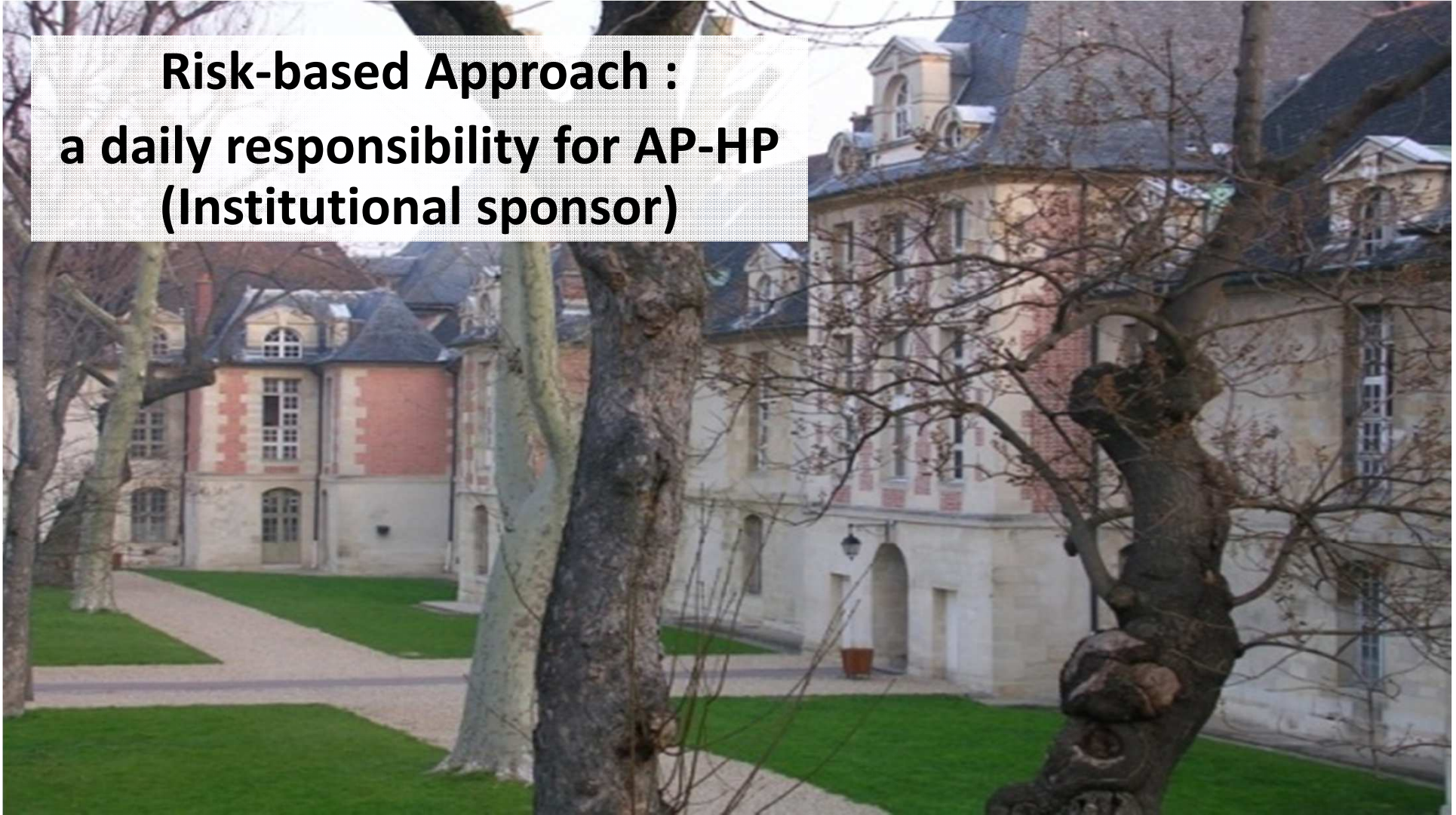


**Risk-based Approach :  
a daily responsibility for AP-HP  
(Institutional sponsor)**



2013

Pr Olivier Chassany, Hôpital Saint-Louis, Paris

# Risk-based approach for monitoring: WHY ?

(risk added by the research)

