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Risk-adapted approach to clinical trial regulation and monitoring

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Risk-based approach for the revision of the 2001/20/EC Directive ?

- 2006 : Consultation on guidance « specific modalities for non-commercial trials »
  - different requirements depending on the sponsor ?
  - or different requirements depending on the risk ?

  Non-commercial sponsors: 12% phase I, 43% phase II, 73% phase IV

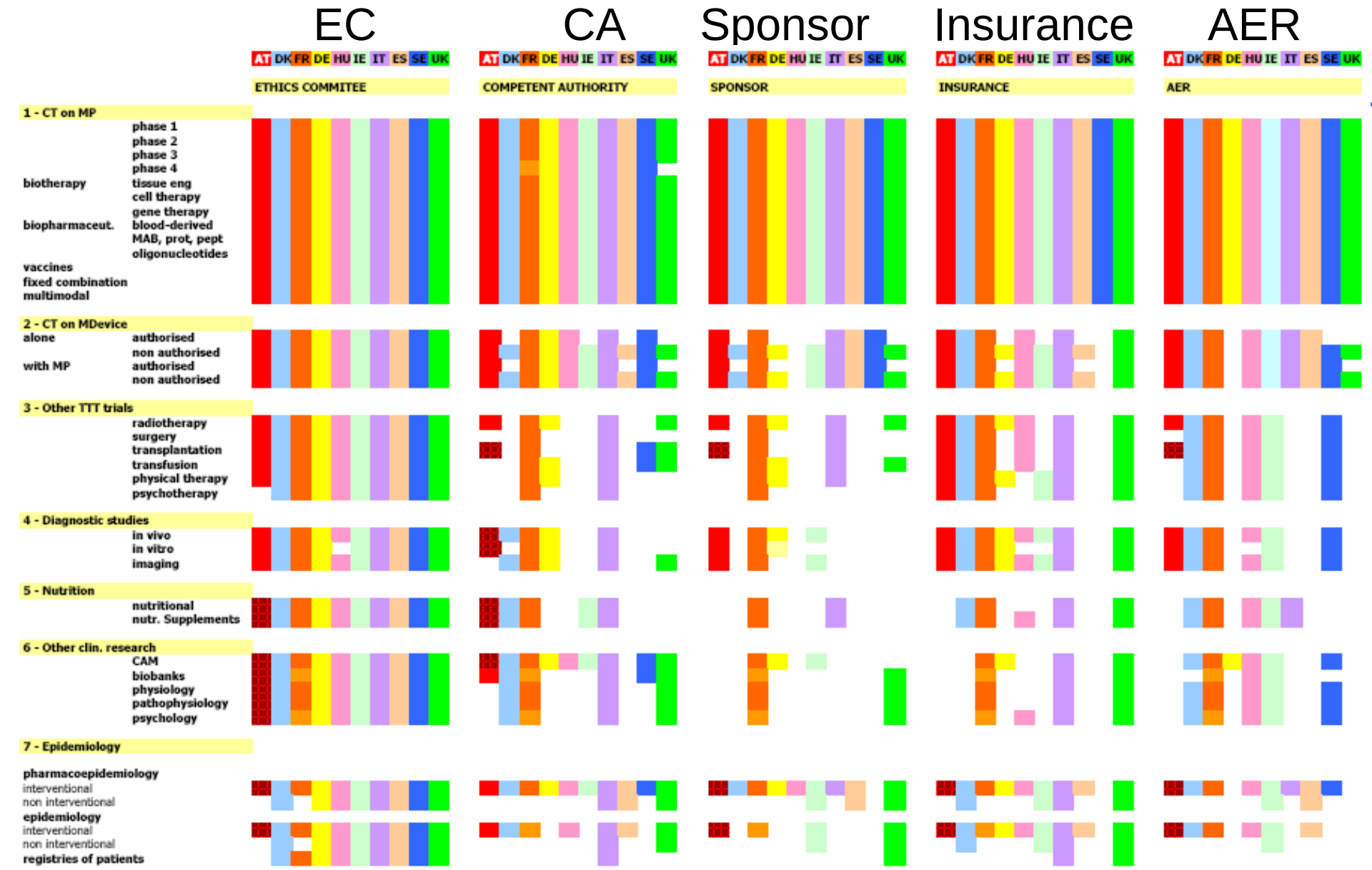
- FP7 ICREL project (2008): increased burden and costs
  www.efgcp.be/icrel

