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Report of the 1st Meeting of the "Vienna Initiative to Save European Academic Research (VISEAR)"

organised by the

Medical University of Vienna

Department Ethics in Medical Research

in collaboration with the

European Forum for Good Clinical Practice (EFGCP)

Vienna School of Clinical Research (VSCR)

European Clinical Research Infrastructures Network (ECRIN)

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Bericht des ersten Treffens der „Vienna Initiative to Save European Academic Research (VISEAR)“ – Wiener Initiative zur Förderung der Europäischen akademischen Forschung

Zusammenfassung. Die EU Richtlinie 2001/20/EC („Clinical Trials Directive“) hatte zum Ziel die klinische Forschung in den Europäischen Mitgliedsstaaten zu „vereinfachen und zu harmonisieren“. Dieses Ziel wurde jedoch nur zum Teil verwirklicht. Die Auswirkungen auf die akademische Forschung in Europa, vor allem für multizentrische länderübergreifende Projekte, brachten zum Teil einen gegenteiligen Effekt. Einzelne Gebiete sind besonders betroffen: Die Frage, wer Sponsor einer klinischen Prüfung sein kann; das Verfahren bei den Ethikkommissionen; der Einschluss von temporär nicht einwilligungsfähigen Patienten in klinische Prüfungen; ein öffentlich zugängliches Register für klinische Prüfungen in Europa; verschuldensunabhängige Versicherungen für die Teilnehmer an klinischen Prüfungen und der Problemkreis der Pharmakovigilanz.

Die bürokratischen Anforderungen haben durch die neuen Regelungen – die EU Mitgliedsstaaten waren verpflichtet bis Mai 2004 die EU Richtlinie in nationale Gesetze umzusetzen – extrem zugenommen ohne dass das den Schutz der Patienten oder Probanden verbessert oder den wissenschaftlichen Gehalt der Prüfpläne erhöht hat. Für die industrielle Forschung bedeutet das weniger Probleme als für akademische Forscher, die nicht über personelle Ressourcen und ein länderübergreifendes Netzwerk verfügen. Damit ist die Durchführung großer akademischer Studien in Europa gefährdet, was zu einer Reduzierung der Anzahl an multizentrischen Studien führt und in weiterer Konsequenz zu einer Reduzierung der Teilnehmerzahlen. Letztlich sind die Europäischen Patienten und die Europäische Forschung die Leidtragenden einer derartigen Entwicklung.

Die „Vienna Initiative to Save European Academic Research (VISEAR)“ bringt Experten aus den verschiedensten akademischen Forschungsgruppen und internationalen Organisationen sowie aus Industrie und Behörden zusammen um die betroffenen Themenkreise zu diskutieren und Vorschläge für eine Verbesserung auf den Gebieten der Organisation, Durchführung und der Finanzierung von nicht industriell gesponserter klinischer Forschung zu erarbeiten. Ein erster Schritt war ein Treffen im Mai 2005 in Wien. Die einzelnen sechs Arbeitsgruppen hatten im Vorfeld die Themen definiert, Resumés erarbeitet und diese anschließend im Plenum diskutiert. Das Ergebnis dieser Veranstaltung wird in zwei Teilen präsentiert: ein Report über die Gesamtveranstaltung mit den Resumés der einzelnen Arbeitsgruppen sowie ein selbständiges position paper mit den Empfehlungen für die Forschung an temporär nicht einwilligungsfähigen Patienten.

Summary. The European Directive 2001/20/EC (“Clinical Trials Directive”) was aimed at simplifying and harmonising European clinical research. The Directive’s attempt represents an important step because many European Member States lack national laws that specifically address details of research, but the goal has been only partly achieved. For academic investigators doing national or multi-national research the new European law and the requirements following its implementation are likely to have the opposite effect. Some areas seem to be of particular concern: trial sponsorship, the ethical review process, the participation of patients who are temporarily not able to consent in clinical trials, in particular the informed consent process, an accepted European registry for all clinical trials, insurance and pharmacovigilance. Furthermore there are fundamental problems of the conduct of clinical trials that could have been foreseen at the time of implementation of the new law, which are impeding academic basic clinical research.

The bureaucratic burden for academic investigators has tremendously increased without representing any contribution to patients’ safety or to the scientific value of research. Furthermore some large European academic trials cannot be conducted anymore due to the new regulations. This results in a reduction in the number of trials and additionally in a reduction of the number of patients enrolled in a study. European research and thus European patients will suffer from the loss of potential benefits of research.

The Vienna Initiative to Save European Academic Research (VISEAR) brings together leading stakeholders from academic research groups and interested parties from industry, international organisations and regulatory authorities to focus on the issues of concern regarding the organisation and funding of academic clinical research in order to improve the development and use of medicines in Europe. The first step of the initiative was a meeting held on May 30, 2005 in Vienna. The resumés of the six parallel working groups are presented in this supplement of the Wiener Klinische Wochenschrift, a position paper with recommendations in relation to the EU Clinical Trials Directive and medical research involving incapacitated adults has been published separately.

