Role of Programmers in Flawless Execution of RBM Trials

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If you are in a shipwreck and all the boats are gone, a piano top buoyant enough to keep you afloat that comes along makes a fortuitous life preserver. But this is not to say that the best way to design a life preserver is in the form of a piano top.

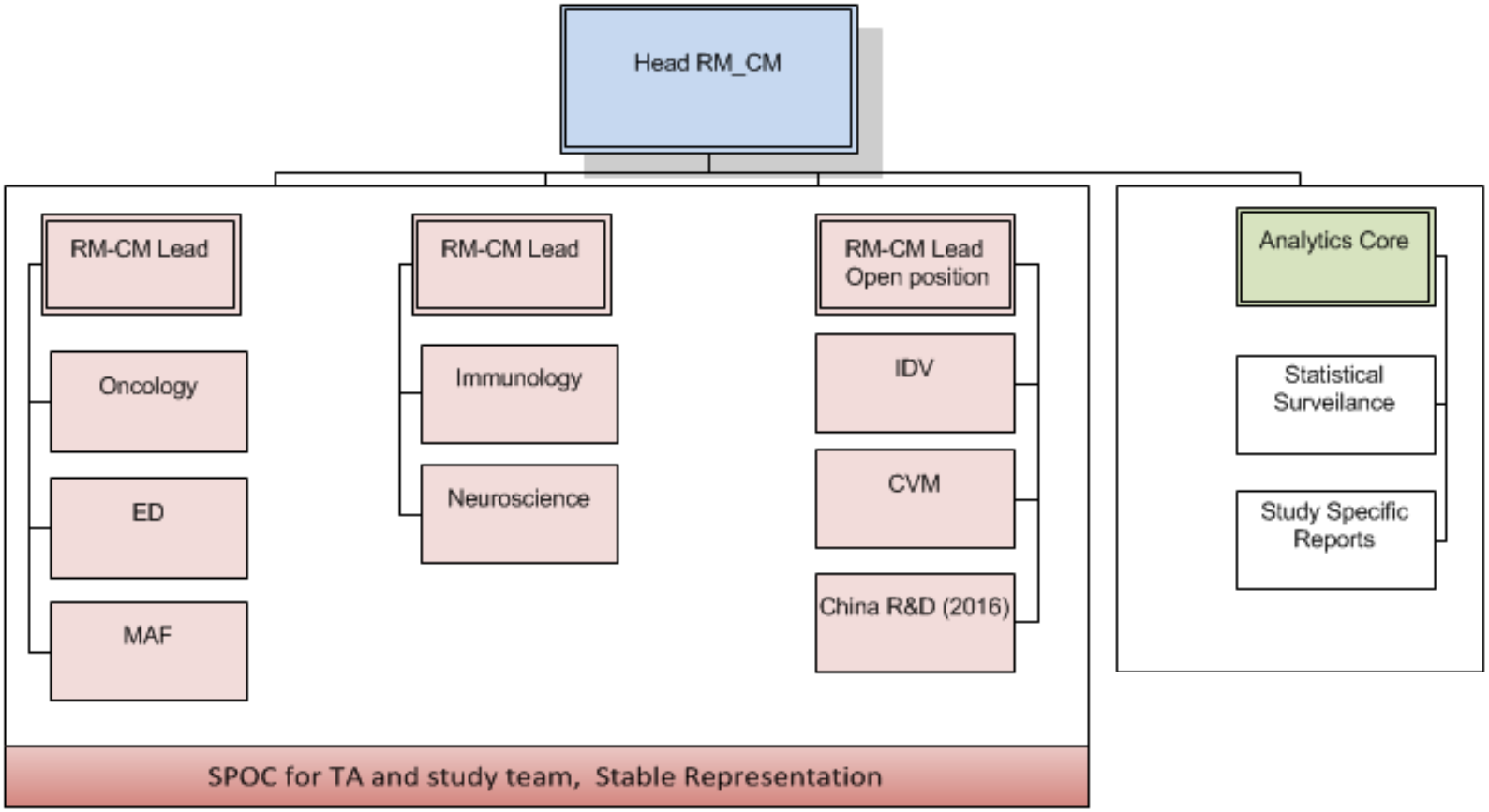
I think that we are clinging to a great many piano tops in accepting yesterday's fortuitous contriving as constituting the only means for solving a given problem.....

