Ensuring quality:
The role of monitoring

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The Role of Quality Assurance

- Overall objective:
  - Improve the availability of reliable information from clinical trials on which to base important healthcare decisions
- Identify and address risks:
  - Risks should be assessed and mitigated throughout the trial life-cycle
  - Risks to participants
  - Risks to reliability of results
- Monitoring should enhance quality
  - Appropriate to the setting
  - Proportionate to the risks
  - Identify threats to design, performance and analysis
  - Stimulate improvement

Criticisms of the traditional monitoring approach

- Largely retrospective
  - too late to address any issues
- Poorly focussed
  - emphasis on checking of individual data points & documents
- Unsustainable
  - inefficient and costly

Monitoring Project

- **Objectives**
  1. Describe the range of current monitoring practices and examine factors that drive their adoption (**What's happening?**)
  2. Define key quality objectives for monitoring clinical trials (**What's the aim?**)
  3. Examine ways to build quality into trials to enable more focused and efficient monitoring (**How can we improve?**)

- **Leaders**
  - Martin Landray PhD FRCP (U. of Oxford)
  - Briggs Morrison MD (Pfizer, Inc.)
  - Rachel Sherman MD (OMP, CDER, FDA)

Results: Survey of Monitoring Practices

- Wide variety of monitoring practices in use
- Choice of monitoring approach depends on type of organizational sponsor
  - on-site monitoring used by ≥80% Industry/CROs; <33% academic centres/cooperative groups/ government organizations
  - ≤33% use centralized monitoring to target/replace site visits

Morrison B. Clinical Trials 2011

Monitoring objectives

Major quality objectives are to:

- Protect participant rights, safety and wellbeing
- Ensure the reliability of the study results
- Maintain adherence to the protocol

Monitoring also provides:

- An opportunity for focused training
- Feedback that can improve study processes

How can we improve?

- Primary focus should shift from post-hoc monitoring / inspection to incorporation of quality into the scientific and operational design of a trial
- No single monitoring approach is appropriate or necessary in all circumstances
- Monitoring approach (which may combine several methods) should be tailored to the needs of the particular clinical trial

Monitoring Recommendations

Build quality into the scientific and operational design and conduct of clinical trials

- Focus on what matters
- Develop a quality management plan
- Assess performance in important parameters
- Improve training and procedures
- Report findings of quality management approach

Ancillary Recommendations

- Share knowledge and experiences
- Encourage appropriate regulatory guidance
- Promote education and awareness
- Seek international adoption and harmonization

