A Risk-Focused Approach to Managing a Pivotal Phase III Critical Care Project Using TrialMaster (Case Study)

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Quality Management: Not Just RBM

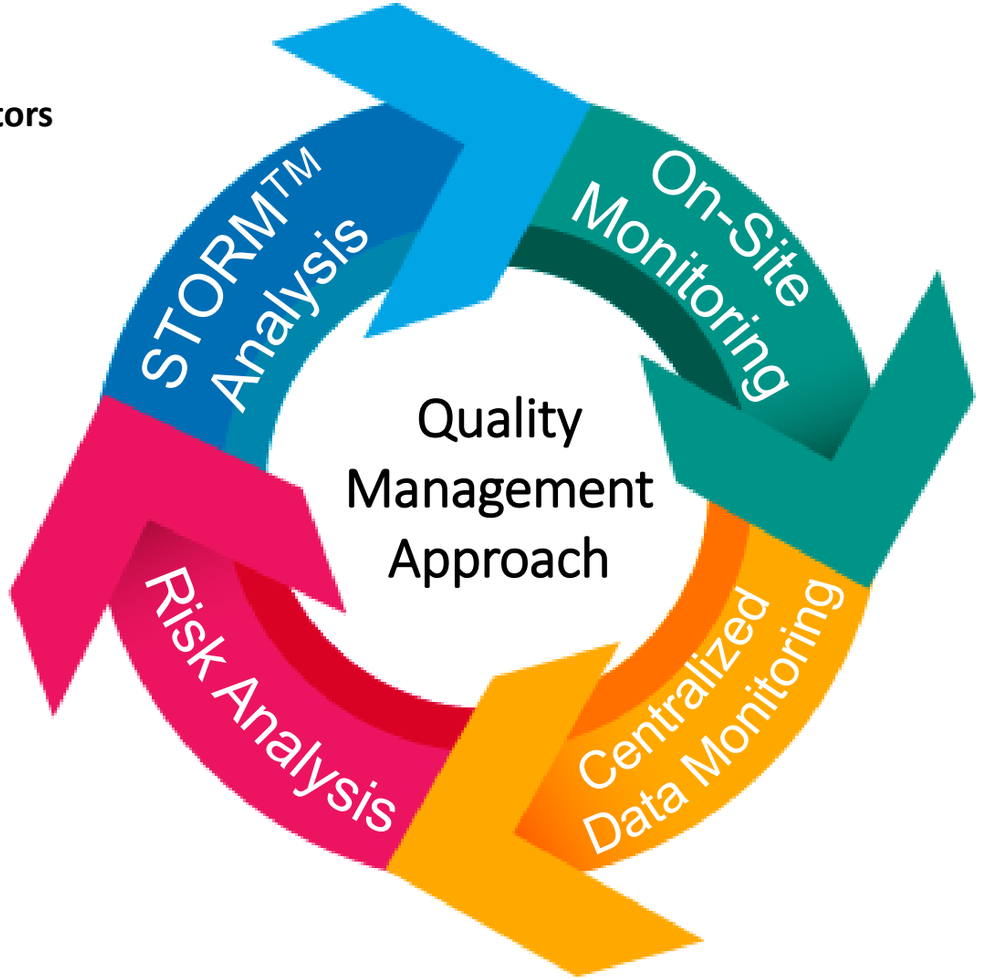
- Brief History
  - Clinical Trials Transformation Initiative recommends Risk-based Monitoring
    - July 2011
  - Draft FDA Guidance for Industry
    - August 2011
  - Final FDA Guidance for Industry: A Risk-based Approach to Monitoring
    - August 2013
    - Guidance documents represent the FDA's current thinking…, "you can use an alternative approach if it satisfies the requirements…"
  - Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6 (R2)
    - November 2016
  - ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1) – Guidance for Industry – catalyst for widespread application of "Quality Management Systems" for clinical trial industry
    - March 2018

Quality Management: Trial Level

- Quality Management [Section 5, E6R2]
  - Focus on activities essential to ensuring human subject protection and the reliability of the trial results
  - Design of protocols, tools and procedures for data collection and processing should be clear, concise and consistent
  - Methods used to control quality should be proportionate to the risks
- Quality Management System (QMS) should use a risk-based approach:
  - Critical process and data identification (1)
  - Risk identification (2)
  - Risk evaluation (3)
  - Risk control (4)
  - Risk communication (5)
  - Risk review (6)
  - Risk reporting (7)

