

Implementing a Scalable Risk-Based Monitoring Strategy

DRIVING QUALITY INTO CLINICAL TRIALS

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Agenda

- Understanding the Importance of RBM
- Defining Your Approach
 - Pre-Study Risk Planning
 - Targeted Site Monitoring
 - Centralized Monitoring
- Managing Change
- Conclusions



Understanding the Importance of RBM

The Motivation for ICH E6 (R2) ...

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to

Study Complexity

68% Increase in average # of procedures

88% Increase in data volume

100% Increase in # of countries

Quality Issues

50% FDA Drug Submissions fail first-cycle review

Up to **32%** of failures due to quality-related issues

14 Month median delay - if approved

Old Processes

1% of eCRF data corrected by 100% SDV

15% of study cost for 100% SDV

A Regulatory Call-to-Action ...

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.



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1 4 August 2011
2 EMA/ING/GCP/394194/2011
3 Compliance and Inspection

4 Reflection paper on risk based quality management in
5 clinical trials
6 Draft
7

Draft Agreed by the CTFG ¹ for release for consultation	31 May 2011
Draft Adopted by the GCP Inspectors Working Group for consultation	14 June 2011
End of Consultation (Deadline for Comments)	15 February 2012

8
9 Comments should be provided using this [template](#). The completed comments form should be sent to
GCP@ema.europa.eu.

10 11 Keywords	Quality Management, Risk Management, Quality Tolerance Limit, Risk Control, Clinical Trial
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FDA CRADA with CluePoints

PUBLIC HEALTH SERVICE
COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

SUMMARY PAGE

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RELEASE THIS SUMMARY PAGE TO THE PUBLIC.

TITLE OF CRADA:	A STATISTICAL TOOL TO ASSESS DATA QUALITY IN MULTICENTER CLINICAL TRIALS
PHS Component (FDA Center):	Office of Biostatistics, Office of Translational Sciences, (Center for Drug Evaluation and Research, FDA)
FDA Principal Investigator:	Paul Schuette, Ph.D.
Collaborator:	CluePoints, Inc.
Collaborator Principal Investigator:	François Torche, CEO

RBM/RBQM Promises Transformative Value ...

	Sample Study
Total Net Value Generated with RBM	\$7,616,000
Central Monitoring Cost (Resources and Technology)	-\$345,000
Value Generated - Site Monitoring Efficiency	\$2,059,000
Value Generated - Improved Quality	\$2,872,000
Value Generated - Shorter Study Timelines	\$3,030,000



Defining Your Approach

3 Core Components to Consider

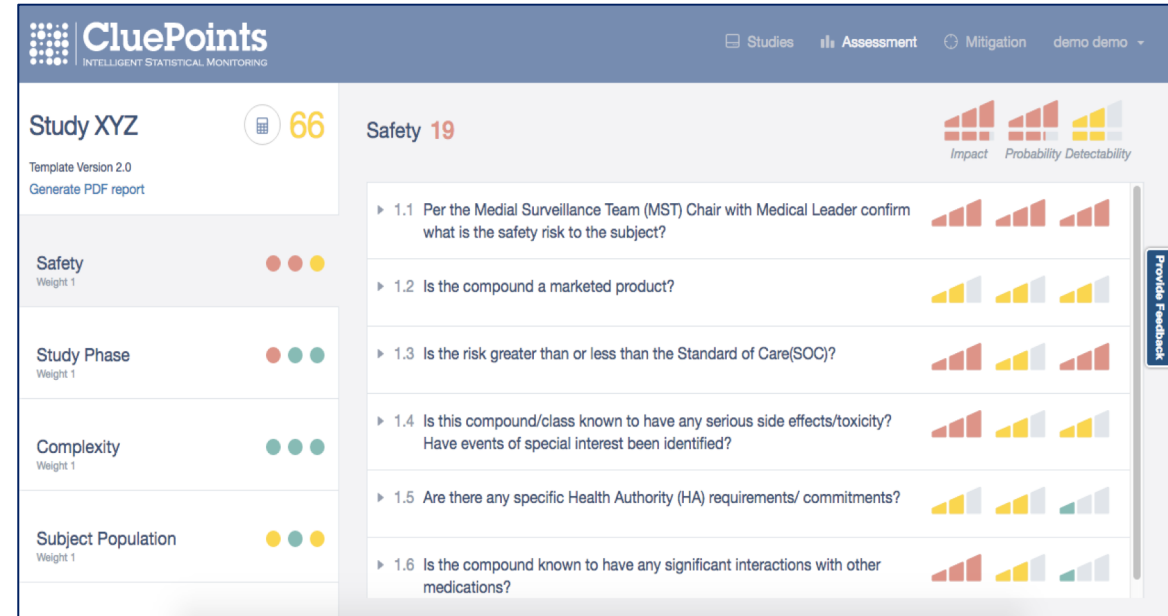
1. Pre-Study Risk Planning
2. Targeted Site Monitoring
3. Centralized Monitoring