Focus on what matters

- "Quality" is defined as the absence of errors that matter

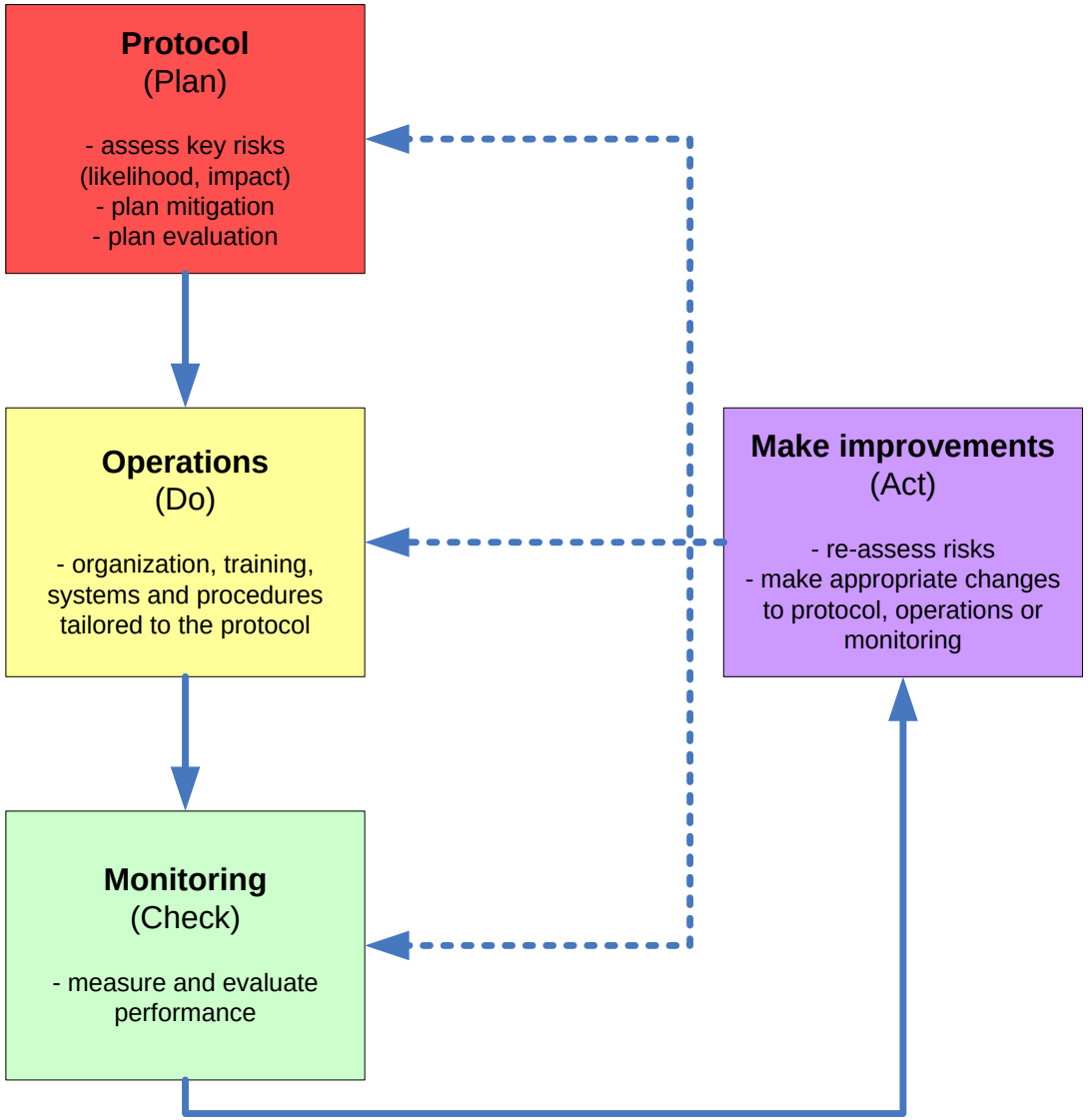
  (i.e. errors that have a meaningful impact on patient safety or interpretation of results)