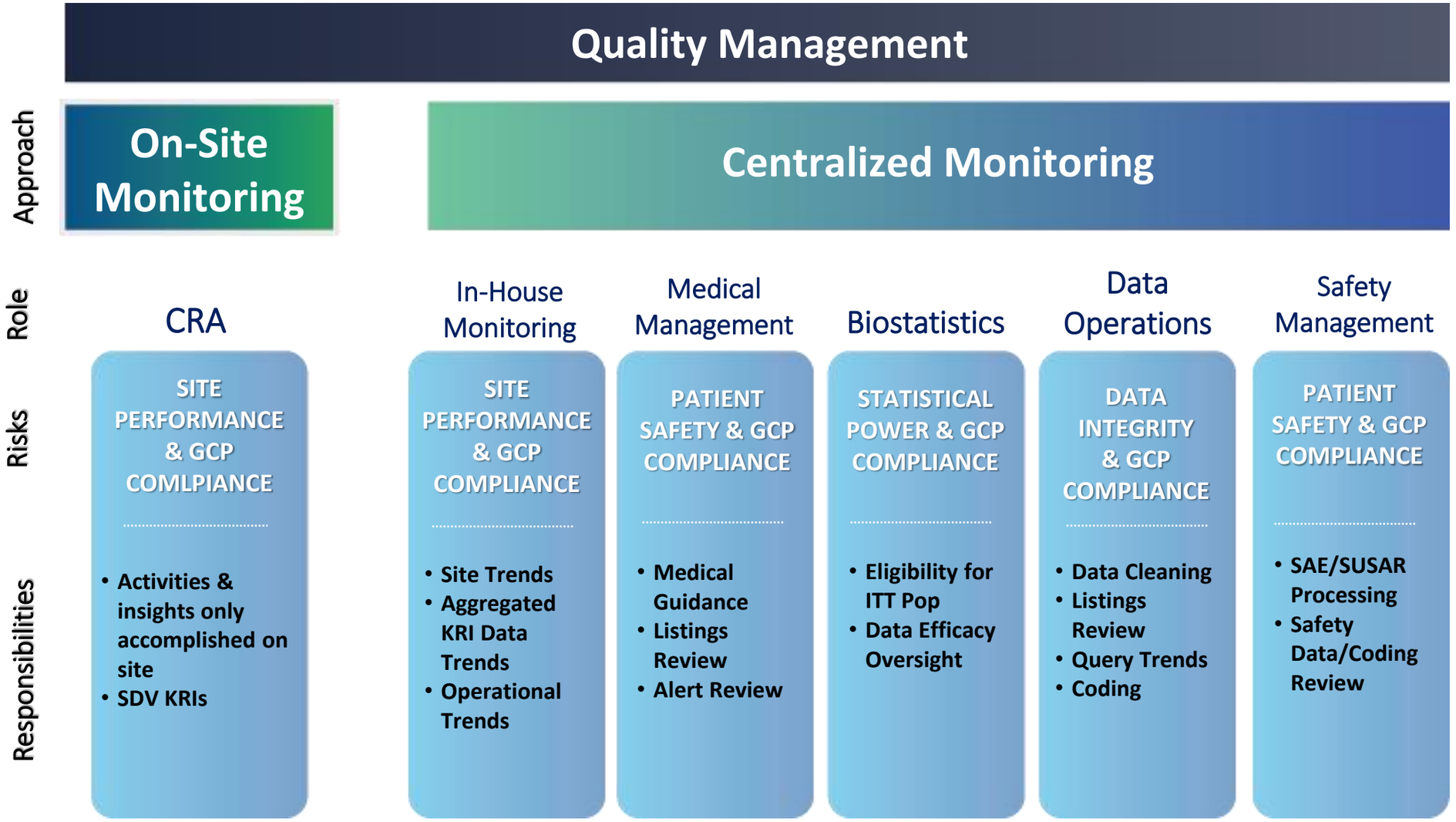
Quality Management: Trial Level

- Joint identification of critical data/key risk factors (1, 2, 3)
- Establishment of initial quality thresholds (3, 4)
- Risk & Issues Mgmt determined (4, 5, 6)
- Central Monitoring Summaries (5, 6, 7)
- Escalation & action planning; summarization of trends (5, 6, 7)
- Ongoing adjustments to QMA; e.g., site mgmt actions, plan revisions, re-training, etc. (1, 2, 3, 4, 5, 6, 7)



- Study Plans focus on data & procedures with greatest potential impact on outcomes of study (4, 5, 6, 7)
- Data and trend reports developed and review schedules determined (6, 7)
- Roles & responsibilities defined for cross-functional data/risk evaluations (4)
- In-house/central data monitoring + field experiences = risk analysis, determine on-site focus (5,6)
- Pool of on-site visits applied based on site risk composite scores from Central Monitoring Logs (5,6)

Quality Management: Trial Level



Data and Procedures Identified as Critical to Quality

- Required data collection and study procedures that have the greatest potential to impact interpretation of the data have been assessed. Site training, traditional on-site monitoring, and centralized monitoring will be performed in order to reduce or mitigate potential errors in the following categories:
  - A. Eligibility Criteria
  - B. IP Administration
  - C. Adverse Events/Serious Adverse Events
  - D. Delayed Cerebral Ischemia
  - E. Radiology Assessments
  - F. Neurologic Assessments
  - G. Compliance with and accurate completion of the GOSE (Extended Glasgow Outcome Scale) and MoCA (Montreal Cognitive Assessment)
  - H. Compliance with maintaining the blind in accordance with the protocol and the Site Blinding Plan
- These data and procedures will be targeted for in-house data review and be the focus for source document review and verification during on-site visits.

