

A statistics-based tool to inform risk-based monitoring approaches

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Agenda

- *Introduction*
- Traditional Monitoring vs. Risk-Based Monitoring (RBM)
Metrics vs. Centralized Statistical Monitoring (CSM)
- Our approach to CSM: Central Statistical Intelligence
- Future steps: Integration with Visualization Platform
- Conclusions

Introduction

- The clinical phase is the most complex part in a drug development process and requires efficient planning, conducting and monitoring of clinical trials to achieve the desired quality and obtain reliable study data that is appropriate for regulatory submission.
- As complexities in clinical trials continue to increase, the **clinical monitoring cost** and, in turn, the trial management cost have risen significantly in order to **achieve higher data quality** and **better monitoring of patient safety**.

Introduction

- What is the cost of monitoring?
 - Monitoring is one of the largest expenses in a clinical trial, accounting for 9 – 14% of the overall budget.
 - Source Data Verification (SVD) can additionally account for up to 15% of the budget, depending on the phase of the trial.
 - These costs are just behind clinical procedure costs (15 – 22%) and administrative staff costs (11 – 29%).⁴

4. <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>

Introduction

- The most recent update (Integrated Addendum E6(R2) - November 2016) to ICH Guideline for Good Clinical Practice encourages “implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results.”¹
- One such approach, to protect the safety of trial subjects and reliability of the data collected, is **risk-based monitoring**. FDA guidance for industry² and an EMA reflection paper³, both published prior to the Integrated Addendum, suggest this approach.

1. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf
2. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>
3. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf

Introduction

- Section 5.18.3 (Extent and Nature of Monitoring) of the ICH E6(R2)¹ has been updated to recommend a risk-based monitoring approach, which includes centralized monitoring.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Introduction

- Section 5.18.3 (Extent and Nature of Monitoring) of the ICH E6(R2)¹ has been updated to recommend a risk-based monitoring approach, which includes centralized monitoring.

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- (a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
- (b) examine data trends such as the range, consistency, and variability of data within and across sites.
- (c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- (d) analyze site characteristics and performance metrics.
- (e) select sites and/or processes for targeted on-site monitoring.

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- Introduction
- *Traditional Monitoring vs. Risk-Based Monitoring (RBM) Metrics vs. Centralized Statistical Monitoring (CSM)*
- Our approach to CSM: Central Statistical Intelligence
- Future steps: Integration with Visualization Platform
- Conclusions

Traditional Monitoring vs. RBM vs. CSM

• Traditional Monitoring

- A Clinical Research Associate (CRA) performs Source-Data Verification (SVD) at each site on a regular bases (i.e. every 6 weeks)
- The CRA also checks that staff at the site are aligned with the study protocol.

• Advantages:

- Catches un-intentional data entry errors.
- May be able to determine if staff are not following study procedures.

• Disadvantages:

- Costly
- Time consuming
- Difficult to detect patterns across visits or subjects

Traditional Monitoring vs. RBM vs. CSM

• Risk-Based Monitoring – using Metrics

- The study Sponsor and Data Manager set thresholds to flag sites or subjects (e.g. > 3 Serious Adverse Events (SAE) per site).
- The Data Manager reviews the data (or data can be reviewed programmatically) as collected and alerts the CRAs/Sponsor when a subject or site meets or exceeds a threshold.
- Data review and preventative/corrective actions are tracked and documented.
- Critical results can be discussed with the study team, so all are up to date as the study progresses.

Traditional Monitoring vs. RBM vs. CSM

• Risk-Based Monitoring – using Metrics

• Advantages:

- Monitoring efforts (including corrective measures) can be focused on sites and subjects approaching the thresholds → a proactive approach to monitoring.
- Data cleaning process can be streamlined.
- Sponsor has a broader view of how the study is progressing and data can be reviewed as soon as the enrollment begins.

• Disadvantages:

- Thresholds are subjective and fixed.
- Sponsor may have a long list of indicators to review.
- Fraud and instrument mis-calibration/malfunction is difficult to detect.

Traditional Monitoring vs. RBM vs. CSM

- Centralized Statistical Monitoring (another approach to RBM)
 - Thresholds are not set at the beginning of the study, rather the results are data-driven.
 - Data is analyzed as collected with appropriate statistical models.
 - Each site or subject is assigned a “risk score” based on the results of the statistical models.
 - Sites or subjects with high risk are the focus of monitoring efforts, including corrective actions.

Traditional Monitoring vs. RBM vs. CSM

Centralized Statistical Monitoring (another approach to RBM)

Advantages:

- Data driven approach creates exceptional data quality checks.
- “Risky” sites/subjects can be flagged sooner, rather than waiting for them to approach a subjective threshold.
- Models can be run at any interval, throughout the study.
- Fraud and instrument mis-calibration/malfunction can easily be detected.