Key words: European Directive 2001/20/EC, clinical trials, academic research, sponsor, ethical review, informed consent, incapacitated patients, clinical trials registry, insurance, pharmacovigilance.

Vienna Initiative to Save European Academic Research (VISEAR)

The European Directive 2001/20/EC was aimed at simplifying and harmonising European clinical research in order to increase competition. The Directive's attempt represents an important step because many Member States lack national laws that specifically address details of research, but the goal has been only partly achieved. For academic investigators engaged in national or multi-national research the new European law and the requirements following its implementation are likely to have the opposite effect. Several areas seem to be of particular concern: trial sponsorship, the ethical review process, the participation of patients who are temporarily not able to consent in clinical trials, in particular the informed consent process, an accepted European registry for all clinical trials, insurance, and pharmacovigilance. Furthermore there are fundamental problems of the conduct of clinical trials that have been foreseen at the time of implementation of the new law but are impeding academic basic clinical research.

The bureaucratic burden for academic investigators has tremendously increased without representing any contribution to patients' safety or to the scientific value of research. Furthermore some large European academic trials cannot be conducted any longer due to the new regulations. This results in a reduction in the number of trials and additionally in a reduction of the number of patients enrolled in a study. European research and thus European patients will suffer from the loss of potential benefits of research.

Objectives

The Vienna Initiative to Save European Academic Research (VISEAR) brings together leading stakeholders from academic research groups and interested parties from industry and regulatory authorities to focus on the issues of concern regarding the organisation and funding of academic clinical research in order to improve the development and use of medicines in Europe.

A first step of the initiative has been a meeting in Vienna on May 30, 2005. 5 working groups had already been established ahead of time to prepare the discussion of the single identified subjects. The working groups assembled and agreed on a resumé and proposed solutions. In the afternoon, these resumés were presented by the rapporteurs and discussed by the plenary. The plenary discussion was chaired by Johannes Huber, chair of the Bioethics Commission at the Austrian Federal Chancellery.

Workshop 1 – Clinical Trial Sponsorship

Chairperson: Christian Ohmann, ECRIN, Germany
Rapporteur: Brian B. O'Neill, EFGCP Clinical Trial Sponsorship and Management Working Party & Roche Pharmaceuticals, Switzerland
Discussants: Christoph Aufricht, Medical University of Vienna, Austria; Ralf Herold, Charité, Germany; Peter Placheta, Pharmig, Austria; Helmut Schuh, Pharmig, Austria; Andreas Zoubek, CCRI St. Anna Children's Hospital, Austria

Introduction

With the implementation of Directive 2001/20/EC, and its sometimes divergent interpretation by national Competent Authorities in its transposition to local law, European research institutions have met new challenges with regard to the sponsoring and management of especially non-commercial clinical trials. The impact of such challenges may well vary in line with the variety of such academic institutions, their location, infrastructure, and their relationships and collaborations with each other and/or industry initiated clinical research, and other supporting/sponsoring bodies. For example, such a variety of academic institutions will range from universities, university hospitals performing national or international studies, and with varying sophistication of infrastructure up to and including larger multinational collaborative groups/study management organizations (SMOs). These academic research institutions may be supported and sponsored by national/transnational research networks and/or other non profit organizations. Such academic researchers are not only interested in industry sponsored clinical trials but also and importantly in non commercial trials and publication of studies which are of public interest and may be publicly funded. These latter may include studies in e.g. mechanisms of diseases, independent evaluation of treatment strategies, off-label use (important in e.g. Oncology), or orphan drug development.

While it is clear that such trials may also be important to the pharmaceutical industry for obtaining essential information related to the safety and efficacy of their products there may be also other priorities for them related to specific trials for new drug applications, novel indications, or novel dose regimens which will impact on the level of support which they can offer to academic researchers at any particular point in time. Industry involvement may, therefore, range from the provision of an unrestricted grant for non specific trial activities to full industry involvement as sponsor of the clinical trial. Notwithstanding the possible level of industry participation there should be a positive and competitive environment for academic researchers to conduct the above specified non commercial studies for the benefit of patients in Europe

and without dependence on industry. Without such an environment there is no doubt that fewer such public sponsored and investigator sponsored non commercial trials will be conducted thus denying possible improved therapies and therapeutic regimens to patients in Europe and decreasing the competitiveness of academic research in Europe.

This report summarizes the concerns and suggestions of academic researchers as expressed related to the sponsorship and management of especially non commercial clinical trials. It aims to cover issues which have arisen, and can arise, in the context of the implementation of Clinical Trials Directive 2001/20/EC, GCP Directive 2005/28/EC, and any specific national modalities documents as referenced in these latter Directives, and including those which may be solely related to non-commercial clinical trials presently under discussion at the EU Commission and by the individual Competent Authorities.

