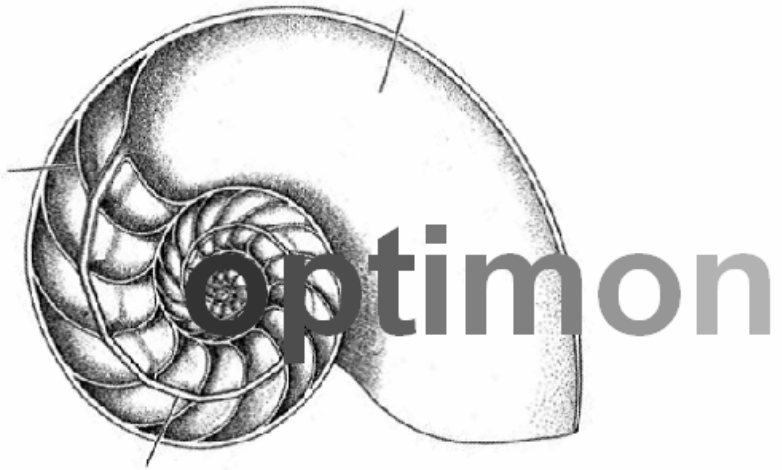
OPTIMON

evaluation of efficacy and cost
of two monitoring strategies
for public clinical research

C·H·U
Hôpitaux de Bordeaux

Inserm
Institut national
de la santé et de la recherche médicale

European Clinical Research
ECRIN
Infrastructures Network



background

Good Clinical Practices

sponsor responsability, via clinical trials unit/CRO
quality should be the same regardless of the sponsor

directive 2005/28/CE

adaptation of monitoring to the academic context

monitoring

responsible for data quality and conformity to regulations
20-40% of research cost

monitoring intensity depending on

benefit/risk ratio, potential impact of the results

Optimon

adaptation and diffusion of patient's risk evaluation
adaptation and standardisation of a monitoring plan

hypothesis

an "optimised" monitoring strategy

may be described *a priori* for each clinical research study
except for highest risk level (D)

may yield results similar to those of a "classical" strategy
for the main quality criteria of a study

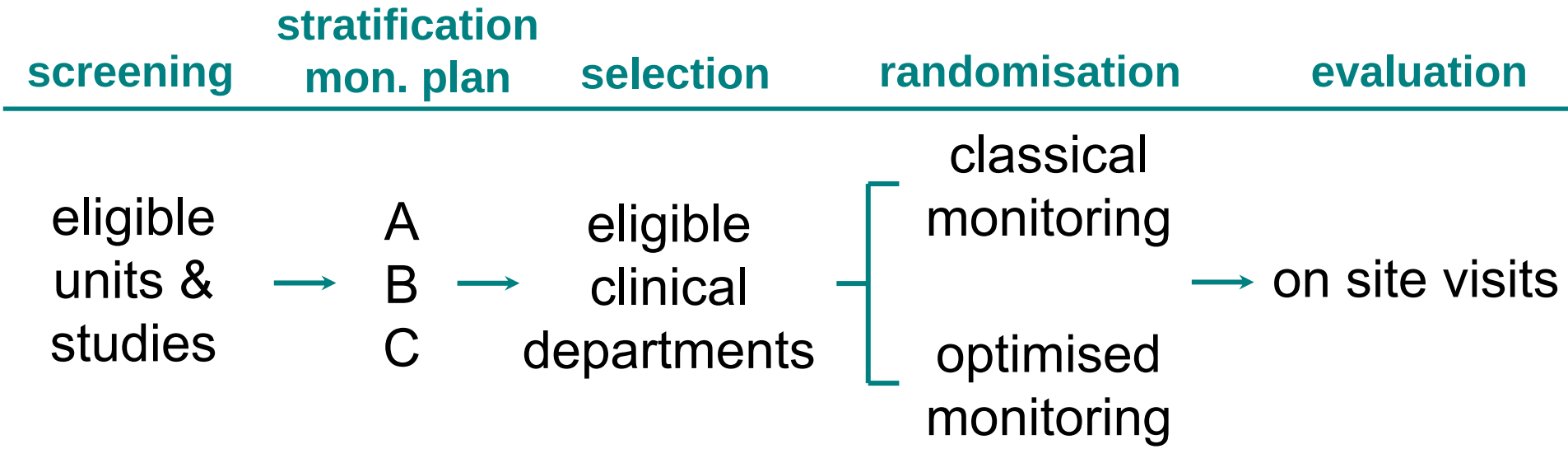
will add value to other aspects such as
research cost and time to results delivery

