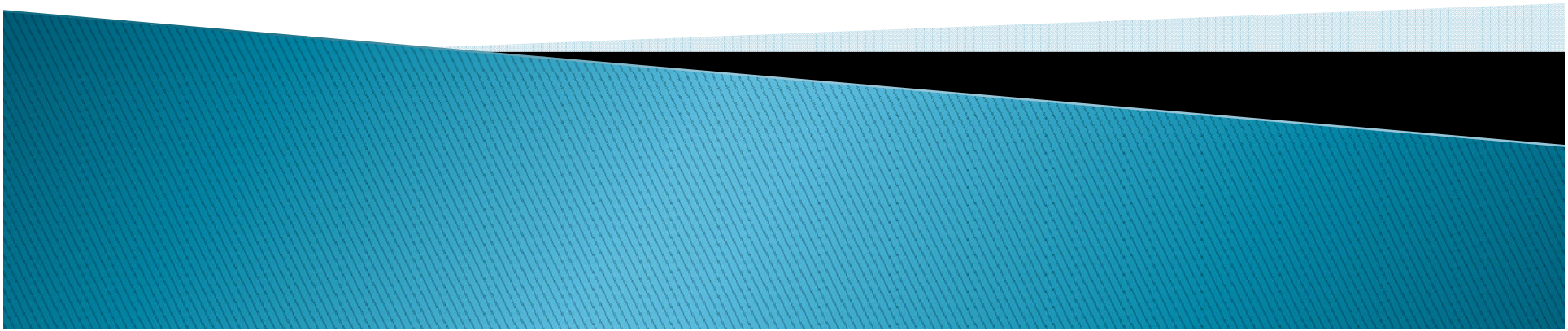
PhUSE Single Day Events, Brussels, April 28th 2011

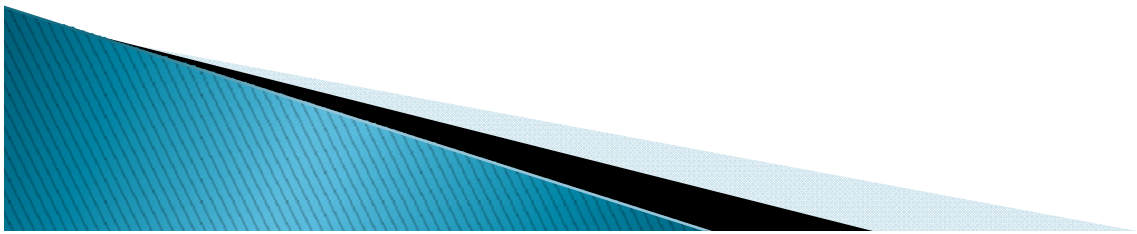
Implementation of Key Risk Indicators for a large scale trial

Erik Doffagne, Biostatistician
IDDI (International Drug Development Institute)



Outline

- Clinical trial monitoring
- Monitoring strategies
- Illustrative example: a Phase III cancer trial
- Conclusions



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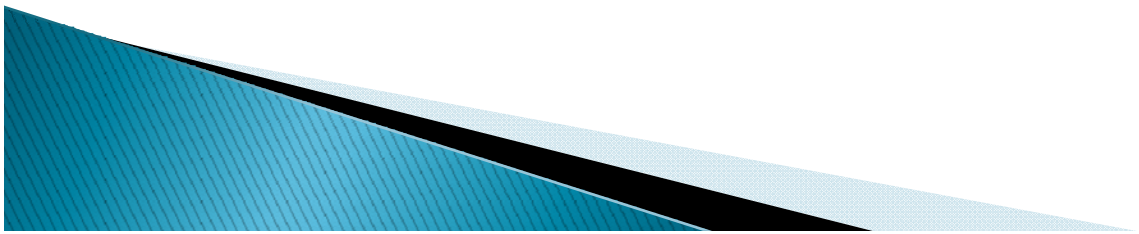
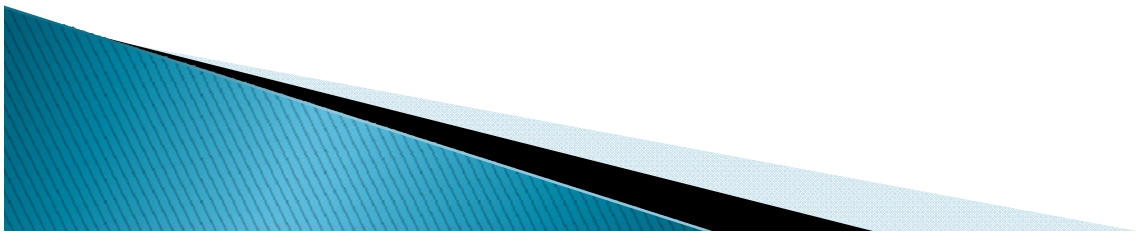


