RISK-BASED APPROACH IN CLINICAL TRIALS

objectives

historical and regulatory context

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French regulation on clinical trials

1947 - Nuremberg Code
1964 - Declaration of Helsinki
1975 - Directive 75/138 Clinical Trials
1988 - Huriet-Sérusclat Act
1996 - GCP guideline (ICH)
2001 - Directive 2001/20/EC Clinical Trials
2004 - Public Health Act
2012 – Jardé Act
2014 - European Regulation
French regulation on clinical trials

1947 - Nuremberg Code
1964 - Declaration of Helsinki
1975 - Directive 75/138 Clinical Trials
1988 - Huriet-Sérusclat Act
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2001 - Directive 2001/20/EC Clinical Trials
2004 - Public Health Act
2012 – Jardé Act
2014 - European Regulation
GCP and Directive 2001/20/EC

Regulatory procedures
- roles and responsibilities
- authorisations
- competent authority
- ethics committee
- informed consent

Monitoring procedures

GCP
§ 5.18.1 **purpose of monitoring**

To verify
- a) rights, safety and protection of human subjects
- b) data accurate, complete and verifiable from source documents
- c) study conduct compliant with protocol, GCP, regulatory requirements

First interpretation of GCP for monitoring = intensive
100% on-site monitoring

Procedure widely implemented in pharmaceutical industries and CROs
  checking of all data = 100% variables x 100% patients x 100% sites
  for detailed completeness and accuracy
  as compared to source documents
  onsite mainly
  → "100% on-site monitoring"

Claimed results
  of the directive
    high improvement in
      safety and ethics for patients
      reliability of data, validity of results
  of the 100% on-site monitoring
    → GCP purpose of monitoring achieved
Consequences of directive 2001/20/EC

Definition and concepts
"monitoring" mostly understood as "data check" rather than "oversight"
100% on-site monitoring = **gold standard** for any type of clinical research

Authorisation process
increase in complexity, costs and delays
+ 100% in costs for staff needs and costs
+ 800% for insurance fees
+ 90% in average delay for launching

Monitoring process
first interpretation of GCP for monitoring = intensive
100% on-site monitoring = 30 to 60% of study budget
Consequences of directive 2001/20/EC

Drastic drop in clinical trials application
Hartmann. Trials 2012.

- 25% between 2007-2012 in Europe

Achievement of GCP purpose by 100% on-site monitoring?
was never demonstrated
risk of loss of discrimination towards specific study objectives
other strategies are satisfactory too, though less on-site intensive
100% on-site monitoring widely rejected

The Optimon trial in France
randomised non inferiority trial comparing 2 monitoring strategies
100% on-site vs. adapted on patient risk
results expected end 2014
https://ssl2.isped.u-bordeaux2.fr/optimon/

Carried by ECRIN in Europe and worldwide
2008 - ESF/EMRC Consensus conference - Investigator-driven trials
2010 - Workshop - Road Map Initiative for Clinical Research in Europe
2011 - OECD/GSF - Facilitate non-commercial trials

Taken over by the USA
2010 - CTTI - Effective and efficient monitoring as a component of quality assurance
5.18.3 **Extent and Nature of Monitoring**

The sponsor should ensure that the trials are adequately monitored. The sponsor should **determine the appropriate extent and nature** of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

In general there is a need for **on-site monitoring, before, during, and after** the trial; however, in exceptional circumstances the sponsor may determine that **central monitoring** in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.

**Statistically controlled sampling may be an acceptable** method for selecting the data to be verified.

- not systematically on-site
- not systematically 100% data
- no systematic rule

→ risk-based approach
Which risks?

For the patient
  safety
  toxicity of interventions and investigations
  risk scales AP-HP, Optimon
categories from Jardé law, UE, OECD, MRC/MHRA (UK)
rights: consent, personal data
  GCP, Data Protection Act

For the data
  validity, power, selection, information or confusion bias
design, Quality-by-Design (CTTI USA)

For public health when implementing intervention in the general population
  risk / loss of chance for patients receiving/not receiving intervention
costs for social security and State

For study stakeholders
  direct stakeholders
  manufacturer, funder, sponsor, investigators, CTU, sites
oversight institutions
  steering committee, independent review board
  competent authority, ethics committee, health institutions and ministries
clinical research institutions
  reputation, funding, career, sustainability
Which monitoring?