- ESF-EMRC Forward Looks on investigator-driven clinical trials (2008-2009) : risk-based approach

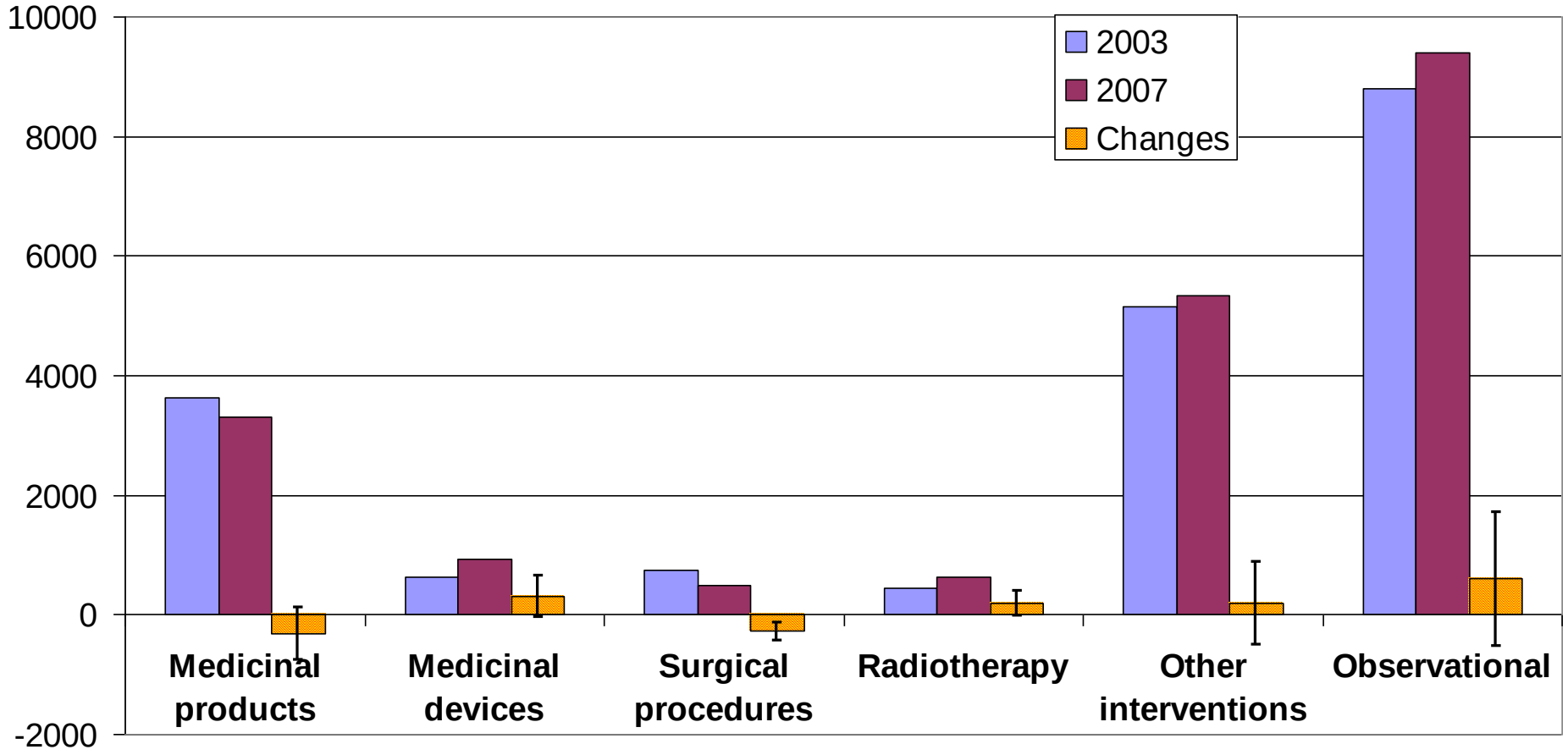
- Roadmap Initiative for Clinical Research in Europe (2009-2010)

