

Investigator-Driven Clinical Trials



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The EMRC has an important role in the future development of medical research in Europe and it invites the European Commission, the European Research Council, learned societies, universities and academic medical centres for debate and action to bring its recommendations to fruition.

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Executive Summary

Investigator-driven clinical trials (IDCT) are clinical trials that are instigated by academic researchers and are aimed at acquiring scientific knowledge and evidence to improve patient care. Such studies deal with potential diagnostic and therapeutic innovations that do not attract or could even be against commercial interest. Typical examples are proof of concept studies, studies on orphan diseases, comparison of diagnostic or therapeutic interventions, surgical therapies or novel indications for registered drugs. IDCT thus have a much broader scope and potential impact than industry-driven clinical trials. IDCTs form a key part of patient-oriented clinical research, and create the basis for continually improving patient care.

Clinical research and especially IDCT are under strain in Europe for a multiplicity of reasons. The European Medical Research Councils (EMRC) of the ESF has therefore undertaken this Forward Look exercise on IDCT to analyse the problems and the needs, and recommend solutions to the challenges identified.

This Forward Look represents what is probably the most comprehensive examination of IDCT in Europe in recent years. A thorough analysis of the problems faced by academic investigators conducting IDCT was carried out through a series of five workshops covering different themes and attended by active and acknowledged experts in the field. These workshops identified specific issues that need to be addressed and recommended a range of possible solutions.

The themes of the five strategic workshops were:

- categories and design of IDCT
- regulatory and legal issues, intellectual property rights and data sharing
- management of IDCT
- education, training and careers, and authorship
- funding and models of partnership

A total of 88 recommendations emerged from the workshops. These recommendations were subsequently processed following the advice of the Forward Look Management Committee, resulting in a list of 26 recommendations.

A consensus conference attended by around 90 delegates was held in September 2008. After debating the recommendations, the individual participants were invited to rank them in order of priority. These rankings were pooled and a final ranking list was obtained.

The top five recommendations to strengthen IDCT in Europe as ranked by the consensus conference were as follows:

- 1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.**
- 2. To increase levels of funding for IDCT.**
- 3. To adopt a 'risk-based' approach to the regulation of IDCT.**
- 4. To streamline procedures for obtaining authorisation for IDCT.**
- 5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.**

A panel of experts subsequently convened to develop a strategy for the sustainable implementation of the recommendations, paying particular attention to the top five ranked recommendations. The advices for developing an implementation plan are presented in this Forward Look report. The four key stakeholder groups in charge of their implementation are:

Group 1:

- Academic research
- Learned societies
- Universities
- Healthcare providers/hospitals

Group 2:

- National and EU funders
- National and EU regulators
- Ministries
- Ethics committees

Group 3:

- Patients
- Philanthropic organisations
- General public

Group 4:

- Private sector

In addition, a separate meeting was held to consider particular problems faced by IDCT in countries of Central and Eastern Europe (CEEC). It was concluded that these countries face broadly similar problems to those of Western Europe, but that the problems tend to be more acute and extreme. A list of recommendations to address the issues specific to CEEC is proposed.

We hope that this Forward Look will be the beginning of interactive discussions between the stakeholders and will generate strategic planning and implementation of the recommendations so that better IDCT and clinical research will improve patient care and health in Europe and worldwide.

Foreword

Improved patient-oriented research in Europe will benefit European citizens and the European medical industry and facilitate the transfer of scientific discoveries from the laboratory bench to the bedside. For Europe and for the rest of the world this effort will be of great importance for the quality of life of individuals and the wellbeing of society as a whole.

To achieve this important objective, the European Medical Research Councils (EMRC) at the ESF mandated the undertaking of a Forward Look on 'Investigator-Driven Clinical Trials'.

This consisted of a state-of-the-art analysis of the current problems faced by academic investigators when initiating clinical trials in Europe and the identification of the investigators' needs. This was achieved by organising a consultation process involving high-level experts already engaged in a similar strategic approach at a national, pan-European or international level and focusing on five main issues:

1. Categories and design of patient-oriented research needed for promoting health research
2. Regulatory and legal issues, intellectual property rights (IPR) and data sharing between stakeholders such as academia, industry and patient groups
3. Management of investigator-driven clinical trials
4. Education, training, careers and authorship
5. Funding and models of partnership

The outcome of the consultation process, including recommendations for how to solve the identified problems and address the specific needs, was presented to and further challenged by a broader high-level audience participating in a consensus conference. This group of acknowledged experts was also requested to prioritise the top five recommendations. This thorough and comprehensive exercise is the basis for the present Forward Look.

The Forward Look makes recommendations on how to strengthen patient-oriented research with the aim of improving clinical research in Europe and thereby securing better health and welfare for the European community. As science is global, strengthened medical research in Europe will also benefit the rest of the world.

As Chief Executive of ESF and Chair of EMRC it is our privilege to express a warm thank you to all who have been involved in this Forward Look process, and to congratulate them for the impressive and important result. We hope that Europe will listen and implement the recommendations, which we believe are urgently required given that clinical research in Europe is under severe pressure. For example in Sweden, the leading country in medical research as measured by production

per capita, serious concerns have been voiced about the future status of the country's clinical medical research. Moreover in January 2009, a group of distinguished peers involved in clinical research in the UK published a warning about the possible extinction of such research in the UK.¹

If we can collaborate on this important issue and improve conditions for clinical research, we can bring better health and prosperity to Europe.

