Risk-Based Monitoring Approach in Clinical Research

Valérie Journot
INSERM U897, Bordeaux, France

on behalf of the
Working Group on Monitoring
European Clinical Research Infrastructures Network
Background

**monitoring objectives**
- data quality → validity of results
- participants' safety

**the "gold-standard" monitoring strategy**
- intensive on-site
  - never assessed for efficacy / efficiency
  - but for on-site initiation visit  
  
- large financial burden

**European directive 2005/28/EC**
- proposed adaptation to academic context
  - monitoring may be centralised and/or on a sample
  - based on study characteristics related to risks
  - → risk-based monitoring approach
- on-site vs remote
objectives

to assess relevance in academic context

to imagine implementation procedure

methods

to identify major issues related to risk-based approach

to identify former experiences and collect feedback

to assess relevance in academic research

to implement

  a risk-assessment tool

  to assess its relevance and reproducibility

  a risk-adapted monitoring strategy

  to define a Policy on monitoring
Major issues

**which study types?**
- trials / epidemiological studies
- commercial / non commercial
- drugs / medical devices / any interventions

**which risks?**
- for participants
  - safety of intervention / investigations
- for study results
  - quality of data / validity of results
- for sponsor / CTU
  - financial loss / legal proceedings / credibility
- for public health
  - impact of results wrt safety / efficacy / efficiency
Major issues

how to assess risk?
- source data
  - characteristics of study / CTU / sponsor
- assessment of risk
  - directly / through assessment and combination of criteria
  - visual analogue scale / categorical scale / …
- risk format
  - continuous / levels / how many levels?
- assessment by
  - anybody / experts / experts committee

how to adapt monitoring?
- on-site / on-site and remote / from initiation to closure
- visits frequency / % participants / % sites
- % variables / key variables
Former experiences

"French" approach
AP-HP (Paris)  http://www.drrc.aphp.fr/
Optimon trial (F)  https://ssl2.isped.u-bordeaux2.fr/optimon/
Adamon trial (G)  Brosteanu. Clin. Trials 2009
study characteristics
→ participant's risk on 4 levels
→ standardised risk-adapted monitoring plan on 4 levels

"British" approach
MRC & Dep† Health (UK)  http://www.ct-toolkit.ac.uk/
several Universities (UK)
study characteristics and risk matrix (likelihood x impact)
→ risk for participant, study, and organisation
→ management strategies
→ study acceptance and monitoring plan definition
Relevance in academic research

Delphi consensus procedure

1\textsuperscript{st} questionnaire
agreement to principle? which risks? which studies?
"I totally / partially agree / disagree"

2\textsuperscript{nd} questionnaire for trials
study characteristics (items) influencing risks?
"no influence / increase / decrease / both"

final meeting
item selection (2/3 agreement) and rewording
→ list of relevant items

participants
no WGM members
any function in clinical research
experienced in different medical fields
<table>
<thead>
<tr>
<th>1st questionnaire</th>
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<tbody>
<tr>
<td>51 respondents from 10 countries</td>
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<tr>
<td><strong>risk-adapted monitoring</strong> agreed by 100%</td>
</tr>
<tr>
<td><strong>types of risk</strong></td>
</tr>
<tr>
<td>for participants 98%</td>
</tr>
<tr>
<td>for validity of results 100%</td>
</tr>
<tr>
<td>for organisation 100%</td>
</tr>
<tr>
<td>for target population and public health 90%</td>
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<tr>
<td><strong>types of study</strong></td>
</tr>
<tr>
<td>trials 92%</td>
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<tr>
<td>diagnostic studies 92%</td>
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<tr>
<td>prognostic studies 88%</td>
</tr>
<tr>
<td><strong>different tool for trials and other studies</strong> 90%</td>
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</table>
2nd questionnaire & meeting

49 respondents from 8 countries

modified items during the final meeting

- rejected: 3
- reworded: 4
- pooled: 24 → 10
- unchanged: 5

19 items in final list

- participants: 5
- validity of results: 4
- study organization: 6
- study governance: 3
- impact on target population and public health: 1
The 19 relevant items

### Study participants
1. Difficulties or incapacity to give informed consent
2. Collection of indirectly identifying or sensitive characteristics
3. Expected inherent hazards related to study interventions or investigations
4. Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
5. Study interventions used outside authorized indication / product license / state of the art or in early stage / phase of development

### Validity of study results
6. Pre feasibility assessment of the study recruitment based on reliable sources
7. Concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations
8. Objective assessment of primary and the main secondary outcomes
9. Complexity of study procedures
## the 19 relevant items