Operating Manual for Spaceship Earth, Buckminster Fuller;*1968*

Clinical trials are essential to the evaluation of promising scientific discoveries, but they are becoming unsustainably burdensome, threatening to deprive patients and health-care providers of new therapies and new evidence to guide the use of existing treatments.

Impediments to Clinical Research in the United States; J M Kramer, P B Smith, R M Califf, *Clinical Pharmacology & Therapeutics* (2012); **91** 3, 535–541

Current Structure of Janssen RM-CM



Current Issues

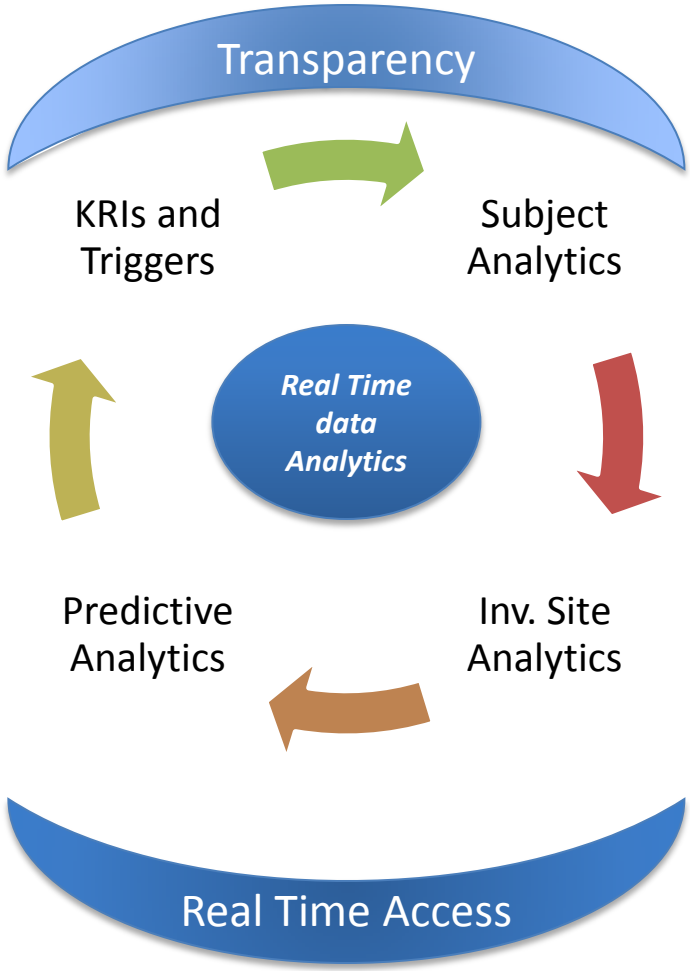
- Successful execution of RBM strategy is dependent transparent dissemination of correct information to the correct level of a clinical operation organization.
- The value proposition in application of risk based management is in identifying risk and implement a mitigation strategy during study set-up.
- The most used metrics and Key Risk Indicators (KRIs) are based on innovation relevant a decade ago.
- Most companies focus on operation metrics and some study specific KRIs without focusing on the full power of available data.
- Data Management and Programming disciplines play an increasing important role in roll out of risk management

Data Quality as a Cornerstone of Drug Development

- A succesfull clinical trial is defined by results that can withstand rigor of scientific and regualtory evaluation for safety and efficacy (data quality/quality).
- Reproducibility is directly corrolated to the error rate. In case of a clinical trial it translate to assurance that deviations from the protocol were minimal.
- The most effective way to assure data data quality is by:
  - Identifying critical data in support of major endpoints and trial objective
  - Understand the link between critical data point and collection process
  - Proactively define reprots that could point to inconsistencies
  - Ensure acess to data from all sources in real time during trial execution

Advantages of a Real Time Reporting

- Operations Risk Management Dashboard
- Study Specific Reports
- Site Specific Reports
  - Data Management Reviews
  - Central Monitor Reviews
  - CRA Reviews



- Site Specific Report:
  - Data Management Reviews
  - Central Monitor Reviews
  - CRA Reviews
  - Medical Review

- Statistical Surveillance
  - Central Monitor Reviews
  - CRA Reviews
  - Medical Review

- Operations Risk Management Dashboard
- Study Specific Reports
- Site Specific Reports
  - Data Management Reviews
  - Central Monitor Reviews
  - CRA Reviews

Study Specific Reporting as an Oversight Tool for Central Teams

- Study Specific Reports (SS-R) are determined as part of RBM process and through protocol review while in development.
- SS KRIs should have a direct link with Critical Data Review and list of Major Protocol Deviations.
- SS-Rs are programmable inconsistencies that draw data from different sources including IV/WRS, EDC, ePRO, etc...
- The information should be actionable and shared across functions responsible for monitoring the trial.