Clinical trial monitoring

- Monitoring is required by Good Clinical Practices (ICH E6)

- Objectives:
  - Ensure patients well being
  - Check data accuracy and completeness
  - Compliance with protocol and regulatory requirements



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- Site management constituting up to 60% of costs in some types of trial.[1]

[1] Eisenstein et al, Clinical Trials 2008;5:75

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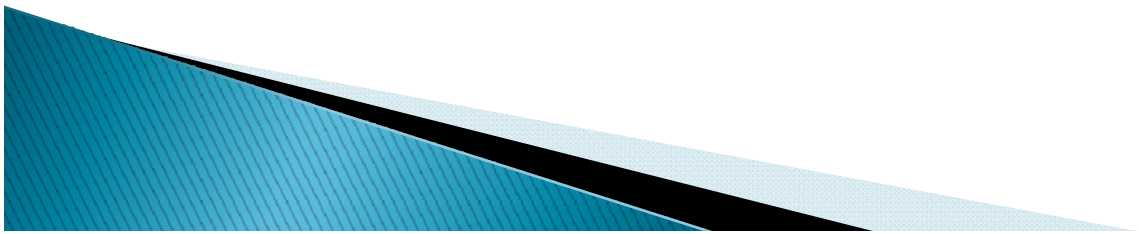
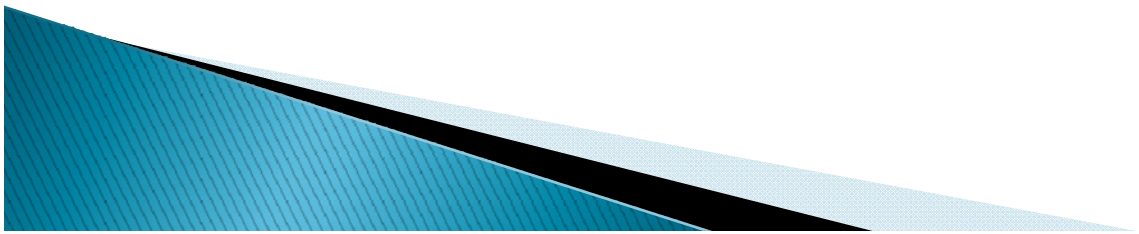


Monitoring strategies

- Extensive monitoring
  - 100% SDV for primary and secondary outcome
- Reduced monitoring
  - Random sampling of centers / patients / outcome to ensure rate of error <x %
- Targeted monitoring
  - Based on Key Risk Indicators
  - Based on central statistical monitoring



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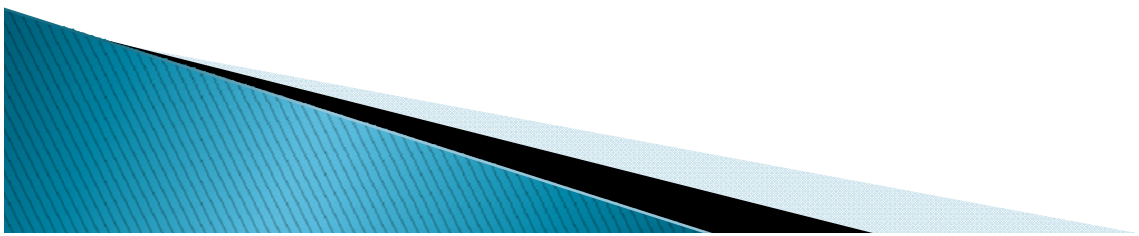

Viewpoint

The Good Clinical Practice guideline: a bronze standard for clinical research

David A Grimes, David Hubacher, Kavita Nanda, Kenneth F Schulz, David Moher, Douglas G Altman