### Study organisation

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<table>
<thead>
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<tbody>
<tr>
<td>10</td>
<td>Education and experience of the sponsor or investigator sites' staff to GCP or study procedures</td>
</tr>
<tr>
<td>11</td>
<td>Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites</td>
</tr>
<tr>
<td>12</td>
<td>Intervention management tracking system run by a qualified organisation</td>
</tr>
<tr>
<td>13</td>
<td>Quickness and security of data entry in the database</td>
</tr>
<tr>
<td>14</td>
<td>Full cleaning of database while study is still in progress</td>
</tr>
<tr>
<td>15</td>
<td>Availability of the appropriate resources at the start of the study</td>
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### Study governance

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<table>
<thead>
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<th></th>
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<tbody>
<tr>
<td>16</td>
<td>Existence of management review organisations</td>
</tr>
<tr>
<td>17</td>
<td>Existence of ethic and scientific review organisations</td>
</tr>
<tr>
<td>18</td>
<td>Influence / interference of a private organisation upon study governance</td>
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### Impact on target population and public health

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<tr>
<td>19</td>
<td>Major impact of study results on target population and public health</td>
</tr>
</tbody>
</table>
Reproducibility

reproducibility / score building study

- collection of real protocols
- academic trials, in English, any clinical field
  + synopsis describing scientific aspects and organisation
- recruitment of assessors
  - same type as in Delphi procedure
- allocation of protocols to assessors
  - partially balanced incomplete block design
- assessment of risks & items through visual analogue scales
  - to be as few restrictive as possible
- objectives
  - assessment of items relevance in real using further selection of the most relevant items
  - building of a n-level risk score
Reproducibility

24 protocols from 9 countries
15 assessors from 9 countries
  7 in study management, QA or RA
  4 methodologists
  5 principal investigators

assessments
  each assessor x 7-12 protocols
  each protocol x 6-8 assessors
  median duration 40 minutes / protocol
Reproducibility

estimated reproducibility (perfect = 1.00)
for risks very bad to bad
   the best one: risk for participants = 0.30
for items: very bad to bad
   but for one: difficulties to give consent = 0.72

high variability between assessors
   free scale allows for variability
   lack of training and experience of assessors
   incompleteness of protocols
   risk is a multifocal and complex notion
   a protocol is a multifocal and complex subject

→ no item selection, no risk score building
Policy on monitoring

**purpose**
- guidance for monitoring plan
- minimum level of monitoring depending on risk level

**sponsor's responsibilities**
- to assess risk
- to define a risk-based monitoring plan
- to provide adequate resources

**proposal for risk assessment**
- guidance to assess risk with practicality advices
- using the 19 relevant items

**template for a monitoring plan**
- recommendation of risk-based approach
- definition of key data
- planning for monitoring activities
### Policy on monitoring

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<thead>
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<th>low risk</th>
<th>medium risk</th>
<th>high risk</th>
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<tbody>
<tr>
<td><strong>on-site</strong></td>
<td>at least 1 visit</td>
<td>at least 2 visits</td>
<td>at least 3 visits</td>
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<tr>
<td><strong>remote</strong></td>
<td>X% SAE queries management</td>
<td>consent notification</td>
<td>idem</td>
</tr>
<tr>
<td></td>
<td>consent notification</td>
<td>other monitoring procedures</td>
<td>idem</td>
</tr>
<tr>
<td><strong>before</strong></td>
<td>ethical &amp; regulatory approvals</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td></td>
<td>protocol specific training</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td><strong>during</strong></td>
<td>100% consent</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td></td>
<td>X% eligibility</td>
<td>+ drug accountability staff &amp; facilities</td>
<td>+ 75% CRF / key data</td>
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<tr>
<td></td>
<td>X% SAE</td>
<td>50% CRF / key data</td>
<td></td>
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<tr>
<td></td>
<td>X% CRF / study endpoints</td>
<td>idem</td>
<td></td>
</tr>
<tr>
<td><strong>after</strong></td>
<td>ethics &amp; regulatory notification</td>
<td>idem</td>
<td>idem</td>
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<tr>
<td></td>
<td>archiving</td>
<td>idem</td>
<td>idem</td>
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<tr>
<td></td>
<td>monitoring activities</td>
<td>idem</td>
<td>idem</td>
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Conclusions and issues

risk-based monitoring approach
large agreement in academic research
a principle to implement

risk assessment
19 relevant items identified = source data
complexity of risk / trial → variability between assessors
risk assessment tool as simple as possible
homogeneity through experts committee
to be formally assessed for validity?
different risks for different applications?

risk-adapted monitoring strategy
few levels, combining on-site and remote monitoring
definition of key data
minimum requirement, flexibility in implementation
Acknowledgments

members of ECRIN Working Group on Monitoring

respondents to questionnaires and assessors