Protocol De-Risking as a Cross-Functional Review

- Protocol de-risking is part of Quality by Design (QbD) principles put forth by CTTI and FDA to proactively identify relevant risk and define a mitigation and monitoring plans.
- It is a cross-functional review meeting that includes medical leader, biostatistics, data management, QA and other applicable functions.
- It involves a thorough review of the protocol to identify CtQ, related data point and associated process .
- The outcome of the review will be documented in an integrated ARBM plan that links with different monitoring plans (e.g. medical monitoring, central monitoring, QM&C plans, etc...)
- The mitigation and oversight plan must include review of data in an integrated system with access to real time data.

Oral Anti-Depressant Dosing

Specific dosing titration schedules for 4 different anti-depressants. This program identifies subjects and time points that have not followed those schedules.

Site	SUBJID	eDC Anti-depressant Medication	Dose for Anti-depressant	Relative Day for Anti-depressant	eDc AD intake Date
Site 1	Subj 1	Sertraline	50	8	10-Nov-15
		Sertraline	100	15	17-Nov-15
Site 2	Subj 2	Sertraline	50	8	2-Nov-15
		Sertraline	50	9	3-Nov-15
		Sertraline	50	10	4-Nov-15
		Sertraline	50	11	5-Nov-15
		Sertraline	50	12	6-Nov-15
		Sertraline	50	13	7-Nov-15
		Sertraline	50	14	8-Nov-15
		Sertraline	100	15	9-Nov-15
	Subj 3	Escitalopram	40	1	14-Nov-15

Protocol defined titrations:

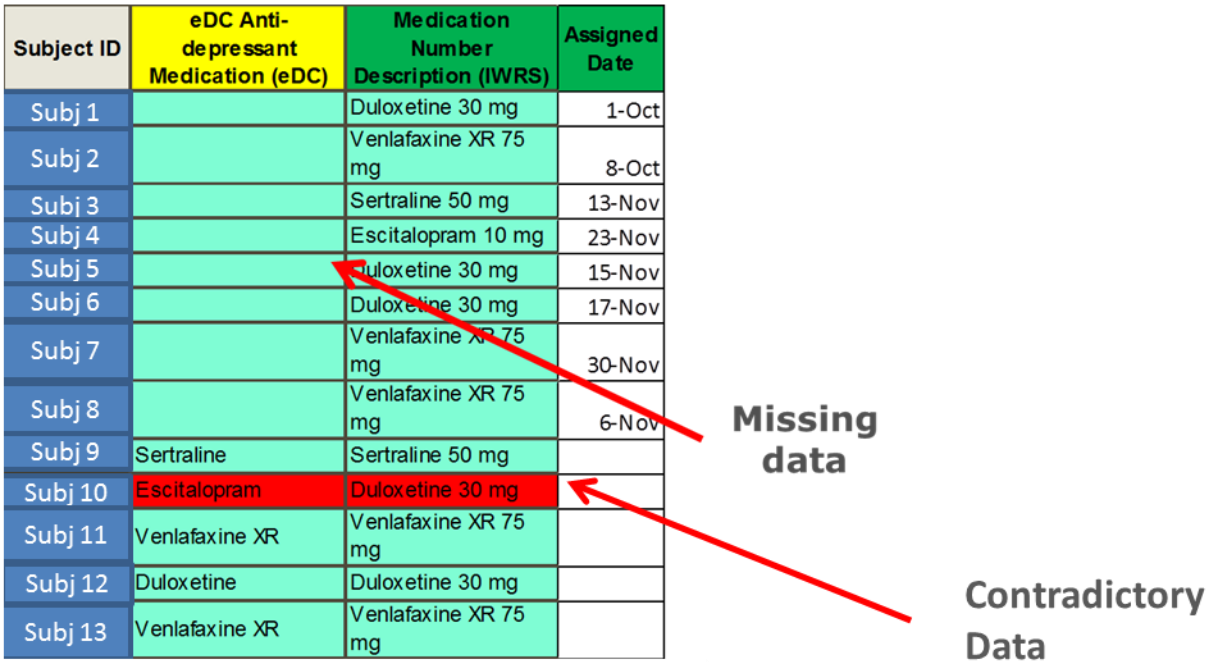
Sertraline: Day 8 = 100mg and Day 15 = 150mg