The main areas addressed in this paper are:

a) Allocation of sponsor responsibilities and requirement or not for a single sponsor in the EU;
b) Specific concerns related to the conduct and management of clinical trials;
c) Proposed solutions for addressing the concerns raised.

Allocation of sponsor responsibilities and requirement or not for a single sponsor in the EU

There is a lack of clarity related to the requirement or not for a single EU sponsor for especially non commercial, non-regulatory, clinical trials, and more particularly how such a requirement is being, or will be consistently interpreted by individual Competent Authorities. Certainly, a rigid single sponsor model more suited to Pharma industry sponsored regulatory trials may not be suited to academic researchers conducting national/international collaborative trials where e.g. single centre availability of specific patients may be an issue. Such rigidity in approach, or indeed any misperception related to this, has discouraged, and will discourage, potential sponsors from accepting formal sponsor responsibility since they themselves may not have the entire necessary infrastructure to take on all the sponsor responsibilities and/or would need time to implement such a complete infrastructure.

There is thus a real need for clear and consistent guidance from the regulators related to how and if sponsors of non commercial trials may meet the Directive's relevant requirements through documented allocation of sets of sponsor responsibilities and legal liabilities based on availability of adequate infrastructure and expertise. Only with such clear guidance will public funding agencies, national research bodies, academic institutions and/or investigators feel comfortable about taking on their respective roles.

It must be clear, however, that even if/when such allocation of responsibility/liability may be allowed a named person must take on each and every legal responsibility of the sponsor. Where tasks related to any sponsor responsibility may be delegated because of lack of specific competencies by the sponsor, the latter still maintains overall responsibility for such tasks and their oversight.

Specific concerns related to the conduct and management of clinical trials

Academic researchers involved in regulatory trials sponsored or supported by industry are well familiar with the requirements necessary in order to conduct and manage these trials according to Good Clinical Practice (GCP). In such cases the management of these trials (monitoring, Adverse Event management and SUSAR reporting, data management, investigational medicinal product (IMP) handling etc.) is normally the responsibility of the industry sponsor, and the academic researcher can normally depend on the latter to provide the necessary support required for the appropriate conduct of the study according to the relevant EU Directives and national legislation. In the case of non commercial clinical trials conducted by academic researchers without the participation of industry the same GCP requirements apply. EU regulators have recognized particular challenges for academic researchers conducting and managing non-commercial clinical trials, and have indicated their willingness to consider waivers to specific GCP conditions as long as patients' safety, legal, and ethical rights are guaranteed, and GCP principles are applied. It must be emphasized here that the principles of GCP apply to all clinical trials, non commercial as well as commercial but what is recognized is that for certain non commercial trials certain of the details of GCP may be unnecessary or guaranteed by other means. Examples given of where such waivers may be applicable relate to manufacture and import of IMP, and documentation to be submitted and archived as part of the trial master file. These waivers will be described in Modalities documents presently under discussion between the EU Commission and individual member states.

It is important therefore, that at this time academic researchers consider, in the context of their infrastructure how these and other aspects of GCP detail related to trial conduct and/or management may be guaranteed by other means. For example, the introduction of rigid approaches to monitoring and pharmacovigilance more applicable to early stage development and regulatory trials may not be appropriate to many non commercial trials on marketed products which are conducted by academic researchers. Requirements must be sought and adopted which are fit for purpose, appropriate to the risks of a particular study, and which will allow acceptable adaptation of the management of a trial depending on trial type and level of risk (e.g. local validated arrangements for Quality Control/monitoring). Consideration must be given to the cost implication of monitoring in non-commercial trials and if/how these may be defrayed by the public health care system.

Pharmacovigilance should be sensibly focused on SUSAR reporting to Eudravigilance after appropriate testing and training.

Concerns related to the supply of IMP to study patients need to be addressed. Guidance is needed as to when access to marketed IMP on same basis as routine treatment may be acceptable and when not. Acceptable methods need to be described for purchasing IMP which are fair and will not put undue burden on either investigator or patient.

Proposed solutions

a) There is a need for guidance from both the EU Commission and Competent Authorities which will provide clarity and especially consistency of interpretation on:
   - Acceptability of allocation of sponsor legal responsibilities and liabilities among a group of academic researchers. There are already examples of divergent interpretations of this aspect in the transposition of the EU Directive 2001/20/EC into local law;
   - Adaptation of the management of a clinical trial depending on trial type and level of risk;
   - Details of GCP which may be guaranteed by other means and taking due cognizance of measures normally implemented in national health care systems or in overlapping patient care structures;
   - When access to marketed IMP on same basis as routine treatment may be acceptable and when not.

b) Modalities documents should be discussed and prepared by individual Competent Authorities which are consistent and harmonized across the Member States.

c) Support structures should be set up to develop a GCP framework and conduct training sessions for academic researchers. This support could be provided either by national research or government agencies or by other independent groups sponsored by national governments or the EU Commission.

d) Governing bodies of academic research institutions need to give serious consideration to funding and infrastructure required for the conduct of clinical studies in their institutions and to the possible need for greater selectivity and prioritization of studies.

e) National "contacts" representing academic researchers should formally input to Competent Authorities and the EU Commission. This would be particularly important during the development of the Modalities documents by independent Competent Authorities.

f) Academic researchers should assure a concerted approach by linking into related initiatives by all stakeholders in different countries.

