Multidisciplinary Workshop on

Research Ethics Committees and Ethical Review in Europe

19th January 2010, Barcelona, Spain

On behalf of the "Road Map Initiative for Clinical Research in Europe"

FINAL REPORT

Introduction:

Research ethics committees (REC) play a central role in the quality of clinical research, protection of the participants and reliability of the results. Based on the Declaration of Helsinki and the ICH-Good Clinical Practice guidance EU Member States (MS) introduced a REC system that fitted their national needs and expectations. Although the Directive 2001/20/EC (CTD) gave provisions for a better harmonisation of their practice between MS, including the single opinion per MS, inconsistent provisions and divergent implementation in the MS resulted in a suboptimal situation:

- Single opinion has not been achieved in all countries
- Requested application dossier content is different in all MS
- In many countries the application dossier has to be provided to all ECs involved in the review – with several copies
- Content of the review is different and of different quality
- Requirements for IC content, liability insurance conditions, site assessment etc. vary from country to country
- Outcome of the ethical review varies from MS to MS
- Integration of different additional requirements in multi-national trials and related substantial amendments prolongs the trial preparation process
- Responsibility for elements to be reviewed by RECs and competent authorities varies from MS to MS
- Safety reporting requirements vary in the MS, overwhelm the RECs and block their capacity
- RECs do not have the capacity nor know-how and tools to judge on the risk-benefit ratio changes in a trial based on the SUSARs they receive
- The quality of the REC organisation and the ethical review is not in all countries ensured
- The required expertise of the REC members, especially for complex IMPs and trials, is not in all MS ensured

The result is that the ethical review process especially in multi-national trials is extremely complex and burdensome; that most RECs are overloaded with administrative tasks and have not enough capacity to focus on their key obligations; that the preparation of multi-national clinical trials is longer than before implementation of the CTD; the costs for the review have increased; and the protection of the trial participants is not improved.

The participants of the Workshop agreed that there is high need to truly harmonise and facilitate the ethical review process, to ensure an equally high standard of the ethical review in all MS, and to improve the protection of the trial participants.

Objective of the Workshop:

The European Commission is currently considering the possibility to revise the clinical trials legislation. The objective of this Workshop was to identify those areas in the ethical review that might need improvement and to provide constructive suggestions for a more efficient and reliable ethical review system in Europe, especially for multi-national clinical trials with IMPs, preserving participants' protection and data quality but improving the scientific competitiveness of Europe in clinical research and fostering its attractiveness for clinical trials. In addition, constructive proposals for the ethical review in two particularly difficult conditions were elaborated: clinical trials in patients temporarily unable to consent and on clinical trials in developing countries.

Executive Summary: Broad Conclusions and Options

- Harmonisation of the ethics review system in Europe would be facilitated by an efficient networking of ethics committees.
- It would be desirable to agree on an electronic application dossier format with the same content in all MS.
- The submission process could be further facilitated by a common electronic submission dossier for RECs and competent authorities (CA).
- The quality and transparency of the ethical review should be harmonised by standardised training of REC members and accreditation of the REC.
- The interaction between investigative site and the responsible local REC in single centre early phase trials should be intensified
- For multi-centre national trials the current single opinion system should be maintained, respectively implemented in MS where this is not yet the case.
- For multi-national clinical trials with IMPs the possibility for a single opinion on EU level should be further explored. Possible options could be:
    - One or several central European REC to review the general ethical, scientific and methodological aspects of the protocol and to incorporate the national input on IC and site assessment
    - General ethical, scientific and methodological review of the protocol by a qualified national REC that ensures the input from all other involved national REC on IC and site assessment. Mutual recognition of this lead opinion in all MS.
- To enable acceptance of a European single opinion system it would be necessary for particularly difficult ethical questions with very different opinions between the MS like e.g. on stem cell research, that consensus on the issues relevant in clinical trials should be sought through a pan-European consensus process amongst experts.
- To avoid duplication of review of the same documents, the responsibilities between RECs and CAs should be clearly defined.
- In case a risk-based approach to oversight of clinical trials would be introduced the REC should decide on the risk level to be applied.
- Expedited SUSAR reporting to RECs should be abandoned, with exception of expedited reporting of SUSARs in early phase single centre trials to the responsible local REC. REC should receive Annual Safety Reports and have access to the EudraVigilance database.
- The role of Safety Data Monitoring Boards in ongoing supervision of the risk/benefit ratio in clinical trials should be strengthened.

