Developing evidence-based approaches to use of on-site monitoring

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Presentation plan

- Background to use of on-site monitoring
- Types of on-site monitoring strategies in use
- Review of ongoing research that will inform future use of these strategies
  - Focus on the MRC CTU's TEMPER study

Background

- ICH GCP "In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances …."
- Frequent site visits costly and of uncertain value
- Regulatory bodies: Increasing reference to risk-based monitoring and central monitoring to guide the use of on-site visits
  - MRC/DH/MHRA Joint project – risk-adapted approaches to the management of clinical trials of investigational medicinal products (Oct 2011)
  - Recent FDA Guidance for Industry also supports targeted on-site monitoring *(Oversight of clinical investigations – a risk-based approach to monitoring August 2013*)

- But … both acknowledge a (current) lack of evidence to support the recommended approaches (see also *Bakobaki et al 2012)*

Strategies for on-site visits

- Non-targeted approaches – routine visits (vs no visit(s))
    - Evaluation (EORTC, START substudy)
- Prospective strategies based (mainly) on baseline risk assessments (vs full on-site monitoring)
    - Evaluation (ADAMON, OPTIMON)
- Dynamic/reactive strategies based on ongoing central monitoring (vs untargeted visits)
    - Evaluation (TEMPER)

Non-targeted approaches -One RCT!

Lienard et al, Clinical Trials 2006

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- Randomised trial embedded within EORTC breast cancer trial
- Sites randomised to on-site visits (initiation, on-going, close-out) vs no on-site visits
- Planned to study impact of all study visits on:
  - Patient recruitment
  - Quantity of data spontaneously reported
  - Quality of data
  - Patients' follow-up time
- Closed early when decision made … to move to targeted monitoring visits
- Only initiation visits carried out in all sites, no close-out visits (could not evaluate impact of repeated visits)

- None of the pre-specified outcomes favoured the visited group

Non-targeted approaches: On-going RCT *(Huppler Hullsiek et al, SCT 2013)*

- RCT embedded in HIV treatment strategy trial (START)
- Study Hypothesis:
  - Adding annual on-site monitoring will improve site performance vs central and local monitoring alone
- Study Design:
  - Cluster randomized study
    - "standard" local and central monitoring vs
    - As above, plus annual site visits
- Composite primary outcome:
  - Major eligibility or informed consent violations
  - Use of an ART drug for initial therapy that is not permitted by the protocol
  - START primary endpoint or serious event reported more than 6 months after the time of occurrence
  - Data alteration or fraud

Ongoing trial

(Huppler Hullsiek et al, SCT 2013)

Potential issues:

- Late addition to START, some sites already visited
- Multiple changes to local monitoring processes
- Variations in regulatory req. and local monitoring practices across 36 countries
- Originally planned to visit 10% of control arm sites to check primary outcome….. Rising!

Status:

- Recruitment complete, follow-up to 2016

Strategies based on baseline risk assessment

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ADAMON

ADAPTIERTES MONITORING

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

http://www.adamon.de/ADAMON_EN/Home.aspx

ADAMON
Design

- Prospective cluster randomised trial, undertaken across 11 clinical studies phase II-IV
- Participating trial sites are randomized to whether the site will be monitored
  - On-site using a specifically adapted monitoring strategy *(Brosteanu et al, Clinical Trials 2009; 6: 585-596)* or
  - Via an intensive monitoring strategy ("full monitoring")
- Primary outcome measure:
  - occurrence of serious or critical findings with respect to patient safety, patient rights or reliability of data
  - To be assessed by a final audit in each trial site

ADAMON
Monitoring class assignment

The potential risk of therapeutic intervention is	Monitoring class	
Comparable to that of standard medical care	**K3 - low** **If there is no patient-related critical indicator that can be controlled by on-site monitoring** **and** **at least one indicator of robustness applies to the trial**	**K2 - intermediate** **In all other cases**
Higher than that of standard medical care	**K2 - intermediate** **In all other cases**	**K1 - high** **If there are patient-related critical indicators that require control by on-site monitoring**
Markedly higher than that of standard medical care	**K2 - intermediate** **If no patient-related critical indicator that can be controlled by on-site monitoring** **and** **at least one indicator of robustness applies to the trial**	**K1 - high** **In all other cases**