- The sponsor should ensure that the trials are **adequately** monitored.
- The sponsor should determine the **appropriate** extent and nature of monitoring

## **NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE**

(CPMP/ICH/135/95) - ICH Topic E 6 (R1) Guideline for Good Clinical Practice

# Risk-based approach for monitoring: WHY ?

- Not enough funding / grant to monitor 100% of data of all studies (institutional)
- Annual budget of Clinical Research Assistant :
  - 35.000-40.000 euros
  - Study over 3 years: Budget > 100.000 euros

# Risk-based approach for monitoring: WHY ?

- Because it is clear, smart and efficient in a time of constrained budget

Everyone can make the difference between these two studies in term of risk added by the research:

- *Decompressive hemicraniectomy for malignant hemispheric infarction*
- Genetic study of the allele x of a given pathology (additional blood tube)

# Current legislation focuses on drugs and is not adapted to the risk-based approach

- **Loi « Huriet-Serusclet » n°88-1138 du 20 décembre 1988** relative à la protection des personnes qui se prêtent à des recherches biomédicales

EN	Official Journal of the European Communities
<b>DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001</b>	
<b>on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use</b>	

- **Loi n°2004-806 du 9 août 2004** relative à la politique de santé publique, concernant les recherches biomédicales
- **Décret n°2006-477 du 26 avril 2006** modifiant le chapitre 1<sup>er</sup> du titre II du livre 1<sup>er</sup> de la première partie du CSP relatif aux recherches biomédicales



# Why clinical research is complex ?

- One-size-fits all regulation for all clinical trials
  - Regulation is not adapted to the **risks/constraints added** by the research
  - European Directive does not include non-drug clinical trials and non-interventional studies (which can evaluate drugs prescribed in usual care)

Regulation – the real threat to clinical research. BMJ 2008



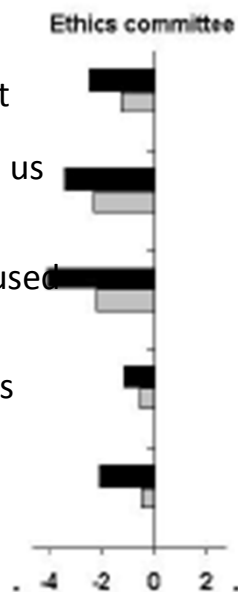
# The burden of European Ethical Review is repeatedly denounced. Ethics Committees must accept to implement a risk-based approach in their review process

## BRIEF REPORT

Intensive Care Med (2009) 35:713-716

### Submission of clinical studies to ethics committees or clinical trials registers: the authors' point of view

- The ethics committee provided good support
- The effort needed to obtain approval caused us to make progress in ethics
- The effort needed to obtain the approval caused us to make scientific progress
- The effort needed to obtain the approval was justified
- The approval was applicant-friendly



## Research ethics paperwork: what is the plot we seem to have lost?

Konrad Jamrozik, BMJ 2004

The standardisation of applications to local research ethics committees seems likely to make ethical approval less efficient and more time consuming for everyone



