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Meetings on the legislative and regulatory frameworks for clinical research in Europe

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Working Group 2: **Transnational Working Group on regulation
and interaction with competent authorities**

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1. Context

In the ECRIN-TWG contract, a meeting was planned, organised with ECRIN, EFGCP, and EMEA, allowing to present and discuss with the commission, stakeholders, regulators and legislators, the current status of harmonisation of clinical research (not only medicines trials) in the EU and the bottlenecks to be addressed. No specific budget was available for this event.

The knowledge developed by ECRIN WP2 on the regulatory context of clinical research in the EU raised a considerable interest and resulted in multiple invitations to participate in and to co-organise meetings, conferences, and workshops on this topics. For this reason, the meeting planned in the work programme was changes into four major events during which ECRIN had an opportunity to express its suggestions regarding the EU regulatory context:

- The EC-EMEA conference on the revision of the 2001/20/EC Directive, held on October 3rd 2007 in London.
- The EORTC - Conticanet – ICREL - ECRIN Workshop “Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors?” on May 21st, 2008, in Brussels.
- The ICREL conference in Brussels, on December 2nd 2008, during which the results of the FP7 ICREL project (coordinated by EFGCP, all the participants in ICREL are also participants in ECRIN-TWG) will be presented and discussed. ICREL is *de facto* a direct consequence of the ECRIN-TWG WP2 activity (www.efgcp.be/icrel).
- The ESF-EMRC Forward Looks conference (Strasbourg, 29-30 September 2008), prepared by a series of 5 workshops.

2. Events, conferences and projects directly derived from the ECRIN-TWG Working Group 2

Knowledge accumulated by ECRIN Working Group 2 has contributed to a set of proposals for the adaptation of national and European legislation in order to promote the protection of participants in clinical research, whilst facilitating clinical research in the EU. For this reason, ECRIN has become an important contributor to a number of discussion groups on EU and national legislation in clinical research. Four major contributions resulted directly from the activity of ECRIN Working Group 2:

2.1. Written suggestions for the Conference on the Clinical Trials Directive, organised by the EU Commission, and held at EMEA, London, October 3rd 2007.

The objective of Directive 2001/20/EC is to harmonise the EU regulatory environment, improve the protection of participants, optimise the use of safety information, and ensure the credibility of data, through stronger responsibility of sponsors and harmonised regulatory and ethical review procedures in the member states. However, this Directive partly missed its harmonisation goal and raised concerns within the clinical research community and industry. In particular, SMEs and academic sponsors have difficulties in fulfilling their duties as sponsors due to the transposition of the Directive into divergent national legislation and increased workload and responsibilities.

The European Commission (DG Enterprises and Industry) and the EMEA organised a conference to discuss possible changes to the current legislation (www.emea.europa.eu/meetings/conference2007.htm). ECRIN was invited to speak on behalf of the academic institutions during this conference, and for this purpose the ECRIN WP2 prepared a written document that was approved by ECRIN as well as many other academic institutions (see appendix 1).

2.2. The EORTC - Conticanet – ICREL - ECRIN Workshop *Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors?* on May 21st, 2008, in Brussels.

More than sixty decision-makers including leaders of academic research organisations, top clinical researchers, legal experts, and representative from the European Commission, took part in the one day workshop, *Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors* held at the EORTC Headquarters, in Brussels on May 21, 2008. The EORTC along with three EU-funded consortiums, the Connective Tissue Cancer Network (CONTICANET), the European Clinical Research Infrastructures Network (ECRIN), and the Impact on Clinical Research of European Legislation (ICREL) organised this event with financial support from the European Commission 6th Research Framework Programme CONTICANET project. All four organisations are working towards a common goal – improving the current EU clinical trials legislation (see appendix 2).

2.3. The ICREL (Impact on Clinical Research of European Legislation) project

ICREL is a one-year project funded by the first call of the FP7 Health Priority. ECRIN, EORTC, the Hospital Clínic of Barcelona and the Ethics

Committee of the Medical University of Vienna are collaborating on this project coordinated by EFGCP (www.efgcp.be/ICREL).

ICREL's aim is to measure and analyse the direct and indirect impact of Clinical Trials Directive 2001/20/EC and EU related legislation on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, ethics committees, and competent authorities. ICREL represents the contribution of DG Research to the debate on the revision of the 2001/20/EC Directive.

ICREL is designed to provide metrics on the impacts of the 2001/20/EC Directive, either direct impact on clinical trials on medicinal products, or indirect impact on other categories of clinical research. ICREL will therefore collect and compare figures from EU member states on clinical trials on medicinal products sponsored by pharmaceutical companies, biotechnology SMEs, and academic institutions, on other categories of clinical research, as well as on the impact on ethics committees, competent authorities, clinical research infrastructure, and on the workload, cost, and funding of clinical trial. Results from the survey will be discussed during a conference in Brussels on December 2nd, 2008 (see appendix 3).

2.4. ESF-EMRC forward looks on investigator-driven clinical trials.

The European Medical Research Council (EMRC) of the European Science Foundation has decided to prepare a strategic document on academic clinical research in Europe. This will be achieved through a 'Forward Looks' process prepared through a series of five workshops on investigator-driven clinical trials (ie, 1 - categories of research, 2 - regulation, 3 - logistics and management, 4 - funding, 5 - education and careers), followed by a consensus conference on September 29 and 30th, 2008. ECRIN participated in all the workshops and in the final conference, and acted as co-chair in the workshops on categories of research and on regulation. This contributed to disseminate the knowledge accumulated by ECRIN-TWG WP2, to validate the categories of research proposed in the survey, and to propose a risk-based approach for regulatory requirements (this was considered as one of the five top-priorities at the consensus conference) (see appendix 4).

Appendix 1

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

ECRIN (European Clinical Research Infrastructures Network)
EORTC (European Organization for Research and Treatment of Cancer)
ESF-EMRC (European Science Foundation - European Medical Research Councils)
CPI (Coordination des Promoteurs Institutionnels)
INSERM (Institut National de la Santé et de la Recherche Médicale)
VISEAR (Vienna Initiative to Save European Academic Research)
ESICM (European Society of Intensive Care Medicine)

Aspects of the Directive 2001/20/EC that work well

- 1) The EU legislation resulted in a **partial harmonisation** of clinical trials on medicinal products in the EU. There is now a need to extend the harmonisation process to all the categories of clinical research in the EU, beyond clinical trials on medicinal products.
- 2) The EU legislation also led to the **integration** of clinical trial identification (through the unique EudraCT number and database) and of adverse event reporting in clinical trials (through the EudraVigilance database). Such databases should now be used to promote transparency, and particularly to develop a European tool for open study registration and reporting.
- 3) The EU legislation promoted a **single opinion** from ethics committees at the national level, and defined the roles and responsibilities of the sponsor and of the state (through the competent authority) in the conduct of clinical trials. There is now a need for a better definition of the respective roles of ethics committees and of competent authorities, and for streamlining their interaction.
- 4) As a consequence of the Directive, some EU countries have invested in the development of a clinical research **infrastructure** and promoted **training** programmes, whereas some public institutions have strengthened their capacity to fulfil the **sponsor's tasks**. This resulted in an improvement in the conduct, in the quality and in GCP compliance of clinical trials. The development of such clinical research infrastructures (at clinical sites, at clinical research centres, at clinical trials units undertaking design, conduct and analysis of clinical research) should now be supported in all the EU member states and coordinated at the EU level.

Aspects of the Directive 2001/20/EC that do not work well

1) *Harmonisation / integration*

The 2001/20/EC Directive and its transposition into national legislation failed to efficiently harmonise the regulatory framework and to facilitate EU clinical trials. It made the initiation and conduct of national, and also of multinational clinical trials on medicinal products more difficult than before the implementation of the Directive. The increased administrative workload and expensive monitoring raised the cost of academic clinical research by 2 to 4 times, and made it impossible to conduct some studies. Moreover, acting as a single sponsor in the EU is impossible for most academic institutions.

Considering the failure of the 2001/20/EC Directive to efficiently harmonise the regulatory framework of clinical trials, and the failure of national legislations and national competent authorities to implement harmonised regulation and practice, we would recommend, whenever possible, an integrated approach (ie, for the competent authority). When integration is not possible (ie, for ethics committees), coordination, guidance, and accreditation should assist and enforce harmonisation. In addition, implementation of such legislation should be coupled to a strengthening of the clinical research infrastructure and of training programmes at both the national and the EU levels.

2) *Directive / regulation*

Some EU member states took advantage of the flexibility in the transposition of the Directive to escape part of its negative impact on clinical research. This resulted in divergent national regulations that made multinational cooperation even more difficult.

In an ideal situation where the new EU legislation would foster rather than hamper clinical research, the issue of a real harmonisation should be addressed by the new legislative framework, either through a Directive, a regulation, with clear implementation guidance. Most participants consider that the regulatory framework for clinical research can be covered by a regulation, avoiding divergent interpretation while transposed into national legislation – in such case, a Directive should be maintained for ethics committees, as ethics is left to the competence of the member states and cannot be covered by an EU regulation.