- Informed consent procedure in clinical trials in patients temporarily unable to consent should follow the national legal requirements in the MS but a harmonised European approach should be encouraged.
- Clinical trials in developing countries should be performed under the same rigorous ethical standards as in developed countries; to avoid exploitation, only trials that fit the standard of care and the conditions for possible follow-on treatment and that can be of benefit to the local population should be performed there.

The Background:

The first point on the agenda was the question whether there is a **need for a centralised ethical review at EU-level for multi-national clinical trials**.

Christiane Druml from the Ethics Committee of the Medical University of Vienna, Austria, presented the broad variability of ethical review systems in Europe and the difficulties in several countries to come to a single opinion per MS. She referred to the well-known deficiencies in the current system as described in the Introduction and defined the elements of a well functioning REC system like a common mission, training of REC members, member appointment standards and transparency, acceptance of payment of members, common IC format, quality assurance (incl. accreditation), and an appeal system as basis for the establishment of a harmonised system.

Rokus De Zeeuw from BEBO Assen, The Netherlands, calculated that a single CTA and a single ethical review in a multi-national trial would reduce the workload for sponsors up to 75%. The most efficient system, however, in his view is the Dutch system where the complete dossier including the IMPD is solely reviewed by a well-trained, competent REC. This system has also been recommended as the most efficient by the "High Level Group of Independent Stakeholders on Administrative Burdens" (the "Stoiber-Group") of the European Commission. Prof. De Zeeuw pointed out that in such a single opinion system the assessment of the local feasibility by local institutions could cover the need for respect of cultural/religious differences. However, most of the discussants in this topic felt that the two-tier system of the current EU system with parallel review by CA and REC would be preferential to ensure optimal competence for the aspects to be reviewed.

The second topic for discussion was on **how to avoid duplication of evaluation efforts** as this is clearly a waste of resources in the current system, especially in multi-national trials.
Chantal Bélorgey from the French AFSSAPS proposed a single submission dossier for all CA involved in a multi-national trial and one for all REC as the basis for well divided responsibilities and raised the question whether it could not even be possible to agree on a common dossier for both parties. (N.B: Such a common dossier is already in place in the UK, entered electronically by the sponsor into "IRAS"). In such a system the responsibility for subject protection, CT relevance/suitability of design and methodology as well as the suitability of the site(s) should be with the REC and the CA should review the elements on IMPs and subject safety (incl. dose, comparator, and pharmacovigilance data). She encouraged the participation of RECs in the Commission's "CTA Ad hoc Working Group".

Xavier Carné from the Hospital Clinic I de Barcelona added that – should a risk-based approach to clinical trial oversight be established in a new regulatory system

– the REC would be the suitable organisation to judge on the risk level to be applied.

In his own presentation on the topic of avoidance of duplication of review efforts Prof. Carné raised the question whether there are really differences of opinion between Barcelona and Helsinki of what constitutes an ethical protocol. The standards provided by widely accepted guidances like the Declaration of Helsinki, ICH-GCP, etc. cover most of the ethical issues in clinical trials. The very few differences in cultural settings seem not justify the enormous effort of parallel reviews and the delay of important trials. He proposed a system with

- Single local REC opinion for mono-centre trials
- Single national REC opinion for multi-centre national trials
- Single EU-wide REC opinion for multi-national trials with national REC input (with exception of highly controversial topics like stem cell research, etc.)

Such a system would require the Europe-wide implementation of well functioning REC systems as described by Dr. Druml, the establishment of common ethical review practices and an agreement on application dossier content and Informed Consent format. Such a common dossier would have to be in English with national translation of the cover letter, the protocol summary, Module 2 and Informed Consent documentation.