Workshop 2 – Ethical Review

Chairperson: Christiane Druml, Medical University of Vienna, Austria
Rapporteur: Francis P. Crawley, EFGCP, Belgium
Discussants: Xavier Carne, University Hopital Barcelona, Spain; Asta Cekanauskaite, Bioethics Committee, Lithuania; Silvio Garattini, Mario Negri Institute Milano, Italy; Jozef Glasa, Slovak Medical University Bratislava, Slovak Republic; Marcel Kenter, Central Committee on Research Involving Human Subjects, The Netherlands

Introduction

The European Directive 2001/20/EC has not given detailed guidance as far as the composition, the working procedures and other relevant structures of ethics committees are concerned. Although the time frames are determined, many other features of ethical review remain in the regulation of the Member States, and even within the different Member States there might be a variety of different types of ethics committees. In some Member States there is particular emphasis on the participation of lay members without abandoning the requirement for ethics committees that one important aspect of the review is the evaluation of the scientific content of the protocol. There is no European wide ethical review procedure for multinational trials. This poses a genuine problem for multinational ethical review for academic infrastructures and investigators conducting multinational research in Europe.

Discussion

What are the similarities and differences between academic and industry-initiated research? Both should strive for the same level of excellence in patient protection. Both should be submitted to the same level of excellence in ethical review. There might be some differences in content, but those might give rise to more procedural ethical problems rather than substantial ethical problems. Both academic and industry research need competent and independent ethical review.

Academic and industry research need each other. However industry could play a more active role in helping academic research to survive. The Directive and its regulations are aimed at industrially driven research taking a new drug through the development process. There has to be more consideration for the vast majority of academic trials which are dealing with registered (old) drugs and involving only minor risks for the participants. One major problem which affects academic researchers much more than the industry is the diversity of the European ethical review system. The additional lack of transparency makes matters worse. The ideal would be a European-wide single opinion, but the members of this working group agree in the discussion that that seems at this point not realistic. The working group is hoping that this would be a topic for the future. Every Member State has different regulations about which committee is the competent Ethics Committee responsible for the decision on a clinical trial. There is wide ignorance among the investigators that such diversities exist. There is no document which informs about such matters. This is a severe handicap for Europe wide research.

The requirement for the "single national opinion" in Article 7 of the Directive leads to even more heterogeneity among the Member States. National systems, which already had a requirement for a single national opinion for multicentric clinical research, had no difficulties in implementing this Article of the Directive, whereas in other

Member States the "local" ethics committees did not want to give up influence over the protection of "their" patients and exercised political pressure to keep matters as they were. Ongoing regionalisation of country and government as for example in Spain lead to separate regulations of ethical review in order to maintain control over their local healthcare facilities and budgets. The actual situation in Europe is a cemented system full of variances with the idea of the Directive which becomes increasingly difficult to handle.

This situation is not a special problem for academic research, it applies to industrially sponsored research as well. But whereas the industry has personnel resources, legal and regulatory departments which can easily deal with such issues, the academic researcher and the scientific societies which operate on an international level do not have the means to investigate these bureaucratic details, information usually only available in the national language and not in English, nor do they have the means to comply with often contradictory requirements.

Conclusion

The working group agreed on the following issues: There is a necessity to establish

1. an information centre on ethical review standards and procedures in each Member State
2. the development of education programs across Members States
3. coordination and interaction between ethics committees at the European-level

Additionally the working group expressed concern that if the registration authority becomes the same authority for all clinical research, they will make the same requirements for academic trials as for industry trials. The high requirements that are expected for a drug to be registered need not be applied in all clinical trials.

- Ethical review is especially a problem in academic research regarding the following issues
  - Bureaucracy
  - Liability/insurance
  - Costs/Time
  - Lack of communication
  - Differing situations in different countries and lack of communication between the countries
  - Quality assurance
- Ethics committees play an important role in the communication between academic and industry research; they help to provide common standards for science and ethics
- There are some principles that should be observed in addressing the problems:

The principles

- There needs to be a legal and regulatory backing
- There should be sufficient funding
- The European perspective and harmonization, placed within a European common research area; seeing Europe as one space where academic research can be carried out in a well defined, ethically and scientific space and a friendly space
- Education of ethics committee members
- Establishment of networking, collaboration, and exchange of information in order to increase transparency
- There needs to be a repository for requirements and practices for ethics committees
  - Information on national ethical review practices, procedures, and documentation
  - The information needs to be communicable and validated
  - A coordinating office is also needed (that would facilitate and provide education)
  - This work should be carried out in cooperation with existing projects in Europe
- Development of "Good Ethical Review Practice (GERP)".