3) *Field of the Directive*

Clinical research is not restricted to clinical trials on medicinal products – this is particularly true for academic research. There is a major disharmony between national regulations regarding clinical research other than clinical trials on medicinal products. This leads to consider the need for extension of the EU legislation to areas of clinical research not covered by the Directive. However some countries fear that such an extension would hamper rather than facilitate such research.

The ideal solution would be a single EU legislation designed to facilitate clinical research in the EU, prepared by DG SANCO, DG Research and DG Enterprise and Industry, adequately and equally protecting the participants in every category of clinical research across the EU (a situation equivalent to the national one where the

Ministry of Health is usually responsible of such legislation). If such a solution is not possible, we would suggest:

- to extend the field of an improved version (assuming that it really facilitates clinical research) of the EU legislation on medicinal products to all the clinical trials on health products (including medical devices, diagnostic products, herbal medicines, nutritional supplements), as they require a common regulatory framework in which the competent authority supervises the health product and the preclinical requirements, and the ethics committees supervise the protection of participants.

- to write a new legislation (also assuming that it really facilitates clinical research) covering all clinical research not involving health products (also reviewing the preclinical development of know-how and procedures), either interventional or observational, in order to ensure harmonised adequate protection of participants and to facilitate clinical research in the EU.

This new legislation should involve DG Research and DG SANCO.

4) ***Competent authorities***

The task of the competent authorities is to supervise the medicinal product, which is the same throughout the EU. There is still a considerable disharmony between requirements for clinical trial authorisation from the competent authorities. The practices differ between countries. There is a redundant assessment of the same product by many agencies, resulting in waste of time, money, and expertise for the agencies, and in multiple submissions for the applicant, and most importantly in a delay for a new therapy to benefit patients.

For multinational trials, the easiest way to circumvent this difficulty would be to obtain a single clinical trial authorisation through a centralised procedure (or a mutual recognition) in which the clinical trial application is managed by one single competent authority, instead of up to 27 national competent authorities. This would save a lot of time and human resources, avoid duplication of protocol and investigational medicinal product (IMP) dossier review, strengthen expertise, and reduce the administrative burden for academic sponsors and investigators. This is merely an extension of what is proposed for first-in-man studies.

For national trials, the clinical trial authorisation could be left to the national competent authority, however, in the long term integration of clinical trial authorisation will make sense (as EudraCT and SUSAR reporting are already integrated) also for national trials.

The governance of EMEA (and/or a new EU competent authority) should be modified towards more consideration of the interests of consumers, public health issues, and research issues – in the member states, the medicines agencies depend on Ministries of Health, not on the Ministries of Industry.

5) ***Ethics committees***

Ethics committees ensure the protection of participants in clinical trials. There is a major disharmony in the assessment of clinical protocols and informed consent forms by ethics committees. This reflects cultural differences in ethical review of clinical research but additional, unnecessary disharmony is due to the lack of coordination, training, and quality assurance systems.

The EU legislation should promote harmonisation of the activity of ethics committees through either a guidance or a change to the Directive implementing an appeal procedure and an accreditation system for ethics committees, ensuring appropriate training and quality assurance, based on EU-wide specification. In addition, a European coordination of ethics committees (under the responsibility of DG SANCO) should promote harmonised training, tools, and practice, including a common template for the informed consent requirements in the EU.

6) *Multiple sponsors*

A single clinical trial authorisation, and a single EudraCT number, should not necessarily require a single sponsor in the EU, only a single applicant at the EMEA/EudraCT level. The requirement for a single sponsor is a major bottleneck to multinational clinical research for academic institutions that lack the capacity to fulfil sponsor's tasks in multinational studies. This is also true for small and medium-sized enterprises (SMEs). In addition, some countries allow multiple sponsors.

There is an absolute need to allow multiple sponsorship, for multinational as well as for national trials, in order to share, on a contractual basis, the roles and responsibilities in the various EU member states, this multiple sponsorship being under the coordination of a single applicant for European regulatory authority.

7) *Definition of categories of research*

Some definitions are open to divergent interpretation, resulting in national differences in the categorization of the same clinical study, particularly the border between interventional and observational studies.

The Directive defines intervention as treatment intervention, diagnostic intervention, or change in follow-up ('monitoring') procedures. This led to divergent interpretations between countries, as some consider diagnostic procedures as intervention in any case, other only if they increase the risk for the patient, whereas other have defined an intermediate category of 'minimally interventional' studies. As a result, the same post-marketing safety study, without treatment intervention but with collection of a blood sample, may be regarded as a clinical trial on a medicinal product covered by the Directive in some countries, and as an observational study in other.

The Directive fails to differentiate categories of research on medicinal products, and does not consider the lower risk associated with some of them, (particularly post-marketing studies, which represent a major part of academic clinical research). Instead, it proposes adaptation for 'non-commercial trials'.

There is a need to clarify the border between interventional and observational studies. Therefore, a workshop should be organised to discuss this point and the potential relevance of defining a category of 'minimally interventional' studies, without treatment intervention and with only low-risk intervention regarding diagnostic or

follow-up procedures, for which approval from ethics committee is required, without full clinical trial application.

There is also a need to harmonise the interpretation on psychological assessment as an intervention.

In a more general perspective, there is a need to refine the definition of categories of clinical research, beyond the phase I-IV classification. The regulatory requirements should take into account the lower risk associated with studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, or trials on off-label use of marketed drugs. This is of utmost importance for the academic community as a considerable part of its clinical trial activity falls into these categories. Developing regulatory requirements based on the risk associated to these categories would be an alternative way to the 'specific modalities for non-commercial trials' that tend to suggest that there are two levels of quality. We strongly oppose the idea that clinical trials should come in different forms regarding their quality, depending on who initiated the trials. If clinical trials are to differ in any regard, this ought to be decided based exclusively on a thorough risk assessment (hazards to the participants, to the trial's data, to public health). A workshop should be organised to help further discuss this critical point.

There is a need to clarify the border between medicinal products, nutritional supplements, and nutrition studies. A workshop should be organised to help further discuss this critical point.

The Directive uses the wording 'subjects' for individuals participating in a clinical trial. This should be changed to 'participants', which better highlights their active role and is non-derogatory.

8) *Definition of 'non-commercial' trials*

The concept of commercial compared to non-commercial trial should be replaced by a better wording (avoiding 'commercial').

In addition, the need for support and for regulatory adaptation may be different for 'non-commercial trials' and for 'trials sponsored by a non-commercial institution'.

There is a need to organise a workshop on the definition of clinical research run by academic institutions (e.g., investigator driven clinical trials), and to determine, with representatives of the academic research community, which adaptation could be proposed, for which type of trial.

Defining 'specific modalities for non-commercial trials' tends to suggest that there are two levels of quality. This should be avoided, and in turn risk-based strategies should be used to improve the cost-effectiveness of clinical trials, especially for monitoring. Therefore developing regulatory requirements adapted to the risk associated to defined categories of clinical trials would be an alternative way.

As stated in (7), most clinical trials sponsored by academic institutions correspond to categories of research associated with a lower risk: studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, trials

on off-label use of marketed drugs, pharmacoepidemiology studies. Academic institutions are also involved in the development of drug treatments for rare diseases, where market incentives fail to drive industry investment. Public-private partnership is frequently used for co-funding or co-development. Specific modalities should be defined for all these categories of research, not for 'non-commercial trials' as a whole.

9) ***Adaptations for academic research ('non-commercial trials')***

Academic institutions acting as sponsors in clinical research face major difficulties in either national or multinational trials, that may be dampened by measures ensuring an appropriate level of quality, and based on support and on regulatory adaptation depending on the risk associated with the category of study (hazard to the patient, hazard to the institution, hazard to the study, hazard to public health).

The guidance document on 'specific modalities for non-commercial trials' mentioned in recital 11 of the 2005/28/EC Directive states that data from non-commercial trials cannot be used for registration, which is a major obstacle to academic-sponsored research and to the development of new indications for marketed medicines, especially in rare diseases. In the future, this may be a threat to all diseases due to the development of personalised treatments.

In some countries, non-commercial trials (or sponsors) are waived to pay fees to competent authorities and to ethics committees. Other countries do not implement such a waiver, or only reduced fees. This waiver system should be harmonised.

Similarly, some countries have implemented a waiver for the sponsor to purchase the IMP (investigational medicinal product) in non-commercial clinical trials, not other, and this initiative should be generalised.

In some countries, the insurance coverage for non-commercial trials is provided by the public health system, by the public hospitals or the university hospitals. This system should be implemented in all the EU member states, with the capacity to cover also investigator-driven trials sponsored by a foreign institution in a EU member state.

National competent authorities should provide free support to academic sponsor in SUSAR reporting and MedDRA coding.

Adaptation of the requirements should be allowed for marketed drugs regarding IMP dossier, and labelling. Alternative methods should be allowed to ensure traceability. Independence of academic trials should not be restricted by the need to ask the marketing authorisation holder to cross refer to an existing IMP dossier.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?

1) ***Interaction between ethics committees and competent authorities***

Various models have been implemented for the interaction between ethics committees and competent authorities: no interaction, a streamlined cross-talk, or a

close cooperation in which the competent authority, not the sponsor, directly interacts with the ethics committee.

