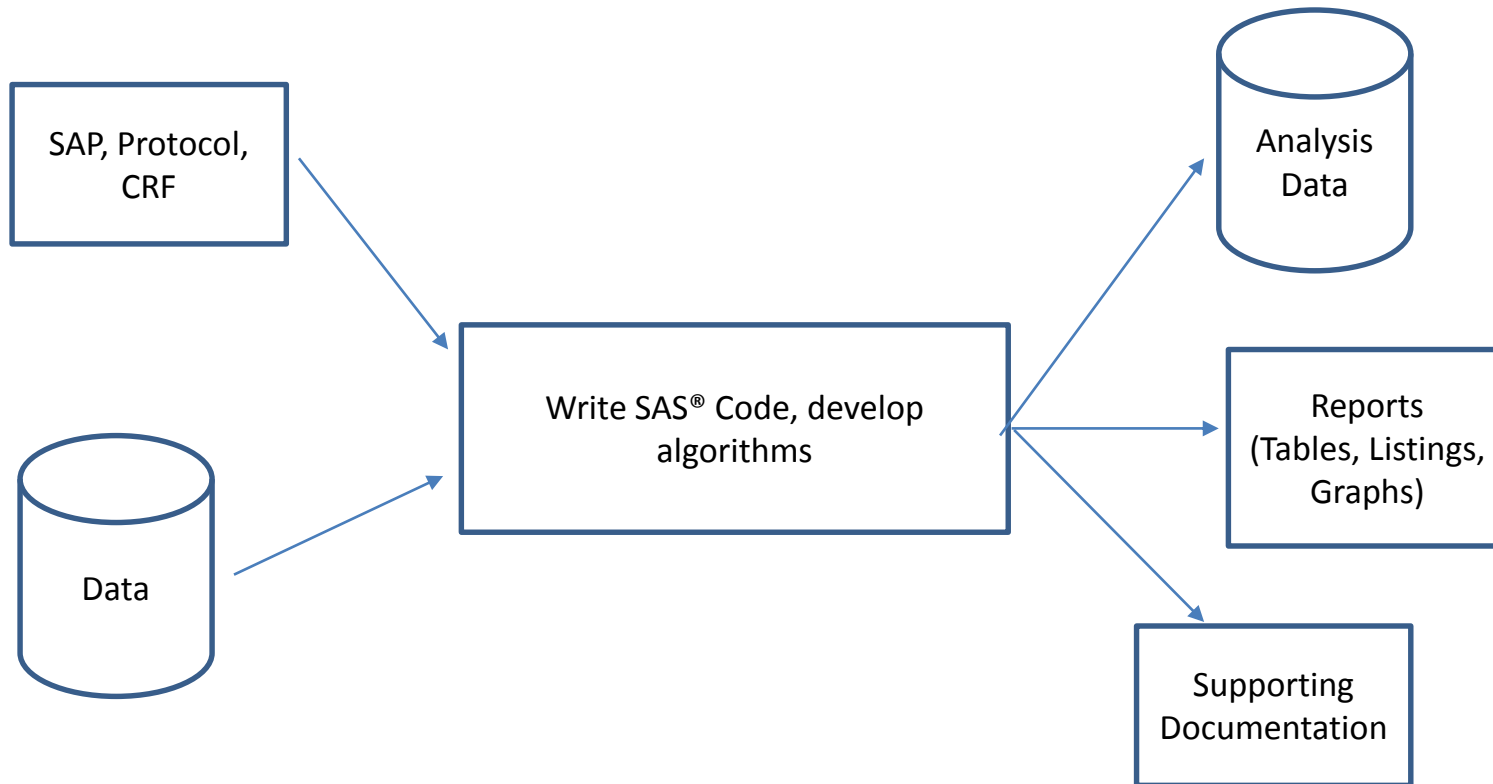


How can I contribute to Risk Based Monitoring?: Statistical Programmer's Perspective

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Perceived Role of Statistical Programmer



What programmers Really do?

Clinical Protocol/CRF Review:

- 1) Thorough understanding of schedule of event and collection of data by end-points.
- 2) Data structure assessment by understanding the trial design, arms, and treatment allocation to patients.
- 3) Data Collection end points as specified in CRF and their traceability and consistency with the information in protocol

Knowing and visualizing the data you will be working on.