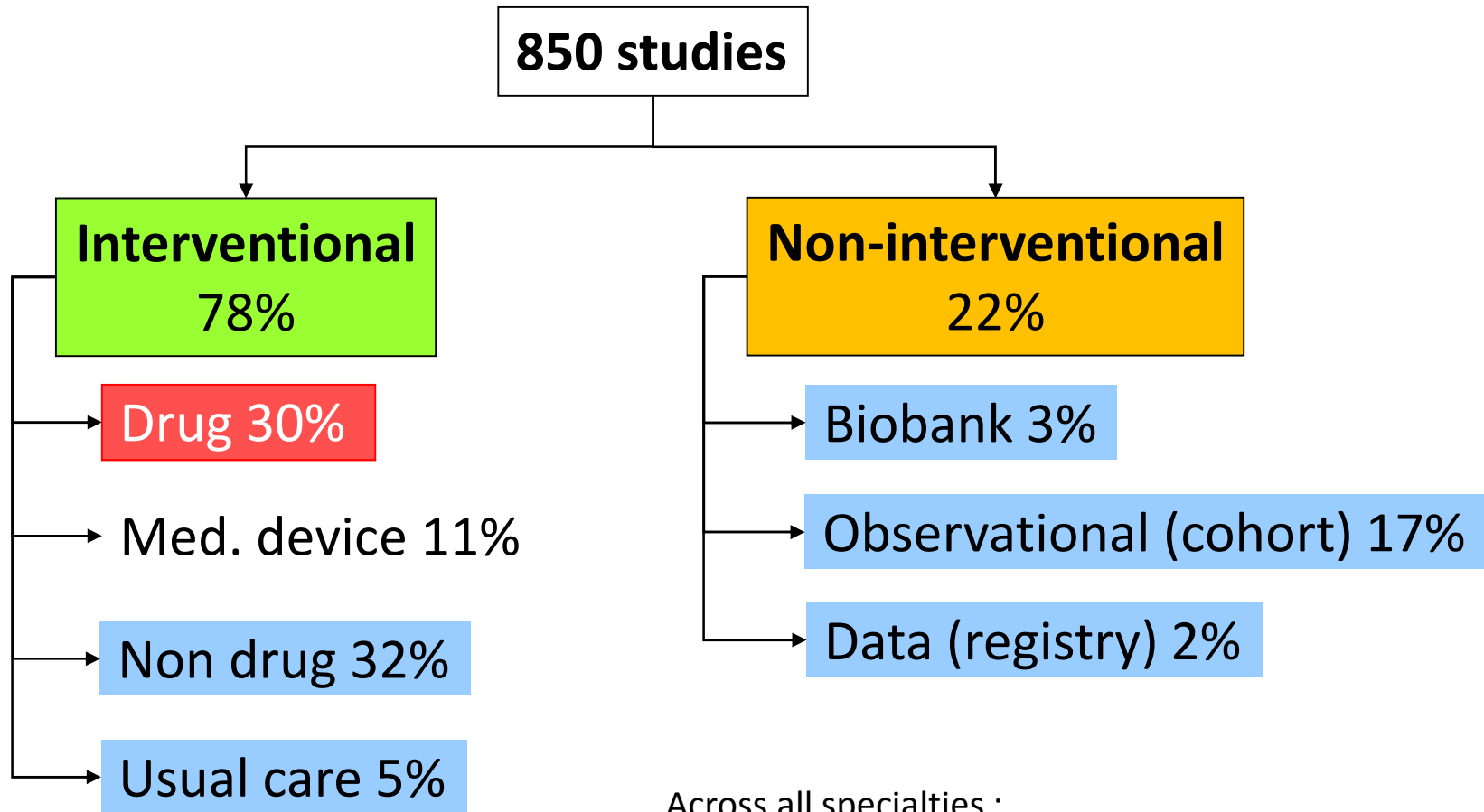
## EDITORIAL

Chassany O. Intensive Care Med (2009)

### Should European Independent Ethics Committees be dismantled ?

# Why clinical research is complex ?

Assistance Publique - Hôpitaux de Paris : institutional sponsor/manager of 850 investigator-based clinical studies



Across all specialties :