- Determine what matters for the specific trial

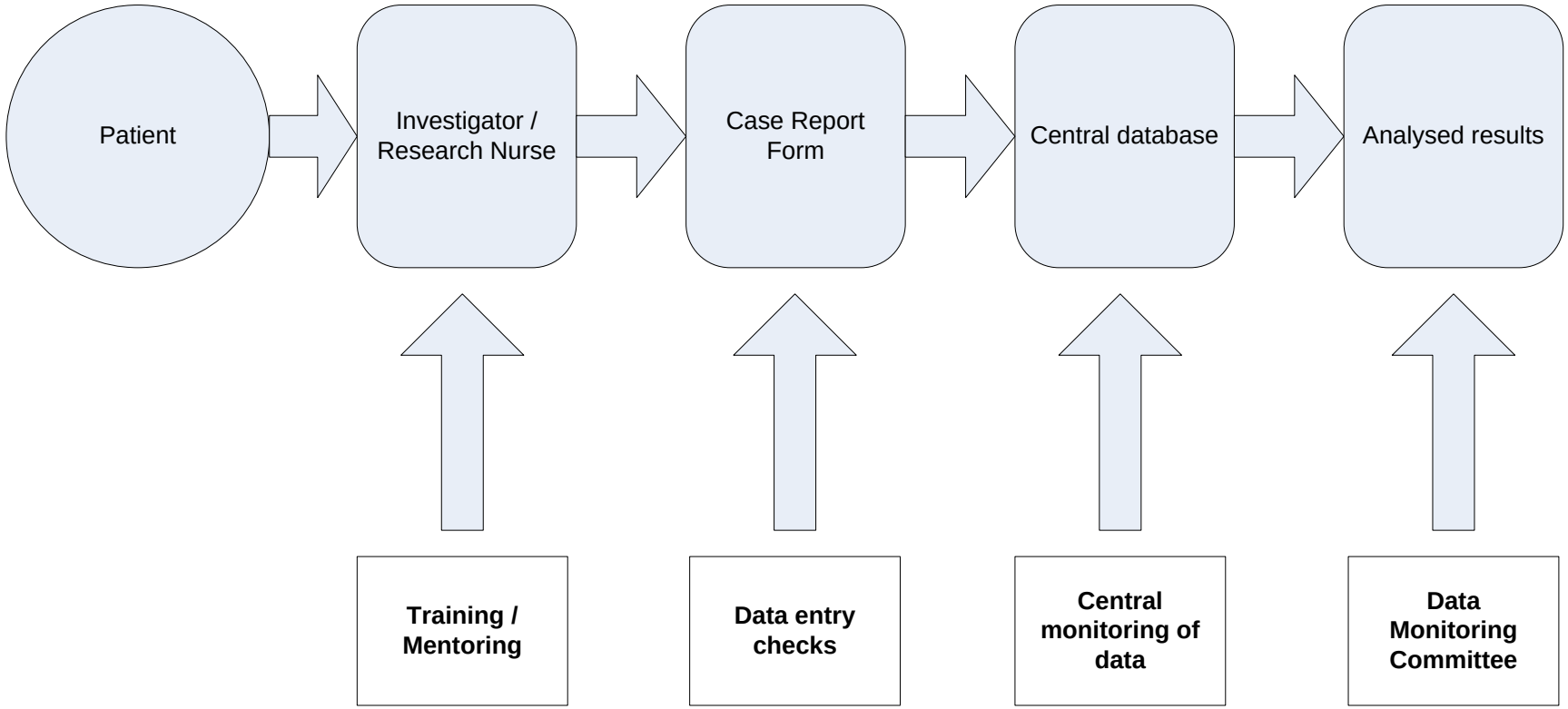
Quality risk management

- Focus on those aspects of greatest importance for the particular trial and consider
  - likelihood of errors occurring in key aspects of study performance
  - anticipated effects of such errors on human subjects protection and reliability of results
- Informs protocol, operations and monitoring approach
- Review/revise in response to new information

Quality by Design (QbD)