Professor Liselotte Højgaard
EMRC Chair

Professor Marja Makarow
ESF Chief Executive

1. Timesonline January 14, 2009

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Thank you to the 150 speakers and participants² of the strategic workshops and consensus conference for their contribution and sharing of their expert analysis and best practices.

We are honoured that the consensus conference was held under the auspices of the French Presidency of the European Union and hosted by *La Maison de la Région Alsace* in Strasbourg, and would like to express our gratitude to the French Minister of Research Mrs. Valérie Pécresse and the President of the Alsace Region Mr. Adrien Zeller.

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We hope that by broadly disseminating this Forward Look to the heads of ESF member organisations, the European Commission directorates and the various stakeholder groups identified in the report, the recommendations will be widely implemented for the future benefit of all European citizens.

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2. All listed in this report in Chapter 11 Committee Members and Annex 2 Speakers and Participants in the Consensus Conference, 29-30 September 2008, Strasbourg, France

1. Rationale

Medical research is the basis for optimal patient treatment in hospitals and healthcare throughout the world. Basic research in biomedicine leads to new insights into the etiology and pathophysiology of diseases, and the discovery and development of new diagnostic tools, new drugs, new technologies and new biomaterials. Translational research brings the ideas from basic research into clinical patient-oriented research and *vice versa*. Clinical patient-oriented research involves testing new discoveries in the clinic by carrying out carefully controlled investigations on patients – known as clinical trials. This includes testing not only new drugs, but also new methods, devices, imaging and surgical procedures. When the research has been published, new methods for the improved treatment of patients can be introduced, based on the findings of the research.

At present clinical patient-oriented research is under strain in Europe. There are a number of reasons for this. For example the demands for greater efficiency in healthcare systems leave little time for medical research; and obstacles are created by an increasing burden of bureaucracy.

This Forward Look analyses the problems and obstacles faced by investigators wishing to set up and run investigator-driven clinical trials (IDCT) – clinical patient-oriented research that is initiated by academic researchers or carried out as a private-public partnership. The Forward Look identifies the specific problems and presents a set of recommendations aimed at solving these problems.

Public Health Needs for Europe

In November 2004 The World Health Organization (WHO) released a groundbreaking report³ which recommended ways in which pharmaceutical research and innovation could best address health needs and emerging threats in Europe and the world. *Priority Medicines for Europe and the World*, commissioned under the Dutch Government's Presidency of the European Union (EU), identified a priority list of medicines for Europe and the rest of the world, taking into account Europe's ageing population, the increasing burden of non-communicable illnesses in developing countries and diseases which persist in spite of the availability of effective treatments. The report looked at the gaps in research and innovation for these medicines and provided specific policy recommendations on creating incentives and closing those gaps.

3. WHO 11/04 Report on Priority medicine for Europe (see <http://www.who.int/mediacentre/news/releases/2004/pr83/en/> and <http://mednet3.who.int/prioritymeds/report/index.htm>)

In addition, the report addressed obstacles which prevented effective medicines from being better delivered to the patient. It emphasised fixed dose combination medicines (medicines which include more than one active ingredient in one pill) as worthy of further research and development. It also examined the needs of particular population groups such as children, women and the elderly, which have frequently been neglected in the scientific or medicine development process.

A list of priorities for future research was identified by the report. These included future public health threats, diseases for which better medicinal products are required, diseases for which biomarkers are absent, diseases for which treatment is absent, neglected diseases or areas and diseases for which prevention is particularly relevant.

The WHO report suggested that Europe can and should play a global leadership role in public health, as reflected by its history of the provision of social services and social safety nets for all citizens. In many developing countries, the poor are increasingly affected by chronic diseases that are widespread in Europe, including cardiovascular disease, diabetes, tobacco-related diseases and mental illnesses such as depression.

For a number of diseases that affect people in all members of the EU, no effective and safe medicinal treatment is yet available, for example Alzheimer's disease and several cancers. For some diseases – such as breast cancer – potentially large markets exist for medicines and pharmaceutical research is likely to become increasingly intensive for these therapeutic classes. For other categories of disease, however, the number of patients is low – for example cystic fibrosis. Here the market-driven pharmaceutical industry does not pursue research and development. A similar situation applies for new medicines against diseases such as tuberculosis, a growing problem in Europe and even more so in the rest of the world.

Priority Setting

For Europe an efficient way of meeting the needs identified by the WHO report is for integrated, EU-wide patient-oriented research, with priorities set by patient needs. Such an approach would reduce fragmentation and duplication of research in Europe and provide a means for carrying out high-quality, multinational clinical studies. Efficient patient-oriented research requires both specialised competences and an advanced infrastructure. Such research is performed in academic medical centres and university hospitals and could also benefit from collaboration with the pharmaceutical industry. Learned societies, academies, disease-oriented net-

1. Rationale

works and organisations all provide support. However infrastructure that supports patient investigations, database management, quality assurance, monitoring and regulatory affairs are lacking.

