



Final Multidisciplinary Workshop

Designing the Future Conditions for Clinical Research in Europe

Diamant Centre, Brussels, Belgium
17 March 2010

Risk-Based Approach Workshop

Presentation & Discussion

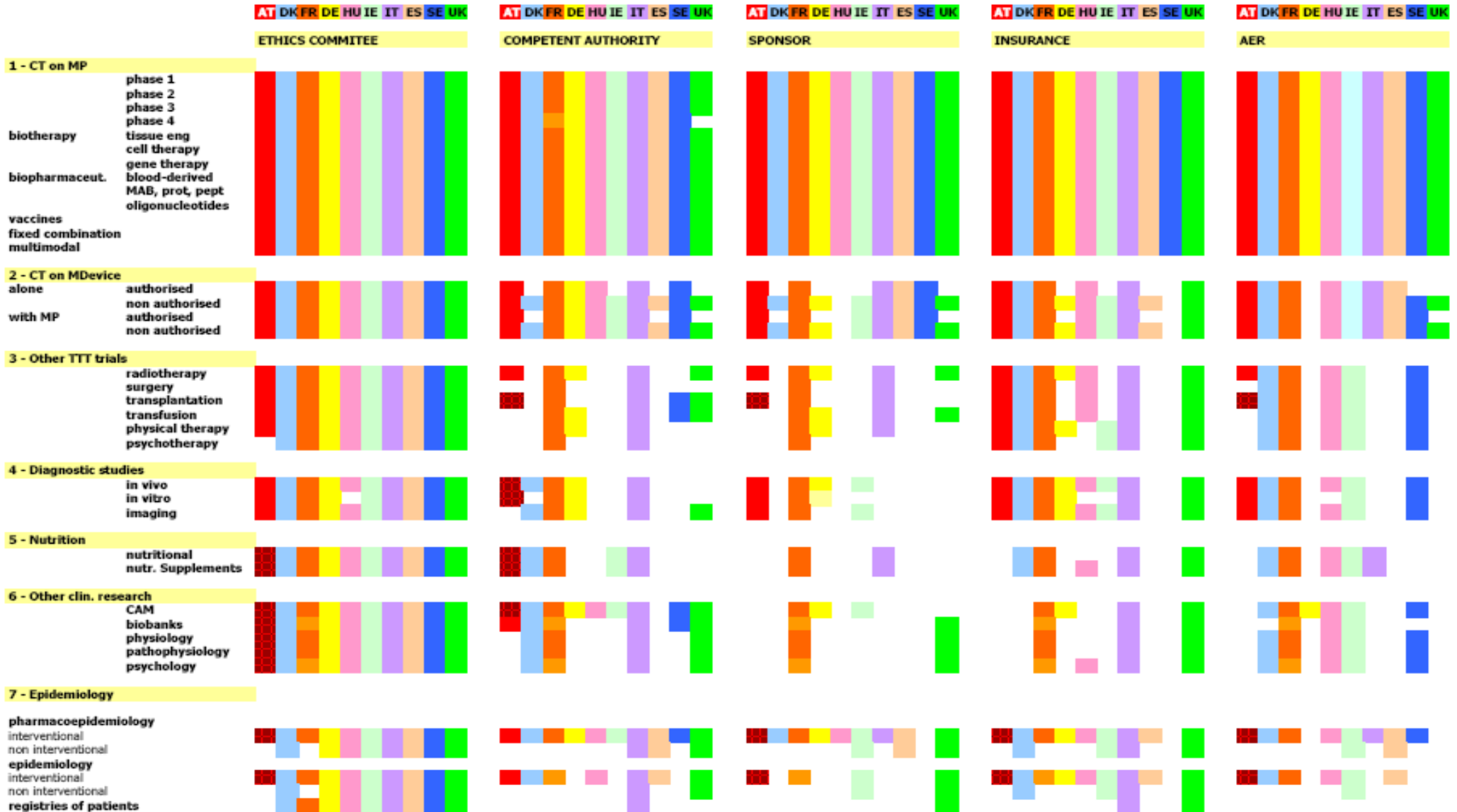
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Comparison of national requirements