Workshop 3 – Clinical trials including patients who are not able to consent; the concept of individual direct benefit from research; informed consent – the temporarily incapacitated patient

Chairperson: Christian Wiedermann, Medical University of Innsbruck & Hospital of Bolzano, Italy
Rapporteur: Kathleen Liddell, University of Cambridge & Cambridge Genetics Knowledge Park, UK
Discussants: Erwin Kompanje, Erasmus University Rotterdam, The Netherlands; Elmar Nimmesgern, Directorate Health, European Commission; Bozidar Vrhovac, Medical School University of Zagreb,Croatia

Contributing by correspondence: François Lemaire (France); David K. Menon (UK), Julian Bion (UK)

Executive summary

(This report in its unabridged version appears in *Wiener Klinische Wochenschrift* 118/5–6)

This report records the views of a working group of the *Vienna Initiative to Save European Academic Research* (VISEAR). VISEAR, an association of European researchers predominantly from the public sector, seeks to improve European regulation of medical research.

This report discusses:

(1) the implementation of the EU Directive 2001/20/EC ('the Clinical Trials Directive') insofar as it related to research involving adult patients unable to consent;

(2) legal, ethical and practical difficulties experienced as a result of implementation of the Clinical Trials Directive; and
(3) possible solutions to the problems experienced.

The report is concerned with a broad variety of research involving incapacitated persons including research about mental illness, intellectual disability, age-related illness, critical care and emergency medicine (e.g. stroke, cardiac arrest, traumatic head injury).

The Working Group makes the following recommendations:

Implementation

1. Member States should monitor the impact of their laws on research involving incapacitated patients, particularly Member States which have applied the conditions of the Clinical Trials Directive to medical research other than clinical drug trials.
2. The European Commission ('EC') and Member States should publish guidance to assist researchers and ethics committees with the interpretation of the Directive and implementing legislation.

Risk assessment

3. The EC and Member States should recognise that in circumstances of clinical equipoise (which is an ethical requirement for enrolling patients in clinical trials) there will be substantial uncertainty whether administering a medicinal product will benefit a patient. The requirement that the trial be expected to produce benefits outweighing risks (or no risk at all) must be interpreted in light of this.
4. The EC and Member States should publish guidance about 'component analysis' to clarify that when assessing whether a trial will produce a benefit to the patient outweighing the risks (or no risk at all), the judgment should be made with reference to the benefits and risks associated with the research component of the trial (rather than components of the trial that reflect accepted medical therapies or treatments in equipoise).
5. In conjunction with component analysis, the EC and Member States should review or clarify the requirement that the trial produce 'a benefit to the patient outweighing the risks or produce no risk at all'. It should allow a protocol to include non-therapeutic components (e.g. scans, chart checks, blood tests) of no benefit to the individual, provided they represent no more than minimal risk, are minimised and proportionate to the knowledge gained.
6. When national legislation implementing the Directive covers more than clinical drug trials, Member States should ensure it permits research with no therapeutic benefit for the individual, provided it poses them no more than minimal risk (for example observational studies, research using human tissue samples or health records, and pathophysiological research).
7. Researchers should document instances when non-therapeutic research has been unwisely prohibited by inappropriate implementation or extension of the Directive.
8. The EC and Member States should support ethical and legal research to develop guidelines for difficult risk comparisons.

Ethics committee review

9. The EC and Member States should increase the resources available for ethics committees to secure members or advisors with specialist knowledge relevant to clinical trials with incapacitated patients.
10. The EC and Member States should develop centralised bodies, guidelines and records of precedent decisions for ethics committees to increase the efficiency, consistency and predictability of their decisions.

Revocation of consent

11. The EC and Member States should clarify the extent of a legal representative's power to revoke the individual's participation in a clinical trial with reference to the future analysis for research purposes of data or tissue already collected.

Permitted investigations

12. Ethics committees should ensure that they interpret the phrase 'research … directly related to a life-threatening or debilitating clinical condition' appropriately, and not too narrowly. The interpretation should permit research in non-neurological conditions accompanied by incapacity, research in settings where incapacity is the consequence of essential therapy, research that addresses the common complications of incapacitating conditions, and research to improve methods of supportive therapy.

Legal representatives for proxy consent

13. Further legal research should be undertaken to ascertain the definitions of 'legal representative' that apply in Member States. This could be used as a resource to ensure the lawfulness of international trials; for the basis of public debates and discussion papers; and to analyse the extent to which current definitions cause problems for research about emergency and critical illness.

Emergency and critical illness research

14. Article 5(a) should be amended or interpreted as necessary to permit and harmonise emergency research involving incapacitated persons where treatment must be commenced as a matter of urgency. It should be possible to waive or defer the requirement for consent.
15. Member States should implement systems for legal representation that are compatible with critical illness research. Countries which ordinarily rely on court appointed representatives should check the system is making timely appointments. Countries which usually rely on family members to act as legal representatives should permit decisions to be made by other persons (unconnected with the research) when family members are too stressed to decide, or should waive or defer the consent requirement.

