RISK-BASED APPROACH

a current application,
the OPTIMON project in France

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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
**Optimon** design

**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
**Optimon**

**design**

**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**

<table>
<thead>
<tr>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>data collection</td>
<td>patients’ accrual</td>
<td>study accrual</td>
<td>available results</td>
</tr>
</tbody>
</table>

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

### Stage I: Identifying the Focus of the Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
</table>
| Clinical trial involving a medicinal product, radiotherapy, gene or cell therapy | - 1st trials in humans (pharmacology, bioequivalence study)  
- Exclusory trial  
- Confirmation trial  
- Product without authorisation  
- Product with authorisation or new combination |
| Surgery                                        | - Minimally invasive technique  
- Technique or biopsy involving an internal organ  
- Generalisation of a new technique  
- Development of a new technique |
| Medical device (including imaging techniques, radiology, radioisotopes) | - CE marking  
  - Class I  
  - Class IIa  
  - Class IIb  
  - Class III  
  - No CE marking  
  - Class I  
  - Non-invasive and inactive  
  - Class IIa, IIb, III  
  - Invasive or active |
| Physiopathology, genetics, other techniques   | - Minimally or non-invasive (including blood sampling) and unrestricting  
- Invasive or restricting |
| Questionnaire, quality of life, psychiatric aspects | - Questionnaire without particular difficulties  
- Disrupting questionnaires for a severe condition |

### Stage II: Identifying One or More Parameters Increasing the Risk

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one of the study interventions presents a particular risk</td>
<td>- Risk of mortality or severe morbidity attributable to the intervention, new indication, potentially dangerous environment, invasive procedure using a route other than natural body orifices (except blood sampling)</td>
</tr>
<tr>
<td>At least one of the study investigations presents a particular risk</td>
<td>- 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)</td>
</tr>
<tr>
<td>The disease or alteration in the target population status aggravates the risk attributable to the intervention or the investigations</td>
<td>- Risk of mortality or severe morbidity attributable to a severe pathological condition; failure or insufficiency of a system or organ; age ≤ 2 years, age ≥ 60 years; pregnant, parturient or breast-feeding woman</td>
</tr>
<tr>
<td>No parameters increasing the risk attributable to the intervention, investigations, or target population status</td>
<td>- 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</td>
</tr>
</tbody>
</table>
Pre Optimon

risk assessment scale

2. to deduce the risk level

<table>
<thead>
<tr>
<th>STAGE III: IDENTIFICATION OF THE LEVEL OF RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOCUS OF THE STUDY</strong></td>
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<tr>
<td><img src="image" alt="Diagram" /></td>
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</table>

<table>
<thead>
<tr>
<th>CONDITIONS FOR INCREASING THE RISK</th>
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</thead>
<tbody>
<tr>
<td>a) At risk procedure, involving:</td>
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<tr>
<td>Risk of mortality or severe morbidity attributable to the procedure</td>
</tr>
<tr>
<td>New indication</td>
</tr>
<tr>
<td>Potentially dangerous situation</td>
</tr>
<tr>
<td>Invasive procedure using a route other than natural body orifices (except for blood sampling)</td>
</tr>
<tr>
<td>b) At risk investigations, involving:</td>
</tr>
<tr>
<td>Risk of mortality or severe morbidity attributable to the investigation</td>
</tr>
<tr>
<td>Use of a radioactive or a relatively undocumented product or product which has not been authorised</td>
</tr>
<tr>
<td>Invasive procedure using a route other than natural body orifices (except for blood sampling)</td>
</tr>
<tr>
<td>c) TARGET POPULATION STATUS ASSOCIATING RISK ATTRIBUTABLE TO THE PROCEDURE OR INVESTIGATIONS, involving:</td>
</tr>
<tr>
<td>Risk of mortality or severe morbidity attributable to a serious pathological condition or the patient's age</td>
</tr>
<tr>
<td>Failure or insufficiency of a system or organ</td>
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<tr>
<td>Age ≤ 2 years, age ≥ 80 years</td>
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<tr>
<td>Pregnant, parturient or breast-feeding women</td>
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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**

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

**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.

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.

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