QBD and RBM => RBQM

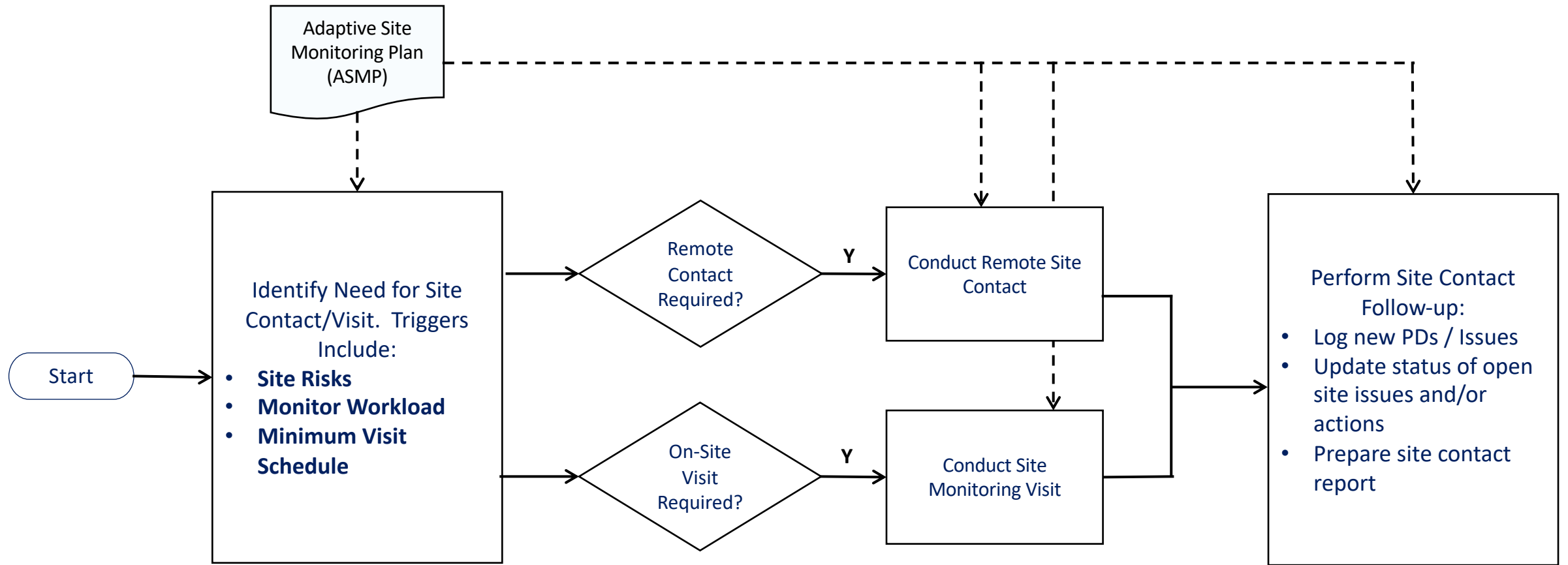


Pre-Study Risk Planning – Keys to Success

- RBM Champions to facilitate and guide study team
- Keep it Simple!
 - Avoid exhaustive review and scoring of numerous risk questions
 - Encourage critical thinking – let the experts speak!
- Ensure mitigation plans are carried out!
 - Tracking and documentation



