RISK-BASED APPROACH
a current application,
the OPTIMON project in France

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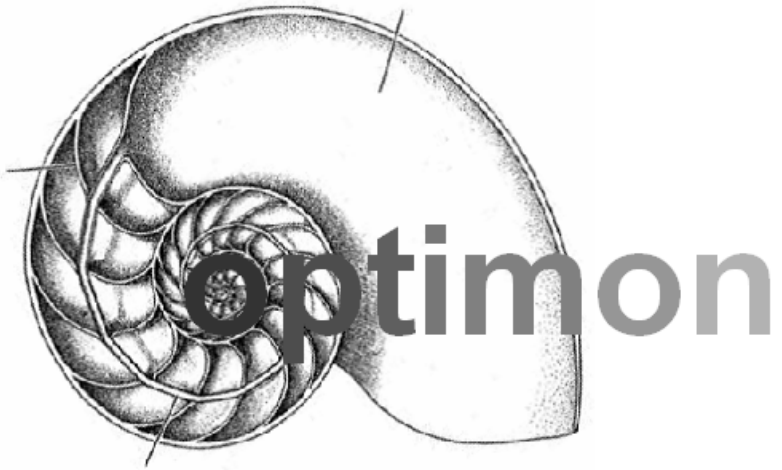
European Clinical Research
ECRIN
Infrastructures Network



Context

in 2005

frame of regulation

directive 2001/20/EC → guideline for GCP
developed for drugs marketing
applied to most biomedical research studies

GCP interpretation

100% data, 100% patients, on-site monitoring
widely spread (mostly industries/CROs), but what about its efficiency?

academic specificities

more varied questions and designs, more studies
limited funding, small organisations

how to optimise the cost-efficiency ratio?

cost	reduction of on-site monitoring intensity
efficiency	maintained fulfilment of regulatory *&* scientific requirements

→ the Optimon trial

objective

to compare two monitoring strategies

optimised (risk-adapted) vs. intensive on-site (“gold standard”)

hypothesis

a risk-adapted monitoring strategy can

. be defined a priori for each study

. yield results similar to the intensive on-site strategy for the main quality criteria of study

. improve other aspects, such as costs or delays

→ a typical non inferiority issue

expected benefits

definition of a standard of monitoring

standardisation of practice

dissemination of optimisation tools to set up a risk-based strategy

. risk assessment scale

. risk-adapted monitoring plan

. centralised monitoring tools and procedures

non inferiority trial

parallel groups	intensive on-site vs. risk-adapted strategy
randomisation	stratified on study, clustered on site
open-label	
accrual unit	study
analysis unit	patient

eligibility criteria

patient	any
study	any design, no highest risk level (e.g. phase I-II…)
sponsor's and investigators' agreements	
schedule and data circuit	
patients' and sites' numbers	
CTU/CRC	academic label, experience, SOPs

outcomes

primary	% pat./no error	. consent form signature, SAEs report, . main eligibility criteria, primary outcome
secondary	errors, delays, costs	

size

1,800 patients, revised to 900 due to recruitment difficulties

accrual

10 included studies → 421 patients expected

8-10 expected studies → 400-500 patients expected

calendar

organisation

investigator	Pr Geneviève Chêne
sponsor	Bordeaux University Hospital
funding	Clinical Research Hospital Program
support	main French university hospitals, INSERM
	French disease-specific institutions & networks
	ECRIN

Pre Optimon

a specific study to develop and validate
- . a risk assessment scale
- . a risk-adapted monitoring plan

methods

working group
- search of literature
- identification of former experiences
  - . Paris Hospital network
  - . MRC toolkit
  - . Giens roundtable 2005
- consulting of experts