→ non inferiority trial

Optimon design

design

randomised, multicentric, open-label, non inferiority trial
cluster (clin. dept.) randomisation stratified on risk level



trial size

1800 patients
up to 360 clinical departments

eligibility criteria

any patient

participating in a study

non D (the higher) risk level (i.e. A, B or C)

agreement to participate in Optimon from
sponsor, ethics comittee and coordinator investigator

unfolding 2006 - 2008

≥ 20 patients

≥ 4 clinical departments (≥ 5 patients by department)

paper CRF

managed by a clinical trials unit

labeled by an public institution

≥ 2-year experience in multicentric trials

SOP finalised before inclusion

monitoring strategies

"classical" monitoring

intensive

frequent on site visits

100% data of 100% patients verified

set for Optimon, whatever the risk level

fully relevant for risk level D

"optimised" monitoring

lightened

the higher the risk level, the lighter the monitoring

100% of the main quality criteria for a sample of patients

detailed definition work still in progress

monitoring strategies (2)

	Classical	Optimised
Initial contact	tel or short meeting	tel or short meeting
Initial meeting	In any case	In any case
Initial on-site visit	In any case	Before inclusion of the 1st screened patient
Interim visits	When the 1st patient is included, then every 2-3 pts	**When the 1st 2 pts have been incl., then if problems arise**
Quality control	100 % data for 100 % pts	100 % key data for a sample of pts
On-site corrections	At each on-site visit	At each on-site visit, restricted to key data
Use of tel, fax, mail	When necessary	Actively
Closing on-site visit	In any case	In any case
Consent	On-site checked	A priori (4th page of a consent)
Re-reading before data entry	In any case	In any case

Optimised by level of risk (A, B, C), study complexity, unicity

outcomes

primary outcome

proportion of patients without error on
- informed consent
- SAR reporting
- eligibility criteria
- primary outcome of the study

assuring regulatory conformity and results credibility

secondary outcomes

each component of the primary outcome
indicators of study completion speed
frequency of errors pre- or post-monitoring
delay of SAR reporting
direct and indirect cost indicators

funding and participation

France

funding national program for hospital research 2005

sponsors main University hospitals
INSERM, ANRS, IGR, INCa, FNCLCC

networks Clinical Trials Units (RFUEC)
Clinical Research Centers (INSERM CIC & CIC-EC)

participating clinical trials units

J.P. ABOULKER (INSERM SC10)
C. ALBERTI (Hôp. R. Debré, CIC-EC)
E. BELISSANT (CHU Rennes, CIC)
J. BENICHOU (CHU Rouen)
F. CARRAT (INSERM U707)
G. CHATELLIER (Hôp. Eur. G. Pompidou, CIC-EC)
G. CHENE (INSERM U593, CHU Bordeaux, CIC-EC)
J.P. COLLET (GEREQ)
D. COSTAGLIOLA (INSERM U720)
J. DEMOTES-MAINARD (CHU Bordeaux, CIC)
F. GUILLEMIN (Hôp. Marin, CIC-EC)
T. LANG (CHU Toulouse)
A. LEIZOROVICZ (Univ. Lyon 1 EA 3736)
N. MOORE (INSERM U657)
J.P. PIGNON (Institut Gustave Roussy)
P.M. PREUX (CHU Limoges)
O. RASCOL (CHU Toulouse, CIC)
P. RAVAUD (Hôp. C. Bernard, INSERM U738)
J.M. TRELUYER (Hôp. Cochin)
E. VICAUT (Hôp. Lariboisière)

starting in September 2006

pre-OPTIMON

validation of a scale evaluating the risk level for patients included in academic clinical research

working group

A. Bouxin-Metro	*ANRS*	V. Journot	*INSERM*
P.H. Bertoye	*AFSSAPS*	E. Mottez	*INSERM*
G. Chêne	*CHU Bordeaux,INSERM*	J.P. Pignon	*IGR*
V. Daurat	*AP-HP*	P. Ravaud	*AP-HP,INSERM*
C. Gaultier	*AP-HP,INSERM*		