Perform Targeted (Adaptive) Site Monitoring



Targeted Site Monitoring Considerations

- Lower frequency of on-site visits
 - Supplement with remote site contacts (web/video conferencing, etc.)
- Minimal reliance on SDV/SDR
 - Not a QC Hammer!
 - Help establish confidence
 - More focus on initial subject(s), critical data
- Remote Monitoring
 - Remote site contacts
 - Targeted review of eCRF data
 - Site risk review & follow-up

SDV/SDR – Keep it Simple!

- Same initial plan across all sites
- Increase scrutiny only for cause - and not permanently
- Consider Setting SDV plan = SDR plan

ICH E6 (R2) – Centralized Monitoring a Key Component

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:

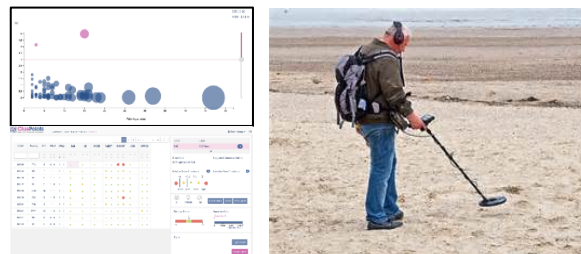
- (a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
- (b) examine data trends such as the range, consistency, and variability of data within and across sites.
- (c) evaluate for systematic or significant errors in data collection and 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.

Centralized Monitoring – Critical New Weapon

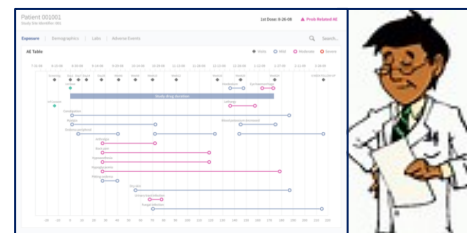
Data Management

Discrepancies
AE/Med Coding
Reconcile SAEs
Lab Data Review

Centralized Monitoring



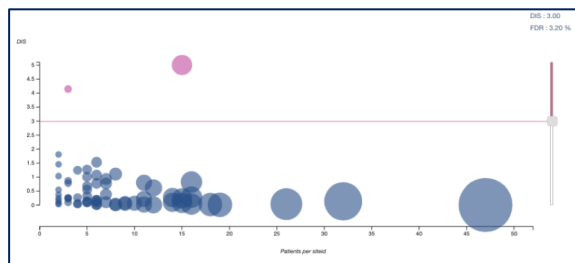
Medical/Safety Reviews



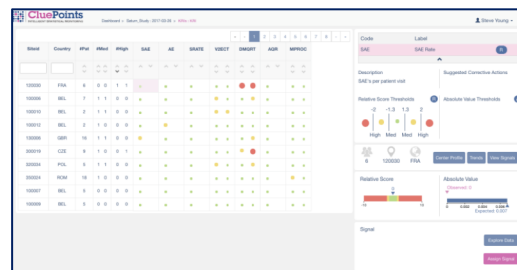
Adaptive Site Monitoring



SDM



KRIs / QTLs



Remote

- Remote Site Contacts
- On-site Visit prep
- Risk Follow-up
- Targeted eCRF Reviews