SAP and Data Review:

- 1) Consistency of data analysis methods in SAP and protocol.
- 2) Ensuring that the actual data received is aligned with the findings from CRF and Clinical protocol review.
- 3) Ensuring that statistical reporting and analysis methodologies are supported by data structure and properties

Conducting analysis and reporting of data.



**Reporting of
Data Quality
issues!**

Risk Based Monitoring and Statistical Programming

Site Monitoring
By CRAs

Query Management
(DMs and CRAs)

- Central monitoring
- Statistical data surveillance
 - Data Validation/Edit Checks

Current Efforts

Why there are risks based on data quality?

- 1) Majority of tools and systems are deployed on sponsor side and not at sites
- 2) Time lag between data collected at site and data integrated into database.

Causes of Continued Issues

Statistical monitoring through-

- 1) Data Analysis
- 2) Report generation process

Trace and report the issues observed in analysis and reporting of data.

Supportive Remediation

Data Issues Reporting vs Data Quality Monitoring

Typical Data
Issues

For patient
10121004, reason for
withdrawal from
study is missing

Missing units for weight
measurements for
patient 10151001 for
day -2, visit-1.

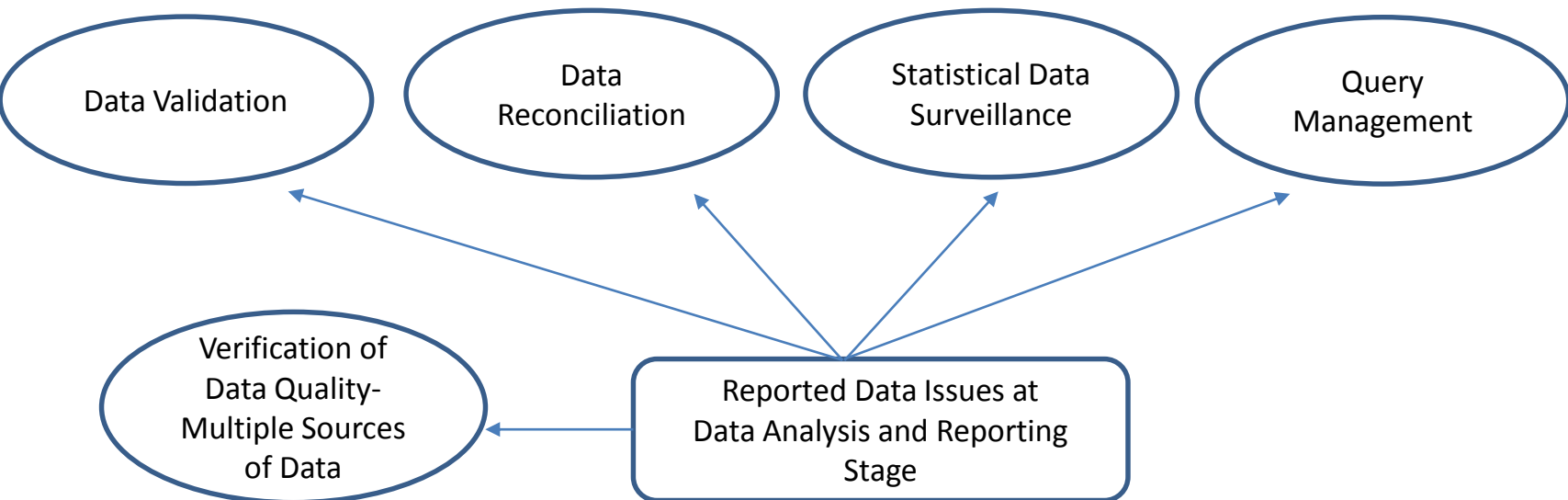
How they are
Identified?

- Edit check programming
- Data review process by Programmer/Statistician

How they are
resolved?

- Query sent to the site for more clarifications.
- Issue resolved after clarification from site.
- Data Updated.

Is RBM same as data issue reporting?



Risk Based Monitoring: Industry Observations

- As per one of the study conducted by TransCelerate Pharma member companies, risk based monitoring is a most important and key influencing factor for redefining strategies on detection of fraud and misconduct in clinical trials.
- Balanced randomization, missing data, and outliers continue to be major indicators of data quality.
- Another study recommended that for efficient and cost effective RBM practices, data validation and query management practices should be at the center of source document verification.