ADAMON

Monitoring strategies

	K1 (high)	K2 (intermed)	K3 (low)
Pre-study visit	Mandatory	Recommended	None
Initiation	Mandatory	Mandatory	Use alternatives
First visit	After 1st pt	After 1-2 pts	None
Further visits (Frequency depends on recruitment and monitoring tasks)	typically 6 p.a.	Assess annually as +/-noticeable problems – yes ≥3 p.a.; no ≥1 p.a.	One per site
SDV			
Existence, IC	100%	100%/100%	100%
Key data	100%	≥50%/≥20%	≥20%
Further data	100% for 10% of pts	100% for 1 pt	None
Further contacts	As required	Structured interview q8/52	As required
Close-out visit	Mandatory	If required	None

ADAMON
Status

- 6/11 included trials have been audited; remainder due 2014/early 2015
- Expected to report end of 2015
- Potential limitations:
  - Crucial factor in interpretation will be how different the two study groups are in practice, ie frequency and nature of on-site monitoring
    - Will depend on risk levels of trials selected for inclusion
    - In K3, review of triggers for for-cause on-site monitoring visits "should be considered" but precisely defined so that "not too many unplanned visits are necessary"

OPTimisation of **MON**itoring

Evaluation of efficacy and cost
of two monitoring strategies for public clinical research

https://ssl2.isped.u-bordeaux2.fr/OPTIMON/default.aspx

OPTIMON
Study design

- Prospective cluster-randomised non-inferiority trial across multiple multi-centre trials, stratified depending on the risk level from the Optimon scale.
- Sites will be randomised to alternative monitoring strategies:
  - **Classical strategy:** based on the practices in pharmaceutical industry
  - **Optimised strategy:** based on the risk level (Optimon scale) with pre-definition of scientific and regulatory priorities.
- **Main outcome:** Proportion of patients' file with at least one severe error (relating to IC, SUSAR reporting, eligibility, data on main outcome)

Pre Optimon risk-adapted monitoring plan

		100% onsite monitoring	risk-adapted monitoring		
			risk level A	risk level B	risk level C
set-up	**initial contact**	systematically and traced			
	site adequation	systematically, remotely if site known and experimented otherwise on site (may be coupled with set-up)			
	initiation	systematically, before inclusion of 1st patient, by phone if site known and experimented, otherwise on site			
data monitoring	**on-site monitoring** data conformity respect of procedures	on site, 100% patients, 100% data, 100% sites (freq. to be defined at study start)	∅	10% patients 100% key points then if major problem	1 visit / site 100% key points then is major problem
	comprehension of circuits	systematically, on site, at 1st monitoring visit (from 1st inclusion)	systematically, by phone after reception of forms of 1st patient at CTU/CRC		
	consents	systematically, on site at next visit	masked copy at inclusion		
			∅	on site at next visit or at closure	
	search for SAEs	systematically, on site	systematically, on site or remotely		
	corrections	at each visit, 100% data queries created remotely or on site	∅	at each visit for key points	
			queries created remotely		
	forms verification	systematically, before entry of forms not checked on site			
	centralized monitoring	systematically, 100% patients, 100% data, 100% sites + respect of procedures			
close-out		systematically, on site 100% patients, 100% sites	systematically, par mail 100% patients, 100% sites		systematically, on site 100% patients, 100% sites

OPTIMON
Status

- Accrual completed end of 2013
- Analysis planned – October 2014
- Issues?
  - As for ADAMON, how different are the 2 groups in practice
  - 22 trials: 8 level A, 4 level B, 10 level C
  - But overall, reduced on-site monitoring cf ADAMON

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Strategies based on central monitoring-directed visits

What are trials groups doing?