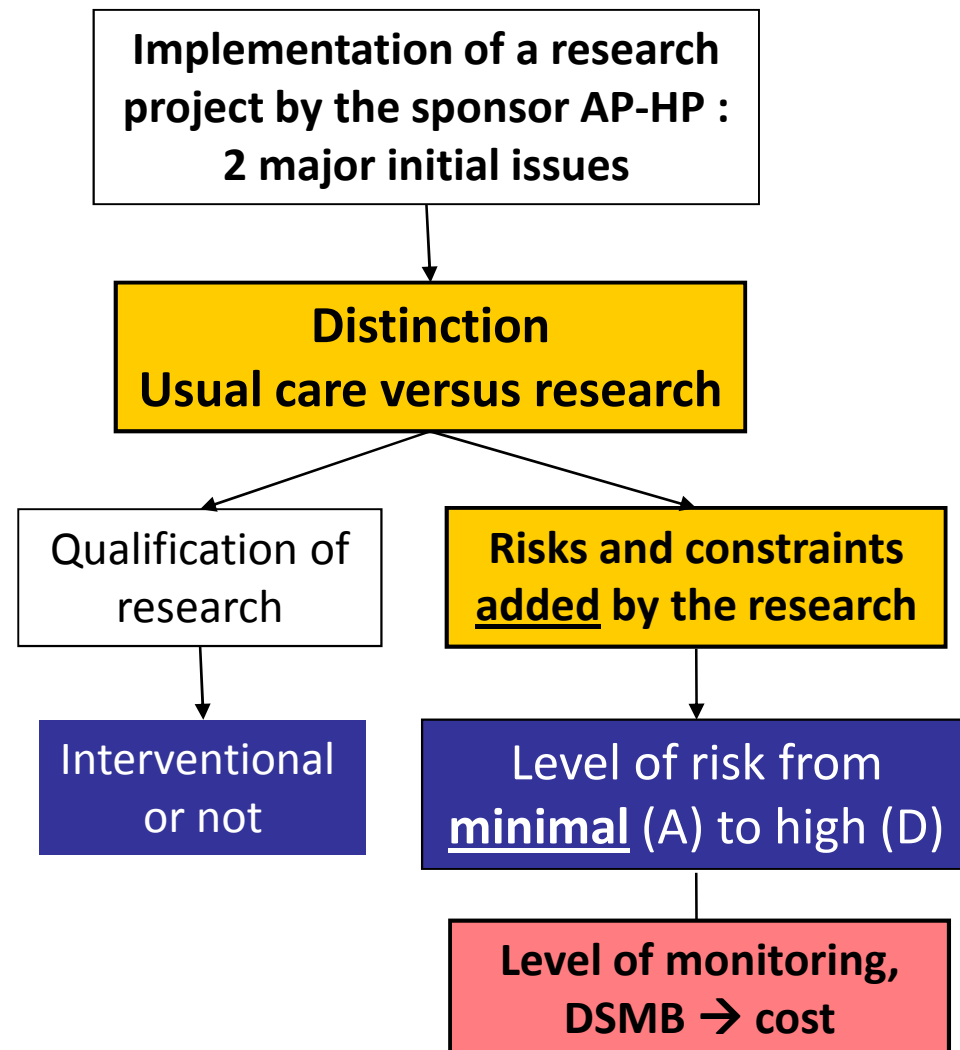
- Hematology, cancerology, neurology
- From physiopathology study to gene therapy trial



# Risk-based approach for monitoring

Such an approach is used since 2003 for all clinical trials by AP-HP (institutional sponsor)

- Who and how to appreciate the risk added by a research ?
- The best expert for setting at first the added-risk level of a research is the sponsor
- Confirmed by Competent Authority and/or EC