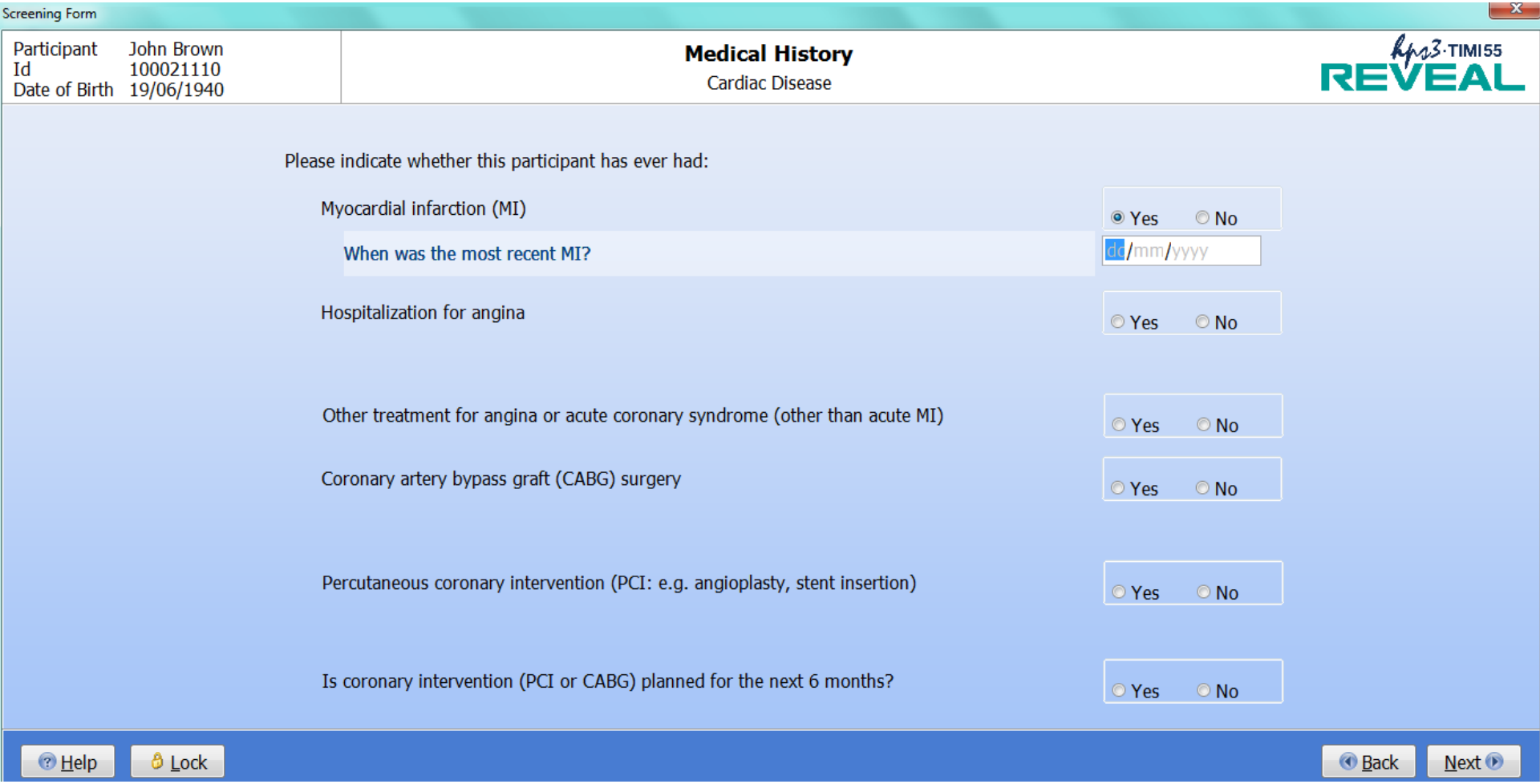
Clinical trial pathway



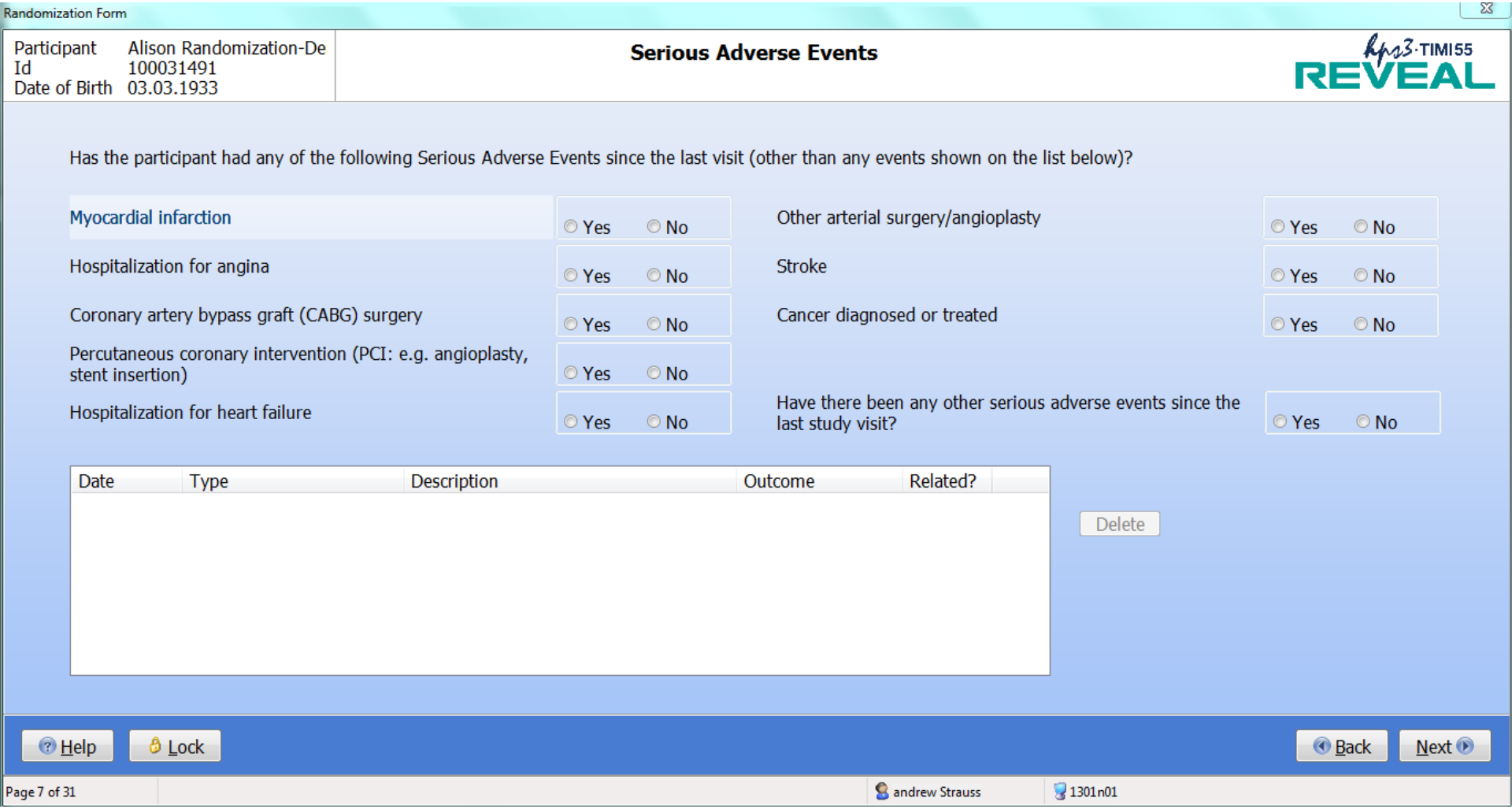
Maximising the potential of IT: More than just data capture

- Comprehensive data collection
  - no missing items, supplementary data sought automatically
  - built-in data coding (at required level of detail)
- Encourage/enforce compliance with the protocol procedures and processes
  - eligibility
  - consent (incl. genetics)
  - safety monitoring & treatment adjustments
  - visit scheduling
- Rapid data transfer to coordinating centre facilitates monitoring of study conduct

Check Inclusion Criteria: ensures complete information is obtained



Record Serious Adverse Events: extra detail sought automatically



Monitoring strategies

- Site visits
  - Observation of trial activities (incl. participant visits)
  - Mentoring: Training, support, motivation
- Remote assessment
  - Central clinical & administrative review
  - Incident alerts & tracking systems
  - Automated detection of potential data issues
  - Verification with external sources (e.g. electronic records)
  - Statistical analyses
- Trial oversight
  - Steering Committee
  - Data monitoring committee