« Monitoring confirms consistency between data collection forms and source documents; if the source documents are wrong because of laboratory, clinical, or clerical errors, then monitoring adds expense without benefit. A common misinterpretation of sponsors is that GCP requires audits of 100% of data; by contrast, random audits might suffice. »

CLINICAL TRIALS

DATA MANAGEMENT AND STUDY CONDUCT

Clinical Trials 2006; **3**: 486–492

Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer

J-L Liénard[a], E Quinaux[a], E Fabre-Guillevin[b,c], P Piedbois[b,d], A Jouhaud[b], G Decoster[e], M Buyse[a], on behalf of the European Association for Research in Oncology (AERO)

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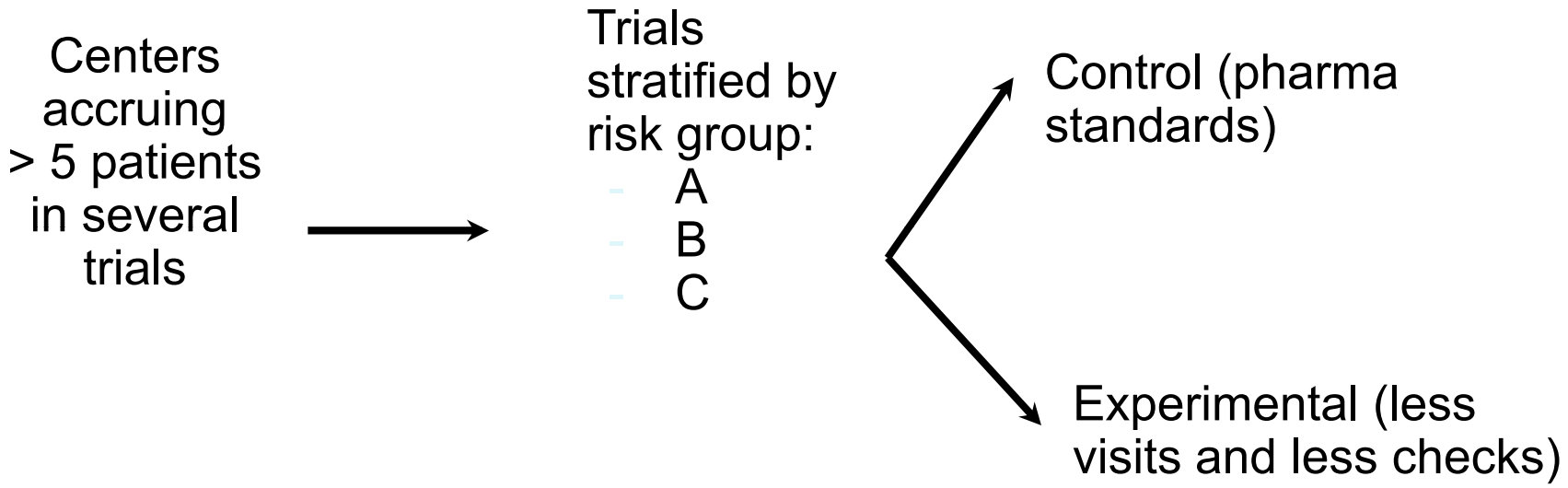
"Systematic on-site initiation visits did not contribute significantly to this clinical trial"

Comparison of monitoring strategies

- OPITMON- University Teaching Hospital Bordeaux

- ADAMON – ZKS Leipzig
  - Prospective cluster-randomized investigation into strategies adapted on a study-specific basis for on-site monitoring in conjunction with additional quality assurance measures.

OPITMON : OPTimisation of MONitoring for clinical research studies



Goal: non-inferiority of the proportion of patients with at least one severe error in informed consent, suspected unexpected severe adverse events reports, major eligibility criteria, or primary endpoint (expected: 95% with non-inferiority margin of 5%).