A guidance is needed to further define the respective tasks of ethics committees (protection of participants) and of competent authorities (assessment of the medicinal product), and how ethics committees and competent authority (either national, or a single EU competent authority) should cooperate in the clinical trial application process and during the conduct of the trial (for instance the model of a direct communication between the competent authority and the ethics committees, resulting in a one stop-shop system for the applicant that interacts only with the competent authority, has to be further discussed). This could reduce redundant work and increase clarity and responsibility.

2) *SUSAR reporting to ethics committees*

SUSAR reporting to ethics committees and to investigators is a major issue raised by ethics committees, investigators, and sponsors. We consider that an improved and streamlined communication between ethics committees and competent authorities could help solve this issue. SUSARs and AER should be reported by the sponsor only to the competent authority, while ethics committees and investigators could have access upon request to the data collected by the competent authority. In addition, a workshop should help discuss how best to make information on risk and benefit also available to participants in order to ensure the long-term validity of the informed consent.

3) *Information on national and EU requirements*

Information on national and EU requirements for clinical trial authorisation should be available, in English, to sponsors and investigators through a dedicated and updated website (at EMEA, or DG SANCO ?), and a helpdesk should be developed to support sponsors in multinational studies.

In addition, electronic documents (.pdf), not only paper documents, should be authorised for clinical trials application and submission to ethics committees.

4) *Investigational medicinal product (IMP) definition*

In the current guidance, only some background treatments are considered as IMP, and this requires case-by-case examination leading to divergent interpretation.

A simple and unambiguous definition of IMP should be provided. This is of particular importance for academic trials, as this has an impact on labelling and traceability, on SUSAR reporting, and as in some countries the academic sponsor still has to purchase the IMP.

5) *Definition of substantial amendments*

The definition of substantial amendments is open to varying interpretation resulting in different status across the EU member states.

A guidance should provide unequivocal definition.

6) *GMP (good manufacturing practice) requirements for biotherapy*

There is a need to harmonise the requirements for GMP manufacturing of biotherapy products.

7) *Education and training of investigators, nurses and other specialised staff*

A guidance should be developed for education and training for investigators and staff in clinical trials, with accreditation of educational programmes. Continuous education

of investigators and staff should be promoted. The issue of a qualification for investigators and staff should be discussed during a workshop.

8) **Methodological assessment by ethics committees and competent authorities.**

The competent authorities and ethics committees play a critical role in controlling the methodology of the protocol and in reducing the risk of errors – risk of design errors, risk of random errors ('play of chance'), risk of systematic errors ('bias'). There is currently a lack of quality assurance requirements and accreditation ensuring that the methodological review of protocols is adequately performed.

Clinical trials methodology should be part of guidance documents, quality assurance, and accreditation processes for ethics committees and competent authorities.

What should a new legal framework look like?

- 1) A **single and comprehensive legislation (directive and/or regulation) covering all clinical research** should be prepared, ensuring **adequate and equivalent protection of participants in any biomedical research in the EU.**

All the biomedical research on human beings, with or without health products, interventional or observational, should be covered by a single, legislative framework prepared under the umbrella of DG SANCO with the contribution of DG Research and DG Enterprises. In order to ensure harmonisation, a Regulation would be preferred to a Directive (whenever possible).

- 2) facilitating high-quality clinical science in the EU and **protecting the participants according to the risk associated to the category of study** (not according to its 'commercial' or 'non-commercial' objective).

Categories of research should be carefully and unambiguously defined, each being associated with regulatory and quality requirements adapted to the risk (instead of adaptation to 'non-commercial trials'). In turn, support should be provided to public institutions acting as sponsors in clinical research (possible co-sponsorship, support to MedDRA coding and SUSAR reporting, information and helpdesk on regulatory requirements, public insurance coverage, waiver of purchasing the IMP, development of the clinical research infrastructure). Workshops are needed to reach an agreement on the definition of, and borders between categories of research, the associated risk, and the resulting requirements.

- 3) with **centralised assessment by a single competent authority** (at least for multinational trials).

Instead of duplicating efforts, assessment of the health intervention should be conducted by a single agency (either centralised, or specialisation of the national competent authorities in a given type of health product, or mutual recognition).

- 4) with **accredited and co-ordinated ethics committees.**

Implementation of a quality assurance and accreditation system, and of an EU coordination under the responsibility of DG SANCO, leading to harmonised training and practice.

- 5) with clear guidance on their **respective roles**, and on the harmonised **interaction between ethics committees and competent authority,**

The national ethics committees should protect the participants in every category of clinical research, whereas the competent authority should assess the health intervention (including a health product if any), using a streamlined and harmonised procedure for interaction between both.

6) and promoting ***trust, transparency and optimal use of data*** in clinical research through open study registration, study reporting, and data sharing.

A clinical trial registration tool, in line with the requirements of the WHO international clinical trials registration portal (ICTRP) and of the ICMJE (International Committee of Medical Journal Editors) is lacking in the EU. The new EU legislation should state that data from the EudraCT database (and/or equivalent) will be used to build a public EU clinical trial register for all interventions (open access to information from EudraCT is already planned in the paediatric regulation). In addition, the EU should take advantage of this registration tool to give open access to study reporting, and to create a repository for anonymised clinical trial data.

Appendix 2



Conticanet

**Report on the EORTC-CONTICANET-ICREL-ECRIN Workshop “Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors?”
May 21st, 2008, Brussels, Belgium.**

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Current European legislation on biomedical research seems to adversely affect pan-European clinical research activities. The impact of the EU Clinical Trials Directive 2001/20/EC has been widely debated since coming into force in May of 2004. Ongoing translational research activities and the growing use of human biological material have exposed additional critical legislative gaps at the European level. The Directive aims to protect the rights and well-being of human subjects enrolled in clinical trials, increase European clinical research competitiveness, harmonise regulatory procedures, and ensure Good Clinical Practices by means of a common legal framework. Member States, however, have interpreted, transposed and implemented the Directive in different ways. The core principles of the Directive on subject protection and general procedural rules are identical at the European level but differ in practice, a result of the various transpositions of those principles into national legislation – thus true harmonisation has yet to be achieved. European researchers must overcome these national discrepancies in order to carry out multi-national clinical trials. This costs time, money and precious resources and has failed to increase trial subject protection and to ensure equal access to innovative research for all European citizens. Both the academic research community and the pharmaceutical industry agree that amendments to the current legislation or new legislation are urgently required if Europe is to remain competitive and patients are to benefit from the latest cutting-edge medical research.

More than sixty decision-makers including leaders of academic research organisations, top clinical researchers, legal experts and representative from the European Commission, took part in the one day workshop, “Biomedical Research in Europe: Which Challenges and Solutions for Academic Sponsors” held at the EORTC Headquarters, in Brussels on May 21, 2008. The EORTC along with three EU-funded consortiums, the Connective Tissue Cancer Network (CONTICANET), the European Clinical Research Infrastructures Network (ECRIN) and the Impact on Clinical Research of European Legislation (ICREL) organised this event with financial support from the European Commission 6th Research Framework Programme CONTICANET project. All four organisations are working towards a common goal – improving the current EU clinical trials legislation.

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Academic Research under Threat from the Clinical Trials Directive

A panel of distinguished experts co-chaired the workshop and presented the position of their respective organisations concerning the EU Directive. Professor Françoise Meunier, Director General of the EORTC [1] opened the meeting by highlighting the key challenges faced by pan-European research organisations today in the conduct of academic multi-national clinical trials. She outlined the task for all in attendance; namely, to work in partnership to find concrete solutions to the issues, to develop a new model of funding for academic research and to convince policymakers that European academic clinical research is essential and not simply a luxury. Professor Meunier deeply regretted the absence of representation on behalf of the DG Enterprise, the source of the Directive. Despite a drop in the number of new cancer clinical trials conducted by the EORTC since inception of the Clinical Trials Directive, the associated rising costs and administrative burden, she remains enthusiastic and positive, commenting that, "it's an exciting time to be working in the field of oncology with over six hundred pharmaceutical molecules now in development. The EORTC's mission is not only to conduct high-quality translational and clinical cancer research but to conduct clinical trials that best serve the needs of future cancer patients." Clinical studies in oncology demanding a high level of scientific expertise and large patient numbers need to be pan-european. Harmonisation of the regulations is therefore of primary importance.

Collaboration with industry is essential for granting patient access to new drugs but the independence of researchers must be safeguarded. Professor Meunier called for more structural and long term funding of academic EU clinical researchers as the only means of guaranteeing scientific research independence and keeping crucial expertise in Europe. A new model of clinical trials is needed for the 21st century that involves all stakeholders including patients, academic researchers, industry, funding bodies and policymakers. Professor Meunier closed her presentation by highlighting three concrete proposals to improve the future of European research, (1) PhD programs should be encouraged and supported, (2) healthcare professionals, namely physicians, clinicians, data managers and nurses should be trained and (3) regulations should be revised and harmonised.

