Road Map Initiative for Clinical Research in Europe

Multidisciplinary Workshop on
Risk Based Approach in Clinical Trials
18th January 2010, Barcelona, Spain

Meeting Report

The Directive 2001/20/EC on clinical trials requires similar provisions for all types of clinical trials with medicinal products. This "one-fits-all approach" , however, appears poorly adapted to the diversity of clinical research, and results under some circumstances in unnecessary burden for investigators and sponsors, especially in post-marketing studies. In its recital 11, the Directive 2005/28/EC on Good Clinical Practice intended to define specific modalities for non-commercial trials. A draft guidance document was released for public consultation in 2006, but was not adopted, as it appeared more sensible to define regulatory requirements based on the risk associated with the study, rather than on its commercial or non-commercial objective. This is critical for investigator-driven clinical trials as 12% of phase 1, but 73% of phase 4 studies in Europe are initiated by non-commercial sponsors.

In-depth discussion on a risk-based approach to clinical trial regulation is therefore necessary:

- as proposed during the EC-EMEA conference on the assessment of the clinical trial legislation in October 2007,
- as highlighted in the conclusions of the FP7 ICREL project evidencing increased burden and costs,
- as given high priority by the ESF-EMRC Forward Looks on investigator-driven clinical trials (2008-2009),
- as promoted in the meeting organised by DG Research 'Can we facilitate investigator-driven clinical trials ?' in November 2009.
- A risk based approach was also a key question in the EC public consultation on the CT Directive (January 2010),
- and the OECD global science forum now considers discussing risk-based requirements at the global level.

Pilot initiatives were already developed in some member states – among others various risk-based approaches to monitoring strategies, a risk based approach to national legislation (but excluding clinical trials on medicinal products), or an expedited review process for ethics committees. And of course risk assessment is central for liability insurance of clinical trials. However there is a need for a more comprehensive approach to compare the underpinning definition of risk (hazard to participants? hazard to data quality? hazard to public health?), the number of relevant risk categories and their definition, and the solutions proposed for implementation of risk-based requirements in each individual clinical trial processes. Among other, this raises the question of who will be in charge of validating the risk level for a given protocol.

This workshop was organised to present the need of investigators and sponsors for a risk-based approach, to discuss how the risk categories could be defined, and which process should be affected by a potential risk-based regulation. It explored how risk-based adaptation of current requirements can be implemented in the various clinical

trials processes (ethical and regulatory submissions, monitoring, safety, insurance, need for a sponsor, labelling, documentation, inspections…). A roundtable discussion allowed all the relevant stakeholders to discuss the acceptability and the feasibility of the solutions proposed, with the ultimate goal to produce ground for recommendations, acceptable for all stakeholders, to create an efficient risk based approach while preserving participants' protection and data quality.

Definition of risk and risk categories

Risk:

Although a number of convergent definitions of risk were proposed by the participants, convergence in the definition of risk should not raise major difficulties, as all the proposed definitions refer to the hazard to clinical trials participants (safety, integrity and rights) and the hazard to data integrity (therefore to public health), stressing the need to provide appropriate protection to participants who will participate in clinical trials, who are participating in clinical trials, and who will be treated with the marketed medicinal products. From the insurance point of view and according to ICH Q9, the risk is proportionate to the probability and severity of harm.

Risk categories:

In turn, defining risk categories applicable to a risk-based legislation and relevant to all the clinical trial processes appeared to be a more challenging task.

- First, the level of risk is a continuous and multidimensional variable, but there is a need for stratification into a restricted number of categories for the purpose of a risk-adapted legislation.
- Second, there are distinct perspectives depending on whether we rather focus on hazard to the participants' integrity and rights (insurance, ethics committees), on hazard linked to the product and participants safety (competent authority, safety reporting), or on data integrity (sponsors, competent authority, monitoring).

As a consequence, it was proposed to make a distinction between:

- what is required for the development of a risk-based legislation (a restricted number of well-defined, discrete categories);
- and what is required for the risk management in individual studies, that should be based on a continuous risk evaluation and take into account, in a systematic approach, the processes and the data, but also the sites and the staff involved. A case-by-case evaluation of risk, using common decision trees would lead to a more accurate and comprehensive assessment of risk (however with a questionable reproducibility) allowing definition of risk-management strategies adapted to each individual process (for instance monitoring as proposed in the OPTIMON and ADAMON studies).

In the perspective of a risk-based legislation, only a few categories should be proposed. In the field of clinical research other than clinical trials on medicinal products, the French legislation defines a category for 'usual care' (2004) or 'minimal risk' (2010) interventional studies (however only based on participants' safety), with specific adaptations of requirements. Similarly, the ethics committee of the Medical University of Vienna uses an expedited review procedure for clinical studies (other than clinical trials on medicinal products) considered as minimal risk studies. Both transpose, for clinical research out of scope of the Directive 2001/20/EC, the concept of minimal risk as defined by the Oviedo Convention, or the US 45 CFR part 46 that defines a listing of minimal risk research, including research using marketed medicinal products and medical devices (all based on participants' safety).

Regarding the European regulatory framework for clinical trials on medicinal products, the discussion led to propose three categories of risk for clinical trials participants, based on the marketing authorisation:

- 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 a fourth category)
- category 2 : clinical trial on IMP with a marketing authorisation in the EU, but for another indication/population/condition. This also raises the question of how to categorise 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.