Increasing demand for efficiency in clinical work in hospitals militates against clinical patient-oriented research, which is time-consuming and labour-intensive. Furthermore, increasing bureaucracy that is required for setting up a clinical trial adds to the burden.

The aim of this Forward Look is to focus on areas where conditions for non-commercial clinical trials can be improved in Europe.

- i) The **funding aspect** is a special problem because it is very expensive to perform large-scale clinical trials. For this reason large-scale clinical trials are mainly undertaken by the pharmaceutical industry for diseases that affect large numbers of people. Rare diseases groups or new indications for established drugs are usually ignored. By the same token, funding for IDCT was and frequently still is lacking, even though such trials are capable of increasing our basic understanding of diseases and improving healthcare. In addition there is increasing pressure on clinical investigators to provide more routine clinical care services thereby decreasing the amount of time they can devote to research. Strategies for increasing the amount of research time available to clinical investigators and increasing funding and overall support for IDCT are thus urgently needed.
- ii) National and EC authorities have **rules and regulations** that govern clinical trials and these are interpreted differently by the different member states. This is an important obstacle for performing clinical research in Europe. The Forward Look describes the problem and recommends a strategy for a common approach to clinical trials between national authorities and EC authorities: Directorate General (DG) Research⁴, DG Health and Consumer Protection⁵ and DG Enterprise and Industry⁶. The mere fact that this area is governed by three different DGs is in itself a significant challenge.
- iii) In many countries there is a general perception that the attractiveness of patient-oriented research as a career has declined and that there is a shortage of qualified researchers. There is also a lack of incentives for qualified personnel to enter the field. An

important obstacle to the development of an optimal strategy for non-commercial clinical trials is the issue of appropriate **career structures** in clinical medicine.

- iv) Another important issue is that of **data ownership**. In commercial clinical trials sponsored by the pharmaceutical industry, data are not owned by and open to researchers and the participating patients. While it is recognised that there are issues of intellectual property, the advancement of knowledge requires data to be shared and more needs to be done to address this.
- v) Clinical and translational medicine requires a solid **infrastructure** comprising research centres and clinical trials units. These are centres of competence and excellence that are founded upon expertise and which provide access to patient-oriented research projects originating from the surrounding scientific community – academic scientists, investigators or industry sponsors. Professional staff trained according to good clinical practice, hospital beds, equipment devoted to patient-oriented research and standard operating procedures ensure that clinical studies are designed and conducted to the highest standards. In Europe there is a lack of enough of such infrastructure for clinical and translational medicine.

A model organisation for an EU-wide integration of patient oriented research is illustrated by the European Clinical Research Infrastructures Network (ECRIN)⁷, funded under the EC's Framework 6 research programme and supported by the European Strategy Forum on Research Infrastructure (ESFRI). Another example is the European Organisation for Research and Treatment of Cancer (EORTC), with its history of 50 years for cancer research, providing a good model of how Europe-wide research can be achieved.

There is a need for the European Union to develop a new strategy to strengthen patient-oriented research, including research across national borders. This will increase the ability of the EU to make significant discoveries through studies involving large patient populations – and initiated by patients' needs and not solely driven by commercial imperatives.

4. DG Research 7 Framework Programme
(see http://ec.europa.eu/research/fp7/home_en.html)

5. DG Health and Consumer Protection
(see the document on "Health in Europe a Strategic Approach" open for consultation at http://ec.europa.eu/health/ph_overview/Documents/strategy_discussion_en.pdf)

6. DG Enterprise and Industry (see regulation for pharmaceuticals at http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm)

7. ECRIN (see <http://www.eclin.org/>)

2. Categories and Design of Investigator-Driven Clinical Trials

As a first step towards developing a strategic framework for IDCT across Europe it is necessary to define the different categories of clinical trials that are needed to turn academic knowledge into new diagnostic, preventive and therapeutic interventions, and the key considerations for designing such trials.

Categories of Patient-Oriented Research

Within the EU there is a lack of harmonisation of regulations for clinical trials other than those that are directly investigating medicinal products, and even the definition of an investigational medicinal product (IMP) is blurred and open to a variety of interpretations. There is a lack of a common definition for categories of clinical research other than clinical trials on medicinal products. For these reasons, national legislation on clinical research other than clinical trials on medicinal products is highly divergent, making it very difficult to conduct this type of study at the multinational level.

What is needed

There is an urgent need for a common categorisation that would make it simple to define national requirements for a given clinical study.

Recommendation

We recommend to regulators that categories of clinical trial are defined in a way that is based on the type of study, as follows:

1. Clinical trials on medicinal products
2. Clinical trials on medical devices
3. Other therapeutic trials (e.g. radiotherapy, surgery, transplantation, transfusion, physical therapy, psychotherapy)
4. Diagnostic studies (imaging, other)
5. Nutrition studies
6. Other interventional patient-oriented research (e.g. physiology, physiopathology, biobanks, complementary and alternative methods, psychology)
7. Epidemiological studies (i.e. observational)

Interventional versus Observational Studies

Within the EU directive on clinical trials of medicinal products, the definition of 'intervention' is unclear and open to interpretation. There is a grey area between 'interventional' and 'observational' studies. For example an 'observational' study that requires the collection of blood samples could be interpreted as interventional in some countries and environments but not in others.

