Randomized evidence on monitoring strategies
the OPTIMON study

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Sponsor       Bordeaux University Hospital
Funding       French Clinical Research Hospital Program
Support       French university hospitals
              INSERM
              French disease-oriented institutions & networks
              ECRIN

https://ssl2.isped.u-bordeaux2.fr/optimon/
Back to 2005

European regulation

directive 2001 Clinical Trials
→ GCP for drug approval trials
in France: any interventional study

GCP § 5.18.3 Extent and Nature of Monitoring
…The sponsor should determine the appropriate extent and nature of monitoring… 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… can assure appropriate conduct of the trial in accordance with GCP...

GCP widespread interpretation (“gold-standard”)
SDV 100% data, 100% patients, 100% sites, on-site monitoring

Protest of (French) academic institutions
100% onsite monitoring = 40 to 60% costs
efficiency still unproved
how to optimise cost-efficiency ratio?
  cost reduction of on-site monitoring intensity
  efficiency maintain of fulfilment of regulatory & scientific requirements

→ the Optimon trial
**objective**

to compare two monitoring strategies
100% onsite vs. risk-adapted

**hypothesis**

a risk-adapted monitoring strategy can
be defined a priori for each study
yield results similar to the 100% onsite strategy for the main quality criteria of study
improve other aspects, such as costs or delays

→ a typical non inferiority situation
non inferiority trial

Risk assessment
Monitoring plan

Screening
CTU ⇔ study ⇔ site

Optimon main eligibility criteria

- patient: any
- study: any clinical field, any design, non risk D level, 20 to 100 patients expected
- sites: ≥ 5 patients expected
- CTU: academic label experience, GCP compliant

Actions by **Optimon team** or by **study team**
non inferiority trial

Risk assessment
Monitoring plan

Screening
CTU ⇔ study ⇔ site

100% onsite

risk-adapted

Stratification = risk level
Cluster = site

Actions by Optimon team or by study team
non inferiority trial

Risk assessment
Monitoring plan

Screening
CTU ⇔ study ⇔ site

100% onsite

Patients’ inclusion and follow-up

risk-adapted

Stratification = risk level
Cluster = site

Actions by Optimon team or by study team
**Optimon design**

**non inferiority trial**

- Risk assessment
- Monitoring plan

Screening

CTU $\Rightarrow$ study $\Rightarrow$ site

100% onsite

Patients’ inclusion and follow-up

risk-adapted

Stratification = risk level
Cluster = site

Final cleaning
Transfert to Optimon

**Actions by Optimon team or by study team**
**Optimon design**

**non inferiority trial**

- Risk assessment
- Monitoring plan

**Screening**

- CTU $\Rightarrow$ study $\Rightarrow$ site

100% onsite

- Patients’ inclusion and follow-up

- Final cleaning
  - Transfert to Optimon

**Optimon outcomes**

- **Primary**%
  - Patient file without error on consent form signature & SAEs report
  - Main eligibility criteria & primary outcome

- **Secondary**
  - Errors, delays, costs

**Actions by Optimon team or by study team**
Optimon design

non inferiority trial

Risk assessment
Monitoring plan

Screening
CTU⇒study⇒site

100% onsite

Risk-adapted

Stratification = risk level
Cluster = site

Patients’ inclusion and follow-up

Final cleaning
Transfert to Optimon

Optimon data collection

Statistical analysis by patient

Actions by Optimon team or by study team
**Optimon design**

**non inferiority trial**

- Risk assessment
- Monitoring plan

Screening

CTU → study → site

100% onsite

Risk-adapted

Stratification = risk level
Cluster = site

Patients’ inclusion and follow-up

Statistical analysis by patient

Optimon data collection

Optimon sample size

\[ \Delta = 5\% / \Pi_{100\text{onsite}} = 95\% / \rho_{\text{intrsite}} = 0.60 \]

→ 1,800 patients

revised to 900 → \( \Delta = 11\% \)

**Actions by Optimon team or by study team**
## Optimon

### Recruitment

**CTU** 11  
**Risk level** 8 A  
4 B  
10 C  
**Design**  
16 trial  
3 cohort  
3 cross-sectional  
**Clinical field**  
6 cancer  
3 liver & gastr.enter.  
3 neurology  
2 nutrition  
2 rheumatology  
1 hematology  
1 infectiology  
1 intensive care  
1 pneumology  
1 tabacco  
1 urology  
**Population**  
14 adults  
4 children  
2 women  
2 elderlies