Risk Based Monitoring: Randomization Issue

Oncology Trial- Randomization Error Detection

Randomization system provided list of patients randomized and treated with following information: Randomization number, stratification factor (presence of disease for less than or greater than 12 months period).

What Statistical programmer did to validate this data?

- Review the Primary diagnosis data (collected and based on CRF design) for disease initiation, and recurrence dates for patients.
- Analyzed this data for 12 month period stratification factor.
- Compared the list of patients per strata obtained from this data against the randomization file.

Risk Based Monitoring: Randomization Issue Continued

Findings-

Investigator incorrectly used the stratification factor to randomize the patient population. This resulted into incorrect stratification of 7% of patient population.

Possible impact of such issue:

- There could have been incorrect conclusions about drug safety and effectiveness.
- There could have be significant impact on labelling of drug
- Regulatory authorities may request additional analyses including risk management plan to mitigate such issues

Risk Based Monitoring Identification of Right Dosing

CNS trial. – Merging of CRF exposure and dose dispensing data showed discrepancies. This comparison was required to identify right amount of dosing given to patient.

Initial assessment- Kit dispensing information entered in CRF not matching with the kit dispensing information coming from randomization system.

What programmer did to validate this?

Reviewed the exposure data coming from database.

There were discrepancies spotted in the kit numbers and entries of kit numbers in CRF.

Reviewed the kit dispensing schedule and matched the bottle IDs against the data coming from database.

Root of this was identified to be the data entry errors/issues with CRF.

Risk Based Monitoring

Identification of Right Dosing

Findings-

- There had been incorrect entries of drug dispensing kits/bottles to patients by site.
- This posed challenges in identifying right amount of dose dispensed to the patients.
- Data management validated the information coming from CRF but could not isolate the errors related to possible data entry issues with CRF.
- Average doses by visit were re-assessed and corrected.

Possible impact of such issue:

- Mis-representation of dosing information
- Questions on integrity of trial data analysis

Risk Based Monitoring

Traceability to CRF Design Issue

- Case: Patients reported through table production were less than the patients randomized and treated.
- Root cause:
 - CRF data showed patients reported were less than number of patients randomized and treated.
 - CRF Design- Drug is dispensed on visit-1, day-1 and findings were gathered on visit-1, day-2.
 - Some patients discontinued after day-1 but received the dispensed drug.....and did not report on day-2. This was discovered from AE log and other data.
- Remediation of such issues: Early detection of issues, more thorough CRF design, and more enhanced central monitoring.

Risk based monitoring: What to Watch for?

- Biostatistician asked for sensitivity and sub-group analysis on data.
- Why would biostatistician do that? – Typical case:
 - Certain patient population is excluded from sensitivity analysis.
 - Those patients did not have presence of disease at baseline as per the data obtained from reviewers and adjudicators from BICR (Blinded Investigator Clinical Review team).
 - Primary investigator on trial analyzed the presence of disease in a different (and possibly incorrect) manner
 - Changes in p-values are witnessed through such analysis.

Statistical Programmer's share to improve trial integrity....

- Thorough understanding of the trial design, schedule of event, and CRF design.
- Objective thinking and multiple level of 'why' questioning to pin-point the real cause of data misrepresentation.
- Be aware of industry trends, practices.....why sponsor would include BICR, IDMCs etc for trial conduct and monitoring? Why biostatisticians may request additional monitoring or analyses of data?
- Quality check on reports and analysis data needs to be extended to reconciliation of data.

Future Efforts and Performance Enhancements

- Trainings and skills upgradation of programming staff
- Re-defining the roles and responsibilities to ensure they focus on quality control with a thorough approach pertaining to statistical monitoring of data.
- Upgradation of scientific and data knowledge
- Development of macro perspective with ability to dive into micro level of every data issue.

Sources and Acknowledgements

References:

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- 2) Tantsyura V., et.al., “Extended Risk -Based Monitoring Model, On-Demand Query Driven Source Data Verification, and Their Economic Impact on Clinical Trial Operations”, Therapeutic Innovations and Regulatory Science, Volume-50, Number-1, J 2016, 115-122.

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Questions/Comments?

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