This lack of common definition makes it complicated and often unnecessarily bureaucratic to organise IDCT.

What is needed

The border between interventional and observational studies needs to be clearly defined, especially for diagnostic interventions.

Recommendation

We recommend that regulators devise a better classification of clinical studies to facilitate the coordination of studies and to prevent problems generated by different national interpretations. This revision needs to better define the border between interventional and observational studies, especially for diagnostic interventions.

Phase I-II-III-IV Categories

The use of phase I-II-III-IV categories does not reflect the variety of studies (and associated risk) conducted by academic institutions, rather it has evolved as part of the classical drug approval process.

What is needed

There is a need to consider the diversity of academic studies, which include:

- long-term safety studies (especially those aimed at identifying rare but serious adverse effects) and efficacy studies;
- head-to-head comparisons, for example for superiority and non-inferiority studies;
- studies aimed at identifying medical endpoints relevant to real-life practice and the needs of patients;
- 'multi-modal' studies aimed at investigating, for example, various combinations of drugs with drugs, or drugs with devices and or surgery;
- studies to identify the most responsive sub-population as part of the broad move towards personalised medicine;
- studies in under-represented populations, such as children, the elderly and people with rare or understudied diseases;
- health economics studies;
- studies aimed at validating operational guidelines;
- meta-analyses using individualised patient data.

Recommendation

We recommend that regulators consider the diversity of academic studies and dismantle the 'phase IV' category, which is very heterogeneous with randomised trials on marketed treatments, as well as pharmaco-epidemiology studies in which the treatment is not assigned by the protocol.

2. Categories and Design of Investigator-Driven Clinical Trials

Commercial versus Non-Commercial Trials

Regulators are willing to create specific modalities for non-commercial trials. However, differentiating between 'commercial' and 'non-commercial' trials regarding regulatory requirements would result in a two-tier model, with one quality standard for industry-sponsored trials and another, presumed to be lower, for investigator-driven trials.

What is needed

Commercial and non-commercial studies should have the same level of quality, credibility and protection of participants.

Recommendation

We recommend that regulators do not distinguish between commercial and non-commercial studies but between commercial and non-commercial (i.e. academic) sponsors, and support should be given to academic institutions acting as sponsors. In turn, regulatory requirements should be adapted to reflect the risk associated with the study, not its commercial or non-commercial objective (see Section 3 below).

Paradigm Shift by Biomedical Breakthroughs

The paradigm shift generated by new biomedical breakthroughs in areas such as genomics, rational drug design and molecular diagnostics is not being exploited fully in current clinical studies.

What is needed

There is a need to better exploit the new biomedical breakthroughs in clinical studies via a fast translational approach.

Recommendation

We recommend that funding agencies, universities and hospitals:

- Rethink the model of patient-oriented research further to the *-omics* paradigm shift (e.g. develop new methodologies, etc.);
- Fully exploit in a more pre-emptive and well planned manner the knowledge produced by new biomedical breakthroughs. This will require the creation of sufficient infrastructure for translational studies (including tissue and sample banks) and harmonisation of regulations for sample storage, sample shipment and use of biobanks;
- Help clinical investigators with good infrastructure and well organised clinical research centres that pro-

vide adequate manpower to plan and execute clinical research and IDCT.

Adequate Scale for IDCT

There is a degree of fragmentation (resulting in 'under-power') and duplication (which leads to redundancy) of biomedical research generally across Europe.

What is needed

New discoveries require an appropriate small-scale approach for proof-of-concept studies. In most cases however it is important to discourage under-powered clinical studies and emphasis should be on correctly powered larger randomised controlled trials (RCTs) as these have the greater potential to change clinical management.

Recommendation

We recommend that funding agencies allow universities, hospitals and learned societies to conduct solid, multi-national, large-scale investigator-driven clinical studies based on the correctly powered scale. This should be facilitated by providing the necessary funding and also by creating an appropriate environment (such as networks, infrastructure, less bureaucracy) to perform such studies. For smaller scale proof-of-concept studies the funding and structure of organisation of the trials should be adapted appropriately.

3. Regulatory and Legal Issues, Intellectual Property Rights and Data Sharing

Risk-Based Approach to Regulating Clinical Trials

Patient-oriented research is developed within the boundaries of various national regulations in Europe taking into account such factors as the role of ethics committees, competent authorities, sponsors and the principal investigator in clinical trials. These regulations are aimed at assuring a high degree of patient protection. These regulations differ between member states and between different categories of clinical trials, making it difficult to construct trans-national trials. An attempt to harmonise these regulations was made in 2001 for one category of clinical trials with the EU Clinical Trials Directive (CTD) on Medicinal Products. There is a widespread feeling that the 2001 directive has failed because the implications of the directive on IDCT were not fully considered. The directive failed to discriminate between different categories of research, which resulted in the lack of an appropriate system for risk assessment for different categories of clinical trials. One consequence of this is that regulations aimed at protecting patients in research that is considered to carry a high risk often need to be applied to 'low risk' research. This results in unnecessarily cumbersome bureaucracy which, in extreme cases, could deter the investigator from launching a trial. Furthermore, the infrastructure, funding and administrative support required to address this bureaucracy are generally lacking.