Source: Geneviève Chêne, University Teaching Hospital Bordeaux
https://ssl2.isped.u-bordeaux2.fr/optimon/Documents.aspx

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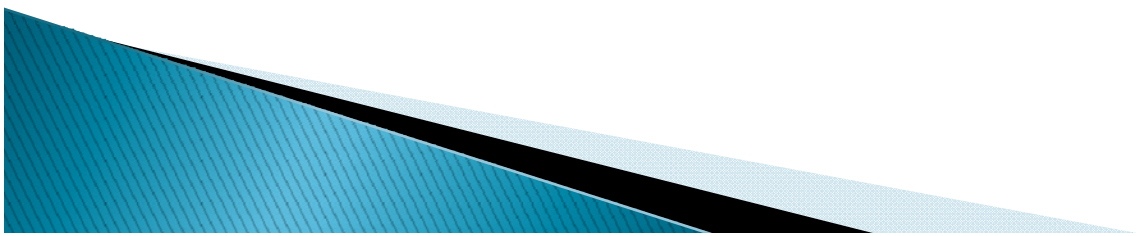
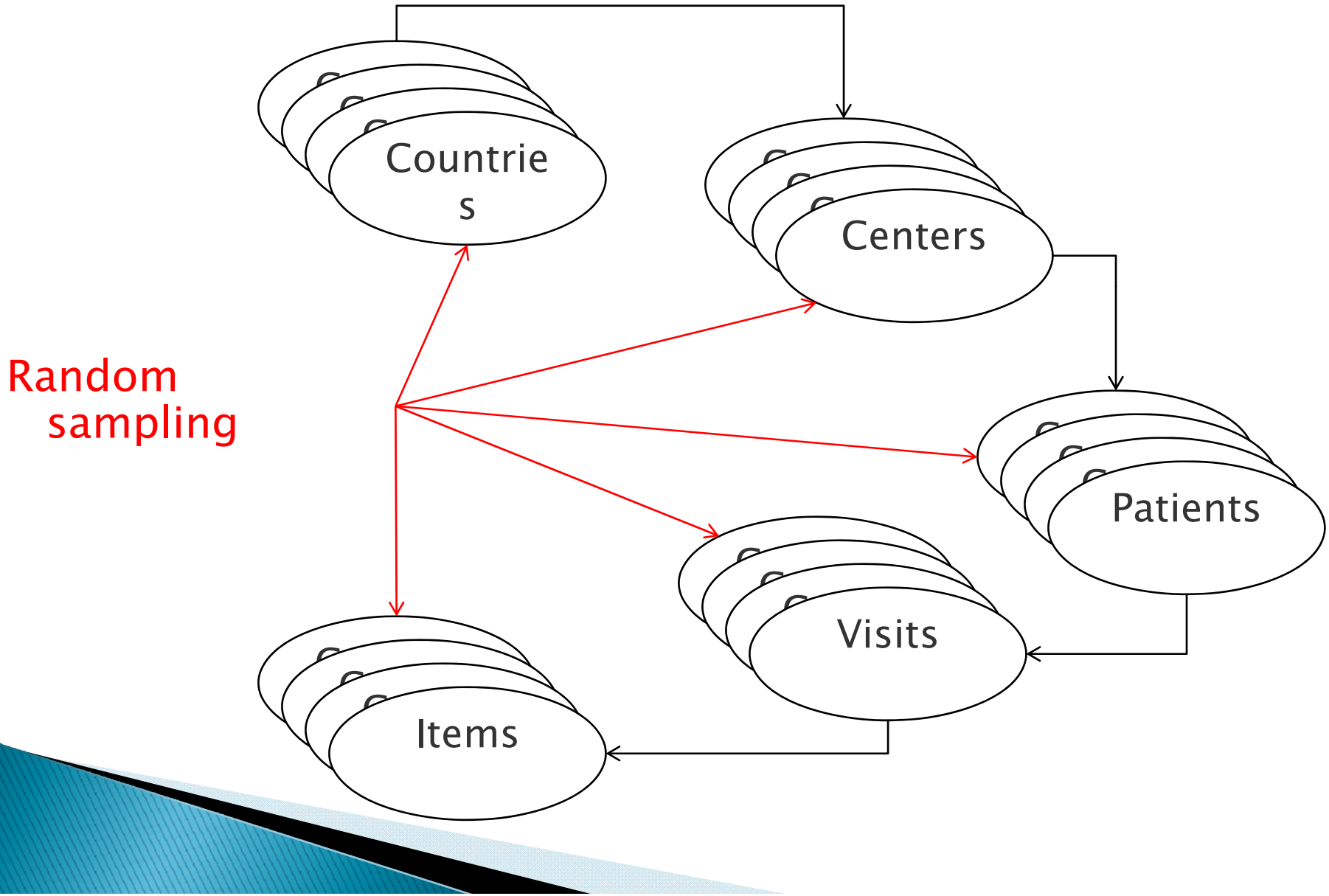