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- Eg CTTI survey *(Morrison et al, Clinical Trials 2011; 8: 342-349*)
  - Electronic survey of monitoring practice
  - 216 organisations/individuals approached; 65 responders including 18 academic, 11 CRO and 36 industry
  - Majority use centrally available data to evaluate site performance
    - but <1/3 "always" use this to guide, target or supplement site visits
  - Most likely factors to trigger a visit (across all all organisation types)
    - Number of protocol deviations
    - Suspected fraud
    - Rate of enrolment
    - Missing CRFs

Variations:

- Key risk indicator approach *(eg Elsa et al, Trials 2011 12 (supp 1)*
  - Examine data distributions for unusual patterns suggesting data may be being fabricated, or training may be required
  - uses cross-site comparisons of specific key study data items (eg SAE rates, visit duration) to identify outlying sites
  - Needs large number of patients per site to be effective

- "SMART" ™ approach *(eg Venet et al Clinical Trials 2012)*
  - Argues all data collected is potentially indicative of data quality
  - Uses multiple analyses across many data items to identify outlying sites

- Evidence that these are effective in identifying problem sites?

TEMPER

TargetEd Monitoring: Prospective Evaluation and Refinement

Evaluating a targeted on-site monitoring strategy for multi-centre cancer clinical trials

Funded by Cancer Research UK
MRC CTU Hub for Trial Methodology Research

October 2013

Study Questions

- **Primary question**: does the targeted on-site monitoring strategy distinguish sites with a substantially higher rate of major/critical findings at on-site visits, compared with untriggered sites?

- **Secondary questions**:
  - Which centrally monitored triggers are most useful in identifying problem sites?
  - Are other site characteristics predictive of on-site findings?

- NB cross-sectional - looking for things we don't know about from central monitoring, not at the impact of the visit

Design

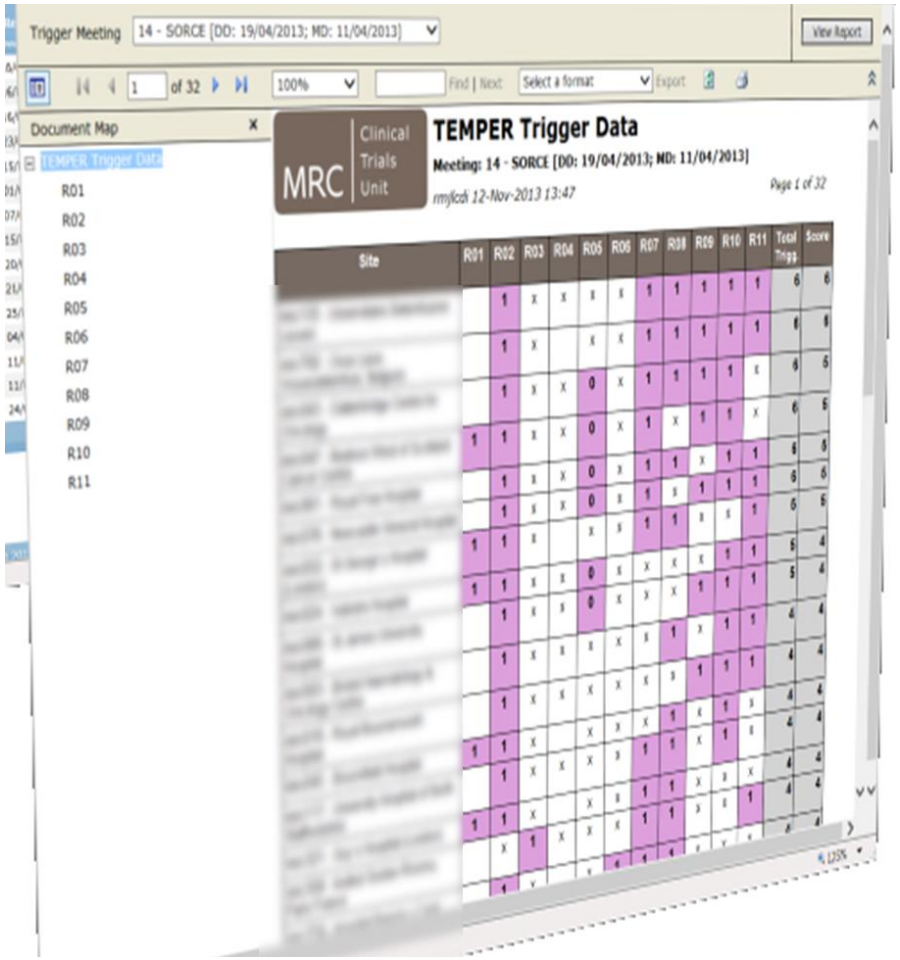
- Prospective, matched pair design: match triggered sites with untriggered and visit both