What is needed

There is a need to make a distinction between studies whose risk is equivalent to standard (usual) care (including randomised trials that compare already marketed and labelled treatments) and those that are aimed at innovation (e.g. testing a new drug). The current classification of trials does not make this distinction and has similar requirements for all categories of interventional trials on medicinal products. A harmonised regulatory approach to clinical trials based on risk needs to be developed and the requirements of different types of clinical trials need to be reviewed. Regulatory requirements need to be adapted depending on the risk, especially where the risk is similar to 'usual care'.

New categories of clinical studies could be developed in which the study is defined based on the aim of the study and on the risk that the study carries to the patient, to the institution and to public health. Each category of risk would have its specific requirements for issues such as submission to competent authority, insurance, need for a sponsor, monitoring of the trial and so on.

Recommendation

We recommend that regulators minimise requirements (submission to ethics committee) for studies whose risk

is similar to usual care, and to use a broad risk-based categorisation. For example:

- Level A – low risk (such as non-interventional pathophysiology, imaging)
- Level B – similar to usual care (equivalent to most phase IV clinical trials)
- Level C – moderate risk (most phase III clinical trials)
- Level D – high risk (most phase I–II drug trials, gene or cell therapy)

and to bear in mind to reduce the administrative burden.

Management by a Risk-Based Approach

There is a general problem with setting up and managing clinical trials in Europe because the regulatory framework has adopted a 'one size fits all' approach; in other words the same regulations apply to all clinical trials of investigational medicinal products (IMPs) regardless of the risk that the trial carries. Thus the requirements for low risk trials with licensed IMPs – which are often almost indistinguishable from standard care – can be prohibitively onerous.

What is needed

Clinical trials should be categorised according to the level of risk that they pose to the patient, investigators and the health service and the regulations governing the clinical trial, including the monitoring procedures, should be adapted to reflect the degree of risk.

Recommendation

We recommend that:

- All procedures and requirements be adapted to the appropriate level of risk, include the risk-based approach in the CTD requirements and consider exempting low-risk IMP studies from the CTD requirements;
- Specific populations (e.g. children) or the use of IMPs outside their licensed indication(s) should not be considered to be automatically 'Level D – high risk'.

Ethics Committee

Ethics committees of the different countries have different roles and functions. In some countries the role of the ethics committee is restricted to the supervision of informed consent, in others the protection of participants includes methodological assessment. In addition their practice may substantially differ, leading to divergent assessment of the same protocol.

What is needed

There is a need to harmonise the mission and role of ethics committees at least at the national level.

3. Regulatory and Legal Issues, Intellectual Property Rights and Data Sharing

Recommendation

We recommend that DG Sanco and national regulators:

- Define a common mission for ethics committees;
- Encourage networking and accreditation of ethics committees;
- Harmonise national procedures for assessment by ethics committees that might lead to a real single opinion per country;
- Increase ethical standards of clinical trials.

Adverse Event Reporting

In clinical trials there is a requirement to report ‘adverse events’. However, the regulations on such reporting are clearly defined only for trials on medicinal products and not for other types of trials; reporting systems and requirements vary between countries.

What is needed

For the reporting of adverse events there needs to be a harmonised reporting and data collection system at the EU level.

Recommendation

We recommend that health authorities:

- Consider how best to facilitate adverse event detection and reporting;
- Consider taking advantage of the EU-wide reporting to Clinical Trials of Investigational Medicinal Products (CTIMPs).

Insurance Requirements

The issues of legal liability and insurance for trials are problematical and there is difficulty in negotiating and paying insurance for trials conducted across several countries. Insurance costs have multiplied sixfold over the past decade.

Across the EU there are significant discrepancies in insurance coverage for IDCT and major differences exist in liability and insurance. In some countries insurance cover for academic trials is provided by the public health system, whereas public institutions have to contract insurance in others. Insurance packages even exist for industry sponsors in some countries (e.g. Sweden).

What is needed

New models of insurance and indemnity for IDCT need to be investigated and appropriate insurance mechanisms need to be developed that allow insurance to be negotiated and paid for in multi-national trials.

Recommendation

We recommend that national funders, ministries of health, insurance companies and relevant government and academic institutions set up a multinational task-force of experts with a clear mandate to:

- Harmonise insurance requirements;
- Set up a not-for-profit insurance organisation for clinical trials;
- Explore the possibility to insure studies through the national public health system;
- Set-up insurance packages.

Intellectual Property Rights

There is a general lack of awareness and sufficiently deep understanding of intellectual property rights (IPR) on the part of investigators and this can stifle the vital dissemination of science. IPR is often cited as a reason why results cannot be disseminated, resulting in a potential conflict between the principle of sharing data and a system that supports wealth-creation by protecting intellectual property. Investigators also display naïveté about what is allowed and what is not allowed, for example under the terms of patent research exemptions.