Case Study: Targeted Source Document Verification (SDV)

Critical Forms for SDV/SDR
Adverse Events
Angiogram
Aneurysmal Subarachnoid Hemorrhage History
CT Scan
Delayed Cerebral Ischemia
Extended Glasgow Outcome Scale
Inclusion/Exclusion Criteria Not Met
Intraventricular IP Administration
Modified Glasgow Coma Scale
Montreal Cognitive Assessment
aNIHSS
Prior and Concomitant Medications
Prior and Concomitant Procedures/Therapies
World Federation of Neurological Surgeons Assessment
Subject Information
Disposition
Hospitalization

Case Study: Central Monitoring Reports

Site Performance Assessment

Rated on 3 point scale:

0 = no action required
1 = attention needed
2 = immediate action required

- Experience of PI and staff (rated initially, then as needed based upon changes or turnover of key staff)
- PI Involvement
- Site Responsiveness

In-House Monitoring Records

Similar ratings applied to routinely monitored data sets based upon:

- Key risk indicators
- Performance metrics
- Outliers or trends identified

The two components are evaluated together to determine:

- Frequency of interim visits
- Other actions/mitigations

Case Study: Central Monitoring Reports

Section 1 – Site Performance Indicators (SPI)

Item #	SP	0	1	2
1.1	Rate prior Sponsor/RPG Experience with site. **(This score is determined by the CRA and should remain the same throughout the study. Refer to CMR Log for previously assigned scores. Newly activated sites that have not yet received a score will need one assigned by the CRA at this time).** • This score is assessed after the SIV occurs and reflects a rating based on Sponsor/RPG prior experience with the site. **The score should remain the same throughout the study.**			
1.2	Rate the experience of the PI and staff and site turnover rate. This should be assessed initially, and thereafter when there are staff changes in the study team. **(This score is determined by the CRA).** • 0 for no staff changes since the previous CMR • 1 indicates moderate concerns about site staff experience or turnover, requiring discussion with the investigator or study coordinator; staff changes that do not impact the site's ability to enroll and/or enter data. • 2 indicates significant concerns about the site staff experience or turnover, requiring escalation to the PM for consideration of actions such as contact with the investigator, or escalation to Sponsor; PI, or staff changes that impact enrollment and/or data entry.			
1.3	Rate impact of changes in key facility, equipment, systems, or procedures at the site. **(This score is determined by the CRA).** • 0 for no staff changes since the previous CMR • 1 indicated changes presenting moderate potential issues (e.g. change in local labs), requiring discussion with the investigator, study coordinator, or pharmacist; changes that do not impact enrollment or data entry			

Case Study: Central Monitoring Reports

Section 2 – In-House Data Monitoring (IHDM) (Key Risk Indicators – Data Operations)

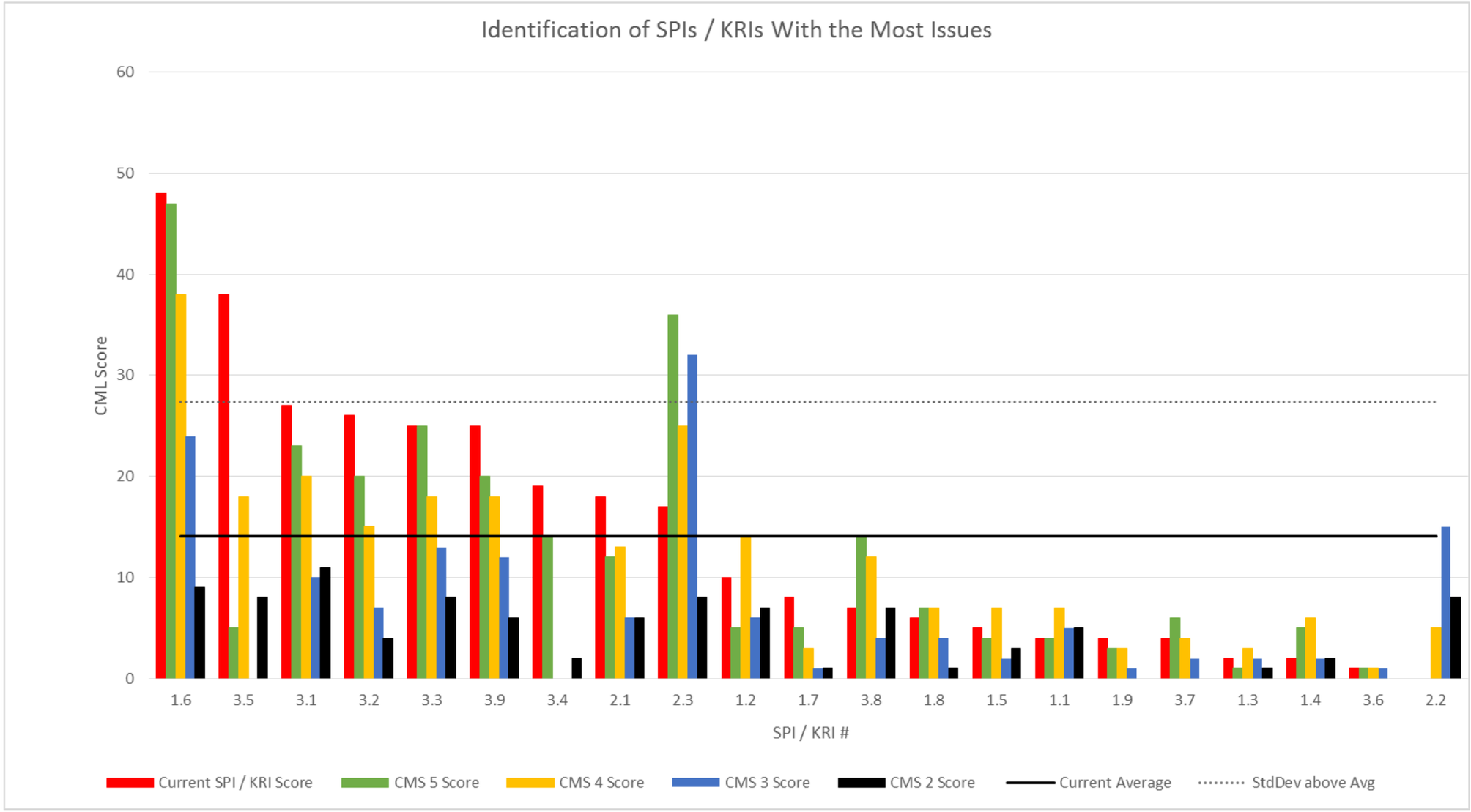
Item #	KRI	0	1	2
2.1	Rate the time to entry of eCRF data. **(This score is determined by the CRA and is based on CRA findings from desktop monitoring, site contacts, and emails sent by the IHDM CRA about missing eCRF data).** • 0 = average ≤3 business days from subject visit to data entry. No action required. • 1 = average of 3-10 business days from subject visit to data entry. Requires a discussion with study coordinator. • 2 = average of >10 business days from the subject visit to data entry. Requires escalation to the PM for consideration of other actions, such as contact with investigators.			
2.2	Provide a rating based on the percentage of eCRF pages that have queries. **(This score is determined by the IHDM CRA).** (Reference the CRF Status Report) – Follow instructions. • 0 = 0.5% of pages have queries, across the site. No action required. • 1 = 6-10% of pages have queries, across the site. Requires discussion with study coordinator. • 2 = >10% of pages have queries, across the site. Requires escalation to PM for consideration of other actions, such as contact with investigators.			
2.3	Provide a rating based on average query resolution time by site. **(This score is determined by the IHDM CRA).** • 0 = <30 days. No action required. • 1 = 30-60 days. Requires discussion with study coordinator.			