Reduced Monitoring



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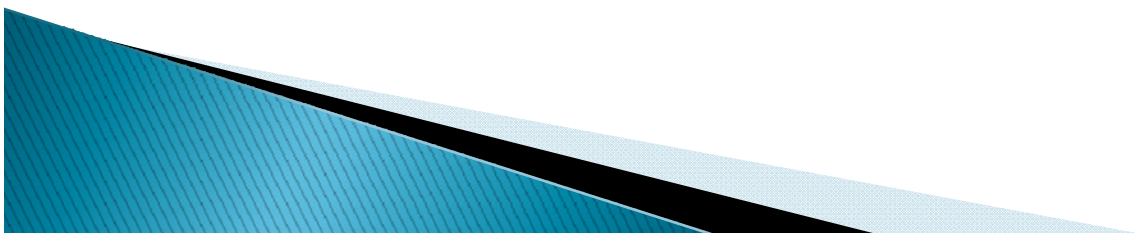
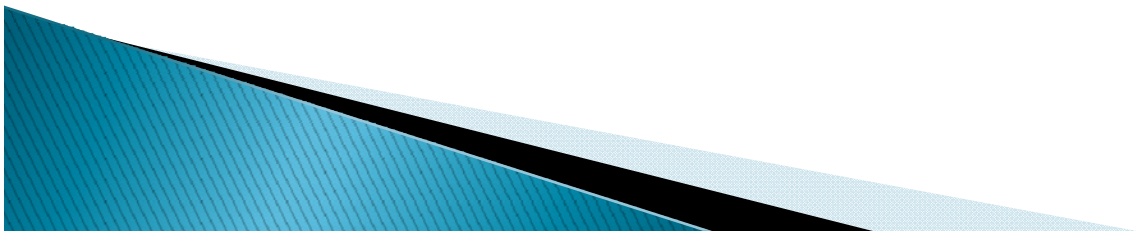


Targeted Monitoring: KRI approach

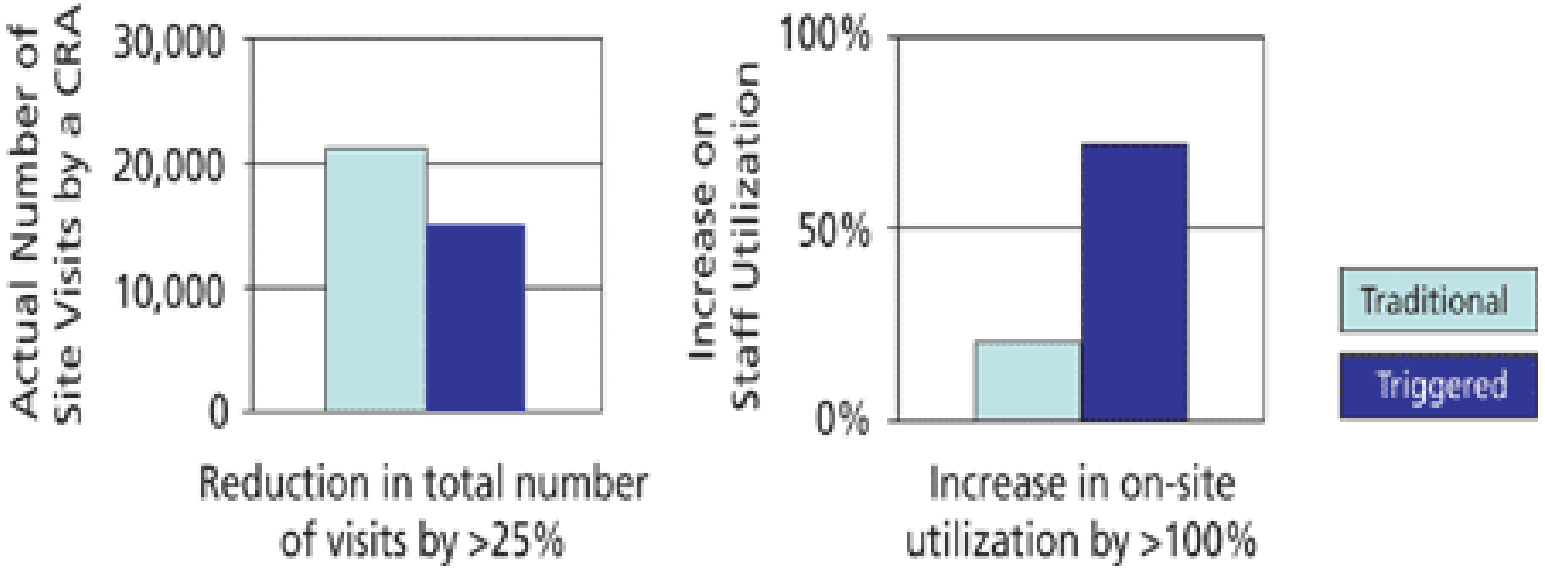
- Predefined metrics are computed for each sites: Key Risk Indicators
- On-site monitoring frequency is adapted based on site performance