There are other problems. New knowledge that could legitimately be protected by IPR is often not detected early enough in a trial. Where IPR is thought to have been breached, protection and litigations costs can be extremely high. There has been a significant increase in the time and complexity of putting in place agreements to start early phase clinical trials on new drugs and to move from phase I to phase II trials, in particular with complex biological treatments such as gene therapy. There are often multiple patent holders for such complex biological systems which results in difficult, protracted and costly negotiations.

What is needed

- There is a need for education on IPR issues;
- There is a need for greater awareness of IPR issues among investigators, who should be given access to more and better information;
- IPR needs to be enforced and funds and support should be made available for this;
- There should be dedicated public support for the complex and expensive negotiations involved in IPR for IDCT;
- There is a need for access for the right IPR support structure;
- It should be made easier to explore innovative approaches on drugs that are already licensed.

Recommendation

We recommend that universities:

- Include a training and specific education in the clinical investigator curriculum on IPR issues;

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- Develop support for technology transfer professional training;
 - Endorse the continued development of standard template agreements, such as the ones developed for trials by the UK Clinical Research Collaboration (note: this need to be used with caution by those who have not received any training);
 - Encourage specifying in agreements the use of alternatives to litigation in the event of dispute, e.g. alternative dispute resolution, mediation;
 - Encourage development of technology transfer professional training and support, and also general education in IP for investigators;
 - Explore the potential for a more liberal regime in terms of providing exemption to patent infringement where research is being carried out for marketing approval by competent authorities;
 - Promote the creation of an affordable pan-European single language patent system.

Data Storage Capacity

Data storage capacity is sometimes inadequate and there is often a lack of commitment to share data. Reasons include issues such as inappropriate ‘architectures’ (the format in which the data is stored and shared), the coding of data or the fact that requests are made by competitors.

It is often difficult to obtain data from drug manufacturers about their licensed drugs if a researcher wishes to investigate the product for purposes of scientific research or to test the drug’s effects on diseases for which the product was not originally licensed.

Data-sharing is complex and requires consideration of issues such as the curation and preservation of data, the ethical use of shared data, consent to use the data and regulatory mechanisms to ensure that the data is used appropriately.

EU legislation of database rights (council directive 96/9/EC) can be used to allow legitimate requests for data sharing to be rejected.

What is needed

Data sharing should be encouraged, facilitated, supported and funded.

Recommendation

We recommend that the following steps are taken in relation to data sharing, with due respect to the right of investigators to use their data for IP protection and publication within reasonable time:

- Make explicit the policy on data-sharing in each trial protocol and consider data-sharing as part of the audit of the trial;

- Continue work to improve access to datasets and to build a clinical trial clearing house (providing information about IDCTs);
- Make available sufficient funding to support data-sharing, to allow, for example, appropriate storage capacity and the installation of relevant architectures;
- Harmonise data management systems by creating a European standard, e.g. by using ESFRI’s European Life Science Infrastructure for Biological Information (ELIXIR) for creating an additional repository for clinical trials data.

Publication of Clinical Trials Results

There is currently no European open database for clinical trial registration. (For further information see www.controlled-trials.com.)

What is needed

There is a need to promote the publication of clinical trial results.

Recommendation

We recommend that:

- Negative results as well as positive results are published;
- Sponsors, funders and all responsible organisations be obliged to register and publish all clinical trial data regardless of the type of trial or the phase;
- The WHO recommendations and the WHO clinical trial platform should be implemented through national governments quickly and registration should be free of charge and done rapidly;
- The quality of data deposited in clinical trials registries be improved;
- The transfer of results into clinical practice be facilitated.

4. Management of IDCT

The process from discovering an innovation from biomedical research to implementing that innovation in the clinic is slow and cumbersome. This is especially true in academia due to the lack of true collaboration among the multiplicity of initiatives, resources and legal frameworks. While funding for medical research at member state level in Europe has increased markedly over recent years, there has been a gradual decline in therapeutic innovation due to the overall increase of funding needed for the discovery process.

Clinical Trial Authorisations (CTA) Process

There is a large number of regulatory authorities across EU member states and a lack of harmonisation in the interpretation of the requirements and the documentation required for the approval of an IMP trial (CTA). This invariably leads to a duplication of effort as submission is required in each country, often with different documentation. Some authorities also assess the methodology, when this is not done by ethics committees (see below).

What is needed

Study approval documentation for IMP trials needs to be harmonised across Europe. Regulatory authorities need to produce a 'one-stop shop' information desk for multinational studies, ideally developing a shared database that feeds into all relevant competent authorities within each country. The competent authorities overseeing clinical trials need to agree on their mission.

Recommendation

We recommend that:

- Procedures for submission of CTAs to the competent authorities are streamlined in a more coherent and efficient way across Europe, ideally requiring only one centralised application or exploring alternative models such as a lead member state with mutual recognition, or specialisation and networking of national competent authorities;
- A system allowing electronic submission and a shared database be implemented.