## Risk-based approach

**It is quite obvious for the sponsor which clinical trials (drugs and non drugs) are risky...**

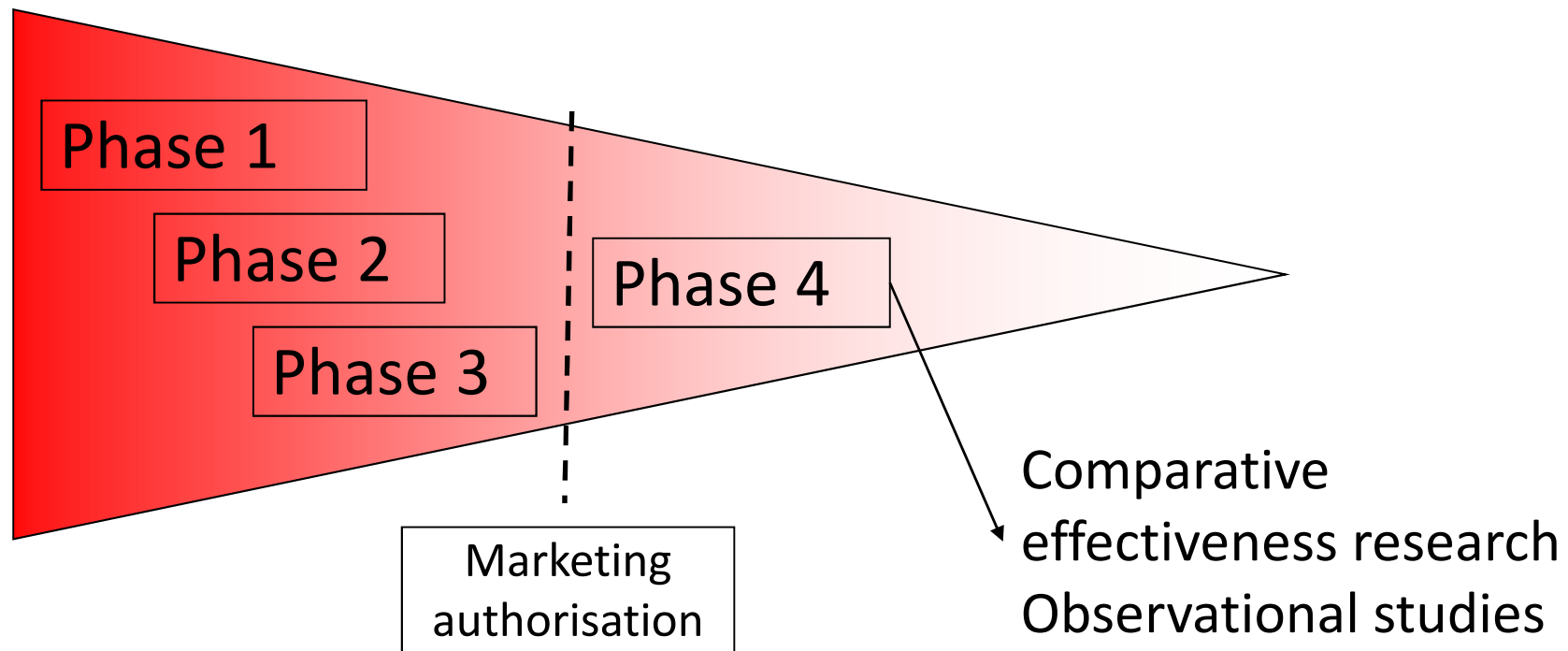
- Trial mobilization with G-CSF stem cells in tissue repair in the acute phase of myocardial infarction
- Randomized "chemotherapy plus thalidomide versus chemotherapy plus placebo" in relapsed myeloma
- Treatment of obstructive hypertrophic cardiomyopathy by distal embolization (septal)
- Multicentric intracerebral grafting in Huntington's disease
- Treatment of severe obsessive-compulsive disorder by bilateral stimulation of subthalamic nucleus
- Decompressive hemicraniectomy for malignant hemispheric infarction