Janet Wisely from NRES, UK, presented the English experience with the **improvement of ethics committee practices**. Four areas turned out to be most important and the way NRES deals with them could be exemplary for other countries:

1. *Transparency* to increase public confidence and to facilitate ethical research can be enhanced by publication of the opinions on the NRES web page
2. *Coordination and harmonisation* can be improved by SOPs, described and monitored standards and implementation of a well functioning application system
3. *Training* to achieve robust and informed review by all RECs includes a mandatory introduction training as well as ongoing training of REC members and operations staff
4. *Quality assurance and accreditation* were implemented against some original resistance but measures like audits, shared ethical debates, user feedback and decision analyses proved to be very helpful in raising the overall ethical review standard in the UK.

The fourth topic of the day was the **involvement of RECs in the ongoing risk/benefit evaluation of clinical trial**s.

Petra Knupfer from the Ethics Committee of Ärztekammer Baden-Württemberg, Germany, made clear that multiple reporting of SUSARs does not improve the safety of participants. In fact, no REC can really handle appropriately the huge number of SUSARs reported to them and decide on a potentially changed risk/benefit ratio in the trial and the overall safety of the IMP. And Dr. Knupfer argued that this, in fact, does not lie in the CTD's intention: RECs are interdisciplinary expert committees that are supposed to give opinions on the acceptability of a trial for the participants but the assurance of the IMP's safety is a sponsor obligation that needs to be centrally supervised by the competent authorities. She recommended to ultimately stop expedited SUSAR reporting to REC

and instead to provide the REC with Annual Safety Reports, SUSAR line listings every 6 months and only information on true changes in the risk/benefit ratio within 15 days. Until such new approach can be implemented, however, Dr. Knupfer encouraged national legislators that we should do in all MS what the current guideline version allows: only expedited reporting to REC of those SUSARs that occurred in the own country.

Beat Widler from Roche, Switzerland, supported these requests. He argued that the current SUSAR reporting system with proactive information of every organisation involved in a trial (partly even with paper copies) is anyway a dinosaur stemming from before the digital age and should be principally overhauled. Responsibility for benefit and risk in a trial has to reside with the sponsor and can be supervised in inspections. He encouraged all players in a clinical trial to utilise more intensively and creatively the flexibility provided in legislation.

Rokus De Zeeuw, however, argued that the local REC needs to stay closely informed on SUSARs occurring at that site to be able to support and advice the local investigator. This seems to be particularly important for early phase, single centre trials.

Chantal Bélorgey emphasised on the need for better signal detection and requested the adequate resources, tools and collaboration between EMA, national CAs and sponsor to ensure the safety of trial participants without double review of actual safety information.

When REC are requested to approve substantial amendments it may be necessary to judge on a new risk/benefit ratio in the trial. Especially in this case it might be helpful for REC to receive access to the EudraVigilance database.

Xavier Carné would like to see a more important role of Data Safety Monitoring Boards for the safety of trial participants. They consist of experts with access to the complete safety information available in a Pharma company and are therefore in the best position to evaluate the safety situation and potentially stop a trial.

Jan Geissler from ECPC, Germany, raised the request to systematically include patients into REC to enable a more adequate risk/benefit assessment and to improve the information to participants. He agreed that patient members in REC would need training and financial support to be able to fulfil their role optimally but patients can more authentically judge on the conflict between the need for research on new treatments and the risk or burden for the individual participant and this important knowledge should not be neglected in the attempt to improve the safety in clinical trials. Obviously, in several countries positive experience has been made.

The fifth topic of the Workshop was the **ethical conditions for clinical trials in temporarily incapacitated patients**.

François Lemaire from Hôpital Henri-Mondor, Créteil, France, pointed out that this research in intensive care and emergency research is particularly needed but rarely done because of the complexity of the informed consent process. Very different solutions have been worked out in different countries making multi-national trials nearly impossible. These approaches reach from waivers to consent (Denmark, Belgium, Netherlands, France, Spain, Norway) to permission for a doctor to act as the legal representative (UK) or a legal representative assigned by a judge (Germany) to no clarification at all (Italy, Poland, Portugal). Harmonisation of the approaches is therefore urgently required.