Disadvantages:

- Every protocol requires statistical input to determine critical data.
- Appropriateness of the model needs to be carefully reviewed by a statistician on an ongoing basis.
- A significant amount of data needs to be collected before the model is considered appropriate.

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Our approach to CSM: Centralized Statistical Intelligence

- Our tool uses a statistical methodology developed around Principal Component Analysis (PCA):
 - It assigns a «risk score» to each site by taking into consideration different types of indicators.*
 - The distribution of all recorded variables at each investigative site are compared with that of the other sites.
 - Critical data can be selected by the Statistician, agreed by the Sponsor and the tool is configured by a Programmer.
 - Once a study has a suitable number of investigational sites, with 10 subjects enrolled per site, the model can be run.

*References for indicator development can be found in the paper associated with this talk.

Our approach to CSM: Centralized Statistical Intelligence

Errors	Approach/Description	Type	Overall Risk
Dates	Detecting visits occurring on weekends and national holidays	proportion	
Univariate Outliers	Identified by using a certain rule (e.g. 3σ rule)	proportion	
Visit Scheduling	Difference between planned study day and actual study day	p-value	
Rounding to Integers	Frequency of rounded values compared among sites	proportion	X
Digit Preference	Trailing digit from all continuous variables – one site compared to all others; P-value for CMH Row Mean Scores Differ; Max percent difference	p-value	
SAE Rate	Frequency per site/number of subjects/time period of reporting	rate	
Systematic Errors	Test on means of one site compared to all others	p-value	X

Our approach to CSM: Centralized Statistical Intelligence

Errors	Approach/Description	Type	Overall Risk
Repeated Measures	Minimum within-subject variability for each test with repeated measures (standard deviation) at each site.	normalized value	X
Multivariate Inliers/Outliers	Mahalanobis distance compared to Chi-squared statistic to classify observations	proportion	X
Missing Values	Proportion of missing values among sites through a Chi-squared test	p-value	X
Neighborhood	Density-based clustering (Minimum Distance to Nearest Neighbor)	normalized value	X

Our approach to CSM: Centralized Statistical Intelligence

USUBJID	SITEID	AGE	SEX	RACE	COUNTRY	AECOUNT	DSSTDT	DIABP_V1	DIABP_V2	DIABP_V3	DIABP_V4	DIABP_V5	DIABP_V6	HR_V1	HR_V2	HR_V3
(	0510	30	M	WHITE	HUN	1	2012-04-21	61	74	73	69	74	78	65	64	73
(	0510	32	F	WHITE	HUN	.	2012-04-21	65	73	69	77	68	77	61	70	75
(	0510	35	M	WHITE	HUN	.	2012-04-23	75	76	87	78	90	.	59	68	64
(	0510	68	M	WHITE	HUN	2	2012-04-24	76	80	83	80	84	78	76	65	68
(	0510	66	F	WHITE	HUN	.	2012-04-24	77	.	.	.	.	.	65	.	.
(	0510	53	F	WHITE	HUN	.	2012-04-24	85	.	.	.	.	.	59	.	.
(	0510	32	M	WHITE	HUN	.	2012-04-26	81	97	80	86	74	.	72	82	82
(	0510	77	F	WHITE	HUN	.	2012-04-26	65	75	70	68	75	.	57	60	60
(	0510	65	F	WHITE	HUN	2	2012-05-03	78	81	94	86	.	.	76	79	83
(	0510	33	M	WHITE	HUN	.	2012-05-08	68	67	79	69	74	.	66	60	78
(	0510	71	F	WHITE	HUN	.	2012-05-08	79	82	70	77	79	.	79	76	86
(	0510	68	F	WHITE	HUN	2	2012-05-08	90	86	82	90	.	.	67	61	78
(	0510	58	F	WHITE	HUN	4	2012-05-08	66	60	.	.	.	.	81	75	.
(	0510	60	F	WHITE	HUN	1	2012-05-08	77	83	75	78	80	.	72	75	67



