Risk-based monitoring approach in academic clinical research

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## Background

<table>
<thead>
<tr>
<th></th>
<th>private</th>
<th>academic</th>
</tr>
</thead>
<tbody>
<tr>
<td>objectives</td>
<td>drug licensing</td>
<td>patients' care strategies</td>
</tr>
<tr>
<td>designs</td>
<td>phase I-IV trials</td>
<td>trials, diagnostic, prognostic,…</td>
</tr>
<tr>
<td>questions</td>
<td>few drugs</td>
<td>many</td>
</tr>
<tr>
<td>resources</td>
<td>large</td>
<td>limited</td>
</tr>
</tbody>
</table>

→ **priorities must be defined**

- cost of scientific aspects not to be reduced
- cost of monitoring aspects?
Background

reference monitoring strategy
- intensive on-site
- never assessed for efficacy/efficiency

European directive 2005/28/CE
- adaptation to academic context
- monitoring may be centralized and/or on a sample based on study characteristics related to risks
→ a risk-based monitoring approach

ESF/EMRC consensus conference (Sept, 2008)
"Investigator-Driven Clinical Trials"
- risk-based monitoring approach 3rd / 26 recommendations
Objective

**Objective**

to build a risk-assessment tool for monitoring adaptation

**Questions**

Are there already existing tools?

Which studies are relevant for risk assessment?
Which risks should be assessed?

How to assess risk?

How to use the risk assessed?
Methods

European Clinical Research Infrastructures Network

network of national networks
clinical research centers
clinical trials units
academic sponsors
ministries
funding agencies

12 countries

funding
the European Community

Working Party
on Monitoring
Methods

**search for literature and networks**
existing tools?
format and field of application?

**Delphi consensus procedure**
1\(^{st}\) questionnaire
agreement to principle? which risks? which studies?
"I totally / partially agree / disagree"
2\(^{nd}\) questionnaire
study characteristics influencing risks?
"no influence / increase / decrease / both"
final meeting
item selection (2/3 agreement) and rewording
→ list of relevant items
Methods

reproducibility study
protocols of academic trials in English, any clinical field
synopsis added: scientific aspects and organisation
protocols assessed by assessors → risks & items (VAS)
partially balanced incomplete block design
→ items relevance
→ items selection?
→ risk score building?

participants to Delphi procedure and reproducibility study
not WPM members
clinical research professionals among ECRIN countries
any function
experienced in different medical fields
Methods

SOP on Monitoring

format defined by SOP of SOPs
drafts and internal revisions
external validation by Working Party on Quality Assurance
→ guidance for development of a monitoring plan
→ minimum level of monitoring depending on risk level
Results – Existing tools

**French approach**
Assistance Publique - Hôpitaux de Paris
http://www.drrc.aphp.fr/
Optimon trial
https://ssl2.isped.u-bordeaux2.fr/optimon/
patient's risk on 4 levels → risk-adapted monitoring plan

**British approach**
MRC & Department of Health – different Universities
http://www.ct-toolkit.ac.uk/
study characteristics and risk matrix
→ study acceptance and monitoring plan definition

**Others**
derived from those from AP-HP and MRC
## Results – 1st questionnaire

<table>
<thead>
<tr>
<th>51 respondents from 10 countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>risk-adapted monitoring</strong> agreed by</td>
</tr>
</tbody>
</table>

### types of risk

| for participants | **98%** |
| for validity of results | **100%** |
| for organisation | **100%** |
| for target population and public health | **90%** |

### types of study

| trials | **92%** |
| diagnosis studies | **92%** |
| prognostic studies | **88%** |

### different tool for trials and other studies | **90%** |
### Results – 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
## Results – the 19 items

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

## Validity of study results

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Pre feasibility assessment of the study recruitment based on reliable sources</td>
<td></td>
</tr>
<tr>
<td>7 Concealment of randomized study interventions, allocated or to be allocated, during allocation, follow-up and investigations</td>
<td></td>
</tr>
<tr>
<td>8 Objective assessment of primary and the main secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>9 Complexity of study procedures</td>
<td></td>
</tr>
</tbody>
</table>
## Results – the 19 items

### Study organization

10. Education and experience of the sponsor or investigator sites' staff to GCP or study procedures

11. 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

12. Intervention management tracking system run by a qualified organization

13. Quickness and security of data entry in the database

14. Full cleaning of database while study is still in progress

15. Availability of the appropriate resources at the start of the study

### Study governance

16. Existence of management review organizations

17. Existence of ethic and scientific review organizations

18. Influence / interference of a private organization upon study governance

### Impact on target population and public health

19. Major impact of study results on target population and public health
Results – Reproducibility study

24 protocols from 9 countries

15 assessors from 9 countries
    7 study management, QA or RA
    4 methodology
    5 principal investigators

assessments
    each assessor assessed 7-12 protocols
    each protocol assessed by 6-8 assessors
    median duration: 40 minutes / protocol
Results – Reproducibility study

**ICC for risks**
0.05 to 0.30
the best one: risk for participants = 0.30

**ICC for items**
0.01 to 0.28
but for one: difficulties to give consent = 0.72

→ no item selection, no risk score building

**high variability between assessors**
VAS allows for variability
lack of training and experience of assessors
incompleteness of protocols
Results – SOP on monitoring

**sponsor's responsibilities**
- to assess risk on a 3-level scale
- to define a monitoring plan
- to provide adequate resources

**definitions**

**template for a monitoring plan**
- principles
- definition of key data
- planning of monitoring activities
<table>
<thead>
<tr>
<th></th>
<th>low risk</th>
<th>medium risk</th>
<th>high risk</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td><strong>remote</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- X% SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- queries management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- consent notification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- other monitoring procedures</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td><strong>before</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ethical &amp; regulatory approvals</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>- protocol specific training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>during</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 100% consent</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>- X% eligibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- X% SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- X% CRF / study endpoints</td>
<td>- 50% CRF / key data</td>
<td>- 75% CRF / key data</td>
<td></td>
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<tr>
<td><strong>after</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ethics &amp; regulatory notification</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
</tr>
<tr>
<td>- archiving</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- monitoring activities</td>
<td>idem</td>
<td>idem</td>
<td>idem</td>
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</table>
Conclusion

What do we have now?
- a problem of scale measurement!
+ a large agreement on the risk-based approach
  experience feedback from organizations already using it
  a synopsis to collect needed information
  19 items to characterize risks
  a risk-assessment committee to reduce variability
  an SOP to handle the approach

Is it a sound approach for academic research? certainly yes

Is it efficient?
Optimon (F) and Adamon (G) randomized trials
  intensive on-site vs risk-adapted monitoring
Acknowledgments

members of ECRIN Working Party on Monitoring

respondents to questionnaires and assessors