- OECD GSF 'Working Group to Facilitate International Cooperation in Non-Commercial Clinical Trials'

Comparison of national requirements

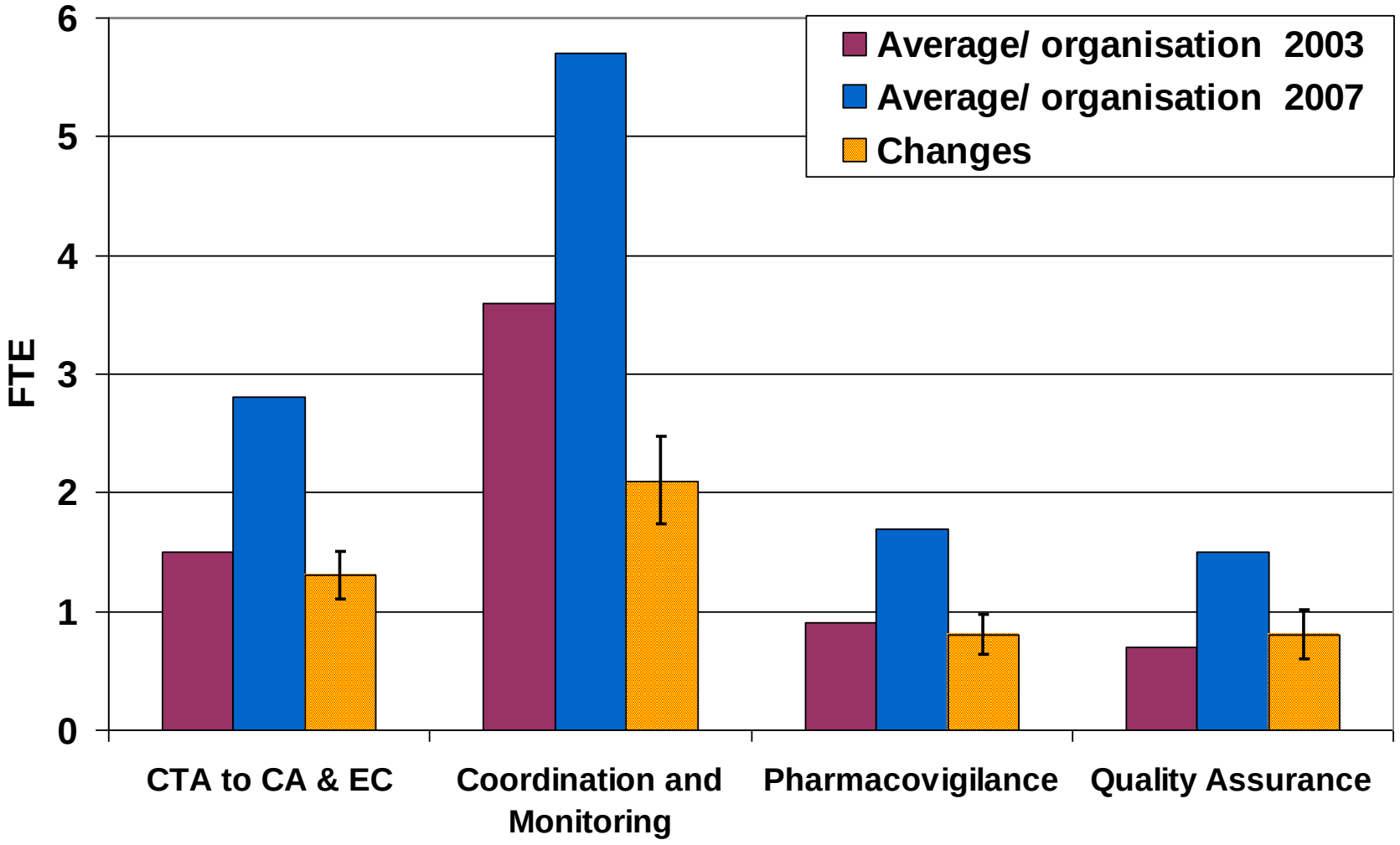


CTs performed before and after the CTD implementation



