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Alternative monitoring procedures in investigator initiated trials

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A risk-based approach to monitoring : the AP-HP experience

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Clinical Research sponsored by AP-HP : a few facts

- 38 hospitals
- 6 medical universities
- 8 **Clinical Trial Units**
- 7 Clinical Research Centers
- 750 medical and technical services
- 18.000 clinicians
- 100 Inserm units
- 30 CNRS units

- > 1970 studies since 1992
- 60.000 patients included since 1992
- 239 patents
- 7.000 publications per year

- **465 on-going sponsored studies**
- 98 studies outside the scope of the biomedical law

Neurosciences	**15 %**
Oncology	**11 %**
Internal medicine	**11 %**
Mother-Child	**11 %**
Surgery, ICU	**10 %**

Source : “Projet” database, 03.06

Institutional sponsor : First objective

- To (re)assess the benefit/risk ratio of each study (intervention & procedures) in order to protect :
  - patients and
  - the public institution AP-HP

- AP-HP is an institutional sponsor, not an industrial sponsor. Its goals and interests (or conflicts of interest) are therefore largely different from a pharmaceutical firm.

AP-HP sponsors some risky trials…

- Gene therapy of human severe combined immunodeficiency CID-X1 disease
- Phase II study : Intramyocardial transplant of cultured autologous skeletal myoblast cells in patients with ischemic cardiopathy
- Stem Cell Mobilization by Granulocyte Colony-Stimulating Factor (G-CSF) in Patients with Acute Myocardial Infarction
- Striatal neural grafting in Huntington's disease patients

N°	SAE	Relationship to study product	Report to AFSSAPS
1	Ventricular Tachycardia	Possible	Yes
2	Ventricular Tachycardia	Definite	Yes
3	Ventricular Tachycardia	Probably related	Yes
4	Ventricular Tachycardia, Sudden Death and Resuscitated (MACE)	Probably related	yes
5	Ventricular Tachycardia	Probably related	Yes

About
- **100 of therapeutic trials (drugs)**
- **15 cellular/gene therapy trials**

AP-HP developed a tailored monitoring procedure

- The sponsor should ensure that the trials are adequately monitored.
- The sponsor should determine the appropriate extent and nature of monitoring.
- The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

AP-HP Tailored monitoring level

Risk Level	Drug trial, cellular or gene therapy	Physiopathology genetic	psychiatry, cognitive study, questionnaires	Radiology, imaging, radiotherapy, isotopes	Surgery
A		Not invasive (blood puncture)	by default	"routine" exam	Usual biopsies : skin, adenopathy, muscle
B	**Phase IV Phase III (combination of marketed drugs)**	Invasive procedure without injection of contrast product	"aggressive" questionnaire in a severe disease	Standard technique, but not completely validated	Routine Surgery
C	**Phase III New indication Risky population**	Invasive procedure with injection of contrast product		New technique, validation study	Generalisation of a new technique
D	**Phase I-II New indication of a risky drug**				Perfecting of a new technique

Also classification for medical devices

AP-HP Tailored monitoring level

	Central	On site		
Risk level	**A**	**B**	**C**	**D**
Preliminary meeting commitment to respect GCP	x	x	x	x
Consent	at the end	x	x	x
SAE, safety, new facts	x	x	x	x
Basis monitoring (6 points)		x	x	x
Primary endpoint		x	x	x
Selected secondary endpoints			x	x
% of dossiers completely monitored		1st/centre 1st/investigator	**10-20 %**	**100 %**

C or D : **constitution of a Data Safety Monitoring Board**

Basis monitoring (6 points)

1. Existence of included patients
2. Existence of signed consents
3. Respect of eligibility criteria
4. Data collection of primary endpoint
5. Declaration of Adverse events
6. Management of products of the study and monitoring in hospital dispensary (pharmacy)

Distribution of level of monitoring

- **465 on-going sponsored studies**

Monitoring*	
A	33 %
B	26 %
C	13 %
D	28 %

* Analysis done on 381 studies, source “Projet database, 03.06

Independently of the safety risk, the level of monitoring is also based on :

- **« media attention » risk**

  (orphan disease, powerful patients' association : Steinert disease, myopathy, Down's syndrome, Gene therapy of human severe combined immunodeficiency CID-X1 disease)
- **Political risk** (unfrequent)
- **Ethical risk**

  (Decompressive hemicraniectomy in major stroke)
- **Partnership risk**

  With a pharmaceutical industry, because the trial may be part of a dossier submitted to Health authorities
- **Impact of results**

  Necessity for a high quality assurance for publication

Other factors politically incorrect…

- **« Investigator » risk**
  (protocol violations : consent, inclusion, SAEs, declaration of centers…)
- **Lack of homogeneity among CTUs**
  (all the monitoring is done by CTUs)
- **Risk of inspection by AFSSAPS**
  Trials with drugs “under the spot”
  Following underfinanced grants given by Afssaps to investigators to conduct therapeutic trials

→ **All of these factors strengthen the level of monitoring**

→ **On-going process : regular reassessment of the benefit / risk ratio, following new SAEs**

French legislation on biomedical research
(decree on the way)

- Opportunity to perform studies on evaluation of standard care of prevention, diagnosis or treatment (excepted drugs and medical devices) outside the scope of the law : without sponsor

AP-HP Tailored management level « Soins courants »

	Evidence of validation	Nature of care	Population and disease	Impact (public health, economic, mediatic…) *
1 pt	High	Non invasive	Normal	Low
2 pt	Medium	a little bit invasive	Protected by law	Probable
3 pt	Low	Invasive	Vulnerable, Orphan disease	High

Points	Level
1-4	A
5-8	B
9-12	C

* Expectation of health authorities

Also classification for medical devices

AP-HP Tailored management level « Soins courants »

Level	A	B	C
Preliminary meeting commitment to respect GCP	**yes**	**yes**	**yes**
Consent	**yes**	**yes**	**yes**
SAE, safety, new facts	**yes**	**yes**	**yes**
Basis validation (5 points)	**TEC**	**TEC or ARC**	**ARC**
Centralized criterion	**no**	**Yes if present**	**yes**
% of dossiers completely monitored	10-40%	40-60%	60-100%

TEC : Technicien d'études cliniques
ARC : Assistant de recherche clinique

Conclusion

- Our major and daily concern is to protect patients
- A reasoned and adequate tailored monitoring is the only way to deal with the numerous studies sponsored and the limited budget granted

- Monitoring is one side of quality control / assurance
- An **audit** unit has been recently set up to control and to improve the monitoring