Professor Peter Hohenberger spoke on behalf of CONTICANET [2]. This Network of Excellence launched in 2006 and funded by the 6th Framework Programme of the European Commission, is dedicated to research on the diagnosis and management of connective tissue tumors. It also seeks to promote a better understanding of these rare tumors, and to harmonise and optimise their treatment on a European level. CONTICANET is generating a critical mass of key stakeholders in order to overcome the current difficulties in terms of lack of data, data fragmentation, and mobility of researchers, heterogeneity of methodologies and legislation and is working to harmonise research projects. In its efforts, the Network has identified various barriers to clinical research resulting from current European legislation. Despite a harmonisation directive on clinical trials, biomedical research on human tissues remains insufficiently regulated. National regulations differ on informed consent for tissue sampling, tissue exchange transfer rights, industry collaboration and financial implications, drug availability, off-label drug usage, reimbursement and non-commercial sponsored studies; as well as the conduct of multi-national clinical trials where the interests of industry are currently favoured over those of patients and researchers. CONTICANET is actively addressing these and other issues in partnership with like-minded research groups by meeting with Health Authorities, detailing specific problems of legislation and ethics faced by European networks of excellence and proposing strategies and an action list to improve harmonisation.

Dr. Ingrid Klingmann presented the ICREL project financed by the European 7th Framework Programme and coordinated by EFGCP in collaboration with ECRIN, EORTC, the Hospital Clinic i Provincial of Barcelona and the Ethics Committee of the Medical University of Vienna. [3] ICREL aims to measure and analyse the direct and indirect impact of the Clinical Trials Directive and related legislations in the EU on all categories of clinical research and the different stakeholders including commercial and non-commercial sponsors, Ethics Committees and Competent Authorities. This work will aid in determining the most relevant pathways for improvement of the directive. Dr. Klingmann pointed out that the new Directive has increased the complexity and administrative work required to conduct clinical trials, introduced new legal requirements not easily to fulfil in the academic environment, and resulted in higher costs for sponsors to perform and supervise clinical trials. Other stakeholders such as Ethics Committees and Regulatory Authorities have also experienced expensive and burdensome new challenges. Dr. Klingmann believes that, “the Directive has the right objectives which justify stronger efforts by all stakeholders but in its current form it has not achieved to encourage European clinical research or to better protect study participants.” In response to multiple complaints, the DG Research awarded the current ICREL one-year project that entails analysing available data and collecting metrics on the impact of the Directive by conducting a pan-European survey of all major stakeholders. ICREL will discuss their fact-based results at a workshop in Brussels on December 2, 2008 and prepare a list of recommendations for changes to the current Clinical Trial Directive for public discussion.

Professor Jacques Demotes-Mainard coordinates the ECRIN projects, funded by the 6th and 7th Frameworks. ECRIN aims to facilitate multi-national European clinical research through the integration of EU research capacity and public funding, the harmonisation of tools, training and practice; by improving quality, credibility and transparency; and the harmonisation of legislative systems. This is achieved by providing support to investigators and sponsors of multi-national trials as well as supporting interaction with Ethics Committees and Competent Authorities. [4] According to Professor Demotes-Mainard, the first challenge to clinical research in Europe is access to patients. The European Unions should take advantage of its population size of over 500 million to increase its competitiveness through multi-national trials, especially in rare diseases. The second problem is of the fragmentation of funding and the need for an integrated approach to clinical research funding. A third issue is the availability of infrastructures. Not all countries have established clinical research and trial centres, disease-oriented networks or national coordination. The first step in the ECRIN process, accomplished between 2004 and 2005, helped identify bottlenecks in multi-national cooperation. Step two (2006-2008) saw trans-national working groups define procedures and guidelines for multi-national studies in the EU. The third step (2008-2011) consists of building a European infrastructure for clinical trials and biotherapy to provide one-stop shop, high-quality services to multi-national clinical research. Improvement in the legislative framework for the conduct of clinical research is required as a critical element and ECRIN is collaborating with others towards revising the EU Clinical Trials Directive.

Dr. Markus Hartmann rounded off the first workshop session presenting the results of his impact analyses of the Directive on academic research. He highlighted the discrepancies and gaps in legislation at the Member State level concerning multi-national multi-modality, surgery and radiotherapy clinical trials—typically the clinical research conducted by non-commercial academic and independent research groups, and where the legal and administrative burdens fall. Drug authorisation statistics pre- and post-implementation from six large EU countries indicate a marked drop in non-commercial academic cancer clinical research within the EU post-implementation.

Drs. Denis Lacombe, Jacques Demotes-Mainard and Carole Moquin-Patthey presented specific examples of how the Clinical Trials Directive influences academic cancer research and proposed strategies for overcoming these challenges. The EORTC, which develops, conducts and coordinates high quality translational and clinical cancer research on a pan-European level has been particularly hard hit by the Directive's failure to bring real harmonisation. This academic organisation conducts clinical trials involving new drugs but more importantly, large-scale multinational trials that evaluate innovative and more effective therapeutic strategies using approved drugs, radiotherapy and/or surgery. The latter type of study may fall under the Directive in some member states if classified as an interventional trial and in all if it involves the use of an investigational medicinal product as interpreted by each Member State's legislation. The EORTC is required to meet and adhere to the legislation of each country participating in a multi-national clinical trial. The complexity of this exercise and lack of EU harmonisation are illustrated by the multi-national EORTC "TEACH" observational study designed to evaluate the risk of thromboembolism in patients receiving chemotherapy. Three EU countries considered this academic trial to fall under the EU Directive, four did not and two countries approved the study without comment—different interpretations of the Directive for the same study. The study was cancelled due to inextricable regulatory issues.

According to Dr. Lacombe, metrics collected by the EORTC over the past decade indicate that the number of newly activated EORTC cancer clinical trials and the number of patients treated have declined precipitously in the post-implementation period. Simultaneously, trial insurance costs have skyrocketed, the overall EORTC budget has increased six fold and the number of EORTC Headquarters staff required to handle the additional administrative burden resulting from the Directive has tripled [5]. The nature of EORTC clinical trials has also changed with fewer academic trials and more industry-sponsored studies. The increasing cost of clinical trials impairs the autonomy and independence of academic clinical research and favours industry. The number of pure academic trials has decreased significantly. The Directive may also result in Europe becoming less rather than more competitive, as exemplified by one EORTC transatlantic US-European study designed to further evaluate important genetic findings from an earlier EORTC brain tumor study. The US research centres, all subject to a common central approval process, were able to initiate patient recruitment twelve months earlier and recruit fifty times more patients into the study compared to their European counterparts. The EORTC continues to collect hard data to support its case for changing the current Clinical Trials Directive.

Professor Demote-Mainard outlined potential solutions and recommendations for the future as proposed by major European research groups and discussed during a conference organised by the European Commission and EMEA in October 2007. Certain aspects of the Directive do work well (partial harmonisation, EudraCT, EudraVigilance, single Ethics Committee opinion, increased quality and GCP compliance). However, harmonisation remains incomplete, interpretation of the Directive is divergent among Member States and the scope of the Directive is indiscriminately all-inclusive failing to recognize the different types and risks of clinical trials. Submission to competent Authorities in multinational trials should benefit from integration and centralisation; Ethics Committees' review process needs more standardisation and their organisation requires accreditation and quality assessment, and the joint responsibilities of multiple sponsorship demands further definition. Academic institutions would benefit from supportive measures including access to data from trials not yet submitted for marketing authorisation purposes, waivers on fees to Competent Authorities as well as for the purchase of investigational medicinal products, public health system insurance coverage, technical support in the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs), development of a

research infrastructure and increased funding. The use of data from trials run by academic institutions should be allowed for marketing authorisation purposes.

Although aspects of the Directive could be remedied, the optimal new legal framework would be a single and comprehensive legislation that covers all clinical “research” which protects participating patients according to trial risk associated with the study, not to the commercial or non-commercial objective of the trial, assessed by one single Competent Authority and accredited Ethics Committees based on clear guidance on their roles and harmonised interactions. This legislation would promote trust, transparency and the best use of data through open registration, reporting and data repositories.

Dr. Carole Moquin-Pathey spoke on the future strategy for medical research in Europe and investigator-driven clinical trials on behalf of the European Science Foundation-European Medical Research Council (ESF-EMRC). The mission of the EMRC is to promote innovative medical research and its clinical application towards improved health; provide authoritative strategic advice for policymaking, research management, ethics and better health services; serve as a consensus voice for all research organisations; disseminate knowledge; and promote the socioeconomic value of medical research to the public and policymakers. In this regard, the ESF-EMRC has produced a white paper aimed at strengthening and improving European medical research for creating new knowledge, better practice of medicine and improved human health and welfare. These are achievable through peer-reviewed funding of research based on excellence, collaboration via the EMRC, revision of the EU Directive to facilitate research, equal opportunities for research and the doubling of public funding of medical research in Europe to a minimum level of 0.25 % of GDP within the next ten years.

Specific to investigator-driven clinical trials, a Forward Look, launched in mid-2007, will provide recommendations on ways to improve coordination of the various national and European initiatives and strengthen investigator-driven clinical trials from an international perspective. Through a series of strategic workshops, European experts have recently addressed: (1) categories and design of clinical trials; (2) regulatory and legal issues, intellectual property rights and data sharing; (3) management and logistics; (4) education, training, career and authorship; and (5) funding and partnership models for investigator-driven trials in cancer, central nervous system, cardiovascular and infectious diseases, inflammatory and metabolic disorders. The workshop findings are currently going through a review and consensus process. In a final conference participants will further refine and agree on a set of recommendations for dissemination to major interest groups.