Case Study: Central Monitoring Reports

Section 3 – In-House Data Monitoring (Key Risk Indicators – Study Metrics & Trends)

Item #	KRI	0	1	2
3.1	Provide a rating based on the average number of AEs per subject at the site compared to the average across the study. **(This score is determined by the IHDM CRA).** (Refer to CMR Metrics spreadsheet). • 0 = an AE incidence within X% of the average across all sites. No action required. • 1 = an AE incidence between X% and up to one standard deviation less than or greater than the average across all sites. Requires a discussion with investigator. • 2 = an AE incidence greater than one standard deviation less than or greater than the average across all sites. Requires escalation to the PM for considerations of other actions, such as further contact with the investigator contact with the Medical Monitor, or escalation to Sponsor.			
3.2	Provide a rating based on the average number of SAEs per subject at the site compared to the average across the study. **(This score is determined by the IHDM CRA).** (Refer to CMR Metrics spreadsheet). • 0 = an SAE incidence with X% of the average across all sites. No action required. • 1 = an SAE incidence between X% and up to one standard deviation less than or greater than the average across all sites. Requires a discussion with investigator. • 2 = an SAE incidence greater than one standard deviation less than or greater than the average across all sites. Requires escalation to the PM for considerations of other actions, such as further contact with the investigator contact with the Medical Monitor, or escalation to Sponsor.			
3.3	Provide a rating based on the AE casualties per subject at the site compared to the average across the study. **(This score is determined by the CRA).** (Refer to CMR Metrics spreadsheet).			

Case Study: CMS Quarterly Comparisons

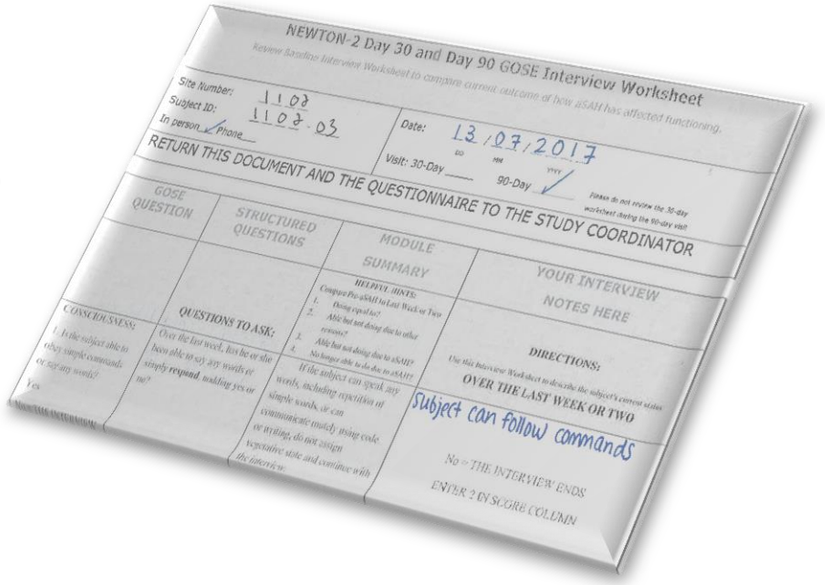


Case Study: Data Collection Challenges

- Need for De-Identified Copies of Assessments to be Available Immediately for Third Party Review
- Protocol Specific Events with Specific Criteria
- Data-Heavy Assessments and Scales
- Complex Randomization Process

Case Study: Need for De-Identified Copies of Assessments

- A field was added via Mid-Study Change that allowed PDFs or JPG files to be uploaded directly into TrialMaster by the Site Coordinators
- Third party reviewers with View Access to EDC were able to compare data directly from source document assessment/scale to confirm it was scored appropriately and entered in EDC correctly


NEWTON-2 Day 30 and Day 90 GOSE Interview Worksheet

Site Number: 1107
Subject ID: 1107 003
In person ✓ Phone
Date: 13/07/2017
Visit: 30-Day 90-Day ✓