Elmar Doppelfeld from the Permanent Working Party of German REC presented the conditions for this type of research developed from the thinking in the Convention of Oviedo and the earlier versions of the Declaration of Helsinki to its latest version of 2008:

Oviedo Convention, Article 2: The interests and welfare of the human being shall prevail over the *sole interest of society or science.*

Declaration of Helsinki, 2008, Article 6: In medical research involving human subjects, the well-being of the individual research subject must take precedence over *all other interests.*

This is of particular relevance for patients unable to consent. This means that this type of research can only be performed if there is direct benefit to the patient or at least only minimal risk and burden.

Professor Doppelfeld recommended for research in this vulnerable patient population today to follow the national law, if there is one, or to consult professional bodies like CA or REC to identify an acceptable approach. However, on the long run, he also supported the implementation of a European regulation for this type of research and recommended to contact the European Commission and the Council of Europe to initiate the process.

The sixth topic of this Workshop was the **role of REC in clinical trials performed in developing countries**. Clara Menendez from the Centre de Recerca en Salut Internacional de Barcelona, Spain, reported of the particular need and ethical problems of clinical trials in developing countries and requested that research in those countries should be performed with the same rigorous ethical standards as in European countries. This has to take into consideration that there is a potential for exploitation if patients take the risk of participating in trials but have no chance to get access to the new treatment afterwards or if there is no appropriate standard of care available to them because basic drugs, equipment or personnel are not accessible. Therefore, only trials that fit the standard of care and the conditions for possible follow-on treatment and that can be of benefit to the local population should be performed in these countries.

The **final discussion** focused on the conditions for a single European opinion for multi-national clinical trials. It became clear that, although a single ethical review for a multi-national clinical trial with national input would be the most efficient approach for multi-national clinical trials but today the national differences in ethical review procedures and content, REC systems, REC member knowledge as well as philosophical/religious viewpoints on complex topics like stem cell research, pre-natal diagnostic, vulnerable populations or contraception in clinical trials make it very difficult to even imagine national acceptance of a single European vote. Several Workshop participants argued that ethics is an analytical method to identify what is right and wrong and that is a regional decision influenced by culture, religion, history and philosophical standpoints of a society and therefore, the current national responsibility for ethical review in clinical trials should remain. But as the rapid development of new treatments through efficiently performed clinical trials is also constrained by the complexity and related costs of the ethical review process, the Workshop participants discussed the possibilities for a step-wise approach to more harmonisation and facilitation:

- Of fundamental importance would be harmonised, efficient training for REC members in all MS, and the implementation of quality management in REC, supervised by an accreditation system in all countries.

- A multi-national expert group, e.g. created by DG Research, could try to find consensus in the above mentioned complex ethical topics as far as they are relevant for the performance of clinical trials.
- The agreement on common content of the application dossier in all MS would be an important step forward, hopefully leading the way to a common application dossier for REC *and* CA in a common database (Janet Wisely offered to provide the English "IRAS" to other countries and/or the EU).
- A single ethical opinion in multi-national clinical trials could be achieved by
    - one or several central European ethics committees (in the 90ies the EERC = European Ethical Review Committee, consisting of clinical research experts from different MS, provided a "pre-opinion" for complex multi-national trials that helped the sponsors to prepare a final protocol that was acceptable to the national ethical reviews), or by
    - mutual recognition of the vote of a competent (accredited) national REC in one of the MS involved in the trial (e.g. in the country of the sponsor)

  In both cases national input at least on Informed Consent and site assessment would have to be ensured from national REC.
- The recommendation was made to establish a multi-national expert group that could work out the best approach to a single ethical opinion in multi-national trials, based on trust, looking for communalities and optimised communication, and strong common interest in providing safe new treatments to patients faster.
- An important facilitation aspect in a new system could be the implementation of a risk-based approach to the extent of ethical review and oversight. Risk criteria would have to be defined and would need to apply to both the ethical *and* competent authority review as far as IMPs are concerned. The decision on the risk level to be applied should be made by the sponsor and approved by the REC.