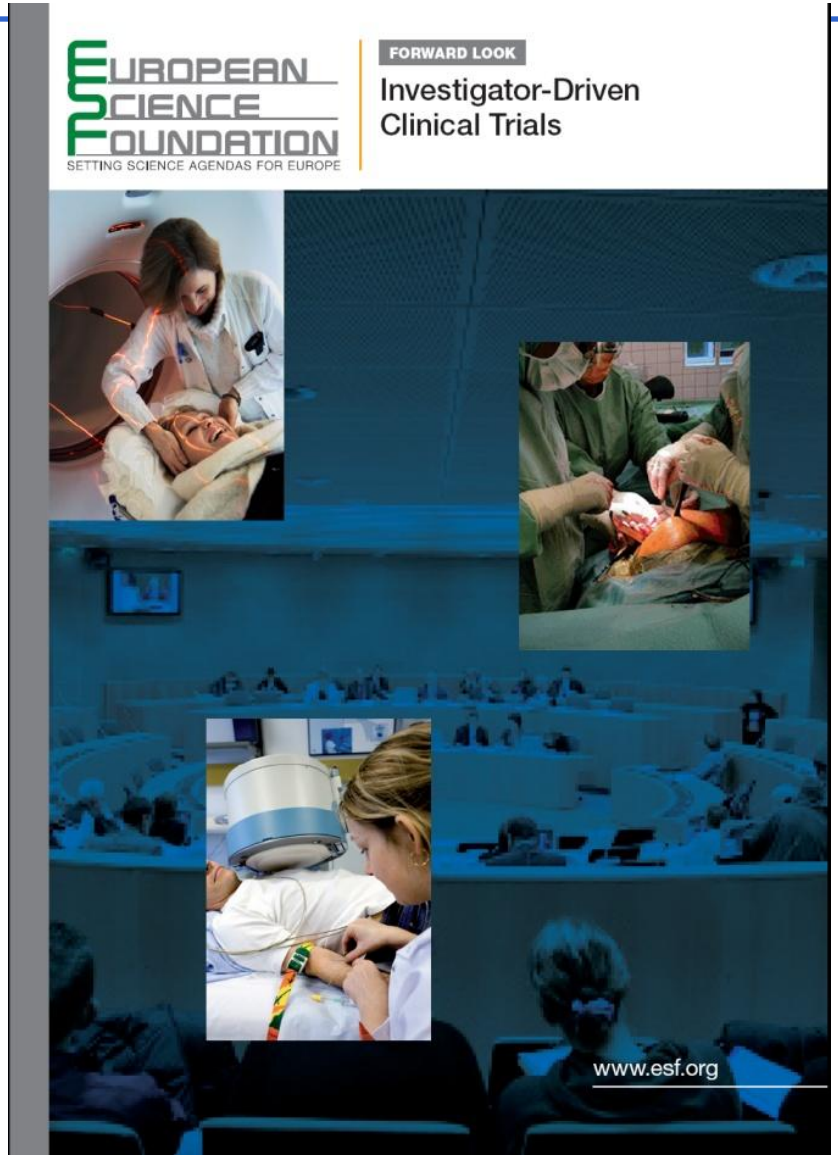
ICREL
Impact on Clinical Research of European Legislation

Workload before and after CTD implementation



European Science Foundation
European Medical Research Councils (EMRC)

Forward Looks ‘Investigator-Driven Clinical Trials’