Such distinction would fit with product-centred adaptations, in line with expectations of competent authorities and safety reporting, but does not consider other dimensions of the risk, including the diagnostic intervention, the complexity of the trial, the overall organisation and the experience of the sites. Therefore, for category 3 there should be a decision tree defining “minimal risk” as discussed above that would allow additional facilitation in some aspects. The proposed categorisation should substantially affect investigator-driven clinical trials: whereas 20% of all clinical trials are non-commercial, 43% of phase 2 (mostly IMP with a marketing authorisation but on new indication/population/condition) and 73% of phase 4 trials (IMP with a marketing authorisation used in the licensed indication) have academic sponsors.

How should risk levels affect each process?

Within such a framework, the panel discussion considered the possible adaptations of requirements to be brought to each process depending on the category. It was proposed that the level of risk could be defined by the sponsor and validated by the ethics committees (with the possibility to ask for advice from the competent authority).

- ***Ethical review***: the discussion led to consider that, for clinical trials on medicinal products, the written informed consent should be obtained in every category (with the possibility of a ‘light’ information in case of marketed products under licensed indication, category 3). The question of expedited review has to be confronted with the current practice in the US IRBs, as there is a need for a methodological review, an assessment of the site and a protection of patients’ rights (particularly if there is merely a notification to competent authority), together with the assessment of data quality.

- ***Assessment by competent authorities:*** A notification for category 3 (IMP with MA under licensed indication) would alleviate the workload and particularly facilitate the multinational studies (this is already performed in the UK under the current legislation). By the way, a harmonised definition of IMP is needed.

- ***Safety reporting***: In category 3 (IMP with MA under licensed indication) only few SUSARs are expected, but their reporting to EudraVigilance Clinical Trials Module (EVCTM) remains necessary, however without expedited reporting, only a simplified (focussed on safety findings relevant to this trial) periodic safety report to national competent authorities, ethics committees,

and investigators. For category 2 (IMP with MA in the EU, but under new indication/ population/ condition), there could be a SUSAR expedited reporting restricted to this particular trial from EVCTM to the competent authority in the sponsor's country, and a simplified periodic safety report to ethics committees and investigators. The sponsor can already ask for limited SUSAR reporting from investigators, based on the indication/ population/ condition..

- ***Monitoring:*** There is a need to build guidance on commonly accepted tools to define the risk of an individual study based on the safety of participants (taking among other into account the categories 1-2-3), and also on data integrity, on the robustness of the process at the centres, based on specific items described in a decision tree, and to define risk-based monitoring strategies adapted to the risk level (this is already possible within the framework of the current legislation). The possibilities offered by central supervision should be considered in the context of new information technology systems.

- ***Requirement for a sponsor***: A sponsor is needed for all three categories (however flexible arrangement should be made easier to allow sharing of responsibilities in multinational studies).

- ***Insurance requirements:*** Principally, there should be a change to no-fault insurance coverage as there is not always a mistake detectable, potentially trial-related problems can occur much later as we know from e.g. paediatric trials, and affected trial participants need to receive the coverage quickly (before the question of guilt is decided). For category 3 (marketed products under licensed indication), when the definition of "minimal risk" can be applied, the need for insurance or indemnity was questioned. In case of diagnostic intervention, it could be the role of the ethics committee to make a recommendation regarding the need for an insurance or indemnity coverage (and it seems that the Directive does not explicitly require and insurance). The insurance coverage in clinical trials with marketed products should be provided by national health care systems as it is the case in Italy and Denmark for national academic sponsors. This should be extended to sponsors of multinational studies. For commercial sponsors, insurance packages as implemented in Sweden appear as an appropriate solution. .

- ***Labelling:*** for category 3 (marketed products under licensed indication), we questioned the relevance of the labelling requirement. If it couldn't be deleted, there is still a need for simplified labelling in current legislation as defined in Article 14 of the Directive 2001/20/EC and in Annex 13. Alternative traceability methods should be explored based on the CRF or patient's diary, on pharmacists' or investigators' documentation. For category 2 (IMP with MA in the EU, but under new indication/ population/ condition), simplified labelling or alternative traceability methods should be made possible.

- ***Documentation:*** for category 3 (marketed products under licensed indication), the IMP dossier (IMPD) is restricted to the SmPC that should be accessible and harmonised between countries, with the possibility to cross-refer to other IMPDs. The trial master file (TMF) archiving could be limited to 5 years in case of no application to a marketing authorisation. For category 2 (IMP with MA, but under new indication), the IMP dossier can be the SmPC plus relevant quality and safety data, with the possibility to cross-refer to other IMPDs.

- ***Inspections:*** the priority of inspections should be adapted to the risk categories (which is already done by competent authorities).

TABLE 1

Clinical trials on medicinal products: proposed adaptations of requirements for each process based on participant's risk categories

Process	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
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
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 ?
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

* Flexibility already possible under the current legislation

In addition to these categories, there is a need to define, for each process, guidance and procedures for shared risk management strategies for specific processes (particularly monitoring) in individual clinical trials.

It turns out that a substantial amount of the proposed solutions are already possible within the framework of the current legislation, pending on adaptation of the guidance documents, or of more flexible transposition into national legislation. There is a need for better information and communication on the flexibility offered by the Directive and related guidance.

Conclusion

These proposals could serve as a basis for further discussion that requires in depth exploration of the definition of:

- the boundaries between the proposed categories
- the decision tree for monitoring strategies (that should take into account the hazard to participants, to data integrity, and the robustness of processes at the investigation sites
- what should be light information, and expedited ethical review
- the SUSAR and adverse event reporting requirements
- what is IMP
- labelling requirements for the different categories
- treatment and diagnostic intervention
- what is “minimal risk”
- and the identification of insurance coverage systems both at the national and pan-European levels.