RETURN THIS DOCUMENT AND THE QUESTIONNAIRE TO THE STUDY COORDINATOR

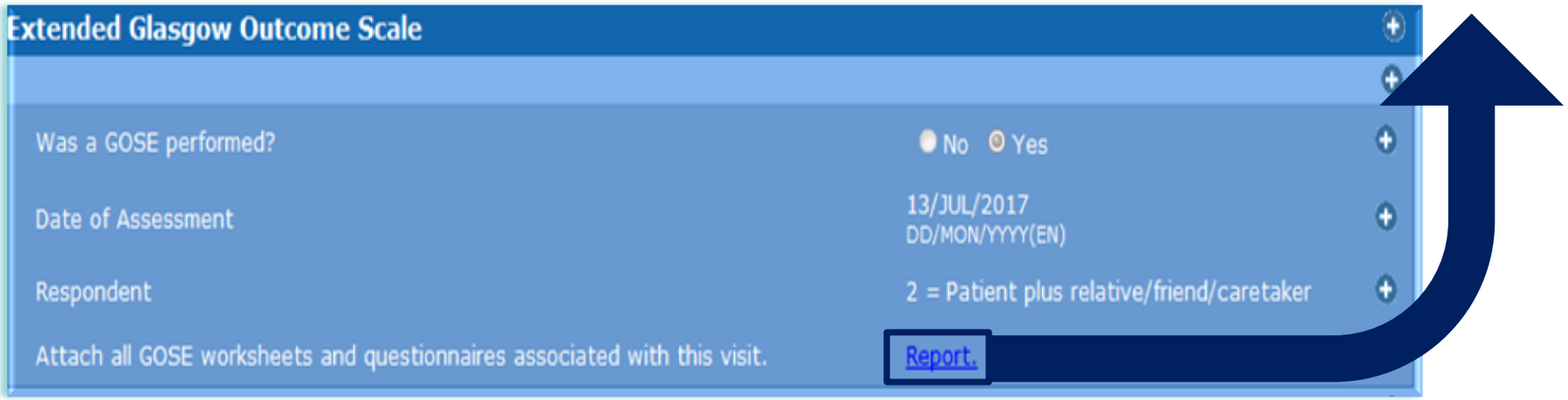
GOSE QUESTION | STRUCTURED QUESTIONS | MODULE SUMMARY | YOUR INTERVIEW NOTES HERE

CONSCIOUSNESS:
1. Is the subject able to obey simple commands or say any words?
Yes

QUESTIONS TO ASK:
Over the last week, has he or she been able to say any words or simply respond, nodding yes or no?

RECALL HINTS:
Compare Pre-aSAH to Last Week or Two
1. Doing equal to?
2. Able but not doing due to other reasons?
3. Able but not doing due to aSAH?
4. No longer able to do due to aSAH?
If the subject can speak any words, including repetition of simple words, or can communicate mutely, using code or writing, do not assign vegetative state and continue with the interview.

DIRECTIONS:
Use this Interview Worksheet to describe the subject's current status
OVER THE LAST WEEK OR TWO
Subject can follow commands
No = THE INTERVIEW ENDS
ENTER 2 BY SCORE COLUMN



Case Study: Need for De-Identified Copies of Assessments

ADVANTAGES

- Third party reviewers were able to view source almost immediately
- A dedicated fax line and/or email address did not need to be set up and monitored
- Listings can be run to easily identify subjects missing their uploaded source documents

POTENTIAL RISKS

- Ensure documents are truly de-identified prior to uploading
- Documents are often not scanned properly and follow-up with Study Coordinators is needed to ensure all pages are visible and complete

Case Study: Protocol Specific Events with Specific Criteria

- Sponsor provided complicated criteria for what events met the criteria of a DCI:

Diagnosis of Delayed Cerebral Ischemia

DCI will be defined by the following:

- For subjects in whom the neurologic scales are assessable: a decrease of at least 2 points on the mGCS or an increase of at least 2 points on the aNIHSS, lasting for at least 2 hours, where other medical or surgical causes (exclusion of any other explanation for the deterioration, such as (increasing) hydrocephalus, recurrent bleeding, seizures (electroencephalography performed in case of suspicion of seizures unless obvious clinically), an infectious disease with associated decrease in consciousness level, hypoglycemia (<3.0 mmol/L) or hyponatremia (<125 mmol/L), metabolic encephalopathy caused by renal or hepatic failure or any other possible cause for deterioration) are excluded.[17] The deterioration is measured relative to the best scores attained after aneurysm repair.
- For subjects in whom the neurologic scales are not assessable: radiological evidence and clinical judgement.

Subjects with suspected DCI should have appropriate radiological investigations perfor
Investigations should be performed to exclude other causes of deterioration. Review ations,
physical examination, CT/CTA and bloodwork are recommended as a minimum. graphy
angiography/CT perfusion (CTA/CTP) is particularly suggested when endovas herapy is
being considered, the diagnosis of DCI is particularly uncertain such as subj
assessable on neurological scales
deterioration may be multifactori

"…and clinical judgement."