Workshop 4 – Registry of clinical trials

Chairperson: A. Metin Gülmezoglu, WHO, Switzerland
Rapporteur: Klaus Lindpaintner, Roche, Switzerland
Discussants: Helene Faure, Current Controlled Trials Ltd, UK; Tsveta Schyns, European Network for Alternating Hemiplegia, Austria

Registry of clinical trials

This report on registries of clinical trials discusses the shortcomings of current European databases and the lack of access and appropriate alternatives for academic researchers.

A registry of clinical trials for human studies serves the principles of transparency of research and could avoid duplication of studies with associated exposure of volunteers to risk. Unnecessary repetition of clinical experiments without a sound reason is considered unethical by the scientific community because of the risks and inconveniences of trial interventions, and also regarding discussions about data privacy. This applies potentially to all clinical research, including observational and retrospective studies.

Since studies by for-profit enterprises are primarily designed to meet regulatory aspects for drug approval, the prerequisites of a study registration to protect proprietary interests may differ from those of researchers in academia. This is irrespective of the common standard for trial conduct as stipulated by GCP and ICH, which forms the basis of approval of study protocols by ethics committees and regulatory authorities. Further, some special regulations have been introduced pertaining to interventional drug trials by the European Clinical Trials Directive 2001/20/EC.

At present, European Clinical Trial registration is accumulating in the EudraCT database, and is associated with a number of significant limitations.

- There is a lack of comprehensive capture of clinical research activities. Currently, only interventional therapeutic trials (as defined by the Clinical Trials Directive) are collected in the database. A study where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation will not be included, as well as other biomedical research projects or studies with medical devices.
- Since the registry is confidential in nature, the potential of providing transparency to the public and the scientific community is not realized. Importantly, not even the independent ethics committees who are asked to judge the scientific content of protocols (including the novelty of the research proposal) are granted access to the EudraCT database.
- The process of obtaining a registration and submitting the form in electronic format and in hardcopy to the competent authorities of the Member States for validation and approval is considered complex and bureaucratic and deters from the potential use of the registry for purposes not related to drug registration.

Thus, the present EudraCT registry as designed for registration of interventional drug trials does not adequately reflect ongoing research activities, nor can it even be regarded as a comprehensive inventory of drug studies. Neither does it fulfil its role to act as a resource for the scientific community nor does it provide the public with research accountability. Finally, the perceived complexity of the registration process with detailed information in the EudraCT form about the investigational product, site for release etc may well discourage clinical investigators to engage in scientifically well-justified clinical intervention studies, to the ultimate detriment of patients and the general public.

Suggestions offered

This working group suggests the following solutions to improve the registry status for academia-initiated studies:

A greater transparency of the EudraCT database is needed. Key information of ongoing and completed (but often unpublished) interventional drug trials should be opened to the public. An access to clinical trial databases is also required by many scientific journal editors to guarantee transparency and accessibility of research information. In addition, the ethics committees should be granted access to all information of the database for their expert review processes.

A definition of (minimal) standards necessary for a valid registration with delineation of a minimum necessary set of data fields, and the establishment of a globally applicable system of unique study identification codes is proposed. The EudraVigilance database may serve as an example in some respects.

Researchers in academia may be confronted to register their projects in different databases for regulatory approval and for future publication of the study results. This additional bureaucracy with duplicate registries has to be avoided and harmonization is needed.

A database for non-interventional studies (as defined by the European Clinical Trial Directive) and other biomedical research including trials with medicinal devices should be implemented. Importantly, adverse drug reactions from these studies may also be collected in the EudraVigilance database and it is necessary to attain an appropriate standard for these studies.

A standardized "tool-kit" consisting of clear instructions and guidance, as well as necessary templates for study implementation, documentation, SOPs, etc would greatly aid the academic research community in their challenge to adopt GCP-compliant processes and procedures. This could be reached, or supported, *inter alia*, by establishing private-public partnerships between the pharmaceutical industry and academic clinical researchers/research centres, in the spirit of creating mutually beneficial collaborative ventures.

An aim to reduce the paperwork applicable to the registration process could significantly lower the hurdles towards launching clinical trials governed by the Directive. A one-stop-shop principle could simplify the administrative workload of clinical research activities for non-commercial sponsors.