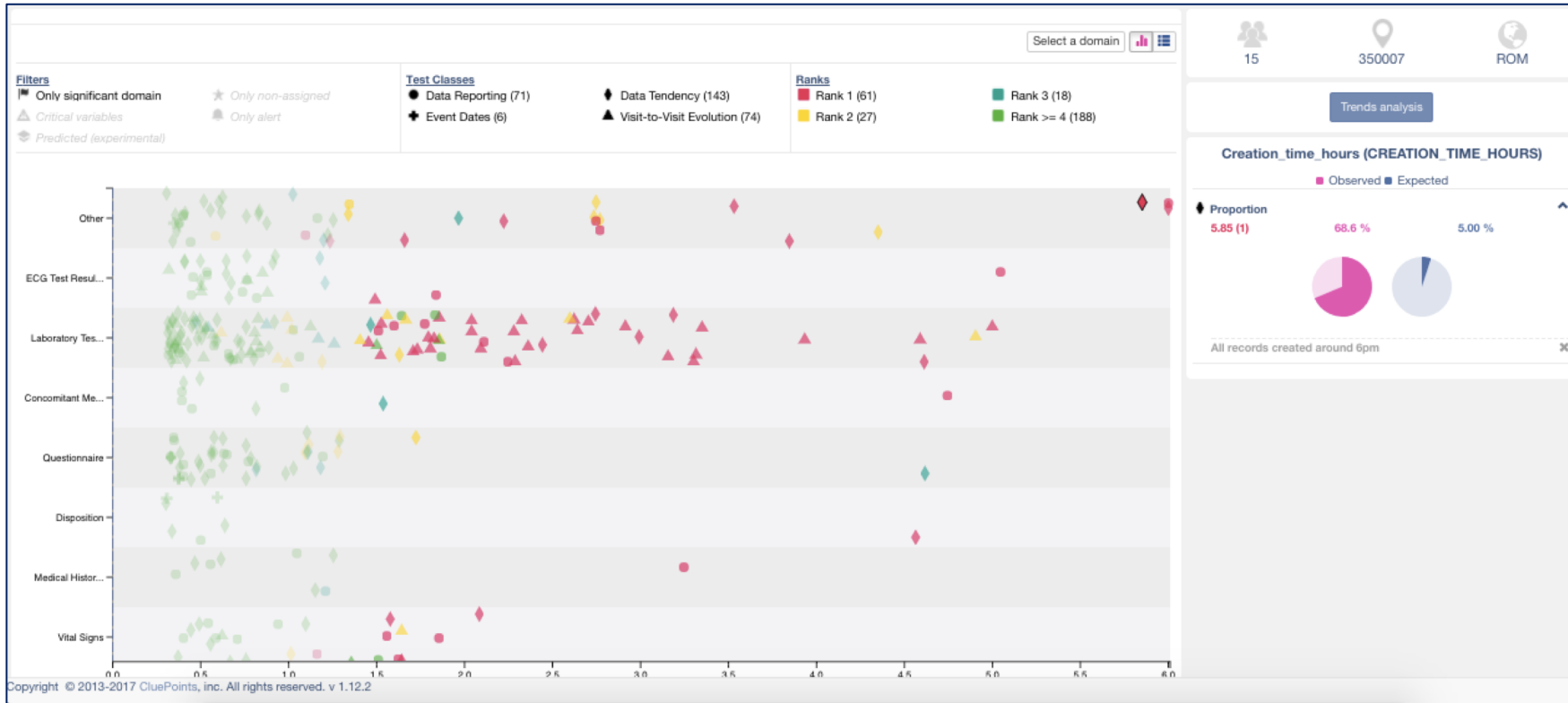
On-Site

- Training/re-training
- SDV/SDR
- Risk Follow-up
- Essential Doc Reviews

Effective Statistical Data Monitoring Uncovers Various Risks ...

Issue Type	Typical examples	Intent
Fraud	- Fabricated patients - Fabricated patient data - Falsified eligibility data - Duplicate patients	Deliberate – financial gain
Tampering and Sloppiness	- Propagated or fabricated vital signs - Under-reporting of adverse events - Procedures or assessments not performed	Limited awareness
Systemic Errors	- Site Training issues - Mis-calibrated study equipment	Unintentional