Sponsorship

Current regulations require that an IDCT has a single sponsor – an agency or organisation that takes legal responsibility and liability for the trial. Many organisations are unwilling to undertake the role of sponsor at a pan-European level for multinational trials. Widely varying regulations and laws on liability between countries makes sponsorship difficult to define. This is one main

difference in Europe currently between academia and pharmaceutical companies, the latter being able to take pan-European sponsorship, while for the former it is extremely difficult. In addition there is no consistent approach to the sponsorship of trials that are not investigating IMPs in Europe.

What is needed

Mechanisms need to be found that enable sponsors to formally/legally share responsibility for IMP trials. A more consistent approach to sponsorship of non-IMP should be developed.

Recommendation

We recommend that:

- Mechanisms are developed to address pan-European sponsorship of IMP trials (e.g. delegating responsibility; shared sponsorship in each EU country, with one leading sponsor collecting the EudraCT number and one single database);
- The issue of sponsorship of non-IMP trials should be addressed.

Investigational Medicinal Products (IMP) Requirements

• Drug Supply:

The requirement to provide all the IMPs in a trial, including post-marketing surveillance and other studies, and control arm(s), may be very high, and this impacts on the research costs of a non-commercial trial.

• Provision of Services:

Within hospital pharmacies resources to satisfy the requirements for IMP trials are often inadequate and the costs of the services high. For placebo controlled trials not conducted with a pharma partner, the production facilities for matching placebo are limited and the costs are usually as high as they are for commercial organisations.

• Regulatory Requirements:

The pharmacy requirements (labelling, etc) relating to unlicensed IMPs also apply to drugs that are already marketed, for example when an IMP is being used for a new indication outside those for which the drug was licensed, such as for a different group of patients or for a different disease.

What is needed

There is clear need for the following:

- Provision of drug in the control arm(s) and post-marketing surveillance studies;
- Resources for a GMP production site including matching placebo and lack of availability of pharmacy

4. Management of IDCT

- resources and expertise for non-commercial trials;
- Pharmacy procedures including drug labeling and drug accountability. Drugs that are already on the market should not be subject to the same requirements for labeling and accountability as for IMP, even if they are being used for a purpose for which the drug was not originally licensed.

Recommendation

We recommend that:

- The possibility be explored for a waiver for drug supply in public- or charity-funded studies and that the EMEA is asked for help to facilitate collaboration between pharma and academic investigators to ensure that adequate post marketing studies are undertaken;
- The resources currently available in Europe and the level of the demand be explored, building on ECRIN's current initiative on biotherapy;
- Marketed drugs provided from routine hospital or clinic supplies be exempted from the same requirements for labeling and accountability in the pharmacy as non-marketed IMP (even if not in the licensed indications).

Pharmacovigilance Reporting

There are inconsistencies in national and international (FDA) requirements for pharmacovigilance for IMPs.

What is needed

Electronic reporting via EudraVigilance needs to be more accessible and coordinated by the regulatory authorities at a national level. Greater consistency in pharmacovigilance requirements for IMPs within Europe and internationally, particularly the US.

Recommendation

We recommend that:

- National interpretations of pharmacovigilance requirements are harmonised within Europe and internationally, especially with the US;
- Effective pharmacovigilance procedures be developed for pan-European non-commercial studies by facilitating electronic reporting via EudraVigilance through the competent authorities with onward transmission to other countries.

Pharmacovigilance Notification

The requirement to notify ethics committees and all investigators of any serious, unexpected reactions immediately may cause confusion and unnecessary concern as such information is very difficult to interpret in isolation. The regular review by an Independent Data

Monitoring Committee (IDMC) of all safety data, and if necessary urgent review of SUSARs, by treatment group should be the preferred option.

What is needed

There needs to be greater consistency and harmonisation in monitoring and reporting adverse events associated with IMPs. Reporting of adverse events should be streamlined so that necessary actions can be taken in a timely fashion and the key role of the IDMC should be identified.

Recommendation

We recommend that:

- Immediate SUSAR reporting to ethics committees and investigators be limited to those reactions which affect the safety of current and future participants;
- The key role of the Independent Data Monitoring Committee (IDMC) be recognised in monitoring the safety of the trial.

Project Management

Clinical investigators often lack the expertise needed to plan all the necessary resources and agreements before starting a clinical trial. In addition, the costs of commercial FDA and EMEA compliant Clinical Data Management Systems (CDMS) are very high and the resources needed to develop in-house systems are often higher.

What is needed

Clinical investigators need the relevant data that will be necessary to support a licensing application in a later stage, and robust data collection methods are needed at a realistic cost.

Recommendation

We recommend that:

- Possible licensing application mechanisms are identified before starting the trial;
- Existing commercial and open source software systems be reviewed with the goal of European level procurement and/or development;
- Systems are developed that incorporate quality assurance and enable compliance with regulations and protocol.

5. Education, Training, Career Tracks and Authorship

Education and Training

Europe is running out of well-trained physician-scientists (physicians who have trained in basic scientific research, “MD-PhDs”) who are capable of working together and with other clinical trial professions. At the same time patient-oriented research is becoming increasingly multidisciplinary, with new technologies constantly appearing. In many cases young investigators are not being sufficiently well trained to cope with this multidisciplinary environment. In a worst-case scenario this situation leads to a real and damaging decline of patient-oriented research and related studies in Europe and greatly reduces the competitiveness of Europe in the field of clinical research and related research on drug development and diagnostics.