Escitalopram: Day 1 = 10mg (maximum = 20 mg)

Oral AD Assignment Issues

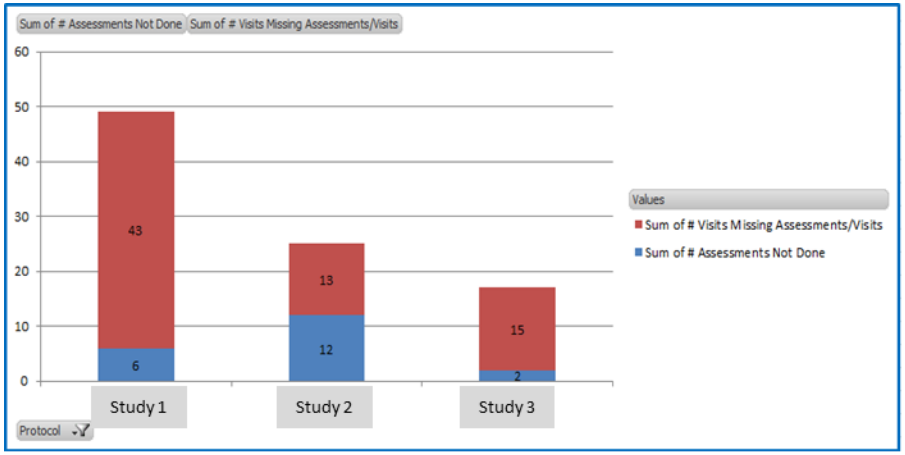
The reports also highlight critical missing data like the Oral anti-depressant dispensed. Without this data we are unable to confirm that the correct Oral AD was administered. In this example, Escitalopram was the incorrect Oral AD based on what was identified for subject 10 in IWRS.

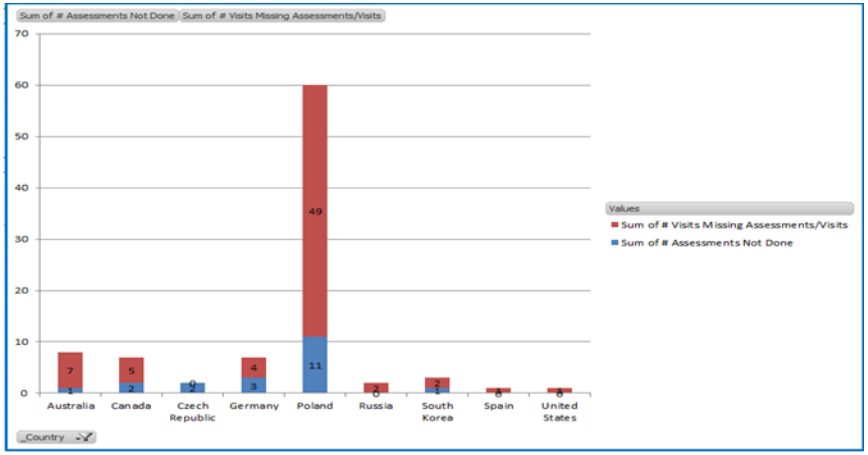
Subject ID	eDC Anti-depressant Medication (eDC)	Medication Number Description (IWRS)	Assigned Date
Subj 1		Duloxetine 30 mg	1-Oct
Subj 2		Venlafaxine XR 75 mg	8-Oct
Subj 3		Sertraline 50 mg	13-Nov
Subj 4		Escitalopram 10 mg	23-Nov
Subj 5		Duloxetine 30 mg	15-Nov
Subj 6		Duloxetine 30 mg	17-Nov
Subj 7		Venlafaxine XR 75 mg	30-Nov
Subj 8		Venlafaxine XR 75 mg	6-Nov
Subj 9	Sertraline	Sertraline 50 mg	
Subj 10	Escitalopram	Duloxetine 30 mg	
Subj 11	Venlafaxine XR	Venlafaxine XR 75 mg	
Subj 12	Duloxetine	Duloxetine 30 mg	
Subj 13	Venlafaxine XR	Venlafaxine XR 75 mg	