- Embedded within ongoing, CR UK-funded cancer trials of IMPs (SWAT)
  - Deemed "Moderate" risk by MRC CTU RGC
  - Use a targeted monitoring strategy

Design

- Typical triggers for on-site visit
  - Poor CRF return
  - Large numbers of queries
  - Specific protocol violations
  - Very low or high SAE rates vs other sites
  - "General concern"
  - (High recruitment)
- Database application developed to aid monitoring of triggers, and to match sites
  - Data drawn from study databases - required further specification/quantification of some triggers
  - Manually add the subjective triggers

TEMPER database application



Application ranks sites according to number of triggers met

Used as a guide as to which visit category each site falls into

TEMPER Visit/Study Strategy

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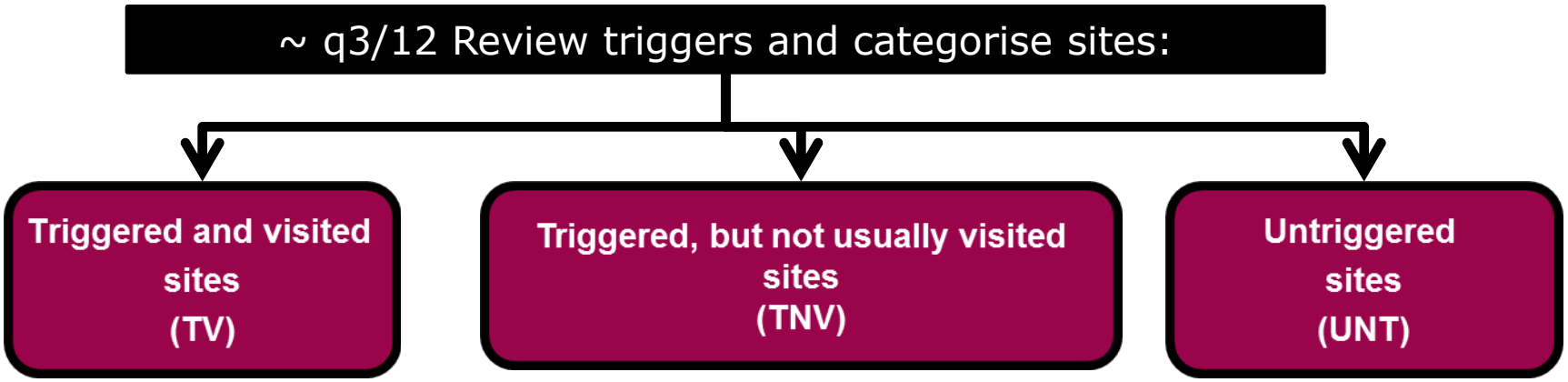
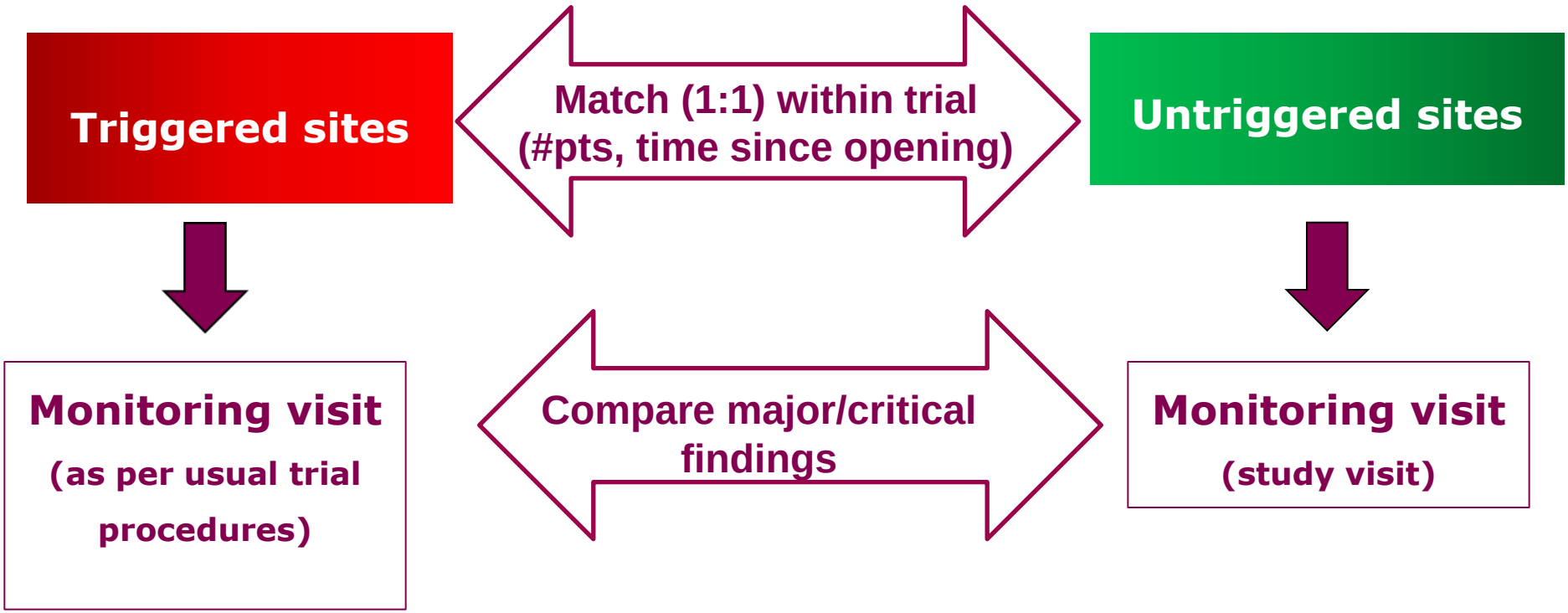
Clinical trial(s) currently using targeted monitoring strategy



TEMPER Visit strategy



- 42 pairs (84 visits) planned
- Powered to detect a 30% difference in the proportion of sites with at least one major or critical finding (eg 60% in triggered sites, 30% in untriggered sites)
- Endpoint review committee adjudicate grade of findings

TEMPER in practice

- CR UK funding covers 2 full time monitors for 2 years - delays in appointing and re-appointing monitors
- Embedding research in ongoing trials - Initial impact on trial teams including trial-specific training of monitors, and concern about capacity to act on findings
- Payback – monitors arrange all visits (triggered and matched), write up findings and chase responses with sites; train trial team members on monitoring; trigger reports

TEMPER Status and future plans

- First matched visits took place in July 2013
- 20/42 paired visits have taken place
- Results: expected within 6 months of last study visit - early 2016

- Adding value – strategy is only as good as our triggers
  - Evaluate the prognostic value of individual triggers to identify sites with problems (refine)
  - Recent enhancements: at time of trigger extraction, apply other statistical central monitoring techniques and compare sites identified by both approaches.
    Potential to extend study to look at visits to sites identified only by these means.

- For further information:

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