Recommendations : ranking

No.	No.	Recommendation	Rank
21	4.1	Education and Training	1
24	5.1	Level of Funding	2
7	2.1	Risk-based approach	3
22	4.2	Careers	4
15	3.1	Clinical Trial Authorisations (CTA) Process	5
6	1.6	Large Scale IDCT	6
1	1.1	Categories of patient-oriented research	7
8	2.2	Management by risk-based approach	8
4	1.4	Commercial versus non-commercial trials	9
26	5.3	Models of Partnership	10
16	3.2	Sponsor	11
25	5.2	Prioritisation and mechanism of funding	12
9	2.3	Ethics Committee	13
11	2.5	Insurance Requirements	13
5	1.5	Paradigm shift by biomedical breakthroughs	15
14	2.8	Publication of Clinical Trials Results	15
17	3.3	Investigational Medicinal Products (IMP) Requirements	17
18	3.4	Pharmacovigilance Reporting	18
20	3.6	Project Management	18
13	2.7	Data Storage Capacity	20
3	1.3	Phase I-II-III-IV categories	21
2	1.2	Interventional versus observational studies	22
19	3.5	Pharmacovigilance Notification	23
10	2.4	Adverse Event Reporting	24
12	2.6	Intellectual Property Rights (IPR)	25
23	4.3	Authorship	26

Roadmap Initiative for Clinical Research in Europe

ECRIN
EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK

ICREL

EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

EF GCP

CLINT: facilitating international prospective clinical trials in stem cell transplantation

ELN European LeukemiaNet

Roadmap Initiative for Clinical Research in Europe

- A single CTA in multinational clinical trials: Dream or option ?
  - Brussels, July 7th 2009
- Research ethics committees and ethical review in Europe
  - Barcelona, January 19th 2010
- Innovative approach to clinical trial co-sponsorship in the EU
  - London, September 21st 2009
- Towards a better future for pharmacovigilance in clinical trials
  - Brussels, February 8th 2010
- ***Risk-based approach in clinical trials***
  - ***Barcelona, January 18th 2010***

Risk categories for legislation vs. for an individual study

- Level of risk is a continuous and multidimensional variable
  - stratification
- Focus on
  - hazard to the participants' integrity and rights (insurance, ethics committees),
  - hazard linked to the product and participants' safety (competent authority, safety reporting),
  - data integrity (sponsors, competent authority, monitoring).

-> distinction between:

- Risk-based legislation:
  - restricted number of well-defined, discrete categories;
- Risk management in individual studies:
  - continuous risk evaluation based on processes and data, sites, staff involved -> common decision trees

Proposed categories for clinical trials on MP

- category 1 : clinical trial on IMP without marketing authorisation in the EU
  - *additional requirements could be proposed for trials with novelty-associated risks, as advanced therapies or first-in-human studies, and this would correspond to 1a and 1b categories ?*

- category 2 : clinical trial on IMP with a marketing authorisation in the EU, but for another indication/population/condition.
  - *also including low-novelty treatments, like drugs already available under slightly different formulation (different salt, different routes of administration, slow release etc) ?*

- category 3 : clinical trial on IMP with a marketing authorisation in the EU, used in the licensed indication/population/condition.

Which processes should be affected by risk-based adaptation ?

- monitoring
- ethical review
- assessment by competent authorities
- safety reporting
- requirement for a sponsor
- insurance requirements
- labelling
- documentation
- inspections

Clinical trials on medicinal products: proposed adaptations (1)

	Category 1 (without MA)	**Category 2** (with MA, new indication/population/ condition)	**Category 3** (with MA, licensed indication/population/ condition)
Ethical review	Full review	Full review	Light patient information Expedited review
Competent authority	Clinical Trial Authorisation	Clinical Trial Authorisation	Notification
Safety reporting	All SUSARs on this product reported to EudraVigilance and to the NCA of the sponsor + Periodic Safety Report to Ethics Committees and investigators	Only SUSARs from this trial from EudraVigilance to the NCA of the sponsor + Periodic Safety Report on this trial to ethics committees and investigators	SUSARs sent to EudraVigilance CTM, no expedited SUSAR reporting + Periodic Safety Report on this trial to NCA, ethics committees and investigators

Clinical trials on medicinal products: proposed adaptations (2)