Several topics were addressed during the morning session general discussion. Workshop delegates questioned whether the role of Ethics Committees includes the review of study protocol methodology. The answer is not clear-cut. Ethics Committees must balance the risks and benefits of any research proposal for the patient. Poor or weak study methodology may prohibit a patient’s benefit from a study or adequate treatment or waste the patients’ participation due to non-interpretable results. The quality of judgements made by Ethics Committees was also questioned and a proposal was put forward to develop accreditation via peer-review committees and a training process for Ethics Committee members.

Delegates agreed that partnership with industry is crucial for obtaining access to innovative drugs but guidelines for collaboration need to be established. The entire academic community that conducts non-registration drug clinical trials should agree on a minimum set of criteria for working in collaboration with industry. The EORTC has proposed rules also applicable to other disease areas, the main tenants being that (1) the study design and methodology should be

controlled by the academic researchers and (2) the database and subsequent analyses should be performed by the academic researchers. National and European academic clinical research funding should be improved. European research is fragmented as a result of the available funds being allocated mainly on a national level. It is estimated that 93% of available research funding in Europe is in the hands of Member States and spent mainly at the national level. Only the remaining 7% of funding is made available for international research such as through the EU Research Framework Programmes.

Human Tissue Research and Biobanking—Is Regulation Necessary?

The afternoon session focused on the legal and ethical aspects of biomedical research on human biological materials. Hildrun Sunseth, Head of EU Policy for the European Cancer Patient Coalition (ECPC) offered insights from the patient perspective. This coalition, launched in 2003, represents 26 EU countries and over 250 full-member organisations. The coalition's main concerns regarding the storage of human bio-specimens or biobanking include the protection of personal information and privacy rights and the use and misuse of tissue samples and data. Patients recognize the potential benefits of biomedical research. Tissue donation must remain a voluntary and informed decision, provide anonymity through the use pseudonyms linking tissue data and donor, provide feedback, and benefit sharing. Consent forms must be explicit rather than implicit as they are today. No one can predict the nature of medical research as science advances and patients need to be aware that tissue donated today may be used for research in the future.

Patients require protection against exploitation when tissues and/or data are transferred, employment and insurance discrimination and stigmatisation when negative hereditary factors are identified. A regulatory framework is needed that governs biobanking but that does not hinder or block research. The Data Protection Directive already exists yet legal and ethical common guiding principles, uniform quality standards, ethical oversight and EU legislation are lacking. The ECPC motto "Nothing About Us, Without Us!" indicates the willingness of patients to move into the future together with researchers but also underscores their importance and power as policy influencers. The Head of ECPC EU Policy commented that, patients "want to work with cancer research organisations to ensure that the balance is correct between patient rights and research interests but the general public is still fearful of bio-banking." Broad public support, realistic and balanced perceptions as well as transparency will help address people's fears and concerns. Steps towards achieving this include (1) registering all cancer trials, (2) lobbying for change—open EudraCT, (3) systematically involving patients in the design of trials and on Ethics Committees, (4) publishing both positive and negative research results, (5) amending the EU Clinical Trials Directive, and (6) keeping clinical cancer research in Europe. Hildrun Sunseth was emphatic in her support of European research stating that, "It is crucial to keep clinical cancer research in Europe as it provides patients with options and access to new treatments. Most patients cannot travel to the US for such treatments."

Three legal experts presented on the ethical and governance issues surrounding human biological tissue research and biobanking, addressing aspects concerning the definition and scope of tissue biobanking, implications for the individual and population at large, current international governance and the best direction forward for Europe. Evert-Ben van Veen believes that the mere definition of tissue banking is problematic, currently spanning the research use of 'leftover' tissue in pathology labs to population-based biobanks. Tissue research and data go hand-in-hand and the type of data associated with tissue (i.e. full or coded anonymity, directly or indirectly identifiable) will determine the legal rules for use of such data. Researchers are interested in

identifying population patterns that emerge from the study of biological materials, not the individual per se. The sharing or flow of tissue and/or data between biobanks requires privacy enhancing technology-coding techniques, which allow for donor anonymity yet remain uniquely discernible. [6] Good research governance is the way forward, striking a fair balance between the interests of all stakeholders. It should encompass strict privacy protection, transparent basic principles for research projects, methods for disseminating research results, conflict of interest policies, and intellectual property rights while at the same time allowing for sufficient flexibility. Researchers together with patient organisations should develop this type of research governance and not look to governments. This will avoid repeating the experience encountered with the Clinical Trials Directive. Harmonisation if any should be 'soft'.

Elisabeth Rynning presented the controversies surrounding access to human biobank materials. There is a lack of agreement on the definition of what constitutes a biobank—is it a collection of human tissue, organs or cells? Is this collection always associated with data? What constitutes a genetic database or a tissue database? Researchers and biobank administrators face the challenge of defining the relevant requirements for biobanking. Policymakers must decide what rules are needed. International activities and cooperation are essential but international legislation is lacking. Many guidelines exist but each country is pursuing its own route. The goals and interests underlying biobanking governance must be balanced, facilitate the justifiable use of human tissue and provide protection of individual privacy and respect for human dignity. Policymakers are struggling to understand whether today's regulations cover the use of human biobank materials, if consistency and harmonisation exist between internal and domestic regulations and whether these comply with external/international requirements.

Blood samples were once considered waste products. Today these samples represent human beings with personal information and a public resource of potential knowledge that should not be wasted. Samples are full of data, ordinary but most importantly genetic information that can affect individuals and families for many generations. UNESCO claims that genetic data is special and needs different treatment. The regulatory issues are multiple. Should biological material be considered a product, an intervention on a body or simply data? When does the tissue stop being a human being and become a research product, data or only information? What forms of regulation are required—local rules, guidelines, international laws, declarations, conventions? Who is better suited to decide the rules that govern the use of biological materials, donors and researchers or politicians and lawyers?

In the realm of international public law, the Council of Europe recognizes the 1950 Convention on Human Rights and Fundamental Freedoms, the 1997 Convention on Human Rights and Biomedicine with its 2004 Additional Protocol on scientific research (not ratified by all countries) as well as the formally non-binding Recommendation (2006) 4 on research on biological materials of human origin. UNESCO and the WHO have non-binding documents that address biobanking issues but the UNESCO Declaration on the Human Genome and Human Rights (1997) and the Declaration on Human Genetic Data (2003) are still relevant. At the EU level, relevant directives already exist for personal data protection, legal protection of biotechnical inventions, implementation of GCP as part of the Clinical Trials Directive, the setting of standards of quality and safety for human tissues and cells as well as regulation on advance medicinal products. The fundamental principle of non-commercialisation or 'no financial gain from parts of the human body' is paramount and biobank materials must not be sold. Issues requiring further attention include payment and compensation, benefit sharing and determining when a sample is no longer deemed a 'part of the human body'.

The scope of EU competency in the field of research is questionable. Is “soft coordination” based on guidelines, recommendations, funding restrictions and European Group ethics and opinions the preferred way to govern human biological materials? Clear definition of the key concepts, analysis of guiding principles and review of the complex systems of relevant national law, public international and EU law will help in determining the most appropriate level, form and content of potential regulation. Biobank research must remain open to continuous debate, show consideration of potentially sensitive ethical and legal issues, especially concerning international cooperation, genetic analyses, and research on minors and incapacitated minors while keeping abreast of developing policies and new laws.

Emmanuelle Rial-Sebbag discussed the Council of Europe and the legal instruments adopted for research on biological materials of human origin, Recommendation REC (2006) 4 of the committee of Ministers to Member States on research on biological materials of human origin. [7] This intergovernmental organisation, comprised of 47 countries, aims to protect human rights, democracy and the rule of the law. It encourages the use of biological materials in research for scientific progress but this must in practice be balanced with the protection of human beings based on the Convention on Human Rights and Biomedicine (Oviedo 1997), the Additional Protocol to this convention concerning biomedical research (2005) and Recommendation 4 on stored biological materials for future research (2006). Binding (national laws, treaties, EU law) and non-binding (international rules, professional guidelines and ethics) instruments contribute to the legal framework applied to biobanks and the associated data.

Within the scope of the Recommendation (2006) 4, ‘data’ are defined as identifiable biological materials (coded and linked anonymised materials) and non-identifiable or all other biological material not traceable back to the individual. ‘Samples’ are biological material directly obtained for research, residual biological materials and biological materials removed after death. There is no specific definition for the term ‘collection’ but may be inferred in REC 4 from references to formal procedures. For the Council of Europe, informed “consent” is an operational ‘principal’ in relation to human dignity whereas the OECD considers “consent” a process or procedure required to carry out some activity. Informed consent for ‘first use in research’ details any unforeseen potential further uses including commercial use of research results, data or biological materials. Informed consent for ‘re-use in research’ provides specific procedures for using human biological materials for other purposes.