<table>
<thead>
<tr>
<th>Year</th>
<th>Study recruitment</th>
<th>Patient recruitment</th>
<th>Data collection</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
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<td>2013</td>
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<tr>
<td>2014</td>
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</tbody>
</table>

59 studies proposed  
33 studies non eligible  
26 studies eligible  
4 studies not included  
1 study awaiting inclusion  
21 studies included  
954 patients expected  
718 patients included 80% of 900 targeted
1. to assess study characteristics without any glance at the resulting risk level

Pre Optimon risk assessment scale


<table>
<thead>
<tr>
<th>STAGE I: IDENTIFYING THE FOCUS OF THE STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Clinical trial involving a medicinal product, radiotherapy, gene or cell therapy</td>
</tr>
<tr>
<td>☐ 1st trials in humans (pharmacology, bioequivalence study)</td>
</tr>
<tr>
<td>☐ Exploratory trial</td>
</tr>
<tr>
<td>☐ Confirmation trial</td>
</tr>
<tr>
<td>☐ Product without authorisation</td>
</tr>
<tr>
<td>☐ Product with authorisation or new combination</td>
</tr>
<tr>
<td>Details</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAGE II: IDENTIFYING ONE OR MORE PARAMETERS INCREASING THE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Surgery</td>
</tr>
<tr>
<td>☐ Minimally invasive technique</td>
</tr>
<tr>
<td>☐ Technique or biopsy involving an internal organ</td>
</tr>
<tr>
<td>☐ Commercialisation of a new technique</td>
</tr>
<tr>
<td>☐ Development of a new technique</td>
</tr>
<tr>
<td>Details</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical device (including imaging techniques, radiology, radioisotopes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ CE marking</td>
</tr>
<tr>
<td>☐ Class I</td>
</tr>
<tr>
<td>☐ Class IIa</td>
</tr>
<tr>
<td>☐ Class IIb</td>
</tr>
<tr>
<td>☐ Class III</td>
</tr>
<tr>
<td>☐ No CE marking</td>
</tr>
<tr>
<td>☐ Class I</td>
</tr>
<tr>
<td>☐ Class IIa, IIb, III</td>
</tr>
<tr>
<td>Details</td>
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<tr>
<th>Physiopathology, genetics, other techniques</th>
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<tbody>
<tr>
<td>☐ Minimally or non invasive (including blood sampling) and unrestricted</td>
</tr>
<tr>
<td>☐ Invasive or restricting</td>
</tr>
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<tr>
<th>Questionnaire, quality of life, psychiatric aspects</th>
</tr>
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<tbody>
<tr>
<td>☐ Questionnaire without particular difficulties</td>
</tr>
<tr>
<td>☐ Disqualifying questionnaire for a severe condition</td>
</tr>
<tr>
<td>Details</td>
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Examples:
- Risk of mortality or severe morbidity attributable to the intervention; new indication; potentially dangerous or unique situation; invasive procedure using a route other than natural body orifices (except blood sampling)
- At least one of the study interventions presents a particular risk
- The disease or alteration in the target population status aggravates the risk attributable to the intervention or the investigations
- No parameters increasing the risk attributable to the intervention, investigations, or target population status
1. to assess study characteristics without any glance at the resulting risk level

Pre Optimon risk assessment scale

STAGE I. IDENTIFYING 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

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 scenarios; 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...
1. to assess study characteristics
   without any glance at the resulting risk level

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<td>Examples</td>
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<td>Details</td>
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| ☐ 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 |
| Details |
2. to deduce the risk level