specific experiments

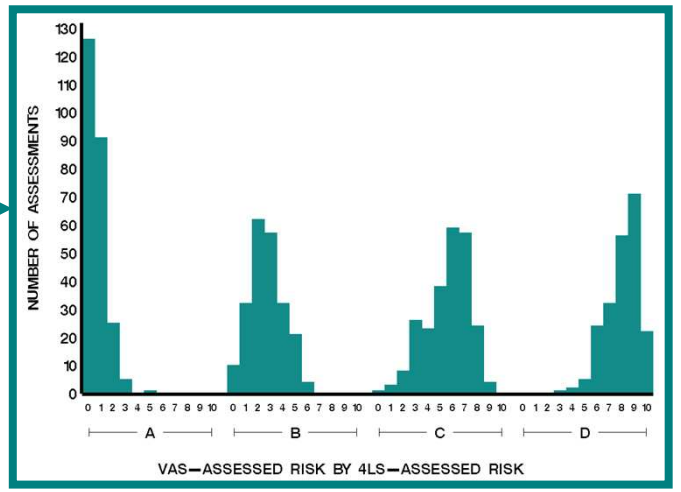
Pre Optimon — risk assessment scale

conception

design by experts group, based on former experiences
patient's risk only

reproducibility study

200 protocols x 49 assessors
good diversity of protocols and assessors
risk assessed with VAS and 4-level scale
good validity
rather good reproducibility (ICC=0,69)
difficulties for 42% assessments
incomplete protocols, scale



proposal

synopsis describing scientific and logistic aspects
improvement of content and format of risk scale

Pre Optimon risk assessment scale

1. to assess study characteristics *without a glance at the resulting risk level*

STAGE I. IDENTIFIYING THE FOCUS OF THE STUDY

❑ **Clinical trial involving a medicinal product, radiotherapy, gene or cell therapy**
- ❑ 1st trials in humans (pharmacology, bioequivalence study)
- ❑ Exploratory trial
- ❑ Confirmation trial
  - ❑ Product without authorisation
  - ❑ Product with authorisation or new combination

Details .....

❑ **Surgery**
- ❑ Minimally invasive technique
- ❑ Technique or biopsy involving an internal organ
- ❑ Generalisation of a new technique
- ❑ Development of a new technique

Details .....

❑ **Medical device (including imaging techniques, radiology, radioisotopes)**
- ❑ CE marking
  - ❑ Class I
  - ❑ Class IIa
  - ❑ Class IIb
  - ❑ Class III
    - ❑ Routine use
    - ❑ Outside licensed indications
    - ❑ With little prior information
- ❑ No CE marking
  - ❑ Class I
  - ❑ Class IIa, IIb, III
    - ❑ Non-invasive and inactive
    - ❑ Invasive or active

Details .....

❑ **Physiopathology, genetics, other techniques**
- ❑ Minimally or non invasive (including blood sampling) and unrestricting
- ❑ Invasive or restricting

Details .....

❑ **Questionnaire, quality of life, psychiatric aspects**
- ❑ Questionnaire without particular difficulties
- ❑ Disquieting questionnaire for a severe condition

Details .....

STAGE II. IDENTIFYING ONE OR MORE PARAMETERS INCREASING THE RISK

❑ **At least one of the study interventions presents a particular risk**
Examples *Risk of mortality or severe morbidity attributable to the intervention; new indication; potentially dangerous weaning situation; invasive procedure using a route other than natural body orifices (except blood sampling)*
Details .....

❑ **At least one of the study investigations presents a particular risk**
Examples *Risk of mortality or severe morbidity attributable to the investigation; use of a radioactive or relatively unknown product, or a product without authorisation; invasive procedure using a route other than natural body orifices (except blood sampling)*
Details .....

❑ **The disease or alteration in the target population status aggravates the risk attributable to the intervention or the investigations**
Examples *Risk of mortality or severe morbidity attributable to a severe pathological condition; failure or insufficiency of a system or organ; age ≤ 2 years, age ≥ 80 years; pregnant, parturient or breast-feeding woman*
Details .....

❑ **No parameters increasing the risk attributable to the intervention, investigations, or target population status**
Examples *No adverse effects attributable to the intervention; adverse effects of no consequence, harmless investigations; no link between the status of the target population and the intervention or investigations*
Details .....

2. to deduce the risk level

STAGE III. IDENTIFICATION OF THE LEVEL OF RISK

FOCUS OF THE STUDY

step 1

① CLINICAL TRIAL OF A MEDICINAL PRODUCT, RADIOTHERAPY, GENE OR CELL THERAPY	② SURGERY	③ MEDICAL DEVICE including IMAGING TECHNIQUES, RADIOLOGY, RADIOISOTOPES
–	Minimally invasive technique	CE marking, class I or IIa, routine use CE marking, class I, use outside licensed indications
Confirmation trial with an authorised product or a new combination	Technique or biopsy performed on an internal organ	CE marking, class IIa, use outside licensed indications CE marking, class IIb or III, routine use No CE marking, class I, non-invasive and inactive
Confirmation trial with a product which has not been authorised Exploratory trial using an authorised product or a new combination	Generalisation of a new technique	CE marking, class IIb, use outside licensed indications CE marking, class IIb or III, with little prior information
Exploratory trial using a product which has not been authorised 1st trials in humans (pharmacology, bioequivalence study)	Development of a new technique	CE marking, class III, use outside licensed indications No CE marking, class I, invasive or active No CE marking, class IIa, IIb or III