Statistical Monitoring

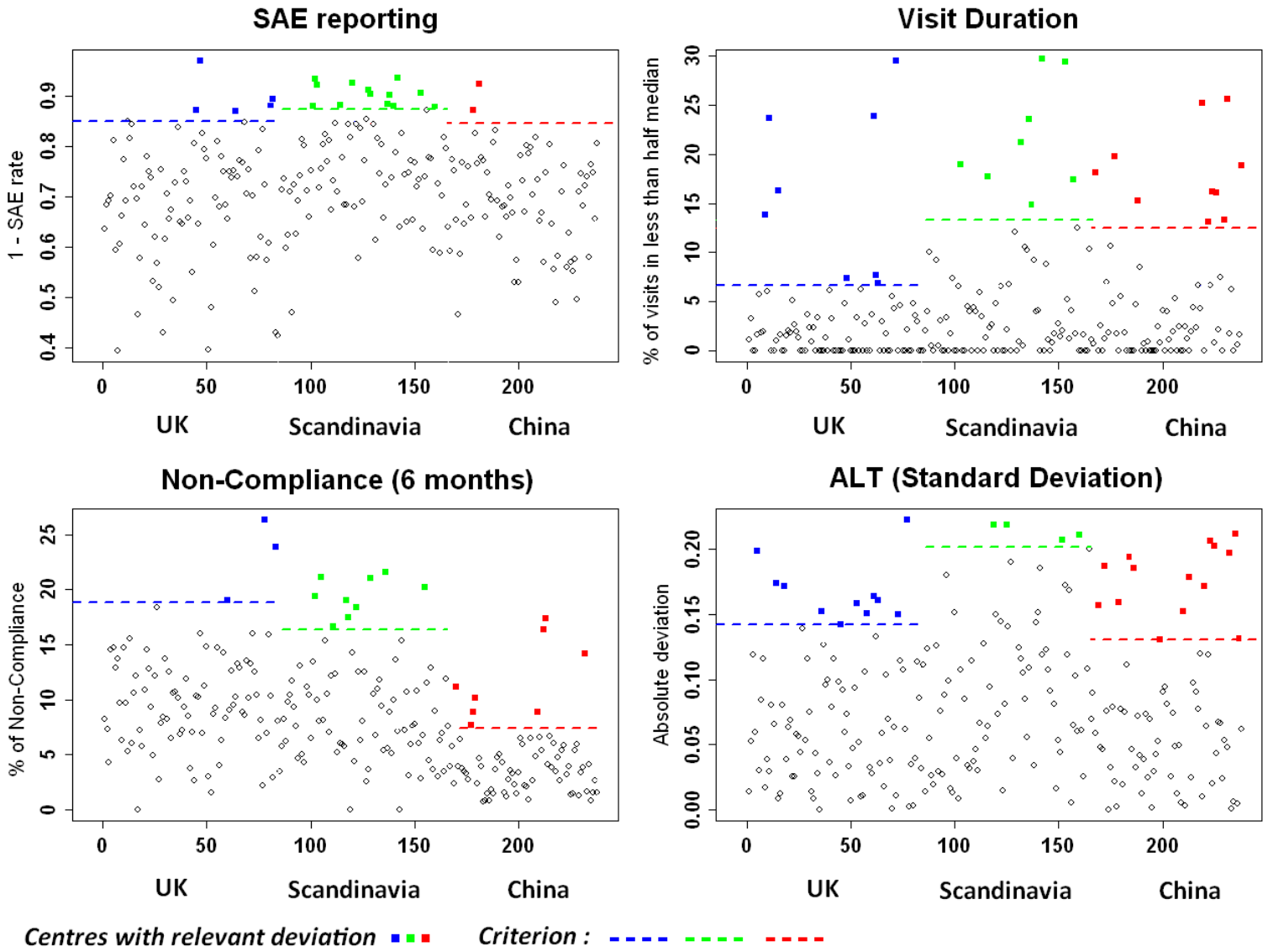
Central Statistical Monitoring can be used to:

- Assist in detecting fraud (data fabrication)
- Prioritize site visits (and additional training)
- Assist in ensuring data quality

