Risk-Based Monitoring Approach in Clinical Research

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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 *Liénard. Clin. Trials 2006*
- 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

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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^{t} 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

- 1st questionnaire
  - agreement to principle? which risks? which studies?
  - "I totally / partially agree / disagree"
- 2nd 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

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%
diagnostic studies	92%
prognostic studies	88%
different tool for trials and other studies	90%

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
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 organisation
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 organisations
17	Existence of ethic and scientific review organisations
18	Influence / interference of a private organisation upon study governance
	Impact on target population and public health
19	Major impact of study results on target population and public health

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

	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

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

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