Article 17 of REC 4 (2006) defines “population biobank” as a collection of biological material with the following characteristics: (1) the collection has a population basis; (2) it is established, or has been converted, to supply biological materials or data derived there from for multiple future research projects; (3) it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; (4) it receives and supplies materials in an organised manner. ‘Collections’ are not synonymous with ‘population biobanks’, depending on the level of organisation and standardised procedures. Likewise, obtaining biological materials does not translate into their use in research projects and consent given for tissue removal is not synonymous with consent to conduct research on the biological material.

Regarding international regulation, the speaker agreed that if this is deemed necessary then the correct avenue must be envisaged and any regulation must be realistic, consensual, anchored to practice and above all applicable. The principle of “mutual recognition” may represent a viable option. If a human tissue sample is used for research in one country, then its use should be

permitted in a second or third country. Any legal framework should not prevent the export of human tissue samples. A point to be stressed is the fact that the patient has given his/her Informed Consent. When questioned as to whether the existing legal texts are responding to any major biobanking past issue, the experts comment that current legislation is purely anticipatory as no major biobanking precedent exists that would justify such legal enforcement.

Workshop Conclusions for Moving the Ship Forward

Workshop delegates agreed that their needs as academic researchers would be best served if all groups speak with one voice when the Clinical Trials Directive is re-opened for discussion. By coming to the table with a prepared common level of consensus, the discussion can start at a much higher level thereby increasing the likelihood of addressing all issues. To this end, each of the four workshop co-organisers agreed to identify and prepare their position on 3-4 key issues for the next round of meetings. The outcomes of the EMEA October 2007 conference prepared by Professor J Demotes (ECRIN) on behalf of non-commercial sponsors, the ESF Forward Look and ICREL findings will be forthcoming in 2008 and will serve to prepare a list of changes to the Clinical Trials Directive to be submitted to regulatory authorities. Final words on the task ahead came in the closing comments from the EORTC Director General, Françoise Meunier when she encouraged delegates to “take up the magic wand and rewrite the Directive as we want it to be—a risk-driven translational research-based directive.”

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Appendix 3

The ICREL project : what should be improved in the current European legislative framework for clinical research ?

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Summary

The Impact on Clinical Research of European Legislation (ICREL) project, due to report later this year, is reviewing evidence and compiling metrics on the competitiveness and ethics of clinical research in the European Union. The project has been prompted by concerns that the European Union Clinical Trials Directive 2001/20/EC (EU CTD) is hampering, rather than helping, academic clinical research.

Data from individual countries, based on different methodologies, suggest that the impact of the European Union Clinical Trials Directive 2001/20/EC (EU CTD) may vary from one country to another (1-4). This variation has not been studied until now, so the Impact on Clinical Research of European Legislation (ICREL) project has been set up to collect data throughout the European Union, using consistent methodology, to help describe and interpret this impact. The results of the project will be publicly discussed on a conference on December 2, 2008 in Brussels and the elaborated conclusions will be included in the Final Report.

The EU CTD (Directive 2001/20/EC (5), prepared and adopted on April 4th, 2001 and implemented by all Member States from May 1, 2004), was introduced to harmonise the legislative framework for clinical research in the European Union, with the objective of harmonising the regulatory systems, of improving the protection of participants, of optimising the use of safety information, and of ensuring the quality of studies and the credibility of data (box 1). The Directive also aimed to strengthen the responsibility of research sponsors and EU Member States in clinical trials, assigning responsibilities to competent authorities, reducing investigators' responsibility, and improving patients' protection (6).

With the EU CTD a single sponsor in the EU, covered by liability insurance for study-related harm to study participants, now has to submit an application for clinical trial authorisation to the national competent authority, and in parallel a request for a single favourable opinion to Ethics Committee(s). The EMEA-based clinical trials database (EudraCT) was also implemented and a section for clinical trials added to the EudraVigilance database.

Although the overall objective of the Clinical Trials Directive has been widely welcomed, various initiatives have challenged its implementation. The European Commission (DG Enterprises and Industry) and the EMEA organised a conference in London, on October 3rd 2007 (www.emea.europa.eu/meetings/conference2007.htm), to learn about the challenges different stakeholders envisage with the new legislation and to discuss possible changes. Concerns expressed by various stakeholders highlighted the need to provide detailed data and metrics on the impact of the Clinical Trials Directive, with the objective of tailoring an adaptation of the EU legislation.

The contribution of DG Research to the debate on the revision of the Directive is ICREL, a one-year project funded by the first call of the FP7 Health Priority. The European Clinical

Research Infrastructures Network (ECRIN), the European Organisation for Research on Treatment of Cancer (EORTC), the Hospital Clínic of Barcelona and the Ethics Committee of the Medical University of Vienna are collaborating on this project coordinated by the European Forum for Good Clinical Practice (EFGCP) (www.efgcp.be/ICREL). ICREL's aim is to measure indicators of implementation in different member states, to compare these metrics, and to interpret them in terms of direct and indirect impact of Clinical Trials Directive 2001/20/EC and EU related legislation on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, Ethics Committees and Competent Authorities.

ICREL will collect and compare figures from EU member states on clinical trials on medicinal products sponsored by pharmaceutical companies, biotechnology SMEs, and academic institutions, on other categories of clinical research, as well as on the impact on Ethics Committees, Competent Authorities, clinical research infrastructure, and on the workload, cost and funding of clinical trials. It will compare the situation before and after the implementation of the Directive. Detailed data obtained through a series of surveys involving structured interviews and questionnaires, focussing on metrics of the impact of this legislation (e.g. on the quantity of clinical trials, on quality and credibility of data, on patient safety and transparency of study results, on cost of monitoring, duration of clinical trial authorisation, clinical trial initiation and progression, on patient enrolment, and on workload for the stakeholders). These surveys will be collected through stratified random sampling of the targeted stakeholder groups "commercial" and "non-commercial sponsors" as well as "ethics committees". The European Competent Authorities will be approached in total. In addition, spontaneous completion of the questionnaires will be sought by posting the questionnaires on the EORTC web page and broad public dissemination of the need to support the project with the provision of data through this tool.

Which problems will ICREL aim to solve?

The implementation of the Directive has been hampered by four major problems (box 2): disharmony of national clinical trials requirements and infrastructures, inadequate protection of research participants except those taking part in drug trials, lack of differentiation between the needs of industry and academic researchers, and increased administrative burden. The specific challenges for different groups are examined below.

Industry and SMEs

On the industry and SME side, the EFPIA expresses five major concerns: differences in the national requirements for clinical trial application; SUSAR reporting to ethics committees; definition of IMP; GMP requirements in some Member States – import, manufacturing site; and the definition of substantial amendments. EuropaBio has released, together with BIA, a White Paper (7) in October 2006 expressing similar concerns of the biotechnology SME sector: lack of harmonisation in clinical trial application; increased bureaucracy and uncertainties due to variable national requirements; different interpretation in the definition of IMP; GMP related issues – import rules, manufacturing license, particularly relevant for active biological ingredients; different requirements for safety reports.

The general consensus is that the Clinical Trial Directive failed to achieve harmonisation, and results in workload that is disproportionate with the objective of protecting safety of trial subjects. The resulting delays and costs are a threat to the EU bioscience industry, and discourage these companies to undertake multicentre trials on a pan-European basis.

Academic institutions

On the academic side, surveys were performed, reported and discussed by some public institutions conducting clinical trials either on a national or on an EU-wide basis. Most of these surveys (8-10) point to a decrease in the number of clinical trials, to an increase of costs, without any obvious change in the level neither of patient protection nor in the quality of data collected. This is even more true for EU-wide trials, as for instance Cancer Research UK no longer believes to be in a position to act as a sponsor in EU multinational studies (10) (although the objective of the Directive was to facilitate these multinational studies). A survey performed by the Federation of European Cancer Societies points to the varying requirements for non-commercial cancer trials across the EU countries, including status and role of the sponsor in national or multinational studies, definition of IMP, free access to marketed drugs, simplified IMP dossier, adverse event reporting, cost of studies and financial support, pharmacovigilance systems and support to MedDRA coding, monitoring strategy, dialogue between competent authorities and ethics committees.

However, these data have to be interpreted with caution as they derive from well-established and professional clinical research institutions. Improvement in patient protection and in credibility of data due to the requirements of the Clinical Trials Directive is more likely to occur in less experienced institutions. Therefore a more comprehensive survey on the impact of the legislation on non-commercial trials is needed.

A very important component of the academic clinical research activity is represented by clinical studies on medical devices, randomised surgery and radiotherapy trials, multimodal trials, diagnostic and imaging studies, genotype-phenotype studies, blood and tissue collection, biomarker studies, physiology and pathophysiology studies, and observational studies. These categories of clinical research are not covered by the Directive 2001/20/EC but partly by national legislations in some EU countries (not in others), with highly variable requirements. It was reported that the transposition of the Directive into national laws had an indirect effect on this legislative framework, and likely resulted in an even more divergent system, increasing the difference between the countries with patient-centred and those with product-centred laws (11). This has to be assessed through metrics on these research activities at both the national and the EU level.