Workshop 5 – Insurance of clinical trials

Chairperson: Ernst Singer, Medical University of Vienna, Austria
Rapporteur: Ingrid Klingmann, EFGCP, Belgium
Discussants: Gerlinde Benninger-Döring, University of Münster, Germany; Harald Etzdorf, Münchner Rückversicherung, Germany; Denis Lacombe, EORTC, Brussels; Ruth Ladenstein, CCRI St. Anna Children's Hospital, Austria; Christian Rittner, Johannes Gutenberg University, Germany; Inga Rossion, Deutsche Krebsgesellschaft, Germany

Summary of discussion

1) Considering the issue of insurance in clinical trials, several types of insurance have to be considered, these are:

- Insurance to cover indemnity for subjects in clinical trials in case of injury or death
- Insurance to cover the liability of investigators
- Insurance to cover the liability of sponsors
- Insurance to cover the product liability of the sponsor
- Insurance to cover the liability of the hospital

Of the types of insurances listed, the first two were discussed in more detail.

Regarding the insurance covering the liability of the investigator it was felt that most investigators are not aware of the type of insurance they have, in particular, whether their insurance covers research activities. Moreover, if their professional liability is covered by a hospital liability insurance it is often difficult and time consuming to receive a copy of the policy. This is not a problem specific to academic studies, however, it is particularly frequent in academic settings. It was agreed that ethics committees may improve this situation by creating awareness of the problem in all parties concerned (hospital, academic investigators).

2) An extensive list of points to be considered and discussed was presented:

- Need for EU-wide agreement on requirements/terms/conditions for professional liability insurance for investigators and sponsors
- Need for EU-wide agreement on criteria for the calculation of required individual subject- and study-related coverage
- Need for availability of multinational contracts
- Need for availability of choice of insurance company
- Need for availability of insurances for investigator initiated trials (IITs)
- Need for availability of insurances for all kind of studies/indications
- Need for transparency of events/costs occurred in insurance cases with clinical trials
- Request for drastic reduction of insurance costs to ensure clinical research (academic and commercial) in Europe
- Opportunity/approaches to cover subject indemnity by other ways than an insurance

In the discussion of theses issues one area of concern presented itself as outstanding and underlying most of the problems, that is the lack of EU-wide agreement on criteria for study risk assessment.

At the moment there is a development to the principle of "strict liability". This creates in a great part of studies a needless coverage of activities that would be covered anyway by other insurance policies. If in a trial 90% of all activities are not study-related but represent routine treatment, there is no need for additional insurance for these 90% but only need to insure the activities of the remaining 10% of the study.

The problem lies in the definition of the study-related risks. One suggestion was that the restriction of coverage to SUSARs could be a viable way of defining those incidences where patients really need the coverage. This would exclude coverage of expected serious events (SAEs). There were also dissenting opinions on this point, stating that SAEs can represent a study-related risk that should be covered by appropriate insurance. A compromise could be formulated as follows: In studies with registered drugs in registered indications only SUSARs should be covered (because all other risks are covered by other types of insurance). In all other studies those SAEs should be included for insurance, for which study-relatedness cannot be clearly excluded.

At any rate, the informed consent must include a detailed description on the nature and severity of expected serious events. This includes the risk of interventions (e.g. surgery, radiation) as part of the standard therapy within the clinical trial protocol.

In the same line of thought is the urgent request of the discussants for a Europe-wide categorization of risks according to different levels of study conditions and study populations. Such a categorization should be detailed enough to allow for the very different types of research. The lack of such a categorization and the lack of clear definition of risks to be insured has e.g. resulted in a decrease of quality assured cancer research:

Until recently, frame contracts were an appropriate way of insuring subjects in clinical trials at a reasonable cost – equal rates for all patients or different rates according to the agreed contract. Lately, clinical trials with special drugs or in special indications were excluded. In Germany and Austria, but also in other EU countries the frame contracts were cancelled and an individual insurance based on risk assessment was introduced. This increased the costs dramatically and is not based on an agreed method of risk assessment. Of note is also the general notion of several discussants that the insurance claims by study participants do not seem to have increased, the costs for insurance policies, however, clearly have.

Another example of insurance problems was given by the representative of a large pediatric oncology unit in Austria. Because of insurance costs the unit is no longer able to participate in some worldwide investigator-driven studies in which established treatments on rare types of cancer are compared (therapy optimizing studies). The consequences of this situation are unfortunate: the chil-

dren are now being treated in the same way as they would have been in the study (thus, the risk of the treatment remains the same. It is also clear that no treatment means certain death); however, which of the available treatments is the best, remains unknown. This is the worst possible outcome imaginable.

A further point discussed as a possible way to reduce costs for insurance was to increase the number of possible insurers. Not only insurance companies should be considered but also other "bodies" who could voluntarily cover study situations: States, universities, industry bodies, hospitals, etc. The solutions need to ensure under all circumstances and on the long run a reliable coverage of protocol-related risks at affordable rates. It was felt that EU guidelines or legislation should explicitly support such approaches.

Conclusion: All discussants were unanimous in their opinion that insurance costs have created a substantial obstacle to investigator-driven research. Ways to reduce these costs include first of all a reasonable assessment of actual study-related risks on an EU-wide basis. Collateral approaches include exemption of certain types of studies (e.g. those in which established treatments are compared) and the possibility of other bodies but insurance companies to cover the risks to which patients may be exposed in a clinical study.