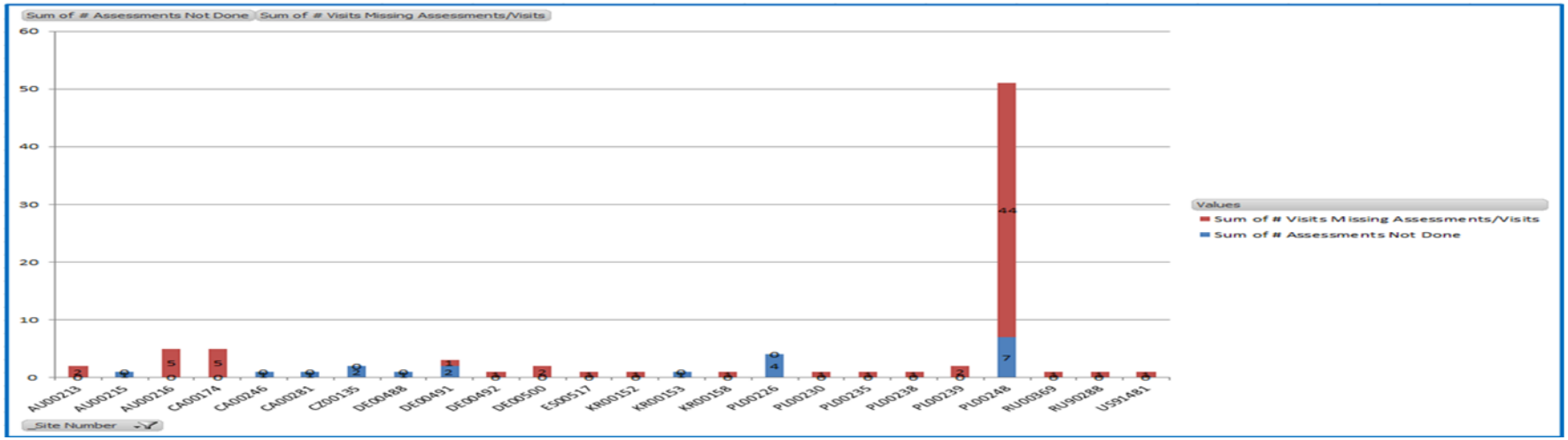


PRO Compliance

- **Missing Assessments/Visits** – There is no assessment data in Study-Works for a given visit. Possible reasons could be: transmission delays, site used paper source and has not submitted DCF, assessment not done.
- **Assessments "Not Done"** – It actually states "Not Done" in Study-Works, as entered by the site.