	Category 1 (without MA)	**Category 2** (with MA, new indication/population/ condition)	**Category 3** (with MA, licensed indication/population/ condition)
Sponsor	Yes (flexible arrangements to share responsibility)	Yes (flexible arrangements to share responsibility)	Yes (flexible arrangements to share responsibility)
Insurance	No-fault insurance by sponsor. Explore coverage by health care system or insurance packages	Explore coverage by public health care systems.	Explore coverage by public health care systems. No insurance required for “minimal risk” category
Labelling*	Current requirements apply but review critically Annex 13 whether there is room for facilitation	Simplified labelling ? or other traceability procedure ?	Simplified labelling ? (CTD Art 14+annex13) Or no specific labelling ? or other traceability procedure ?

Clinical trials on medicinal products: proposed adaptations (3)

	Category 1 (without MA)	**Category 2** (with MA, new indication/population/ condition)	**Category 3** (with MA, licensed indication/population/ condition)
Documentation*	IMPD	IMPD = harmonised SmPC + quality / safety data Cross-reference to other IMPD Facilitate definition and access to suitable SmPC	IMPD = harmonised SmPC Cross-reference to other IMPD 5-years retention of TMF if no MA application Facilitate definition and access to suitable SmPC
Inspections	Current practice	Medium priority. Adapt inspection to risk definition in protocol	Low priority. Adapt inspection intensity to procedural risk as defined in protocol
Monitoring* (also takes into account the hazard to data integrity)	Decision tree for risk definition, and adapted monitoring strategy	Decision tree for risk definition, and adapted monitoring strategy	Decision tree for risk definition, and adapted monitoring strategy

Risk-based monitoring

-> Decision trees taking into account hazard to participants, to data integrity, and the robustness of processes at the investigation sites

Existing models

- MRC model *(www.ct-toolkit.ac.uk)*
- TMF model *(Brosteanu. Clin. Trials 2009)*
- AP-HP model (*www.drrc.aphp.fr)*

4 levels of expected risk-to benefit (for the patient)

- Level A : low risk
  - Ex non-invasive pathophysiological / imaging
- Level B : similar to usual care
  - ex phase IV CT
- Level C : substantial risk
  - Ex phase III CT
- Level D : very high
  - Ex Phase I-II drug CT, gene/cell therapy

Risk-based monitoring strategy
AP-HP model (2001)

Risk level	A	B	C	D
Activation meeting, GCP training	X	X	X	X
Informed consent	end	X	X	X
SAE-new facts	X	X	X	X
Basic monitoring source, inclusion-exclusion, drug dispensing	-	X	X	X
Secondary endpoint	-	-	X	X
Records exhaustively monitored	-	1/centre 1/invest	10-20%	100%

+ more recent version taking into account other risk factors

ECRIN WG on monitoring
19 relevant items

Study participants

1 Difficulties or incapacity to give informed consent

2 Collection of indirectly identifying or sensitive characteristics

3 Expected inherent hazards related to study interventions or investigations

4 Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population

5 Study interventions used outside authorized indication / product license / state of the art or in early stage / phase of development

Validity of study results

6 Pre feasibility assessment of the study recruitment based on reliable sources

7 Concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations

8 Objective assessment of primary and the main secondary outcomes

9 Complexity of study procedures

ECRIN WG on monitoring
19 relevant items

	Study organisation
10	Education and experience of the sponsor or investigator sites' staff to GCP or study procedures
11	Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites
12	Intervention management tracking system run by a qualified organisation
13	Quickness and security of data entry in the database
14	Full cleaning of database while study is still in progress
15	Availability of the appropriate resources at the start of the study
	Study governance
16	Existence of management review organisations
17	Existence of ethic and scientific review organisations
18	Influence / interference of a private organisation upon study governance
	Impact on target population and public health
19	Major impact of study results on target population and public health

Beyond the legislative framework

- For each process
  - guidance and procedures for shared risk management strategies for *individual* clinical trials.