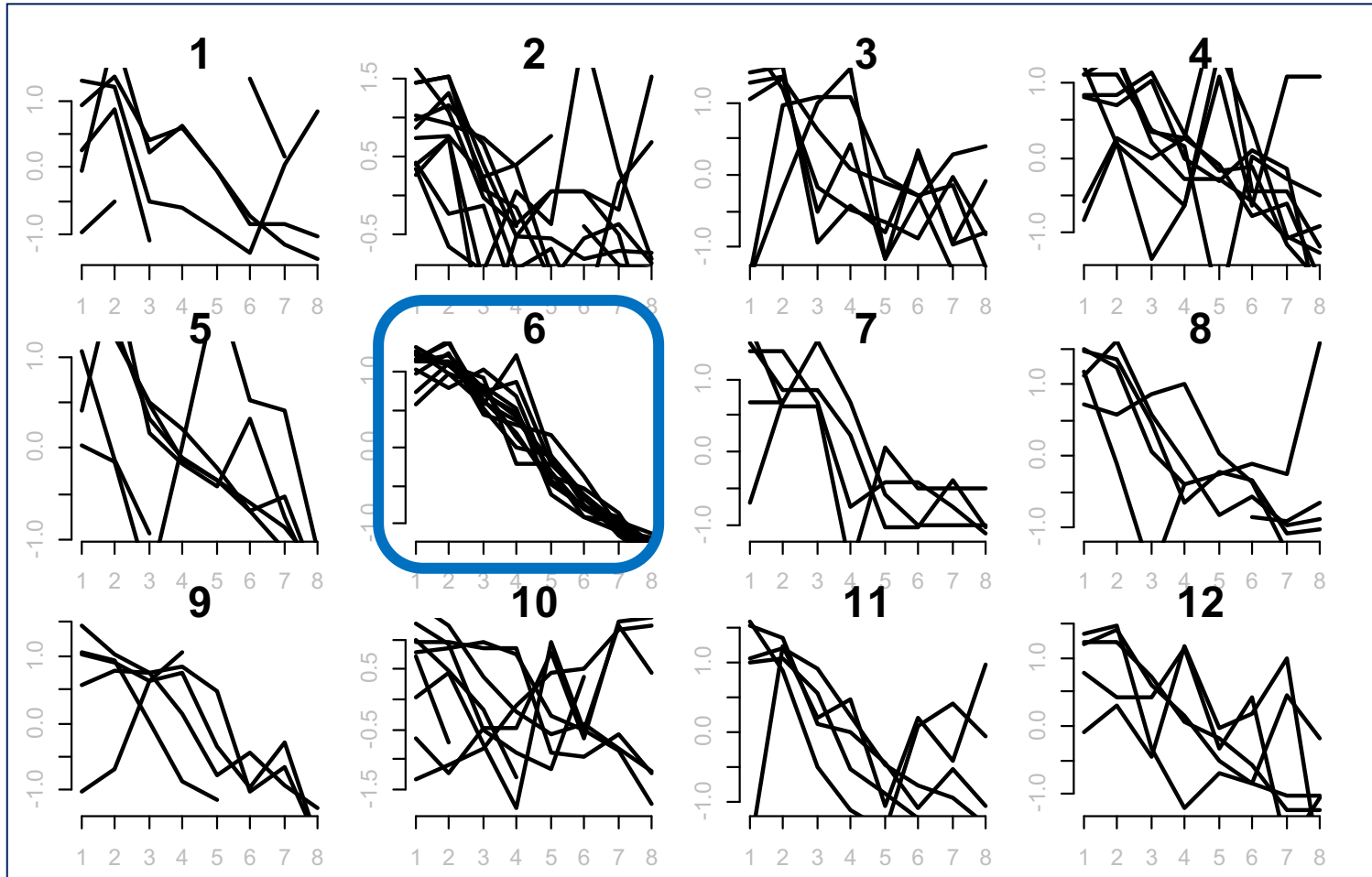
CM Example: Fraud



Phase 3 Study – Chronic Disease

Site with 15 patients – all ePRO diary entries done by site: Same time of day, same day for all patients. Sponsor removed all 15 patients from analysis.