Workshop 6 – Pharmacovigilance

Chairperson: Michael Wolzt, Medical University of Vienna, Austria;
Rapporteurs: Nicola Fabris, C.I.R.M. – Consorzio Italiano per la Ricerca in Medicina, Italy
Discussants: Sabine Brosch, EMEA, UK; Alexander Hönel, AGES, Austria; Bettina Schade, Pharmig, Austria

Shortcomings, identification and analysis

In an effort to harmonize pharmacovigilance reports from clinical trials, the Clinical Trial Directive 2001/20/EC has introduced a distinction between suspected unexpected serious adverse reactions (SUSAR), suspected serious adverse reactions and other serious adverse events. Requirements for notification of Competent Authorities and ethics committees within and among Member States varies greatly, even though a common reporting point with compulsory electronic submission environment (*Eudra Vigilance Gateway*) is being implemented and electronic data interchange from the EudraVigilance Clinical Trial module (*EV-CT*) will enable a rapid information exchange of all parties involved.

For non-commercial sponsors several difficulties have been identified: event coding is compulsory and has to follow MedDRA terminology, which requires subscription with yearly renewal and training. Eudraviligance data entry needs nomination of a responsible "named person" to assess the *EV-CT*, with completion of a 3-days training course and registration to the electronic gateway. Finally, additional forms are generated by Competent Authorities and ethics committees to comply with the new adverse event classification.

Since introduction of the Clinical Trial Directive the number of SAE reported to ethics committees has approximately doubled. On the other hand, the number of sponsors reporting to *EV-CT* is small. The roll-out of training programs has only started and is not available in all Member States. Costs for investigators in academia are substantial, despite a fee reduction in place. The current implementation status in Member States is unknown and the cases added so far in the EudraVigilance database represent merely a fraction of SAE in clinical trials.

Consequences

Information from the *EV-CT* module is not accessible for independent investigators and protected by proprietary interests of the industry. In order to secure confidentiality Sponsors can only get access to *EV-CT* for their own trials. Only data entries into the database for individual case safety records (*EV-PM*) will be available for additional information on the product safety accordingly.

In contrast to guidance on the EudraCT form, reporting to EudraVigilance does not require submission in English. This leads to administrative burden and delay for database management at the EMEA data warehouse, where entries are translated and retranslated accordingly. Reports are checked for quality of content, but proper report classification as SUSAR is not evaluated.

The new legislation has multiplied the workload for Sponsors. Heterogenous requirements among Member States with different local regulations, language barriers and lack of data management infrastructures severely hamper appropriate reporting of adverse events. Thus, commercial third party providers may be necessary to comply with these requirements in academia.

Proposed solutions

Greater harmonization among Member States is pivotal to avoid redundancies or even contradictions in procedures or interpretations. The undisputed need for adverse event reporting should be matched by feasibility for investigators in academia. At present data management requires a substantial amount of infrastructure (personnel, training, offices …) for non-commercial sponsors.

The Clinical Trial Directive should be amended to facilitate reporting requirements for non-commercial research and thereby prevent underreporting. Further, the amount of reports currently submitted by commercial sponsors to ethics committees prevents continued safety monitoring of ongoing studies.

The following urgent measures are proposed:

– Introduction of a mutually accepted and harmonized form for reporting (adapted from CIOMS) according to E2B format as well as harmonization of reporting requirements in the EU Member States.

- Implementation of pharmacovigilance centers within Member States for non-commercial research with a designated and trained (e.g. MedDRA) person responsible for safety data entry and administration to improve reporting quality.
- One-stop-shop for reporting, equivalent to EudraCT: the Competent Authorities of the Member State concerned shall enter SUSAR into the EV-CT, e.g. by means of a Clinical Trial Registration Department (already existing in some countries) in their local office. This single model procedure would also be applicable for adverse event notification from clinical trials for drugs, devices, gene & cell therapy, transplantation, procedures etc.
- Unrestricted access to the EudraViligance database for ethics committees involved in non-commercial trials, as identified in the EudraCT form. These committees already receive updated reports from the industry and have to protect intellectual property accordingly. Conversely, all regulatory authorities and competent ethics committees of Member States will be automatically informed of SUSAR entries into the database by "flagged" identification in the EudraCT form. Capture of competent ethics committees is already guaranteed in the present version of the clinical trial application forms.
- Harmonization among Member States requires consistent and continued education by means of common tools, at all levels, for investigators, study nurses and, if organized, epidemiologic figures.

A local epidemiologic/public health approach for pharmacolovigilance centres is faced by severe restrictions and would need a significant financial and logistical support. A solidarity fee by the industry and/or public funds would be required to account for the mutual interest to improve report quality, in particular for orphan diseases, pediatric studies or surveillance of registered drugs.

Conclusion

All participants agreed that awareness has to be raised in order to make European academic research competitive again and continually to be challenged. This first meeting will have a follow-up meeting in the year 2006.

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