<table>
<thead>
<tr>
<th>FOCUS OF THE STUDY</th>
<th>Step 1</th>
<th>Step 2</th>
<th>INTERMEDIATE RISK</th>
<th>QUESTIONNAIRE QUALITY OF LIFE PSYCHIATRIC ASPECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL TRIAL OF A MEDICINAL PRODUCT, RADIOTHERAPY, GENE OR CELL THERAPY</td>
<td>Minimally invasive technique</td>
<td>Minimally or not invasive (including blood sampling)</td>
<td>Questionnaire without particular difficulties</td>
<td></td>
</tr>
<tr>
<td>Confirmation trial with an authorised product or a new combination</td>
<td>CE marking, class I or IIA, routine use CE marking, class I, use outside licensed indications</td>
<td>Not restricting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmation trial with a product which has not been authorised</td>
<td>Technique or biopsy performed on an internal organ</td>
<td>Invasive or restricting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory trial using a product which has not been authorised</td>
<td>Generalization of a new technique</td>
<td>Disquieting questionnaire for a severe condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory trial using a product which has not been authorised 1st trials in humans (pharmacology, bioequivalence study)</td>
<td>Development of a new technique</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONDITIONS FOR INCREASING THE RISK**

a) AT RISK PROCEDURE, involving:
- Risk of mortality or severe morbidity attributable to the procedure
- New indication
- Potentially dangerous worsening 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 ATTRIBUTABLE 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 breastfeeding women

**FOCUS OF THE STUDY**

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.

**FINAL RISK**

If condition c is fulfilled, increase the risk by one level.
2. to deduce the risk level

Pre Optimon risk assessment scale
2. to deduce the risk level

<table>
<thead>
<tr>
<th>FOCUS OF THE STUDY</th>
<th>INTERMEDIATE RISK</th>
<th>PHYSIOPATHOLOGY OTHER INTERVENTIONS</th>
<th>QUESTIONNAIRE QUALITY OF LIFE PSYCHIATRIC ASPECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL TRIAL OF A MEDICINAL PRODUCT, RADIOThERAPY, GENE OR CELL THERAPY</td>
<td>Minimally invasive technique</td>
<td>Minimally or not invasive (including blood sampling)</td>
<td>Questionnaire without particular difficulties</td>
</tr>
<tr>
<td>SURGERY</td>
<td>CE marking, class I or IIA, routine use</td>
<td>Not restricting</td>
<td></td>
</tr>
<tr>
<td>MEDICAL DEVICE including IMAGING TECHNIQUES, RADIOLOGY, RADIOISOTOPES</td>
<td>CE marking, class I, use outside licensed indications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>confirmation trial with an authorised product or a new combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>confirmation trial with a product which has not been authorised</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>exploratory trial using an authorised product or a new combination</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONDITIONS FOR INCREASING THE RISK**

- **a)** AT RISK PROCEDURE, involving:
  - Risk of mortality or severe morbidity attributable to the procedure
  - New indication
  - Potentially dangerous symptomatic situation
  - Invasive procedure using a route other than natural body orifices (except oral)
- **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 with increased toxicity of an invasive procedure using a route other than natural body orifices (except oral)
- **c)** TARGET POPULATION STATUS AGRIPPIN RISKS ATTRIBUTABLE TO THE PROCEDURE, involving:
  - Risk of mortality or severe morbidity attributable to a serious pathological situation
  - Failure or insufficiency of a system or organ
  - Age ≥ 2 ≤ years, age ≥ 80 years
  - Pregnant, parturient or breast-feeding women

