ESR Response
REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
CONCEPT PAPER

May 2011

Introduction

The European Society of Radiology (ESR) is an apolitical, non-profit organisation, dedicated to promoting and coordinating the scientific, philanthropic, intellectual and professional activities of Radiology in all European countries. The Society's mission at all times is to serve the health care needs of the general public through the support of science, teaching and research and the quality of service in the field of radiology. The ESR is the European body representing the radiology profession with over 52,000 individual members and acts as the umbrella organisation of all national radiological societies in Europe as well as Europe's subspecialty organisations in the field of radiology. The ESR is registered in the European Commission's transparency register.

The ESR welcomes the approach by the European Commission to revise the existing Clinical Trials Directive 2001/20/EC.

We want to emphasize that it is essential to develop strategies for accelerating the clinical translation of new (molecular) imaging probes. In the next 10 years, a number of molecular imaging probes are expected to be introduced into clinical practice including probes used for the imaging of metastatic lymph nodes, vulnerable atherosclerotic plaque, macrophages in inflammatory and neurodegenerative diseases (e.g., multiple sclerosis, polyarthritis and osteomyelitis), andnamyloid plaques in Alzheimer's disease. However, many more probes are on the horizon.

At present, the expense of clinical development and the regulatory process are the major rate-limiting step in probe development. The design of molecular imaging probes must take into account pharmacokinetics, biocompatibility and toxicity, on the one hand, and imaging modality sensitivity, speed and resolution on the other. The development process usually produces numerous candidates, of which only a few pass preclinical evaluation with the promise of clinical utility. The most suitable substances have to undergo in-depth toxicological evaluation before clinical trials can even begin. Collaboration between academia, industry, medical societies and government regulators can help to address these problems and streamline probe develop.

An important issue that's missing in this directive is some kind of **Fast Track Development Program** that accelerates the approval of new investigational drugs and probes. Such status should be given to agents that show promise in treating or diagnose serious, life-threatening medical conditions for which no other drug either exists or works as well.
This fast track should be a process designed to facilitate the development, and expedite the review of drugs to treat or probes to diagnose serious diseases and fill an unmet medical need.

The purpose is to get important new drugs and probes to the patient earlier. Fast track addresses a broad range of serious diseases. Determining whether a disease is serious is a matter of judgment, but generally is based on whether the drug or probe will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

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Item-by-item responses

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1. Single submission with separate assessment

Consultation item no. 1: The ESR is in favor of a single submission of the application for clinical trials and agrees with this appraisal.

Consultation item no. 2: The ESR is against an independent separate assessment by each Member State concerned and agrees with this appraisal.

1.2. Single submission with subsequent central assessment

Consultation item no. 3: The ESR would be in principle in favor of a central European assessment of applications for clinical trials, considering that also ethical perspectives may be not so different across European countries and that, in the rare case that "sensitive" trials would be proposed, such differences may be considered and resolved by a well-balanced central authority. However, ESR agrees that – at the present time – this perspective cannot be adopted and that a single submission with a coordinate assessment procedure (CAP) is the best way to deal with this issue, This choice will allow for: a) accelerating and simplifying the initiation of a clinical trial, and b) considering the risk benefit assessment as well as the ethical and local aspects of such trials.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

Consultation item no. 4: The catalogue is complete, even though, in ESR's view, compliance with rules on personal data protection should be shifted in section b), being more related with ethics than with "national" issues.

Consultation item no. 5: The ESR does not agree to include only the aspects listed under a) in the scope of the CAP. ESR makes efforts for harmonization and homogenization of clinical practice of radiology across all the European countries. In this view, clinical trials are a strong tool to promote shared highest levels of good practice, also regarding ethical issues. In this view, we think that ethical issues should be evaluated as much as possible in the CAP context. Moreover, in a historical phase where information on clinicians' profile can be easily retrieved on the Internet, also the suitability of the investigator (first point of list c) could be evaluated within the CAP context. Thus, only suitability of clinical trials sites and insurance issues should be left to a local ("national") evaluation.