AP-HP scale

risk classification for monitoring intensity adaptation
set in 2001, never formally validated

	clinical trial genic or cellular therapy	physiopathology genetics	questionnaire quality of life psychiatry	imaging radiology radiotherapy isotopes	surgery
A	—	non invasive (blood sample)	—	routine	usual biopsies cutaneous, ganglionic
B	phase IV phase III combination of products with MA	invasive accord. to act injection accord. to product	specialized questionnaire in severe pathology	standard technique but ill-knowned	routine
C	phase III new indication population at risk	invasive accord. to act injection accord. to product	—	learning phase	generalisation of a new technique
D	phase I or II	—	—	perfecting of a new technique	perfecting of a new technique

design

discussion of items relevance

reproducibility

validity

discussion of items relevance

litterature search of scales

AP-HP, EORTC, MRC, « Giens » workshop

working group discussion

→ items and scale adaptation

survey

critical review of items & scale presentation

47 professionals experienced in clinical research

→ a new scale

proposed new scale

STUDY TOPIC					
① CLINICAL TRIAL OF MEDICINAL PRODUCT RADIOTHERAPY GENIC OR CELLULAR THERAPY	② SURGERY	③ MEDICAL DEVICE **among which** IMAGING, RADIOLOGY, RADIO-ISOTOPES		④ PHYSIOPATHOLOGY GENETICS OTHER THERAPY PROCEDURES	⑤ QUESTIONNAIRE QUALITY OF LIFE PSYCHIATRY
–	technique little invasive	marqued CE, class I or IIa, routine use marqued CE, class I, out of indication	→ **A** ←	non invasive (among which blood sample) non constraining	questionnaire without any particular difficulties
confirmatory study on product with authorisation or new association	technique or biopsy on internal organ	marqued CE, class IIa, out of indication marqued CE, class IIb or III, routine use not marqued CE, class I, non invasive and non active	→ **B** ←	invasive or constraining	questionnaire disturbing in a severe pathology
confirmatory study on product without authorisation exploratory study on product with authorisation or new association	new technique generalisation	marqued CE, class IIb, out of indication marqued CE, class IIb or III, with few distance	→ **C**		
exploratory study on product without authorisation 1st studies on manship (pharmacology, bioequivalence)	new technique perfecting	marqued CE, class III, out of indication not marqued CE, class I, invasive or active not marqued CE, class IIa or IIb or III	→ **D**		

CONDITIONS OF INCREASE OF THE RISK LEVEL

a) THERAPY PROCEDURE AT RISK, among which:
risk of mortality or severe morbidity related to the therapy procedure
new indication
potentially dangerous weaning
invasive act with penetration by another way than a body orifice

b) EXAMINATION PROCEDURES AT RISK, among which:
risk of mortality or severe morbidity related to the examination procedure
use of a radioactive product, few knowned, without autorisation in the indication
invasive act with penetration by another way than a body orifice

c) POPULATION AT RISK, among which:
risk of mortality or severe morbidity related to a severe pathology or to the age
failure or insufficiency of a system or an organ
age ≤ 2 years, age ≥ 80 years
pregnant, parturiente or breast-feeding woman

STUDY TOPICS ①, ② OR ③
If at least one of the conditions **a)**, **b)** or **c)** is fullfilled, increase the risk by one level, or even by two if the concomitance of several conditions strongly increases the risk.

STUDY TOPIC ④
If the population is at risk, increase the risk by one level.

FINAL RISK

reproducibility

sample size

200 study protocols
40-60 evaluators

design

balanced incomplete blocks

statistical analysis

estimation of scale reproducibility
identification of sources of disagreement

balanced incomplete blocks design

blocks of 2 evaluators	blocks of 10 protocols																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	x	x																		
2		x	x																	
3			x	x																
4				x	x															
5					x	x														
6						x	x													
7							x	x												
8								x	x											
9									x	x										
10										x	x									
11											x	x								
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16																x	x			
17																	x	x		
18																		x	x	
19																			x	x
20	x																			x

with
random allocation
of
protocols & evaluators
to
blocks

validity

design

analogic visual scale x scale

52 study protocols x 15 evaluators

statistical analysis

Is there a risk continuum ?

Are the scale-determined risk levels correctly ordered ?

Are there really 4 distinct risk levels ?

proposal

looking for a consensus among ECRIN

necessity for a common scale

achieving consensus by the Delphi method

Cf. Standards for Reporting of Diagnostic Accuracy

BMJ 2003;326:41-4

organisation

under the aegis of ECRIN / monitoring working package

design

constitution of a steering committee

circulation, critical review of the translated scale

1-2 days meeting of experts from various interest groups

small groups / plenary sessions

→ consensus on optimal format and phrasing

more information

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Optimon Web site

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