- Some of the proposed solutions are already possible within the framework of the current legislation, pending on
  - adaptation of the guidance documents
  - more flexible transposition into national legislation.

Conclusions

Need for in-depth exploration and common definition of:

- what is “minimal risk” ?
- the boundaries between the proposed categories
- treatment and diagnostic intervention
- who should validate the level of risk ?
- what could be “light information” ?
- expedited ethical review
- the SUSAR and adverse event reporting requirements
- what is IMP ?
- labelling requirements for the different categories
- decision trees for monitoring strategies
- best practices for insurance/indemnity coverage both at the national and pan-European level.

OECD GSF Working Group to *Facilitate International Cooperation in Non-Commercial Clinical Trials*

->Two major models:

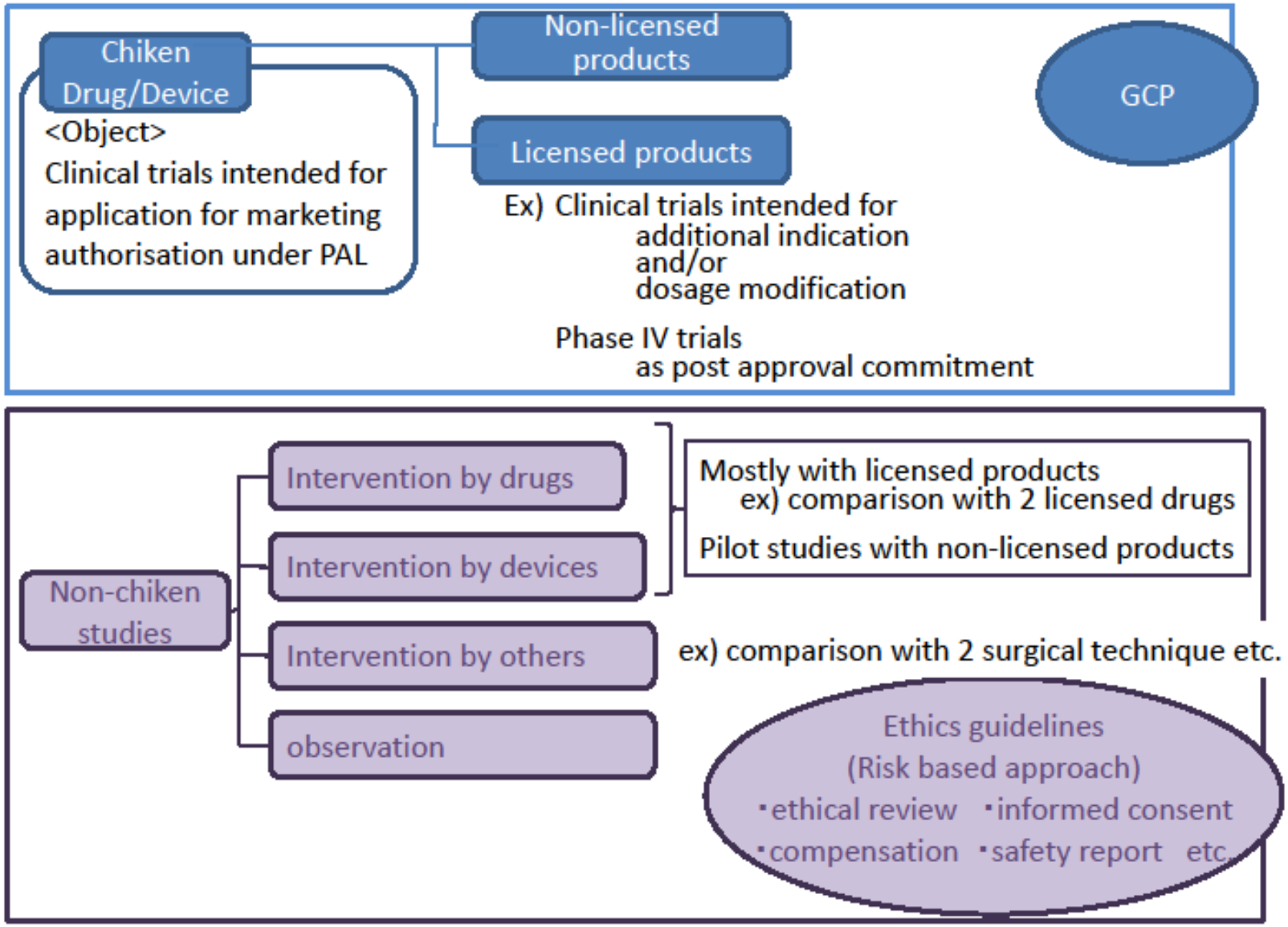
1. Registration vs. non-registration trials