*Final Risk*
## Pre Optimon

### risk-adapted monitoring plan

<table>
<thead>
<tr>
<th></th>
<th>100% onsite monitoring</th>
<th>risk-adapted monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>risk level A</td>
<td>risk level B</td>
</tr>
<tr>
<td><strong>initial contact</strong></td>
<td>systematically and traced</td>
<td></td>
</tr>
<tr>
<td><strong>site adequation</strong></td>
<td>systematically, remotely if site known and experimented</td>
<td>otherwise on site (may be coupled with set-up)</td>
</tr>
<tr>
<td></td>
<td>initiation</td>
<td>systematically, before inclusion of 1st patient, by phone if site known and experimented, otherwise on site</td>
</tr>
<tr>
<td><strong>on-site monitoring</strong></td>
<td>on site, 100% patients, 100% data, 100% sites</td>
<td>10% patients</td>
</tr>
<tr>
<td>data conformity</td>
<td>(freq. to be defined at study start)</td>
<td>100% key points then if major problem</td>
</tr>
<tr>
<td>respect of procedures</td>
<td>systematically, on site at 1st monitoring visit (from 1st inclusion)</td>
<td>systematically, by phone</td>
</tr>
<tr>
<td></td>
<td>systematically, on site at next visit</td>
<td>after reception of forms of 1st patient at CTU/CRC</td>
</tr>
<tr>
<td><strong>comprehension of circuits</strong></td>
<td>systematically, on site at next visit</td>
<td>systematically, on site or remotely</td>
</tr>
<tr>
<td><strong>consents</strong></td>
<td>systematically, on site at next visit</td>
<td>masked copy at inclusion</td>
</tr>
<tr>
<td></td>
<td>systems</td>
<td>on site at next visit or at closure</td>
</tr>
<tr>
<td><strong>search for SAEs</strong></td>
<td>systematically, on site</td>
<td>systematically, on site or remotely</td>
</tr>
<tr>
<td><strong>corrections</strong></td>
<td>at each visit, 100% data queries created remotely or on site</td>
<td>at each visit for key points</td>
</tr>
<tr>
<td></td>
<td>queries created remotely</td>
<td>queries created remotely</td>
</tr>
<tr>
<td><strong>forms verification</strong></td>
<td>systematically, before entry of forms not checked on site</td>
<td></td>
</tr>
<tr>
<td><strong>centralized monitoring</strong></td>
<td>systematically, 100% patients, 100% data, 100% sites + respect of procedures</td>
<td></td>
</tr>
<tr>
<td><strong>close-out</strong></td>
<td>systematically, on site</td>
<td>systematically, par mail</td>
</tr>
<tr>
<td></td>
<td>100% patients, 100% sites</td>
<td>100% patients, 100% sites</td>
</tr>
<tr>
<td></td>
<td>systems</td>
<td>systems</td>
</tr>
<tr>
<td></td>
<td>systematically, on site</td>
<td>systematically, on site</td>
</tr>
<tr>
<td></td>
<td>100% patients, 100% sites</td>
<td>100% patients, 100% sites</td>
</tr>
</tbody>
</table>
# Pre Optimon: Risk-Adapted Monitoring Plan

<table>
<thead>
<tr>
<th>100% Onsite Monitoring (= risk D)</th>
<th>Risk-Adapted Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>risk level A</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## On-Site Monitoring

<table>
<thead>
<tr>
<th>on site, 100% patients, 100% data, 100% sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>(freq. to be defined at study start)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10% patients 100% key points then if major problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 visit / site 100% key points then is major problem</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
# Pre Optimon

## risk-adapted monitoring plan

<table>
<thead>
<tr>
<th>100% onsite monitoring (= risk D)</th>
<th>risk-adapted monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>risk level A</td>
</tr>
<tr>
<td></td>
<td>risk level B</td>
</tr>
<tr>
<td></td>
<td>risk level C</td>
</tr>
</tbody>
</table>

### on-site monitoring

| on site, 100% patients, 100% data, 100% sites  | Ø                        |
| (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 |

- **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

### centralized monitoring

- systematically, 100% patients, 100% data, 100% sites + respect of procedures
Rationale
high inter-assessor variability observed in Pre Optimon
need for risk assessment independent from sponsor
→ validation committee
  → 2 clinicians, 2 methodologists, 2 sponsor representatives
  independent assessment
  consensus search if needed

Summary of results
24 studies assessed
initial consensus reached for 2/3 studies
sponsors tend to a higher risk level
→ collective risk assessment
  by trained assessors
Remote checking of consent form

Clin Trials 2013.10(3):445-55 & 446-8
Remote checking of consent form

Clin Trials 2013.10(3):445-55 & 446-8

TO BE CHECKED
- Trial identification
- Consent form version
- Participant anonymization
- Name
- Date of signature
- Signature
- Investigator signature
- Name
- Date of signature
- Contact info.

→ something visible, not legible

OPTIMON – V. Journot
Society for Clinical Trials, Boston, 20 May 2013
Limits
- guesstimated sample size and power
- risk for participant only / one-for-all strategy
  ≈ outdated

Strengths
- randomized clinical trial
  - high level of evidence
  - only 2 such trials: Optimon and Adamon
- risk for participant only
  - minimal level of monitoring
- one-for-all strategy
  → proof of concept
- movement for development of the approach
  ECRIN, OECD, FDA, EMA, EC → (drug) trials
  Optimon → any study design or phase
Randomized evidence on monitoring strategies
the OPTIMON study

Valérie Journot
INSERM U897 & CIC-EC 7, Bordeaux, France

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https://ssl2.isped.u-bordeaux2.fr/optimon/