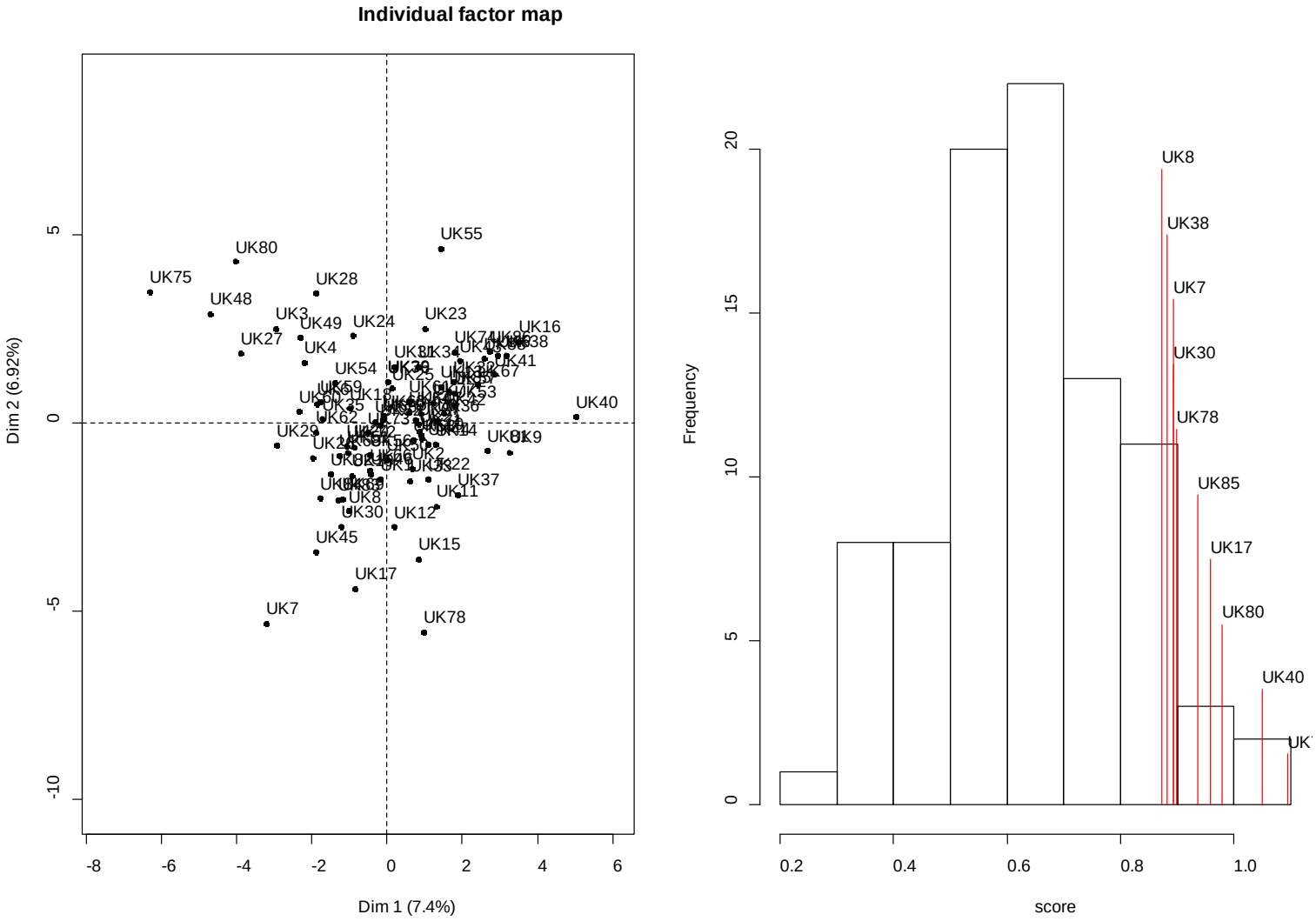
Approaches:

- Supervised - Key Risk Indicators
- Unsupervised - Data derived (e.g. SMART)

Central statistical monitoring



SMART Example (UK)



Conclusions: Risk-based quality assurance

- Assess the important risks to human subjects protection and reliability of results
- Design quality in to the trial protocol and procedures
- Use monitoring as a tool for improvement
  - Introduce from the start of the study when problems are more likely to occur
  - Tailor monitoring approaches to the risk-assessment and trial design
  - Direct visits to sites that have been identified with potential problems by central monitoring
  - Focus study visits on mentoring local study staff (and not on "box-ticking" and paperwork)
- Be open about quality assurance (including management plans and issues identified) with key stakeholders

Regulations & their interpretation (2009)

- Regulations should set out the quality objectives that are common to all trials
- Regulations should NOT specify the methods for meeting these objectives
- The interpretation and implementation of the regulations must be flexible, if their objectives are to be fulfilled

Regulations & their interpretation (2012)

Progress

- US FDA: Draft Guidance on a risk-based approach to monitoring (2011)
- EMA: Reflection paper on risk based quality management in clinical trials (2011)
- MRC/DH/MHRA Joint Project report on risk-adapted approaches to the management of clinical trials of investigational medicinal products (2011)

Challenge

- Ensure that these very helpful initiatives are widely propagated, understood and adopted.