# Études interventionnelles à risque (contraintes) négligeable

- Étude de l'influence de la composition du repas du soir sur la glycémie à jeun chez le diabétique de type II
  - Surveillance accrue / contraintes : **1 nuit d'hospitalisation** (prélèvements sanguins nocturnes)
- Dépistage et intérêt du traitement des troubles respiratoires du sommeil au cours de l'hypertension artérielle pulmonaire (HTAP)
  - Interventionnel : Polysomnographie
  - Contraintes : **1 nuit d'hospitalisation**
- GRIPMASK : Essai randomisé évaluant l'efficacité du port de masques chirurgicaux dans la prévention de la transmission secondaire de la grippe A dans les foyers
  - **masque ou pas masque pendant 5 jours (= intervention)** (port à domicile durant la journée)

# Risk-based approach of drug clinical trials

## Added-risk of drug clinical trials



# Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003) – drug clinical trials

Risk level	Drug clinical trials	Level of monitoring
<b>A</b>		Consent
<b>B</b>	<p><b>Phase 4 : licensed drugs in their indication</b> (comparative effectiveness research, optimization, observational)</p> <p>Phase 3 : Combination of licensed drugs in their indication</p>	Basic data* in all patients + monitoring of all relevant data in a few dossiers
<b>C</b>	<b>Phase 3 : new drug under development or licensed drug in new indication</b>	Basic data* in all patients + monitoring of all relevant data of 10-20% of Case Report Forms
<b>D</b>	<b>Phase 1 or 2 : new drug under development</b>	<b>100% of Case Report Forms</b>

\* Consent, Serious Adverse Event (SAE), eligibility, primary endpoint...



# **Examples of drug clinical trials with minimal added-risk for the patients, in which the drugs are given in usual care in their licensed indication**

Studies specifically promoted by institutional sponsors

## **Optimisation of therapeutic strategies**

- Comparison of 2 antibiotic duration (no optimal duration of treatment is indicated in the Summary of Product Characteristics) :
  - Erysipelas
  - Pneumopathy

## **Comparative Effectiveness Research**

- Comparison of 4 treatments in plantar wart
  - One of the treatment is the old salicylate vaseline
- Comparison of 2 antivirals in Influenza
- Comparaison of 2 drugs in malaria

# Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003) – non drug trials

Risk level	Gene or cell therapy	Physiopathology, imagery	Psychiatry	Radiotherapy isotopes, surgery	Medical device (MD)
<b>A</b>		<u>None</u> invasive, e.g. blood puncture, imagery without injection of contrast agent	Non risky use of patient questionnaires	<u>Routine</u> technique or surgery, non severe biopsy (skin, ganglion)	The risk depends : <ul style="list-style-type: none"> <li>• Of the <u>grade</u> of the MD (I, IIa, IIb, III)</li> <li>• Whether <u>invasive</u> or not</li> <li>• Whether use in or outside the approved <u>indication</u></li> <li>• Of the <u>novelty</u> of use in practice</li> <li>• Whether availability of the <u>CE</u> conformity marking</li> </ul>
<b>B</b>		<u>Slightly</u> invasive procedure Imagery with injection of contrast agent	Use of patient questionnaires with a risk of destabilizing the patients	<u>Generalization</u> of a new or recent technique	
<b>C</b>		<u>Invasive</u> procedure		<u>Learning</u> phase of a new technique	
<b>D</b>	Gene or cell therapy			<u>New</u> technique	

# Monitoring level tailored to the risks & constraints added by the research (AP-HP, since 2003): What is monitored ?

Risk level →	A	B	C	D
Initial meeting, commitment to comply with good clinical practice (GCP)	X	X	X	X
Monitoring of consent	X	X	X	X
Monitoring of SAE	X	X	X	X
Basic monitoring (6 points)	-	X	X	X
Monitoring of primary endpoint	-	X	X	X
Monitoring of selected secondary endpoints	-	-	X	X
% of CRF monitored at 100%*	-	1 <sup>st</sup> /centre 1 <sup>st</sup> /investigator	10 - 20 %	100 %