siteid	PNONIN	PNONOUT	P2_WIL_DIA BP	P2_WIL_HR	P2_ST_DIA BP	P2_ST_HR	PNONMISS	RES	NORMINDIS	RM_DIABP	RM_HR	PNINT	SAERATE
0101	1	1	0.340583	0.292254	0.027412	0.060220	0.36111111	0.52242907	0.14977135	0	0.2	0.5	.
0102	1	1	0.453984	0.230121	0.040636	0.123274	0.32407407	0.18539394	0.23426050	0.5	0.5	0.53846153	0.00143678
0104	1	1	0.647944	0.426102	0.992185	0.391543	0.30555555	0.16151759	0.20987225	.	.	0.375	.
0105	.	.	.	.	.	.	0	8.512895E-1	.	.	.	.	.
0109	1	1	0.060232	0.631866	0.929926	0.036944	0.39583333	0.86032131	0.16791164	0	0.2	0.57142857	0.00378787
0110	1	1	0.015343	0.018973	0.621630	0.992750	0.38888888	0.99003208	0.27713750	0	0.28284271	0.6	.
0111	1	1	0.396430	0.509249	0.230154	0.237105	0.24444444	0.00527143	0.09345206	.	.	0.42857142	.
0112	1	1	0.340798	0.594545	0.421364	0.422641	0.35	0.47581674	2.5443109E-	0	0	0.5	.
0113	1	1	0.931917	0.032826	0.010425	0.517340	0.33333333	0.19121811	0.17560948	0	0	0.52631578	.
0114	1	1	0.037793	0.658093	0.500656	0.931690	0.36111111	0.58047917	0.15491011	0	0.2	0.6	.
0206	1	1	0.180980	0.062883	0.826488	0.473733	0.22222222	0.00368530	0.31471832	1	0.4	0.66666666	.
0401	1	1	0.029738	0.001206	0.830100	0.002615	0.44444444	0.11381251	0.16564193	0.40824829	0.32659863	0.53125	.

Our approach to CSM: Centralized Statistical Intelligence

- Principal Component Analysis (PCA) is run on the matrix of indicators.
- Principal components are selected based on
 - How much variance is explained
 - What the components represent
- Risk score is computed by Euclidean distance to the center of the PCA space.
- Thresholds are used to classify sites into low, medium, high risk groups.

Our approach to CSM: Centralized Statistical Intelligence

- Some notes about the PCA methods:
 - Cross-validation is used to determine the number of PCs and the statistician will review the PCs that result to determine if any mainly describe the imputation.
 - With ongoing studies, missing data tends to cause problems with traditional PCA methods.
 - Our solution is to use one of two methods:
 - Bayesian PCA
 - SVD imputation followed by traditional PCA
 - Implemented in SAS/IML®

Our approach to CSM: Centralized Statistical Intelligence

Selected principal components

Risk score



COL1	COL2	siteid	risk_score	riskgrp	label
0.0013312833	0.0001473398	0101	0.00133941	1	
-0.003131401	-0.000146713	0102	0.00313483	1	
-0.003691843	-0.000114924	0104	0.00369363	1	
-0.00045117	0.0000225063	0105	0.00045173	1	
-0.000575571	2.4526349E-6	0109	0.00057557	1	
0.0008465473	0.0000188269	0110	0.00084675	1	
-0.002247063	-0.000073529	0111	0.00224826	1	
-0.000160458	0.0000496094	0112	0.00016795	1	
0.0009245525	0.000121491	0113	0.00093250	1	
-0.000375269	-0.000014265	0114	0.00037553	1	
-0.0011918	-0.000122452	0206	0.00119807	1	
0.0005579704	-0.000065321	0401	0.00056178	1	
-0.005789353	-0.000326536	0402	0.00579855	2	0402
0.0013987431	0.0000601151	0404	0.00140003	1	
0.0022995453	0.000350005	0405	0.00232602	1	