Key Risk Indicators

- Study Conduct
  - Screening rate, accrual rate
- Treatment Compliance
  - % of dose reduction, % of dose delays
- Safety Reporting
  - Rate of AE, SAE
- Data Management
  - % of overdue forms, query rate, query resolution time

Cost-savings from targeted monitoring



Source: Quintiles.

Ref: S. Cooley & al. Triggered Monitoring. *Applied Clinical Trials* 2010:08:01

BMJ

RESEARCH

Carbon cost of pragmatic randomised controlled trials: retrospective analysis of sample of trials

Katy Lyle, research fellow,[1] Louise Dent, acting principal research fellow,[1] Sally Bailey, senior programme manager,[1] Lynn Kerridge, chief executive officer,[1] Ian Roberts, professor of epidemiology and public health,[2] Ruairidh Milne, director of strategy and development[1]

"**Conclusions** CO2 emissions from pragmatic randomized controlled trials are generated in areas where steps could be taken to reduce them. A large proportion of the CO2 emissions come from travel related to various aspects of a trial."

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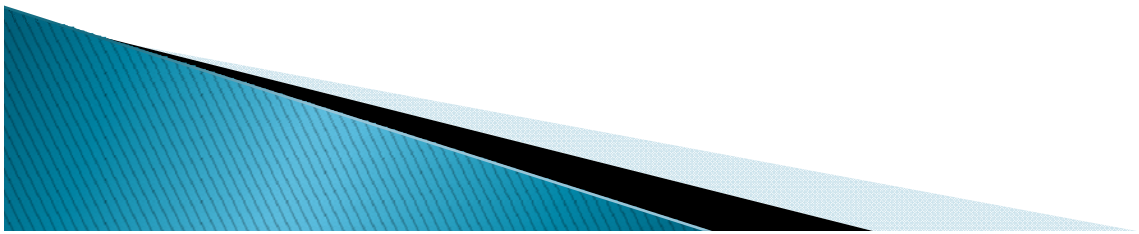
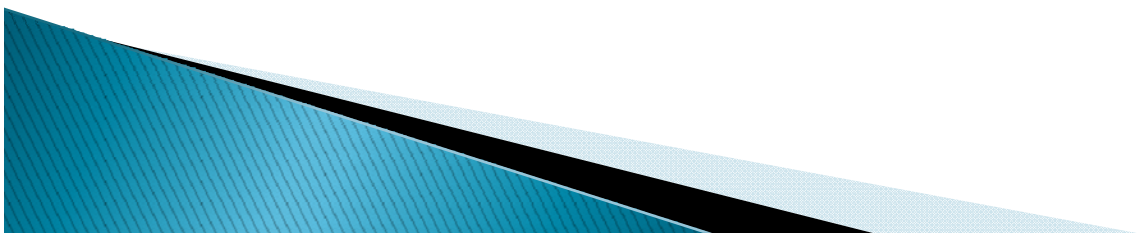


Central statistical monitoring

- In multicentric trials, the distribution of many/all variables can be compared between each center and all others

- In particular, aspects not captured by KRIs can be checked, such as:

  - Data consistency (across CRFs/time/patients)
  - Data plausibility (outliers, inliers, striking patterns)
  - Outlying centers can be identified
  - Overall reliability and quality of data can be assessed



