

Health Professionals / Ethics Committees' Perspective

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Risk-based approach

1- The facts :

- 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

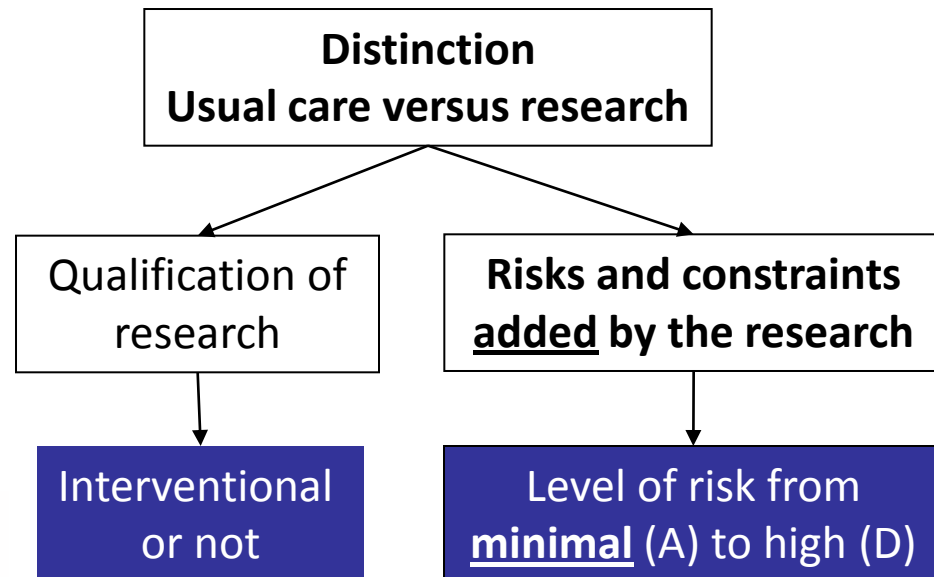


Stewart P, et al.

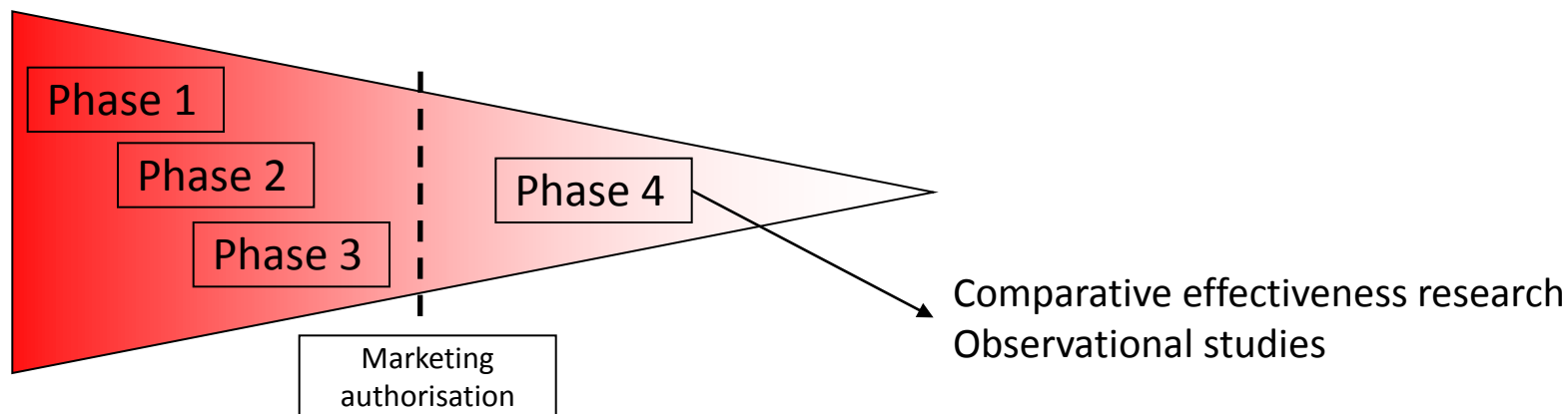
Risk-based approach

2- Who and how to appreciate the risk added by a research ?

- **Responsibility of sponsors to set the level of risk**
- Confirmed by Competent Authority and EC



Added-risk of drug clinical trials



Risk-based approach

2- how to appreciate the risk added by a research ?

3-level classification

- **Type A : no higher than the risk of standard medical care**
 - Licensed drugs in their indications, dosage & form
- **Type B : Somewhat higher than the risk of standard medical care**
 - Licensed drugs used in a new indication
- **Type C : Markedly higher than the risk of standard medical care**
 - Not licensed drugs, new drug under development

ADAMON Project

MRC/DH/MHRA Joint Project : Risk-Adapted Approaches to the management of clinical trials of investigational Medicinal Products. October 2011

Monitoring level tailored to the risks/constraints added by the research (AP-HP, since 2003)

Risk level	Drug clinical trials	Level of monitoring
A		Consents
B	Phase 4 : licensed drugs in their indication Phase 3 : Combination of licensed drugs	Basic data in all patients + monitoring of all data in a few dossiers
C	Phase 3 : licensed drugs in new indications	Basic data in all patients + monitoring of all data of 10-20% of Case Report Forms
D	Phase 1 or 2	100% of Case Report Forms

* Consent, SAE, eligibility, primary endpoint...

Risk-based approach

2- how to appreciate the risk added by a research ?

It is quite obvious which trials 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

Can we reduce the regulatory requirements for studies in which the drugs are given in usual care in their licensed indication ? = minimal added risk

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

Can we reduce the regulatory requirements for studies in which the drugs are given in usual care in their licensed indication ? = minimal added risk

- Non-supply & alleged traceability of drugs
- Alleged notification of side effects
- Expedited review by Competent Authority ?
- **Expedited Review by Ethics Committees ? Already applied :**
 - US Code of Federal Regulations – Policy for Protection of Human Research Subjects
 - **46.110 Expedited review procedures for certain kinds of research involving no more than minimal risks (2009)**
 - **Protocols in expedited review : tackling the workload of ethics committees – experience of Vienna EC (Intens Care Med 2009)**

French law Jardé under discussion : Finally, a regulation based on risks added by the research

Recherches	Interventional with some risk (nothing changes)		Interventional trials at minimal added risk	Non-interventional studies
	Health products	Non health products	Drugs are excluded !	Observational
Sponsor	Yes	Yes	Yes	Yes
Ethics Committee	Yes	Yes	Yes	Yes
Consent	Yes	Yes	Yes*	Information
Insurance	Yes	Yes	Yes	NO
Competent Authority	Yes	Yes	NO	NO
Data protection	NO	NO	Not anymore	Not anymore

* Possible exemption given by EC

Ideal composition of Ethics Committees (EC) ?

Based of their 2 major roles :

benefit/risk ratio : it is worth including patients in the research ?

e.g. is it ethical to let patients under placebo during 12 weeks and having a cancer pain resistant to analgics ? It depends :

- Which patients will be included ?
- How is defined a pain resistant to analgics
- In fact, add-on treatment, i.e. all patients continue a background treatment against pain
- What are the stopping rules for a patient ...

→ Scientific review

Review information & consent forms

→ Civil society representatives

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 ?