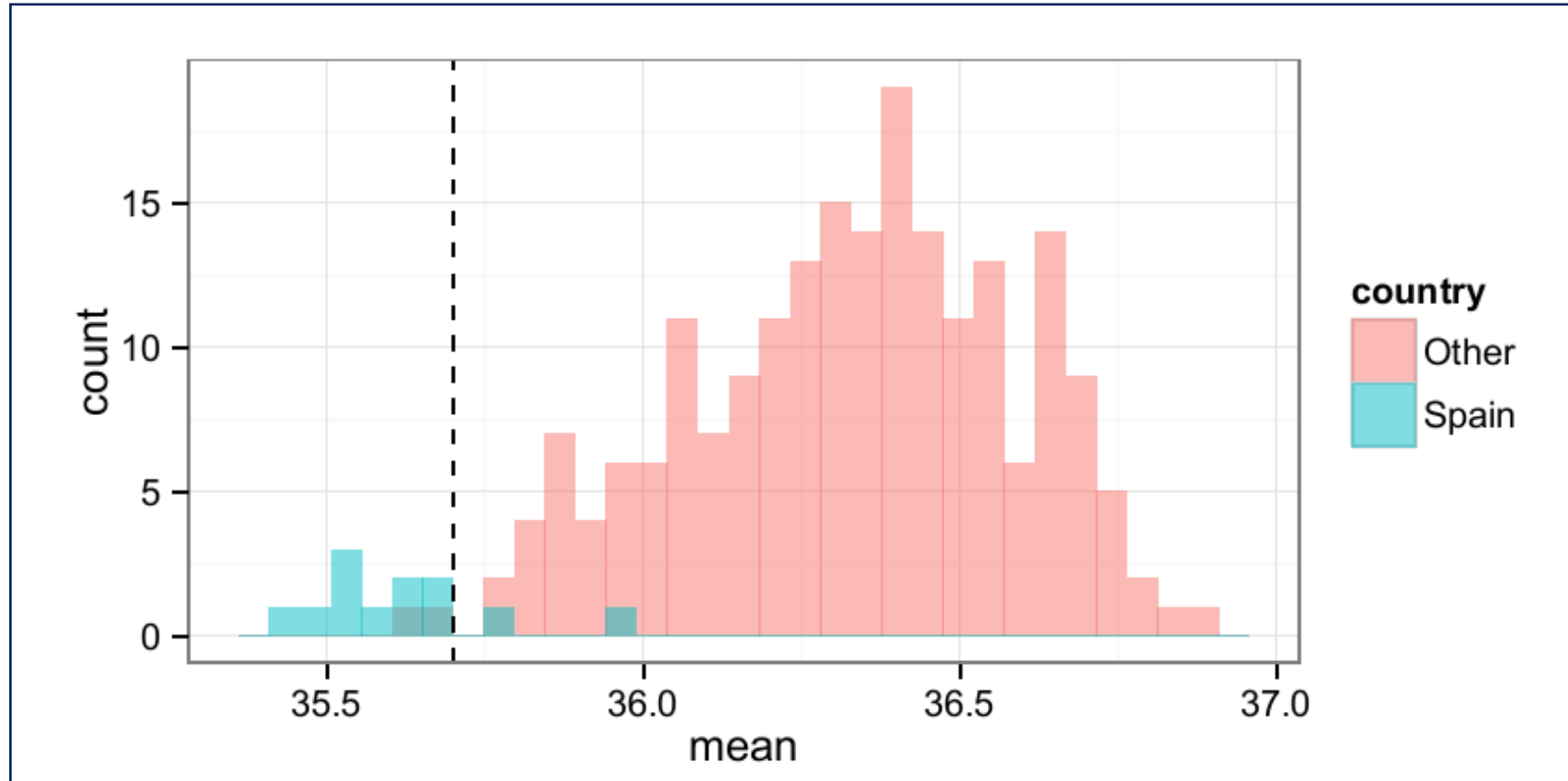
CM Example: Tampering/Sloppiness



Diabetes Study – 55 sites, 300 patients

Site found with unusual lack of variability across patient weight measurements. Staff were “inventing” missed weight measurements by interpolating.