CA Sponsor Insurance AER



Assessment of the 2001/20/EC (& 2005/28/EC) Directives

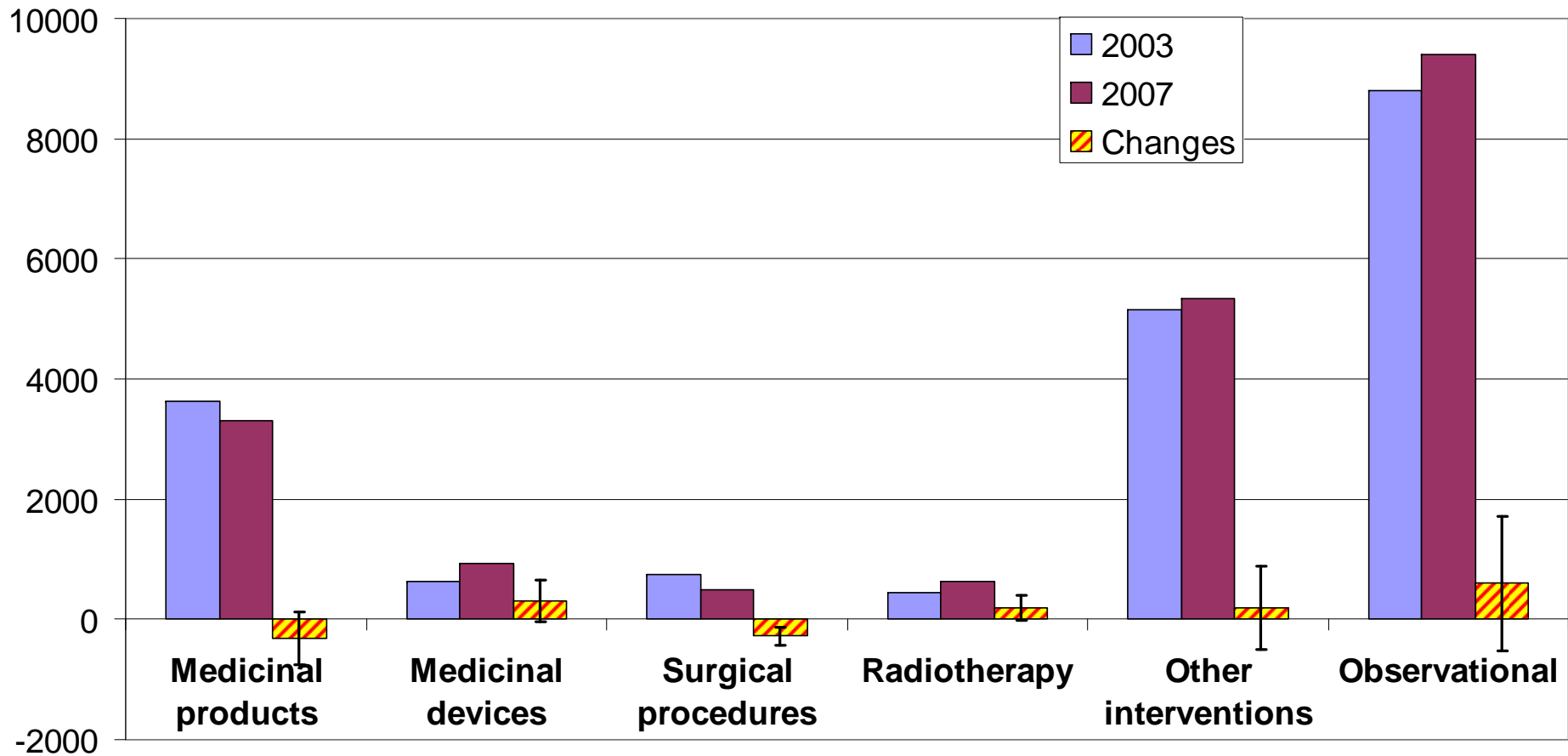
- October 2006 : Consultation on the guidance document on « specific modalities for non-commercial trials »
 - different requirements depending on the sponsor ?
 - or different requirements depending on the risk ?

Non-commercial sponsors:

12% phase I, 43% phase II, 73% phase IV

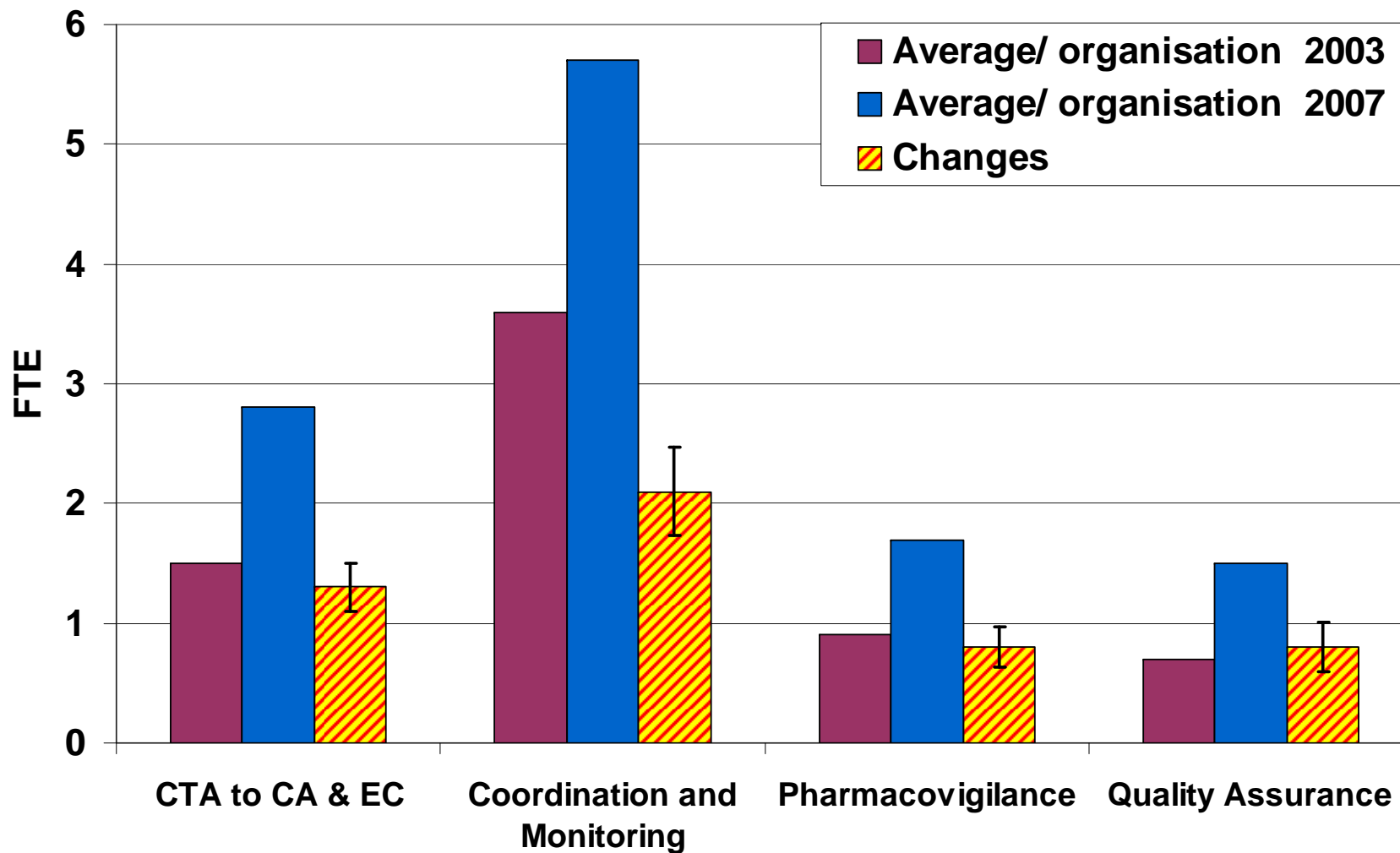
- EC-EMEA conference, October 2007
- FP7 ICREL project (2008): increased burden and costs

CTs performed before and after the CTD implementation





Workload before and after CTD implementation



Assessment of the 2001/20/EC (& 2005/28/EC) Directives

- ESF-EMRC Forward Looks on investigator-driven clinical trials (2008-2009) : risk-based approach = high priority
- DG Research (10 Nov 2009) : Can we facilitate investigator-driven clinical trials ? Risk-based regulation
- EC public consultation on the CT Directive (Jan 2010)
- Roadmap Initiative for Clinical Research in Europe (2009-2010)

Risk-based approach to clinical trials legislation

- *Lessons from risk-based monitoring*
- How to define risk ?
 - Hazard to patients
 - Hazard to data quality
 - Hazard to public health
- How to define risk categories ?
 - How many categories ?
 - Which boundaries ?
 - « Mechanistic » vs. « case per case » approach ?

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

Questions raised by the risk-based approach

- For each process, what should be the risk-adapted requirements ?
- Is it possible to find a definition of risk levels suitable for all these processes ?
- Who should propose a level of risk, and who should validate the risk level for each study ?
- Clinical trials on medicinal products vs. clinical studies without medicinal product ?

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 of clinical research

- 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.

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.

Next steps

- Towards a consensus
 - with ALL stakeholders
 - in ALL world regions
- Review of EU legislation : Directive vs. guidance
- Review of national legislation
- OECD initiative 'Establishing a Working Group to Facilitate International Cooperation in Non-Commercial Clinical Trials'
- Other initiatives