Competent authorities, pharmacovigilance, monitoring, infrastructure and funding

The EU CTD had a major impact on the structure, procedures and activity of most of the national *competent authorities*, leading to the need of additional resources and the charging of a fee to the sponsor for clinical trial applications and substantial amendments. In turn the competent authorities can provide a lot of valuable and measurable information on clinical trial activity (number, type, timelines, patient enrolment, substantial amendments, SUSARs, etc...).

As the Directive was implemented in a different way in the different EU Member States, varying practice in competent authorities and in the dialogue with the ethics committee resulted in significant differences in clinical trial application procedures (for instance, whereas the parallel submission by the sponsor is the rule in most countries, Hungary uses a one-stop shop approach in which the competent authority, not the sponsor, interacts with the central ethics committee).

As the staff and budget capacities vary in the different competent authorities, the management of *SUSARs* notified to the competent authorities, their practices to support MedDRa coding and to send electronic notifications to the EudraVigilance database differ. In addition, the EU Member States' requirements for dissemination of *SUSAR* information varies and thus the impact of these processes on patient protection will be of interest.

Some countries develop strategies for cost-effective, risk-based *monitoring* in non-commercial trials, and some provide logistic and financial support to this monitoring activity for investigator-initiated studies. This project will investigate the impact of these different approaches on data quality, costs and patient safety.

Increased responsibilities of the investigator-sponsors, increased workload and GCP requirements for the investigators led to foster the development of the national *infrastructure* for clinical research: clinical research centres, clinical trials units (12), national networks (13), and EU-wide infrastructures networks (14) or disease-oriented scientific networks (15-16). In addition, initiatives were developed to facilitate the conduct of industry-sponsored trials in some countries (the UK Clinical Research Collaboration, the CeNGEPS in France). This indirect impact of the Directive, tending towards professionalism and a rational structuring of clinical research activity, has also to be considered in this survey.

Of course, structuring the support to clinical research and meeting the quality requirements results in extra costs for both industry and academic sponsors. As a result, academic researchers claimed for *public funding* to clinical research (17), and in the recent years some opportunities arose at the national level, including initiatives from the Italian competent authorities, from science ministries in some countries (e.g. Germany), and health ministries in other (e.g. France). Simultaneously the FP7 health priority funds some clinical trials, whereas the Innovative Medicine Initiative will also support biomarker studies and post-marketing safety studies. This project will aim to find out whether the current funding practice is matching the costs required by the new regulatory environment.

Ethics committees, protection of participants and transparency of study results.

The impact of the Directive on the *ethics committee* was major as it requires delivering a single opinion in each EU country. However, this was implemented in very different ways in the EU Member States, and often the single opinion still requires multiple submissions of information and review as well as extended delays (18). Differences in the interaction between ethics committees and competent authorities, in processes, composition, training, fees, number and activity of ethics committees, in their independence, and in the cultural context of ethical review result in major discrepancies between countries in protocol and patient information requirements, review timeframes, costs and acceptability for a single protocol (19) in a multinational study. Moreover, ethics committees and sponsors complain about the workload due to the useless notification of SUSARs. Compilation of all existing information and an additional survey in this project will help clarifying the impact of having different national ethics committee systems on clinical research in Europe. Finally, information gathered from ethics committees will provide the other surveys with metrics and a lot of valuable information on the number and type of studies conducted in EU countries.

The EU Directive was designed to improve the *protection of participants* in clinical research. This point will also be assessed by the survey, with the involvement of both ethics committees and patients associations. However, national legislations still differ in the protection of vulnerable populations (e.g., the waiver of consent in emergency care is possible in some countries, not in other) (20). Finally, the indirect impact on transparency will be explored: data collected by national competent authorities or by EudraCT may be used to promote an EU clinical trial registry. Other approaches like the new French legislation requiring the sponsor to inform the participants on the overall outcome of the study will be compiled. And finally, the EU CTD's impact on speed and comprehensiveness of study result publication will be explored.

Outputs from ICREL

This work is expected to help improving Europe's attractiveness and competitiveness for clinical research by delivering the facts for proposing pathways for improvement of the clinical trial environment in the EU, allowing better balance of high level of patient protection, optimal use of safety information, high quality and credibility of data, with minimal cost and workload for investigators, sponsors, ethics committees and competent authorities, for both national and multinational studies in the EU. Together these improvements should increase the competitiveness of the academic EU clinical research and its attractiveness as a place for commercial clinical trials compared with emerging investigation sites in Eastern Europe and in Asia-Pacific (21).

Box 1

History of the EU Clinical Trials Directive

One of the consequences of the Nuremberg trial (1947) was a statement on the need to collect informed consent prior to the participation of human beings in biomedical research experiments (22). This principle was enlarged and refined in the Declaration of Helsinki (1964) and its various revisions, and adopted as a standard for clinical trials on medicinal products run by drug manufacturers for registration and post-marketing purposes. Based on a harmonisation agreement covering the three main geographic areas where clinical development was prominent (European Union, United States of America and Japan), the International Conference on Harmonisation (23) good clinical practice guideline (ICH-GCP-E6) from 1996 defined the standard for all type of clinical research (*“The principles established in this guideline may also be applied to other investigations that may have an impact on the safety and well-being of human subjects”*) (24) but only adopted by industry as a standard for commercial trials. But whereas drug regulatory agencies required compliance to ICH-GCP in trials intended for submission to competent authorities, there was no mechanism of enforcement for compliance to ICH-GCP in non-commercial trials. The ICH-GCP guideline was implemented in the context of clinical trials for marketing authorisation of medicinal products. Clinical trials on medical devices for registration purposes have to follow the ISO14155. However, no requirement existed to enforce the implementation of the Helsinki principles and to ensure appropriate protection of participants in non-commercial clinical research.

During the 80's and 90's, some countries developed national legislation to enforce protection of participants in all categories of clinical research. For instance the pioneering Huriet Law (25) in France (1988) covered the participation of patients and healthy volunteers in any 'interventional' clinical research (defined as therapeutic interventions, but also as any invasive investigation), requiring a sponsor responsible for the study, an insurance coverage, an approval by the ethics committee, a collection of informed consent, a notification to the competent authority, and a mechanism for adverse event reporting. Other laws in other countries also resulted in an improvement in the protection of participants; however the type of clinical research covered by these laws and the nature of the protection widely varied between countries. Some countries developed legislation centred on the patients, with an equivalent level of protection in any type of biomedical research, whereas other countries adopted legislation centred on the product, focusing on the credibility of data used for registration purposes, and in which the protection of participants is restricted to clinical trials on medicinal products (and often on medical devices) (11). This resulted in major challenges

for drug manufacturers involved in multinational studies in the EU, and also for academic institutions conducting clinical trials: for instance, a randomised surgery trial will require in some countries a sponsor, a liability insurance for trial-related harm to study participants, a submission to ethics committees and to a competent authority, and the reporting of adverse events, and nothing in some other countries. The situation is similar for radiotherapy (with for instance a specific legislation steered by the Ministry of Environment in Germany), and for non-therapeutic clinical research.

Box 2

Four major problems with EU CTD implementation:

1 -The fact that the clinical trials legislation was established as a Directive required transposition of its principles into national legislation. Since most of the EU countries already had their own legislation and practice before the adoption of the Directive, their interpretation of the Directive and the changes brought to the national legislation were highly dependent on this pre-existing framework. As a result, the harmonisation target was partly missed for clinical trials on medicinal products.

2 - Due to the structural singularities of the European Commission it was in the remit of the Directorate Enterprises to implement clinical trials legislation, and thus the scope of the EU CTD centred on the product, failing to protect participants in clinical research other than clinical trials on medicinal products. However, several EU Member States choose to implement the EU CTD in their new clinical research legislation with a wider scope than the Directive's. And as the revision of the national legislations covering other types of clinical research was performed without any EU coordination this process resulted in totally divergent systems. For instance, France extended the system recommended for medicinal products to all 'interventional' studies (requirement for a sponsor, insurance, approval from ethics committees and competent authority, definition and notification of SUSARs), while other 'patient-centred' legislations only rely on ethics committees for the protection of participants in the same studies. Other countries adopted 'product-centred' legislations covering only health products (drugs and devices) or only drugs (a strict translation of the Directive). Especially the performance of large multi-national clinical trials suffers from this lack of harmonisation.

3 - In an attempt to achieve the same quality standards for all types of clinical trials with medicinal products almost similar requirements for all types of clinical trials with medicinal products were introduced. The Directive does not consider the different categories of clinical research performed by the commercial (registration studies on new treatments) vs. the non-

commercial sponsors (mostly studies comparing treatment strategies and combinations using marketed drugs, or exploring the potential for new indications). Using similar rules and requirements for all types of studies reportedly leads to major obstacles to academic research (26-28), whereas it was discussed that case-by-case, risk-based strategies taking into account the hazard to the patients and the hazard to public health would probably help ensure quality and protection with less administrative burden and lower costs. A guidance document on non-commercial trials (as stated in recital 11 of the Directive 2005/28/EC), open to public consultation before 1st October 2006 and still awaiting publication, as well as Q&A documents, were drafted to dampen this effect. But this concept of specific modalities for 'non-commercial trials' is challenged by the academic community as data from these trials would not be accepted for registration purpose. In addition, the increase in sponsor's responsibilities and tasks was not a major obstacle for big pharmaceutical companies, but SMEs including small biotechnology companies, face major difficulties in acting as a single sponsor on the EU level for their commercial trials, mostly early proof-of-concept trials, often in rare diseases. Also multi-national non-commercial trials are difficult to organise in an efficient way because a sponsor based at an academic institution in one EU Member State has not the institutional coverage to take over legal responsibility for clinical trial activities performed at an academic institution in another EU Member State. In addition, in different EU Member States academic investigators do not have at all the legal coverage to play the role and endorse the responsibilities of a sponsor according to the requirements of the EU Clinical Trials Directive.