\* Important data

# Distinction between the monitoring level adapted to the added-risk versus the quality control of data

- **Monitoring level adapted to the risks & constraints added by the research for the patients**

→ for ensuring the protection and rights of patients

- Information, consent process
- Protocol deviations
- Serious adverse events

→ May lead to modifications of the protocol, the follow up of patients, the administration modalities of the health product; may lead to a premature stop of the study (Role of the Data Safety Monitoring Board – DSMB ++)

- **Quality control of the data of studies which may be risky or not**

→ For ensuring the veracity and authenticity of data

# Distinction between the monitoring level adapted to the added-risk versus the quality control of data

For each clinical trial, the AP-HP sponsor sets 2 levels :

1. **Minimal level of monitoring** to achieve (A, B, C et D) **according to the risks & constraints added by the research**
    - This classification is recognized by the insurer which sets the insurance cost depending of the level of risk declared by AP-HP
  
  2. **Necessity or not of a higher level of quality control** of data (in practice: a 100% of monitoring of data), if :
    - Partnership with industry (possibility of a dossier submission for drug approval)
    - Potential impact of results : modification of management, high ranking publication, important public health issue
    - Media risk, orphan diseases...
- In practice, a trial may be declared to the insurer and to the Competent Authority with an added-risk level of A (minimal risk), but with a 100% quality control of data for other reasons



## Monitoring level: risk added by the research for the patients versus quality of data

Study	Risks for the patients	Impact of the study : quality of the data
Sleep in pulmonary arterial hypertension	Interventional study at minimal risk (no risk : A)	No
Cohort evaluating tolerance of biotherapies in skin diseases	No risk added by research : observational study	Yes ++ → monitoring
face transplant	<b>Risky surgery</b>	<b>Yes +++ : 100% monitoring</b>

## The risk-based approach of the AP-HP sponsor is not limited to the monitoring level, but also to the management of serious events and the DSMB

- For clinical trials with minimal added-risk (Level A)
  - No serious adverse event due to the research is expected
  - A death occurring in a study where the only additional procedure of the research is a blood puncture, an additional blood tube, or a chest x-ray, is not a serious side effect, but an event unrelated to the research
  - For these studies, the protocol should/must specify that no serious adverse event has to be reported to the sponsor (even in case of a death)
- For risky clinical trials (Level D), a **Data Safety Monitoring Board (DSMB)** is systematically created
  - Discussed on a case by case basis for clinical trials with a level C
  - There is no DSMB in clinical trials with a A or B level

# Risk-based approach : a shared approach



- MRC/DH/MHRA Joint Project : **Risk-adapted Approaches** to the Management of Clinical Trials of Investigational Medicinal Products
- FDA Guidance for Industry - Oversight of Clinical Investigations - A **Risk-Based Approach** to Monitoring
- European Community : Proposal for a revision of the Clinical Trials Directive (2001/20/EC)
- EMA Reflection paper on **risk based quality** management in clinical trials
- OECD - Facilitating multinational cooperation in non-commercial clinical trials : Sub-working group on **risk-based approach** to clinical trial regulation

**French law Jardé on clinical research voted (Feb. 2012) :  
Finally, a graduated regulation based on the added-risk  
of the research**

Type of research Requirement	Interventional with some risk		Interventional trials at minimal added-risk	Non-interventional studies
	Health products	Non health products	Drugs are excluded !	Observational
<b>Sponsor</b>	Yes	Yes	Yes	Yes
<b>Ethics Committee (EC)</b>	Yes	Yes	Yes	Yes
<b>Consent</b>	Yes	Yes	Yes *	Information
<b>Insurance</b>	Yes	Yes	Yes	NO
<b>Competent Authority</b>	Yes	Yes	NO	NO
<b>Full Data protection review process</b>	NO **	NO **	Not anymore **	Not anymore **

\* Possible exemption given by EC, \*\* if no “sensible” data is collected