In 2001, the Department of Clinical Research and Development of the Paris - Ile-de-France region of the Assistance Publique - Hôpitaux de Paris (AP-HP) developed a grid, using information available at the onset of the study, in order to class clinical research projects depending on the level of risk they represent for patients. Four levels of risk were identified:

- Risk A: low or negligible risk anticipated
- Risk B: risk anticipated close to that of normal care
- Risk C: high risk anticipated
- Risk D: very high risk anticipated

This classification system has been used for several years by AP-HP, then by other French trial sponsors, but has never been officially validated.

We decided to undertake formal validation in the context of the Optimon trial. In the first instance a workgroup met several times to discuss various items of the classification grid and to modify it. This modified grid was then sent to various research professionals in the French clinical research field, and their remarks were included to produce the final version of the grid presented below together with a user guide, several examples that will help you familiarise yourselves with the grid and its use, and a glossary.

**ORGANISATION OF THE WORKGROUP**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annie BOUXIN-METRO</td>
<td>HIV Clinical and Therapeutic Research Unit, National Agency for Research on AIDS</td>
</tr>
<tr>
<td>Pierre-Henry BERTOYE</td>
<td>Inspection and Companies Directorate, AFSSAPS (French Agency for the Safety of Health Products)</td>
</tr>
<tr>
<td>Geneviève CHENE</td>
<td>Methodological Support Unit for Clinical and Epidemiological Research, Bordeaux University Hospitals CIC-EC and Unit 593, INSERM</td>
</tr>
<tr>
<td>Véronique DAURAT</td>
<td>DRRC Ile-de-France, AP-HP</td>
</tr>
<tr>
<td>Claude GAULTIER</td>
<td>DRRC Ile-de-France, GHU Nord, AP-HP</td>
</tr>
<tr>
<td></td>
<td>CIC (Clinical Investigation Centre), INSERM</td>
</tr>
<tr>
<td></td>
<td>Robert Debré Hospital, AP-HP</td>
</tr>
<tr>
<td>Valérie JOURNOT</td>
<td>INSERM, Unit 593</td>
</tr>
<tr>
<td>Jean-Pierre PIGNON</td>
<td>Biostatistics Department, Institut Gustave Roussy</td>
</tr>
<tr>
<td>Philippe RAVAUD</td>
<td>North Paris Clinical Research Unit, AP-HP</td>
</tr>
<tr>
<td></td>
<td>Bichat Hospital, AP-HP</td>
</tr>
<tr>
<td></td>
<td>Unit 738, INSERM</td>
</tr>
</tbody>
</table>
### STAGE I. IDENTIFYING THE FOCUS OF THE STUDY

<table>
<thead>
<tr>
<th>Clinical trial involving a medicinal product, radiotherapy, gene or cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; 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>
</tbody>
</table>

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
  - No CE marking
    - Class I
    - Class IIa, IIb, III

Routine use

Outside licensed indications

With little prior information

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**
### Stage III. Identification of the Level of Risk

#### Step 1

<table>
<thead>
<tr>
<th>Clinical Trial of a Medicinal Product, Radiotherapy, Gene or Cell Therapy</th>
<th>Surgery</th>
<th>Medical Device including Imaging Techniques, Radiology, Radioisotopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive technique</td>
<td>CE marking, class I or IIa, routine use</td>
<td>CE marking, class I, use outside licensed indications</td>
</tr>
</tbody>
</table>

- Confirmation trial with an authorised product or a new combination
- Technique or biopsy performed on an internal organ
- Generalisation of a new technique
- Development of a new technique

#### Step 2

**Intermediate Risk**

- **A**
  - Minimally or not invasive (including blood sampling)
  - Not restricting

- **B**
  - Invasive or restricting
  - Disquieting questionnaire for a severe condition

- **C**
  - Minimally or not invasive (including blood sampling)
  - Not restricting

- **D**
  - Invasive or restricting
  - Disquieting questionnaire for a severe condition

#### 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 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 breast-feeding 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.

- If condition **c** is fulfilled, increase the risk by one level.

**Final Risk**
INSTRUCTIONS FOR USE

STAGE I: Identify the focus of the study and its characteristics. Describe them.

STAGE II: Identify all parameters that increase the risk. Describe them.

STAGE III: Determine the level of risk using the grid and information collected in stages I and II:

Step 1. Enter the grid via the focus of the study, identified during stage I.

Step 2. Determine the intermediate risk level of the study according to its characteristics identified during stage I.

Step 3. For columns ① to ③, increase the risk by one level if the study involves an at-risk intervention, an at-risk investigation method, or a target population status that aggravates the risk attributable to the interventions or investigations. Possibly increase the risk by two levels if more than one condition greatly increases the risk. For column ④, increase the risk by one level if target population status aggravates the risk attributable to the interventions or investigations.