- Product-centred legislation, focus on data credibilty for the registration of health products
- US (IND), Japan (chiken), other world regions
- Implicit risk based approach : distinct requirements
  - when no health product
  - or when already marketed product
  - supervision by IRB/ECs, no legislation

2. No difference between commercial or non-commercial trials

- Participant-centred legislation, focus on patient whatever the objective of the study
- Europe (2001/20/EC Directive)
- Limited flexibility for risk-based adaptation
- Not exploited by national legislation
- Only for clinical trials on medicinal products

【Categories of Clinical Studies in Japan】



Agreement on the definition of risk

- hazard to participants
  - hazard to participants' rights
    - informed consent
    - personal data protection
  - hazard to participants' safety
    - safety of health product / treatment intervention
    - protocol-related diagnostic / follow-up intervention
    - population/context-related
- hazard to trial results
  - credibility of data
  - robustness of study design and analysis

Risk assessment

- Objective vs. subjective
  - "systematic evaluation of research risks" (SERR)

  (Rid et al. JAMA 304:1472-9, 2010)

- Incremental risk
  - compared to usual care or "no-research"
  - better informed consent forms : focus on additional risk

Action : two parallel processes

- Stratified approach
  - defines discrete risk categories for the purpose of the legislation
  - alignment of legislations across the world -> similar regulatory framework for a given trial across the world
  - ‘competition’ between legislation
  - based on the safety of the health product :
    - limited to CT with health products
    - does not consider other risk determinants

- Personalized approach
  - considers all the risk determinants
    - participants right & safety
    - data and results
  - encompasses all the categories of clinical research
  - require a complex decision tree and individual assessment of each protocol
  - ICH-like panel
  - GCP-like guidance

Stratified approach

	Cat 1: new health product	Cat 2: marketed, new indication	Cat 3: marketed, licensed indication
Europe	DIR	DIR	DIR
USA	IND	IND	Non-IND
Japan	Chiken	Chiken	Non-chiken

Who validates ? *EC/IRB ? Competent authority ?*

Stratified approach

- category 1 : clinical trial on health products without marketing authorisation
  - *additional requirements could be proposed for trials with novelty-associated risks, as advanced therapies or first-in-human studies*
- category 2 : clinical trial on health products with a marketing authorisation, but for another indication/population/condition.
  - *low-novelty treatments, like drugs already available under slightly different formulation (different salt, different routes of administration, slow release etc) ?*
- category 3 : clinical trial on health products with a marketing authorisation, used in the licensed indication/population/condition.

Stratified approach

- Which process should be risk-adapted ?
  - ethical review
  - assessment by competent authorities
  - safety reporting
  - requirement for a sponsor
  - insurance requirements
  - labelling
  - documentation
  - inspections
  - monitoring ?

Personalized approach

- considers all the risk determinants, including risks to data quality and credibility fo results
- all the categories of clinical research
- guidance /decision tree for individual assessement of protocol
- ICH-like panel
  - Industry
  - Regulators
  - Academics
  - IRB/EC
  - Patients
  - All the world regions
  - All categories of clinical research
- Principles for risk categorisation
- Impact on each CT supervision process

Recommendations

- Stratified approach to clinical trial legislation
- Individual approach to risk-based adaptation of the protocol

  -> monitoring
- Assessment of risk (incremental) and training (objective vs. subjective)

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SEVENTH FRAMEWORK PROGRAMME

Thank you !