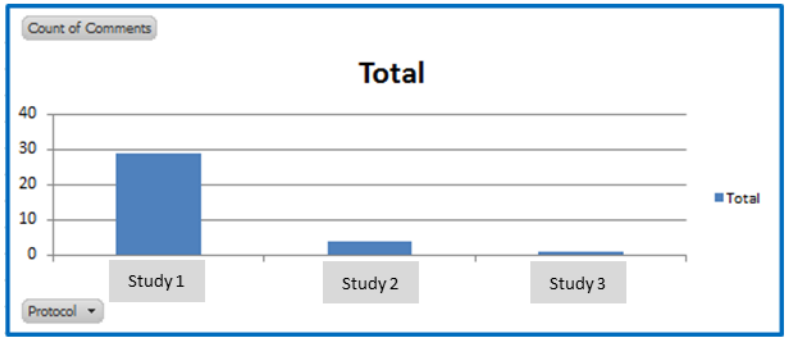


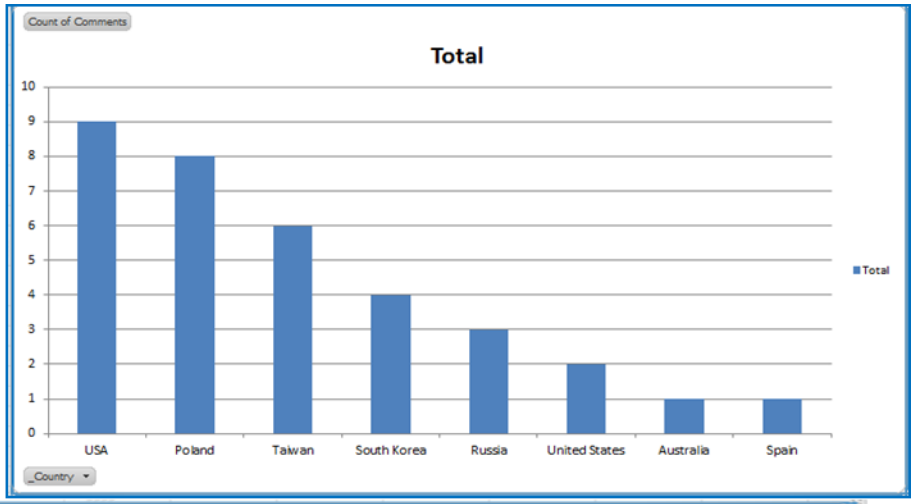


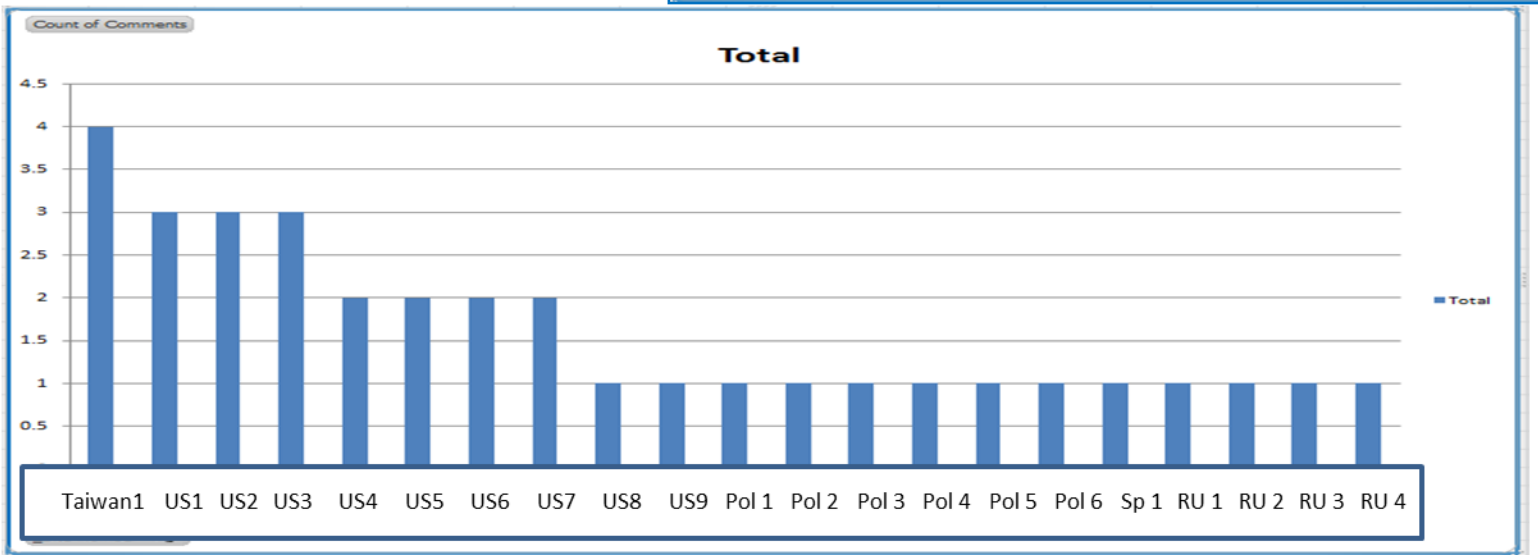


Subject Eligibility Trends (Labs)

Charts below represent subjects that had an Exclusionary Lab Result and no retest results available in LabLink







Conclusions

- A review of protocol deviation rates for studies using SS-Rs has shown significant reduction comparing to traditionally monitored studies.
- Risk management in clinical trials is cross-functional undertaking requiring close coordination during set up and execution.
- A successful implementation requires access to critical data sources in real time.
- Use of SS-Rs in a well-defined risk management process can support identification of critical protocol compliance issues proactively in real time.