Case Study: Protocol Specific Events with Specific Criteria

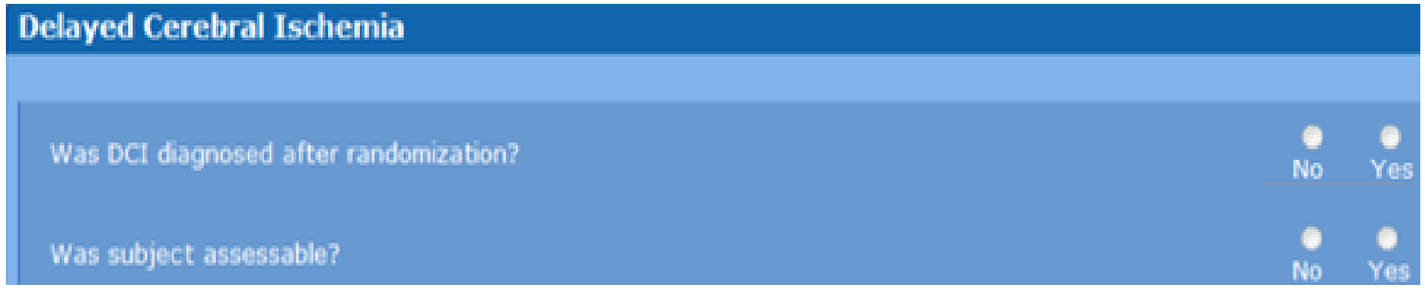
Strategy

TDS

EDC

Two main questions were utilized in the Dynamic Rule: "Was DCI Diagnosed after randomization?" and "Was subject assessable?

Delayed Cerebral Ischemia [DCI]			
Item Name/SAS Variable	Front End Form Question Text	Control Type	Codelist Name
[DCI]	1 of 1		
DCIPERF[DCIPERF]	Was DCI diagnosed after randomization?	RadioButton	NY
DCIASSES[DCIASSES]	Was subject assessable?	RadioButton	NY



Case Study: Protocol Specific Events with Specific Criteria

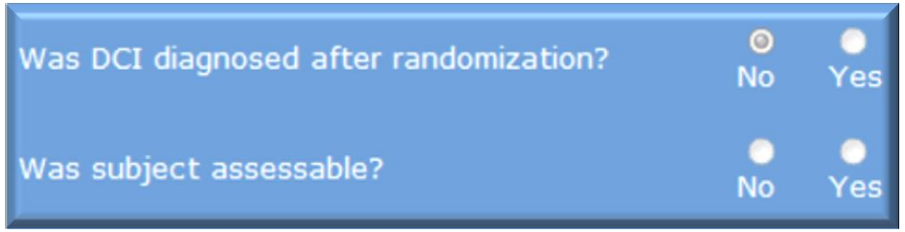
Was DCI diagnosed after randomization?

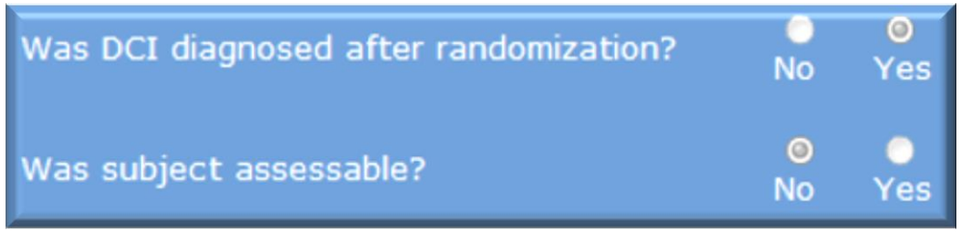
Was subject assessable?

Case Study: High Volume AEs & Protocol Specific Events

- This was accomplished by the use of Dynamic Rules using HIDE Edits

Edit Numbe	Visit Name	SAS Variable	Edit Type	Condition	Error/Warning Message Text
DCI42	Delayed Cerebral Ischemia	DCISPEC	HIDE	DCIPERF is not Yes or DCITERM = null or DCINON is checked or DCIOTHER is not checked	NO ERROR MESSAGE
DCI57	Delayed Cerebral Ischemia	DCIDESC	HIDE	DCIPERF is not Yes or DCITERM = null or DCISER is not Yes	NO ERROR MESSAGE
DCI58	Delayed Cerebral Ischemia	Datagroup [DCI4]	HIDE	DCIPERF is not Yes or DCITERM = null or DCISER is not Yes	NO ERROR MESSAGE
DCI62	Delayed Cerebral Ischemia	DTHDAT	HIDE	DCIPERF is not Yes or DCITERM = null or DCISER is not Yes or AESDTH is not checked	NO ERROR MESSAGE
DCI94	Delayed Cerebral Ischemia	DCISPEC3	HIDE	DCIPERF is not Yes or DCITERM = null or DCIACN2 does not equal Other	NO ERROR MESSAGE
DCI96	Adverse Events	DCIRSPEC	HIDE	DCIPERF is not Yes or DCITERM = null or DCIREL is not Suspected	This item is required.