N.B.: If the study focuses on two different topics (for example: comparison of a surgical technique and use of a medicinal product), the risk level should be determined for both topics, and the highest of the two final assigned to the study.

EXAMPLES

<table>
<thead>
<tr>
<th>Aims / Methods / Comments</th>
<th>Use of the grid</th>
</tr>
</thead>
</table>
| Multicentre protocol for treatment of acute myeloblastic leukaemia in children and adolescents (aged 0 to 18 years) with interleukin 2 (no marketing authorisation for use in children); risk of severe morbidity attributable to interleukin 2 | Trial of a medicinal product  
|                                            | Confirmation trial using an unauthorised product  
|                                            | Intervention and population at risk  
|                                            | final risk |
| Comparison of the efficiency (number of stools/day in the 8th postoperative month) of sphincter function following neo-rectum surgery using two classical surgical techniques: J-pouch versus coloplasty-pouch | Surgery study  
|                                            | Techniques involving an internal organ  
|                                            | No additional risk  
|                                            | final risk |
| Evaluation of the use of resting splints in rhizarthrosis: randomised prospective controlled study | Medical device  
|                                            | Class I medical device with CE marking  
|                                            | No additional risk  
|                                            | final risk |
| Physiopathological study: to determine reference values for the difference in nasal potential and short circuit current measurements on rectal biopsies in healthy children (age: 3 months to 3 years) and children with cystic fibrosis (risk of inhalation and dehydration) | Physiopathological study  
|                                            | Invasive intervention  
|                                            | Additional risk because population at risk  
|                                            | final risk |
| Perinatal psychiatric cohort: study of anxiety disorders during pregnancy and post-partum, of the consequences for the mother, the infant and on the development of the young child | Questionnaire  
|                                            | Questionnaire without particular difficulties  
|                                            | No additional risk  
|                                            | final risk |
GLOSSARY

Authorisation: Marketing authorisation for a medicinal product, authorisation to use a radioisotope, for a specific indication; the authorisation is valid only for this indication.

Surgery

Generalisation of a new technique: Technique being spread to a large number of centres.

Development of a new technique: Technique being developed by a small number of centres.

Medical device


Medical device: The term ‘medical device’ defines any instrument, apparatus, appliance, material, or other article, except products of human origin, or other article, whether used alone or in combination therapy, including any accessories and software for its proper functioning, which is intended by its manufacturer for use for medical purposes for human beings and which does not achieve its principal action by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medical devices designed to be totally or partly introduced into the human body or placed in a natural orifice, which rely for their functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity, are defined as active implantable medical devices.

These medical devices are intended to be used for:
. Diagnosis, prevention, control of treatment or alleviation of disease
. Diagnosis, prevention, control of treatment or alleviation or compensation of an injury or handicap
. Investigation, replacement or modification of the anatomy or of a physiological process
. Control of conception

CE marking: A visible CE symbol which certifies that the medical device complies with a list of items called "essential requirements", compulsory since 14th June 1998, and in force in France and all other member states of the European Union or signatories of the agreement on the European Economic Area, valid for 5 years.

CE marking classes: There are 4 classes (I, IIa, IIb, III) corresponding to rising levels of risk. Classification is according to 18 rules divided into 4 subgroups (Appendix IX of Book Vb of the Public Health Act (Code de la Santé Publique): version 2003):
. Rules for non-invasive devices
. Rules for invasive devices
. Other rules for active devices
. Special rules

Criteria used for the classification of medical devices:
. Duration of use (temporary, short-term, long-term)
. Invasive character of the device and invasive impact
. Possibility of re-use of the device
. Therapeutic or diagnostic use of the device
. Dependence on an energy source
. Part of the body in contact with the medical device

Body orifice: Any natural opening of the body, as well as the external surface of the eye, or any permanent artificial opening, for example a stoma.

Invasive medical device: Device that is totally or partly introduced into the body, either via an orifice, or through the surface of the body.

Active medical device: Any medical device that relies for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and functioning by use of this energy. Medical devices intended to transfer energy, substances or other elements, without significant modification, between an active medical device and the patient are not considered to be active medical devices.

Confirmation trial: A study which focuses on efficacy; conducted after exploratory studies; trials of phase II or III in the development of a medicinal product.

Exploratory trial: A study which focuses on safety, tolerance, feasibility, exploring doses, activity; conducted after the first studies in humans; phase I or II trials in the development of a medicinal product.

Intervention: procedure, product or topic being studied.

Other interventions: for example, clinical examinations, patient management, patient diet, physical activity, etc.

Investigation: Any means to evaluate the status of the patient, of the condition being studied or the effects of the intervention being studied.

Severe morbidity: Aggravation of the basal state of a condition.