Step 2

INTERMEDIATE RISK

	④ PHYSIOPATHOLOGY GENETICS OTHER INTERVENTIONS	⑤ QUESTIONNAIRE QUALITY OF LIFE PSYCHIATRIC ASPECTS
A	Minimally or not invasive (including blood sampling) Not restricting	Questionnaire without particular difficulties
B	Invasive or restricting	Disquieting questionnaire for a severe condition
C		
D		

CONDITIONS FOR INCREASING THE RISK

a) AT RISK PROCEDURE, involving:
Risk of mortality or severe morbidity attributable to the procedure
New indication
Potentially dangerous weaning situation
Invasive procedure using a route other than natural body orifices (except for blood sampling)

b) AT RISK INVESTIGATIONS, involving:
Risk of mortality or severe morbidity attributable to the investigation
Use of a radioactive or a relatively undocumented product or product which has not been authorised
Invasive procedure using a route other than natural body orifices (except for blood sampling)

c) TARGET POPULATION STATUS AGGRAVATING RISKS ATTIBUTABLE TO THE PROCEDURE OR INVESTIGATIONS, involving:
Risk of mortality or severe morbidity attributable to a serious pathological condition or the patient's age
Failure or insufficiency of a system or organ
Age ≤ 2 ≥ years, age ≥ 80 years
Pregnant, parturient or breast-feeding women

Step 3

FOCUS OF THE STUDY ① OR ② OR ③
If at least one of the conditions **a**, **b** or **c** is fulfilled, increase the risk by one level, or even two if more than one of the conditions strongly increases the risk.

FOCUS OF THE STUDY ④
If condition **c** is fulfilled, increase the risk by one level.

FINAL RISK

Pre Optimon risk-adapted monitoring plan

conception

design by experts consulting through Delphi process

content

study initiation & closure

simplification & standardisation

on-site monitoring

. lower intensity depending on risk

. identification of key data

. early remote consent check through modified form

feasibility study

40 protocols: 10 / risk level

feasibility scale: 0-easy to 4-impossible

0,2 to 0,9 in average depending on risk level

assessment difficulties due to incomplete protocols

. treatments, samples, and SAE report circuits

. scheduled on-site visits frequency

Pre Optimon risk-adapted monitoring plan

		intensive monitoring (= risk D)	optimised monitoring		
			risk level A	risk level B	risk level C
set-up	**initial contact**	systematically and traced			
	site adequation	systematically, remotely if site known and experimented otherwise on site (may be coupled with set-up)			
	set-up	systematically, before inclusion of 1st patient, by phone if site known and experimented, otherwise on site			
data monitoring	**on-site monitoring** data conformity respect of procedures	**on site, 100% patients, 100% data, 100% sites** (freq. to be defined at study start)	∅	**10% patients 100% key points** then if major problem	**1 visit / site 100% key points** then is major problem
	comprehension of circuits	systematically, on site, at 1st monitoring visit (from 1st inclusion)	systematically, by phone after reception of forms of 1st patient at CTU/CRC		
	consents	systematically, on site at next visit	masked copy at inclusion		
			∅	on site at next visit or at closure	
	search for SAEs	systematically, on site	systematically, on site or remotely		
	corrections	at each visit, 100% data queries created remotely or on site	∅	at each visit for key points	
			queries created remotely		
	forms verification	systematically, before entry of forms not checked on site			
	centralised monitoring	**systematically, 100% patients, 100% data, 100% sites + respect of procedures**			
administrative closure		systematically, on site 100% patients, 100% sites	systematically, par mail 100% patients, 100% sites		systematically, on site 100% patients, 100% sites

key points key data, respect of procedures

key data patient's existence, consent form signature, primary outcome, main eligibility criteria, main exams and visits, main secondary outcomes