CM Example: Mis-Calibrated Equipment

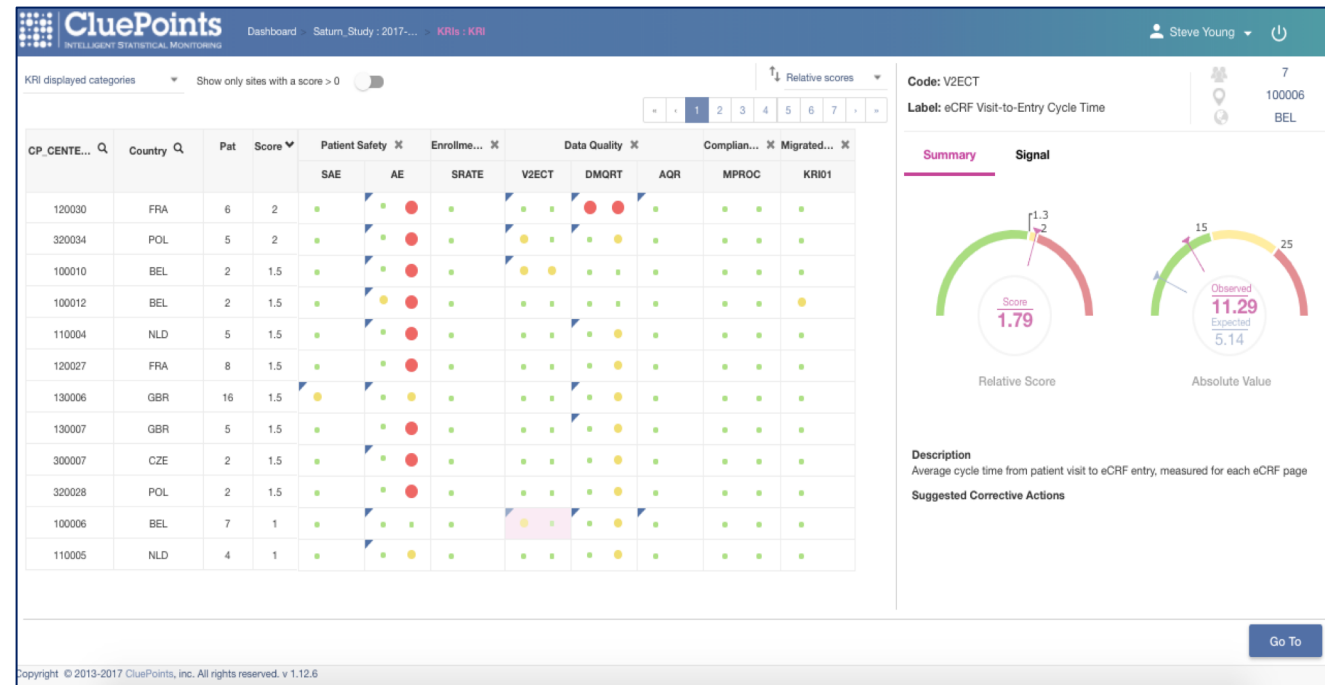


Phase 3 Study – Vaccination
200 Sites, 16000 Patients

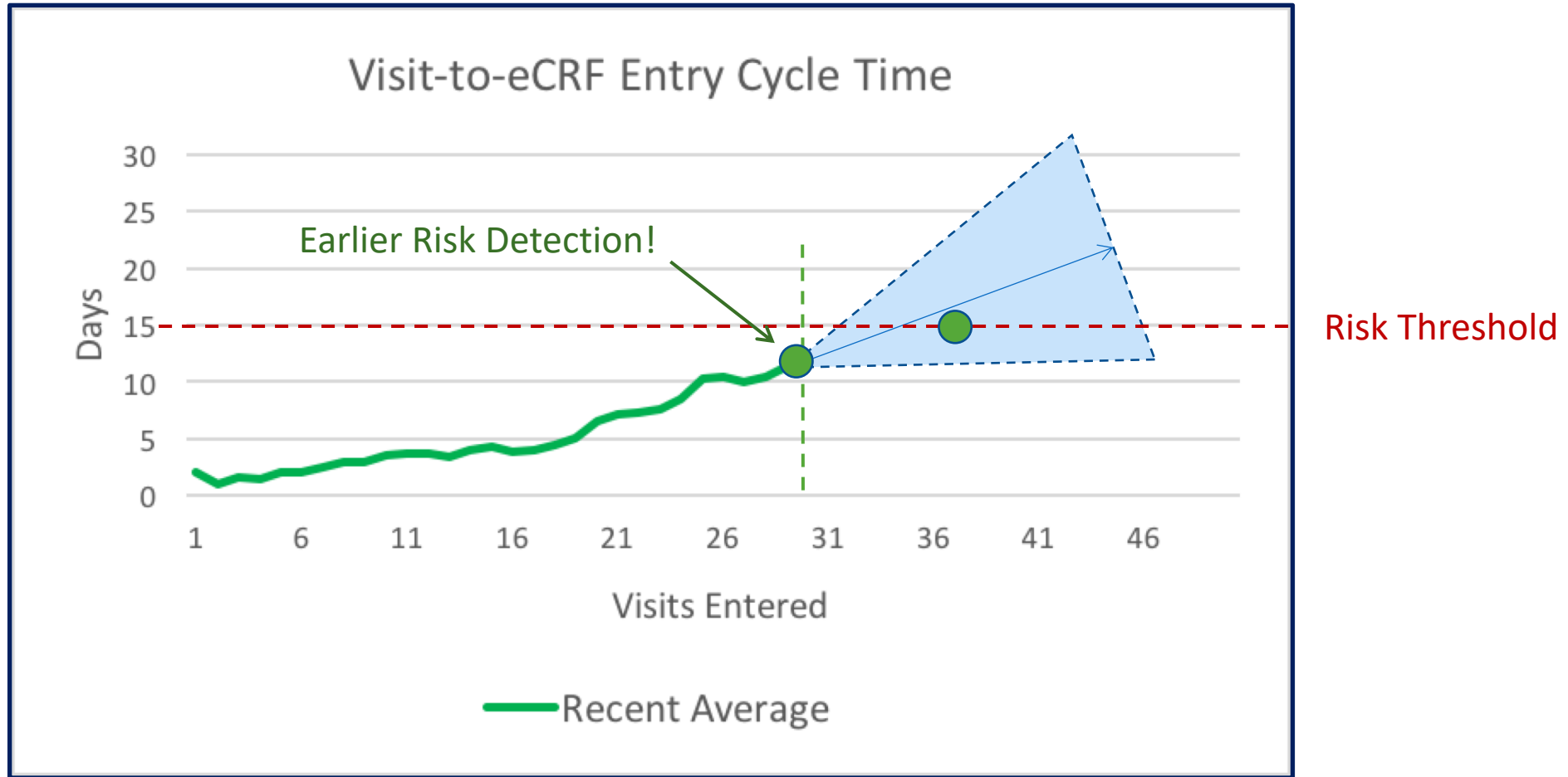
Temperatures for all sites in Spain consistently in a lower range. Investigation revealed mis-calibrated thermometers shipped to all sites in Spain.

KRIs / QTLs – Targeted Risk Detection

- ≤ 20 Total KRIs
 - ✓ Avoid signal overlap => signal noise
 - ✓ Scalability
- Standard KRI Library
- Focus on Reliability
 - ✓ Minimize false signals
- Focus on Early Detection
 - ✓ Predictive vs. Retrospective



Looking Forward – Predictive Analytics



Conclusion

- Heart of RBM/RBQM – Continuous Risk Assessment and Mitigation
- Keys to Success
 - Keep it Simple!
 - Keep it Thoughtful
- Huge opportunity!

| Thank You

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