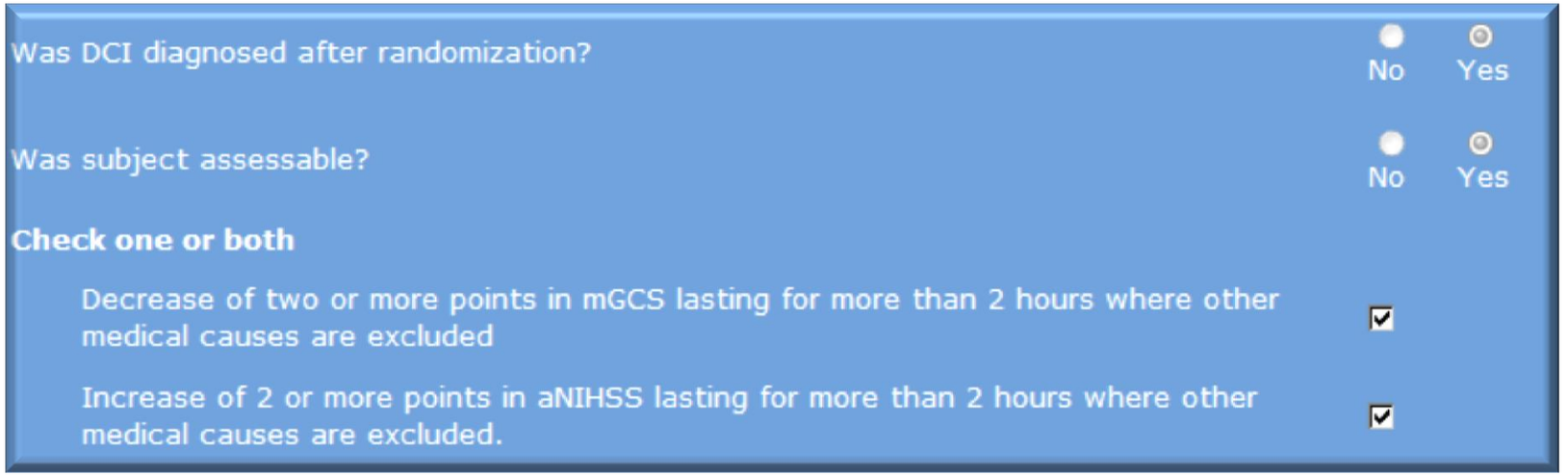




Case Study: High Volume AEs & Protocol Specific Events

- The inverse was also accomplished using Dynamic Rules with ENABLE Edits.

Edit Numbe	Visit Name	SAS Variable	Edit Type	Condition	Error/Warning Message Text
DCI04	Delayed Cerebral Ischemia	DCILBL	ENAB	DCIPERF = Yes	NO ERROR MESSAGE
DCI06	Delayed Cerebral Ischemia	DCIGCS	ENAB	DCIPERF = Yes and DCIASSES = Yes	NO ERROR MESSAGE
DCI07	Delayed Cerebral Ischemia	DCINIHSS	ENAB	DCIPERF = Yes and DCIASSES = Yes	NO ERROR MESSAGE
DCI08	Delayed Cerebral Ischemia	DCILBL2	ENAB	DCIPERF = Yes	NO ERROR MESSAGE
DCI09	Delayed Cerebral Ischemia	DCINONE	ENAB	DCIPERF = Yes	NO ERROR MESSAGE
DCI11	Delayed Cerebral Ischemia	DCICTA	ENAB	DCIPERF = Yes and DCINONE is not checked	NO ERROR MESSAGE
DCI12	Delayed Cerebral Ischemia	DCMRIMRA	ENAB	DCIPERF = Yes and DCINONE is not checked	NO ERROR MESSAGE



Case Study: Data-Heavy Assessments and Scales

- Study endpoints depended on data collected from two complex scales
- Extended Glasgow Outcome Scale (GOSE) utilizes 9 questions in a structured interview format to rate subject's status:

POST DISCHARGE
STRUCTURED INTERVIEW FOR GOSE

Respondent: ☐ 0 = Patient alone 1 = Relative/friend/caretaker alone 2 = Patient plus relative/friend/caretaker

Conciousness:

1. Is the head-injured person able to obey simple commands or say any words?

◯ Yes ◯ No (VS)

Note: anyone who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff and/or other caretakers. Confirmation of VS requires full assessment.

Independence at home:

2a. Is the assistance of another person at home essential every day for some activities of daily living?

◯ Yes ◯ No (VS) **If no: go to 3**

Note: for a NO answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone overnight.

2b. Do they need frequent help of someone to be around at home most of the time?

◯ Yes (lower SD) ◯ No (upper SD)

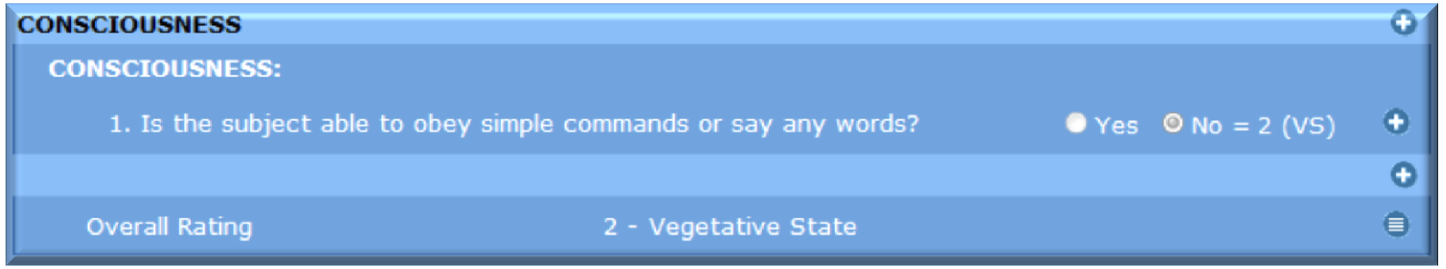
Note: for a NO answer they should be able to look after themselves at home up to eight hours during the day if necessary, though they need not actually look after themselves