Optimon Committee — set-up

rationale

high inter-assessor variability observed in Pre Optimon
need for risk assessment independent from sponsor

committee members' professional field

2 clinicians, 2 methodologists, 2 from regulatory affairs

functioning

risk assessment by sponsor (with help of investigator)
independent risk assessment by committee
6 independent assessment → 6 initial opinions
if 4/6 agreeing initial opinions
or discussion (F2F, TC) → 6 final opinions
→ consensus reached
in any case, final decision belongs to sponsor

Optimon Committee progress

initial opinions

16 studies with finished (14) or on-going (2) risk assessment

sponsor assessment

6 A, 3 B, 5 C, 2 D

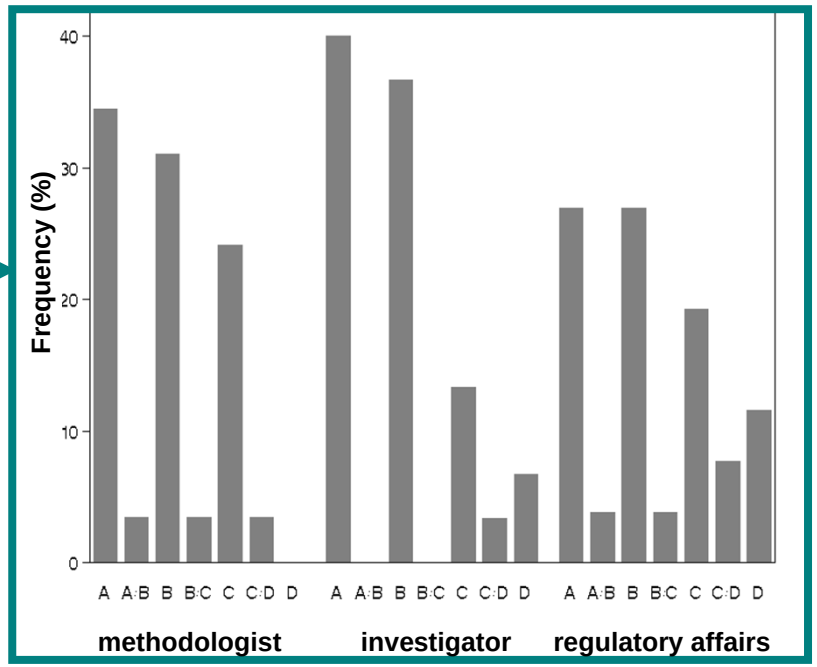
committee initial opinions (n=16)

. complete agreement 6 (38%)

. 2 (adjacent) opinions 4 (25%)

. 3 (adjacent) opinions 6 (38%)

depending on professional field →



committee vs. sponsor (n=14)

. complete agreement 12 (86%)

. 2 (adjacent) opinions 2 (14%)

collaborations

ECRIN Monitoring - Study characteristics influencing risk

attempt to define a risk assessment tool

any type of risk — patient, validity of study results

organisation, governance, target pop. & public health

identification of 19 study characteristics influencing risks

24 protocols x 15 assessors

very high variability → no tool definition

recommendations — training of assessors, collective assessment

ECRIN Monitoring - Risk-adapted monitoring toolbox

to identify, assess, and validate tools

risk assessment tools, tools for centralised monitoring…

Bordeaux University Hospital

use of Optimon tools in current practice

yet, in some occasions, re-intensification on-site monitoring

study not to be renewed, high economic impact, available funding

to define decision rules for re-intensification of on-site monitoring

final remarks

strengths of the risk-based approach

no unique strategy → study-specific monitoring plan
reasoned approach → “focus on what matters” (see CTTI)
reduction of costs (still to be demonstrated)

remaining issues

protocol complex and incomplete → synopsis
risk assessment
. several risks
. different tools available
. high variability to be expected

personnel feedback

assessment on protocol and synopsis
trained assessors
collective and independent assessment
2-step process?
. patient's risk assessment → minimal on-site monitoring intensity
. other study characteristics → re-intensification

publications

Validation of a risk-assessment scale and a risk-adapted monitoring plan for academic clinical research studies - The Pre Optimon study.

Journot et al. *Contemp Clin Trials* 2011. **32**(1): 16-24.

Early remote check of signed informed consent form highly reduces the frequency of non conformity before enrollment: feedback from a 4-year experience in a French academic clinical trials unit.

Journot et al. submission to *J Clin Epidemiol*

Risk-based monitoring approach in academic clinical research.

Journot et al. 30th Annual Meeting of the Society for Clinical Trials. Atlanta 2009.

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