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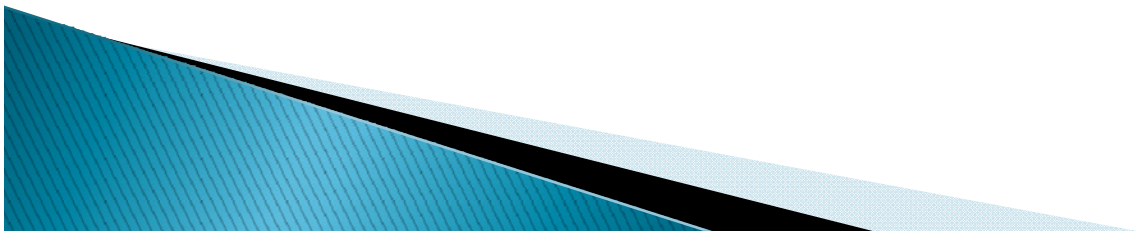
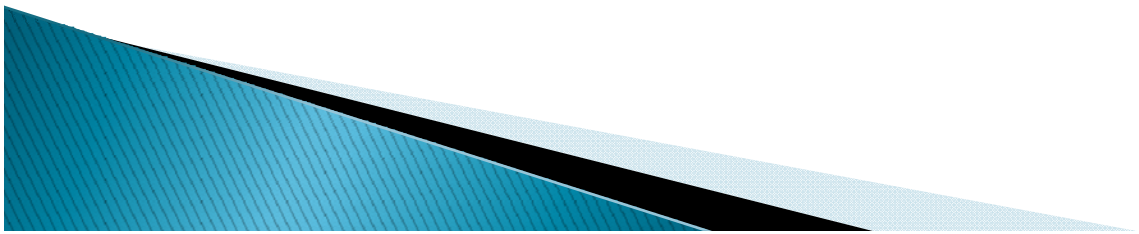


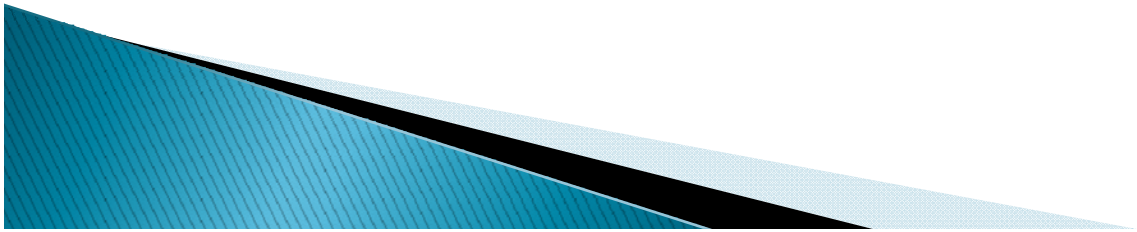
KRI implementation illustration

- International, multi-center, open-label, randomized Phase III trial (breast cancer)
- Academic research groups and industry sponsor
- ~ 3000 patients, ~1000 sites
- Different monitoring groups



SAS Implementation

- Analysis to be performed every 6 months
- Data from heterogeneous sources (clinical DB, Rando, various XLS sheets)
- Presentation of results for decision makers



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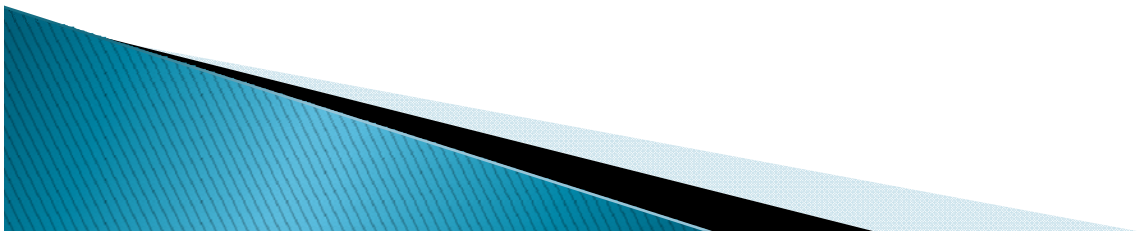

Conclusions

- Current clinical research practices (such as intensive monitoring and 100% source data verification) are not useful, effective, or sustainable

- Risk based approaches of clinical trials monitoring can help to reduce trial costs without loss in quality.