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD -
4	Upper severe disability	SD +
5	Lower moderate disability	MD -
6	Upper moderate disability	MD +
7	Lower good recovery	GR -
8	Upper good recovery	GR +

Case Study: Data-Heavy Assessments and Scales

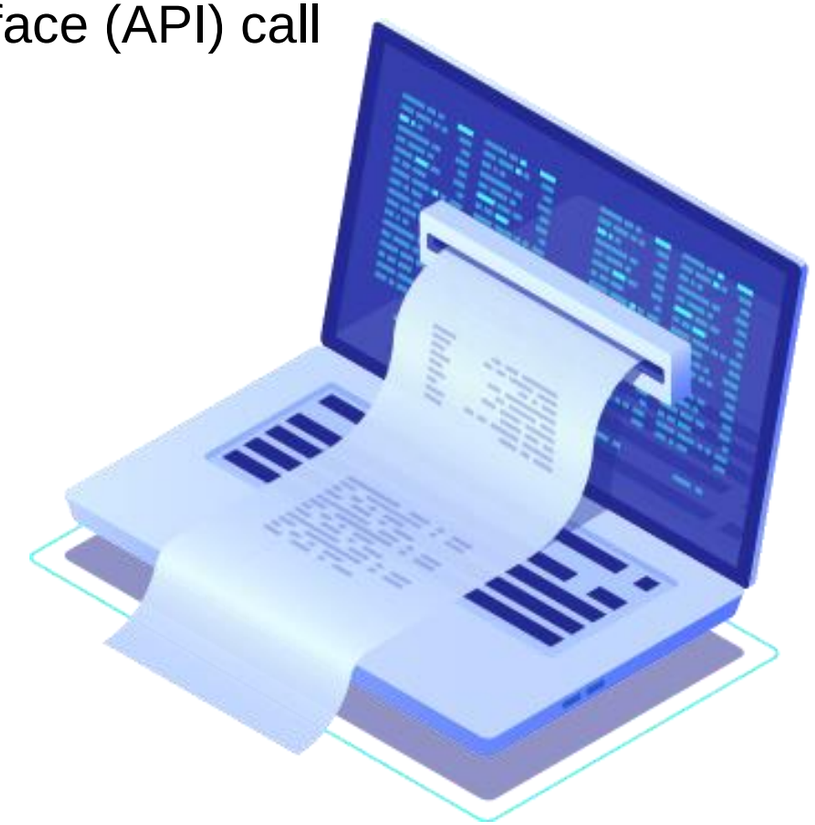
- Derivations utilized to facilitate correct data entry of scale rating

Edit Number	Visit Name	SAS Variable	Edit Type	Condition
				When EGOPERF = Yes and EGO01 = 'No = 2 (VS)', populate EGORRES with 2 -
				When EGOPERF = Yes and EGO01 = Yes and EGO02B = 'Yes = 3 (lower SD)', populate EGORRES with 3 - Lower SD. **When** EGOPERF = Yes and EGO01 = Yes and EGO02B = 'No = 4 (upper SD)', or EGO03A = 'No = 4 (upper SD)', or EGO04A = 'No = 4 (upper SD)', populate EGORRES with 4 - Upper SD. **When** EGOPERF = Yes and EGO01 = Yes and EGO05B = 'Able to work only in a sheltered workshop or non-competitive job or currently unable to work = 5 (Lower MD)', or EGO06B = 'Unable to participate: rarely, if ever take part = 5 (Lower MD)', or EGO07B = 'Constant – Daily and Intolerable = 5 (Lower MD)', populate EGORRES with 5 - Lower MD. **When** EGOPERF = Yes and EGO01 = Yes and EGO05B = 'Reduced work capacity = 6 (Upper MD)', or EGO06B = 'Participate much less: less than half as often = 6 (Upper MD)', or EGO07B = 'Frequent – Once a week or more, but tolerable = 6 (Upper MD)', populate EGORRES with 6 - Upper MD. **When** EGOPERF = Yes and EGO01 = Yes and EGO06B = 'Participate a bit less: at least half as often as before the hemorrhage = 7 (Lower GR)', or EGO07B = 'Occasional - Less than weekly = 7 (Lower GR)' or EGO08A = 'Yes = 7 (Lower GR)', populate EGORRES with 7 - Lower GR. **When** EGOPERF = Yes and EGO01 = Yes and EGO08A = 'No = 8 (Upper GR)', populate EGORRES with 8 - Upper GR. If any the fields listed above is null, do not derive EGORRES. EGORRES is to be derived based on lowest number selected.
GOSE67	Day 30, Day 90, Unscheduled	EGORRES	DVA	



Case Study: Complex Randomization Process

- Pre-Randomization and Randomization process was lengthy
- Pre-Randomization data used for stratification and could not be changed once established
- Sponsor wanted to minimize data entry errors by EDC receiving data imports from IRT via application programming interface (API) call
- Data included:
  - Subject Number
  - Informed Consent: Date & Time
  - Randomization: Date & Time
  - Randomization Number
  - Demographics: Date of Birth, Age, & Sex
  - World Federation of Neurological Surgeons Assessment (WFNS) data



Case Study: Complex Randomization Process

GOAL

Less Data Entry Effort for Sites

REALITY

- MSCs required additional testing & updates to IRT
- Data entry delays when IRT issues arose
- Additional reconciliation for DM & CRAs
- Sites had to submit multiple DCFs to IRT to have errors corrected

Integrated Quality Management