**To be done onsite**
- visual checks
  - site adequation: premises, circuits, organisation
  - patient’s existence
  - data conformity to source documents (except eCRF)
  - compliance with procedures and regulatory requirements
- take opportunity of the face-to-face situation
- establish a collaboration relationship
- discuss difficulties, non conformities, circuits, organisation

**May be done remotely**
- eCRF - CTMS
  - check of completeness, integrity and consistency
  - computerised calculation of grades, scores…
  - query management
- fax, mail, email
  - staff and organisation adequation
  - query management
  - compliance with procedures and regulatory requirements
  - reminders, accrual stimulation…
- phone
  - discuss difficulties, non conformities, circuits, organisation
Which data to be checked remotely?

Consent
validation of a procedure for early and remote check (Journot. Clin Trials 2013)
collection of consents by secured envelop

SAE reporting
non reporting of some types of SAEs
closed questions for the most frequent or most relevant SAEs
computerised calculation of grades for lab events
computerised consistency checks
drugs x events
lab results x events

Study data
computerised real-time checks (eCRF) or by frequent batch
completeness, integrity, consistency

Non-study data
computerised and statistical checks → errors, discordances, changes
connexion identifiers to eCRF, filling of correction date, queries flow, accrual flow,
error rate, SAE reporting rate…
→ warnings, quality indicators (ANRS)
Risk-based approach

Regulatory procedures
application to competent authority, ethics committee, insurance
→ simplification of procedures when risk is low or as standard of care
definition of 2 to 3 research categories
adaptation of procedures for each category
UE low intervention → expedited procedure
no additional insurance fee

Oversight procedures
multitask activities study conduct
data management monitoring
to assess and focus on key points → optimisation
CTTI USA "focus on what matters"
Risk-based approach

OCDE/FMS
recommendation - Governance of clinical trials (published March 2013)
http://www.oecd.org/sti/sci-tech/oecdrecommendationonthe governanceofclinicaltrials.htm
→ adaptation of study oversight depending on risk
assessment of risk by sponsor and investigator
3 categories for regulatory procedures

FDA
guideline – Risk-based approach to monitoring (published August 2013)
focussed on monitoring = tool for trial oversight
relevance of centralised monitoring, therefore of eCRF
→ study-specific monitoring plan

UE
regulation on clinical trials of drugs for human use and repealing directive 2001 (→ 2014)
→ GCP compliance
→ 2 categories for regulatory procedures
adaptation of oversight procedures depending on risks
Risk-based approach

**EMA**

EMA proposal

Adapted from
ICH Q9 - Quality Risk Management → drug manufacturing
ISO 31000 – Risk management

Principle = Deming wheel
improvement of quality
Plan
Do
Check
Adjust

quality management system
EMA proposal
EMA proposal

Appendix in progress

Practical procedures?
  - how to identify risks?
  - how to assess risks?
  - how to establish priorities among risks?
  - how to adapt study conduct, data management plan, monitoring plans?
  - how and when to check?
  - how and when to adjust?

Who does the assessment? Who decides? Who revises?
  - competent authority, ethics committee
  - sponsor, investigator, steering committee, independent review board
  - CTU
  - sites
  - service provider
Definitions

Risk
- ISO 31000: the risk is the effect of incertitude on the objectives.
- The effect may be positive or negative.
- The objectives must be clearly defined.

Risk management
- Culture, procedures, and governance to achieve a desired result while managing harms.
- Risk management is a cross-disciplinary activity.

Objectives of risk management
- Not to suppress risk.
- But to understand it so as to minimise harm.
F-CRIN  WP4 Common tools development
WP4d Risk management

Newsletter
news, experience feedback, decoding, debates

Workshop
24 September 2013 – Paris
information, training, awareness

Guideline on risk management in clinical research
analysis of existing de documents
ISO 31000:2009  Risk management - Principles & guidelines on implementation
books on risk management
draft of a guideline on practical implementation
which procedures, which steps to plan?
which tools, which techniques may be of use?
which governance to implement?
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