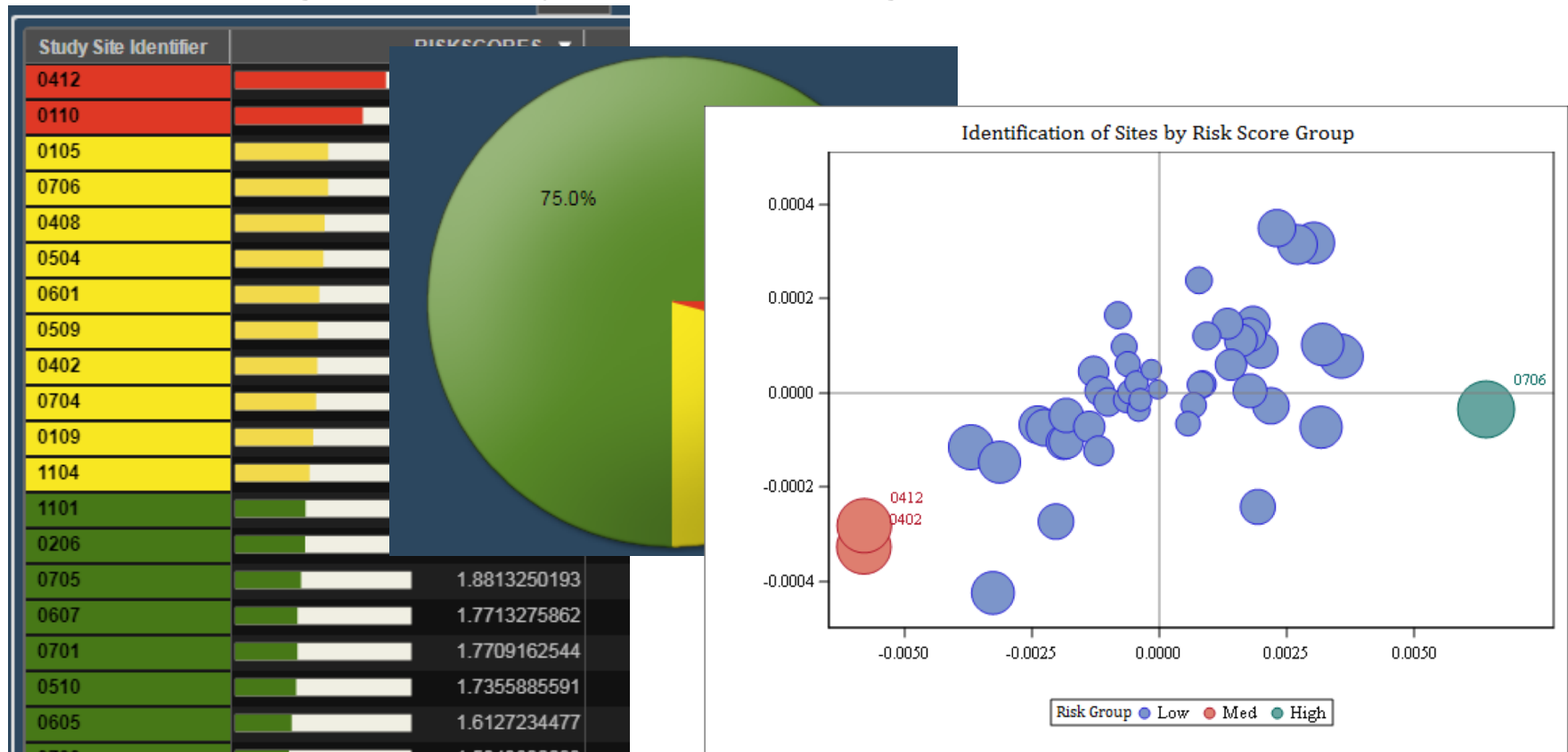
A moderately risky site

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Future Steps: Integration with Visualization Platform

- Considering several options including SAS VA



Future Steps: Integration with Visualization Platform

- Tools in the visualization platform
 - Integrate RBM Metrics with CSI
 - Easy to navigate for clinical staff (e.g. legends, labels, data tabs)
 - Drill-down capabilities (e.g. view a single site or subject)
 - Email alerts
 - Tracking of corrective and preventative actions

Add Alert

Expression Subscription and Notification

Specify alert context

☒ Create new expression

Column: Profit

Operator: >

Value: 500,000

☐ Use existing condition

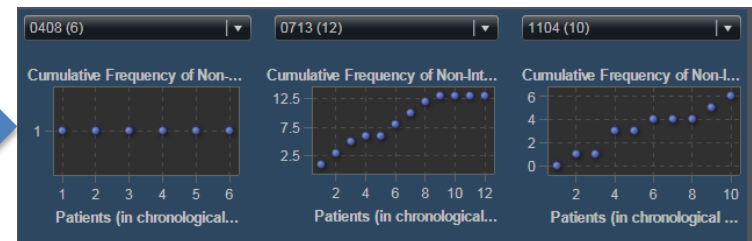
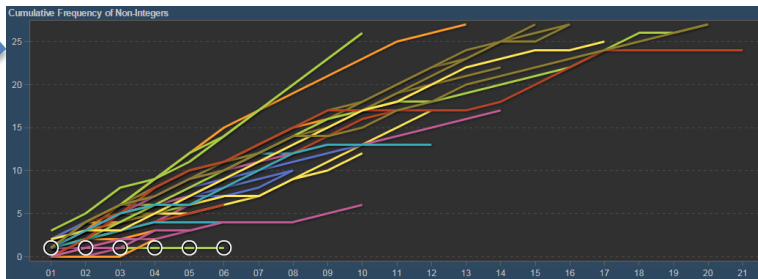
Options

Select how often to query the system

☐ Use the system default

☒ Query the system every: 1 Hour

OK Cancel



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Conclusions

- Guidance from regulatory bodies around the world suggest taking a risk-based approach to the monitoring of clinical trials.
- “Risky” sites may compromise subject safety or overall quality of study data; centralized monitoring tools identify these sites for targeted monitoring efforts.
- Data driven approaches provide a scientific safety net.
- Data review is enhanced by using data visualization.
- Cost-effective way of meeting regulatory requirements.

Background References

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Thank You!

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