Consultation item no. 6: The ESR is in favor of the second option: Member States concerned vote on the issue and decide by simple majority.

Consultation item no. 7: The ESR considers CAP as mandatory for all multinational clinical trials. In principle, in the ESRs view of homogenization of clinical research in the EU, we would be in favor of mandatory CAP for all clinical trials, including those performed only in one individual Member State. However, at the present time, this would create a huge amount of work for the EU institutions. Thus, a preliminary phase of CAP mandatory only for multinational trials can be adopted.

Consultation item no. 8: The point (b) of the proposed pre-assessment is quite difficult to work in practice. How the CAP people can define that an additional risk is “insignificant”? We strongly discourage the use of this term in this context. In fact, in clinical research, “significant” and “not significant” are terms always related to statistical analysis. However, depending on the sample size, a finding can be statistically significant but not clinically relevant. We suggest correcting “insignificant” into “not clinically relevant”. However, this change of terms does not solve the problem consisting in the need of a wide spectrum of specialized clinical expertise within the people who will have to do a CAP. This problem deserves high attention by the EU institutions. The ESR is ready to assist EU offices when radiology is involved in clinical trials, also when radiological or imaging procedures are used “only” as surrogate end-point for the efficacy of drugs, as is commonly for research concerning anticancer drugs.
Notably, It is crucial that the time line for low-risk clinical trials is shortened, which can be identified in a pre-assessment procedure. It should be shorter than the suggested 60s days (e.g. below 30 days). Also a tacit approval for these low risk clinical trials is conceivable.
Better adaptation to practical requirements and a more harmonized, risk-adapted approach to the procedural aspects of clinical trials
The harmonization, simplification and clarification of the rules for all clinical trials is a very good and important approach but special attention should be paid at the collaboration between academia and industry. There is a need for a special status for clinical trials done under the umbrella off academia and industry. These collaborations will a motor to drive the research in the future. Therefore the clinical trials directive should have special rules for this kind of collaboration e.g. see below fast track development programs, but also the option for multiple sponsorship and not only for a single sponsorship

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1. Limiting the scope of the Clinical Trials Directive

Consultation item no. 9: The ESR agrees with this appraisal.

Consultation item no. 10: The ESR agrees with this appraisal.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item no. 11: The ESR agrees with this appraisal.

Consultation item no. 12: In the ESR's view, there is a key aspect concerning clinical radiological research which presents peculiar aspects to be addressed: the research on the use of contrast materials for clinical indications different from those for which an initial authorization has been obtained. As a matter of fact, radiological clinical practice is characterized by a relatively large off-label use of such medicinal products, in particular for contrast-enhanced magnetic resonance imaging and ultrasound. This a particular area for which the EU should stimulate high-quality research, considering these trials as "Type A, low-risk trials".

2.3 Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item no. 13: The ESR agrees with this appraisal.

2.4. Insurance/indemnisation

Consultation item no. 14: In the ESR's view, "low or minimal risk" is absolutely different from "no risk". This statement is thought with reference to very rare events such as fatal reactions to intravascular administration of contrast materials. As a consequence, while we strongly support the idea of an easier procedure for low- or minimal-risk clinical trials, we are also in favor of well-adapted insurance/indemnization rules also for those trials.

2.5. Single sponsor

Consultation item no. 15: The ESR does not agree with this appraisal. Option 2 is preferable: multiple sponsorship/joint sponsorship/shared sponsorship should be possible, especially in order to make trials sponsored by multiple academic institutions possible across European countries.

2.6. Emergency clinical trials

Consultation item no. 16: The ESR agrees with this appraisal. It is important to make European clinical research in the emergency setting easier to be planned and performed. This is relevant for getting data on the use of contrast-enhanced imaging procedures in the emergency setting from randomized controlled trials.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: The ESR agrees with this appraisal: results of clinical trials performed in third countries should be accepted for EU marketing authorization only if the trial has been registered in the EudraCT.

4. FIGURES AND DATA

Consultation item no. 18: No other data to be added.

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