4 - Several of the EU CTD-related requirements were reported to have led to an increase in administrative tasks for all stakeholders leading to a need for increased resources with the related cost generation, delays in study preparation and performance and the danger of reduced protection of the trial participants as ethics committees reported to have reduced capacities to cover their patient protection responsibilities due to overwhelming administrative tasks, especially in the area of expedited safety reporting.

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Appendix 4

Programme of the ESF/ EMRC Forward Looks Conference on Investigator-Driven Clinical Trials



**EUROPEAN
SCIENCE
FOUNDATION**
SETTING SCIENCE AGENDAS FOR EUROPE

FORWARD LOOK

Consensus Conference Investigator-Driven Clinical Trials

29-30 September 2008
Maison de la Région Alsace
Strasbourg, France



Chair: Professor Jürgen Schölmerich (DFG, Germany)
Co-Chairs: Professor Håkan Billig (SRC, Sweden)
Professor Roger Bouillon (FWO, Belgium)
Coordinator: Dr. Carole Moquin-Pattay (ESF, France)
www.esf.org/emrc/idct

ESF: Professor Marja Makarow (Chief Executive)
ESF-EMRC: Professor Liselotte Hejgaard (Chair)

www.esf.org

Preliminary Programme

Rationale

Various categories of patient oriented research are necessary to develop academic knowledge into new diagnostic, preventive and therapeutic interventions, each associated with different risks. These include advanced therapy, proof-of-concept, first-in-man studies, impact measures and also post-marketing trials aimed to optimise treatment strategies and to assess the safety and the cost-effectiveness of new interventions through medico-economic studies.

The overall objective of the Forward Look launched by the ESF and managed by the EMRC is to develop a strategy and make recommendations for strengthening public-sponsored and investigator-driven clinical trials (IDCT) to best address health needs in Europe in an international perspective.

Main Objectives of the Conference

The conference will focus on addressing the concerns expressed in the EMRC White Paper about "Present status and future strategy for medical research in Europe" with a special emphasis on the specific needs of patient oriented research and the identification of the main problems faced by investigators when initiating a clinical trial in Europe with the aim to produce problem-solving recommendations.

We are honored that Professor Jürgen Schölmerich, Professor Roger Bouillon and Professor Håkan Billig have agreed to chair this conference aimed to challenge to a high level audience the recommendations produced at the occasion of five strategic workshops, organised in the frame of the Forward Look exercise, i.e.:

- **'Categories & Design of IDCT'** chaired by Professor Harry Janssen (Erasmus MC, Netherlands), and co-chaired by Professor Jacques Demotes (ECRIN, France)
- **'Regulatory, Legal Issues, Intellectual Property Rights & Data Sharing'** chaired by Professor Sally Davies (DH, United Kingdom), and co-chaired by Professor Jacques Demotes (ECRIN, France)
- **'Management of IDCT'** chaired by Professor Janet Darbyshire (UKCRN & MRC CTU, United Kingdom), and co-chaired by Professor Stefan Bielack (Olgas Hospital Stuttgart, Germany)
- **'Education, Training, Career & Authorship'** chaired by Professor Eero Vuorio (University of Turku, Finland), and co-chaired by Professor Pierre Lafolle (Karolinska Institute, Sweden)

- **'Funding & Models of Partnership'** chaired by Professor Christian Bréchet (Mérieux-Alliance, France), and co-chaired by Professor Richard Sullivan (London School of Economics, United Kingdom)

For each strategic workshop, experts were asked to present from their perspective the main challenges they encounter and propose possible solutions based on examples.

Deliverables

After completion of the five strategic workshops a draft Forward Look report was produced under the coordination of their chairs in preparation of the Consensus Conference. The final report of the Forward Look activity 'Investigator-Driven Clinical Trials' will highlight the consensus reached on the key recommendations to strengthen patient oriented research in Europe.

The EMRC has an important role in the future development of medical research in Europe through its science policy and through dialogue with the European Commission, the European Research Council, Learned Societies, Universities and Academic Medical Centres. We firmly believe that a concerted and collaborative effort will have a positive impact for health and welfare in Europe and the rest of the world. We invite debate and action to bring our proposals to fruition.

1. EMRC White Paper 'Present Status and Future Strategy for Medical Research in Europe', Dec. 2007 at: www.esf.org/emrc/whitpaper

Conference Preliminary Programme

Monday 29 September 2008

13:00-14:00 **Welcome Buffet and Registration**
Maison de la Région Alsace, 1 place du Wacken 67070 Strasbourg – www.region-alsace.eu

14:00-14:20 **Welcome and Introductory Remarks**
Professor Marja Makarow
Chief Executive, European Science Foundation (ESF), Strasbourg, France
Professor Liselotte Højgaard
EMRC Chair and Professor and director, Clinical Physiology, Nuclear medicine & PET,
Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

14:20 - 16:00 **Day 1 - First Session**

Chair: **Professor Jürgen Schölmerich**
Vice-President, Deutsche Forschungsgemeinschaft (DFG) and Professor,
University Medical Center, Regensburg, Germany

14:30-15:45 **Categories and Design of Investigator-Driven Clinical Trials**
Professor Harry L.A. Janssen
Professor, Erasmus Medical Center, Rotterdam, The Netherlands
Round table discussion – Dr. Amy Patterson
Director, Office of Biotechnology Activities, National Institutes of Health,
Bethesda, USA

15:45-16:00 **Coffee Break**

16:00-18:00 **Regulatory and Legal Issues, Intellectual Property Rights and Data Sharing**
Professor Jacques Demotes
Coordinator, ECRIN, Paris, France
Dr. Chris Bird
Solicitor, The Wellcome Trust, London, United Kingdom
Round table discussion – Professor Kent Woods
Chief Executive, Medicines and Healthcare Products Regulatory Agency (MHRA),
London, United Kingdom

18:00 **End of Day 1**

19:30-22:30 **Conference Dinner**
Château de L'île, 4, quai Heydt 67540 Ostwald
Transportation organised by bus from Hotels –
Departure 19:15



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Conference Preliminary Programme

Tuesday 30 September 2008

08:30-09:00 **Welcome Coffee and Registration**
Maison de la Région Alsace, 1 place du Wacken 67070 Strasbourg - www.region-alsace.eu

09:00-12:30 Day 2 – First Session

Chair: Professor Håkan Billig
EMRC Core Group Member for the Swedish Research Council and Professor,
Göteborg University, Göteborg, Sweden

09:00-10:00 **Management of Investigator Driven Clinical Trials**
Dr. Sarah Meredith on behalf of Professor Janet Darbyshire
UKCRN and Clinical Trial Unit, MRC, London, United Kingdom
Professor Stefan Bielack
Professor, Olga Hospital, Stuttgart, Germany
Round table discussion

10:00-11:00 **Education, Training, Career and Authorship**
Professor Eero Vuorio
Chancellor, University of Turku, Turku, Finland
Professor Pierre Lafolle
Professor, Karolinska Institute, Stockholm, Sweden
Round table discussion

11:00-11:30 Coffee Break

11:30-12:30 **Funding and Models of Partnership**
Professor Christian Bréchet
Vice President for Medical & Scientific Affairs, Mérieux Alliance, Lyon, France
Professor Richard Sullivan
Professor, London School of Economics, London, United Kingdom
Round table discussion

12:30-13:00 Lunch

13:00-15:00 Day 2 – Second Session

Chair: Professor Roger Bouillon
EMRC Core Group Member for the Fonds voor Wetenschappelijk Onderzoek (FWO) and
Professor, Leuven University, Leuven, Belgium

13:00-15:00 **Point of view from European Learned Societies**
Professor Stephanie Dimmeler
European Society of Cardiology (ESC) and Professor, Molecular Cardiology,
University of Frankfurt, Frankfurt, Germany
Professor Jes Olesen
President, European Brain Council (EBC) and Chief, Danish Headache Center, Copenhagen, Denmark
Professor José Baselga
President, European Society for Medical Oncology (ESMO) and Chief, Medical Oncology Service,
Barcelona, Spain
Professor Markus Büchler
Past-president, International Hepato-Pancreato-Biliary Association (IHPBA) and
Chairman, Department of General Emergency and Visceral Surgery, Heidelberg, Germany
Round table discussion

15:00-15:30 **Closing Discussions**
Chair: Professor Liselotte Højgaard
Chair, EMRC and Professor and director, Rigshospitalet, University of Copenhagen, Denmark

15:30 End of Day 2



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