Risk-based monitoring approach in academic clinical research

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Background

	private	academic
objectives	drug licensing	patients' care strategies
designs	phase I-IV trials	trials, diagnostic, prognostic,…
questions	few drugs	many
resources	large	limited

→ **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

but for initiation visit: *Lienard. Clin. Trials 2006*

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

1st questionnaire

agreement to principle? which risks? which studies?

"I totally / partially agree / disagree"

2nd 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

51 respondents from 10 countries

risk-adapted monitoring agreed by	100%
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

	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 randomized 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

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

Results – SOP on monitoring

	low risk	medium risk	high risk
on-site	at least 1 visit	at least 2 visits	at least 3 visits
remote	- X% SAE - queries management - consent notification - other monitoring procedures	idem	idem
before	- ethical & regulatory approvals - protocol specific training	idem	idem
during	- 100% consent - X% eligibility - X% SAE - X% CRF / study endpoints	idem - drug accountability - staff & facilities - 50% CRF / key data	idem - 75% CRF / key data
after	- ethics & regulatory notification - archiving - monitoring activities	idem	idem

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

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respondents to questionnaires and assessors

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