What is needed

- Patient-oriented research should be acknowledged as an important part of the medical education curriculum, which should also include comprehensive coverage of ethical and regulatory issues;
- Provision should be made to allow physicians to train as researchers, with postgraduate programmes for patient-oriented research and key core facilities and infrastructure such as clinical trials centres, and biobank and bioinformatics resources;
- There should be lifelong training in ‘good investigator practice’;
- There is a need for trained and experienced personnel to design, carry out and analyse studies. There is also a need for chief investigators, clinical investigators at the site, statisticians and project managers. There also needs to be a sufficient number of experienced members to constitute independent data monitoring committees.

Recommendation

We recommend that:

- Universities establish new clinical investigator programmes, strengthen existing ones and include a training and specific education on IPR issues;
- Universities, health care providers, regulators and the pharmaceutical industry increase international co-operation in education relating to patient-oriented research by building a European Medical Research Academy; there should be harmonisation of European training programmes for clinical investigators and other patient-oriented research professionals by agreeing on a common training syllabus for clinical investigators at all levels (as suggested in the ESF publication *A European Syllabus for Training Clinical Investigators* – see Annex 4);
- Universities, healthcare providers and regulators establish quality control mechanism for clinical

investigator training and training facilities by giving accreditation (a “driver’s licence”) to clinical investigators, and promote life-long training of clinical investigators by establishing mandatory training courses in appropriate subject areas;

- Funding agencies establish programmes supporting visits of clinical investigators to centres of excellence in different countries.

Careers

In many countries there is a general perception that the attractiveness of patient-oriented research as a career has declined over the years and that this has resulted in a shortage of qualified researchers. Part of the problem has been ascribed to a lack of job security and uncertain future prospects, and the absence of a clear, well-defined and predictable career path for clinical investigators. In Western Europe the healthcare system tends to suffocate research – there is simply too little time available to pursue research. Participation in research usually does not bring a competitive salary and may even be a disadvantage at several stages of the career of a clinical investigator or clinician practitioner. Academic freedom appears to be diminishing with researchers being constrained by regulations and guidelines and an increasing demand for efficacy, which leaves less latitude for imaginative, innovative research.

In addition there is a lack of mobility of researchers between the industrial and academic sectors and there appears to have been a reduction in the movement of researchers internationally.

What is needed

- More incentives should be given to attract high quality personnel into patient-oriented research, with appropriately resourced training facilities put in place;
- There must be an appropriate career structure for academic clinical investigators: the most innovative questions frequently come from the clinic or the laboratory, not from ‘big pharma’;
- There is a need to encourage young people into research as an attractive career option and to create the optimal conditions for such career opportunities;
- Patient-oriented research is difficult and time-consuming and requires familiarity with a large amount of information on issues such as regulation and ethics. A lot of paperwork is required and often administrative and expert support for researchers is lacking. This acts as a disincentive to pursue research as a career.

5. Education, Training, Career Tracks and Authorship

Recommendation

We recommend that:

- Universities, hospitals and/or funding agencies create full and attractive career opportunities for clinical scientists at all stages throughout their professional development: as young scientists during their clinical research training and finally as independent clinical researchers.
- Universities, hospitals and learned societies present patient-oriented research as an attractive career option by providing predictable career paths (with transparent promotion criteria) for clinical investigators and by offering them sufficient time to carry out clinical research and to maintain and update their clinical skills. Innovative models of employment should be tested to attract clinicians into research, to create individual career paths to attract young clinicians and to promote mobility of clinical investigators between academia and industry;
- Universities and hospitals build clinical research infrastructure such as hospital clinical trial units and provide better administrative support for clinical investigators;
- Funding agencies and learned societies should sponsor high-level European prizes for patient-oriented research to promote the visibility of such a career path for clinicians as well to highlight the importance of clinical research to the wider public.

Recommendation

We recommend that:

- Clinical researchers and medical journal editors closely follow current recommendations relating to authorship and contributorship. Contribution should be based on the International Committee of the Medical Journals Editors' requirements (see <http://www.icmje.org/sponsor.htm>);
- Universities, hospitals and funding agencies develop strategies to improve listing of academic merits in the CVs of clinical investigators (e.g. by including registration numbers of clinical trials) and recognise the contribution of all who take part in clinical trials, including those who recruit participants.

Authorship

Many clinical trials are conducted without the results ever being published. This means that the trial has no academic merit for the researchers involved and that the results of the trial never become known to the scientific community. There is also inadequate recognition of clinical investigators in multicentre trials. There is a general belief that an authorship in a clinical trials publication is more demanding than in basic sciences, and that in the publication of papers from clinical trials the distinction between 'author' and 'contributor' is often blurred.

What is needed

- All contributors to clinical trials, whether the trials are published or not, should have their contributions acknowledged and documented;
- There need to be mechanisms to reflect more accurately the academic input into clinical trials. The professional and intellectual input into a clinical trial is sometimes not reflected in the publication of the trial results – these can have less academic impact than more conventional publications or studies.

6. Funding and Models of Partnership

Analysis of funding statistics contained in the recently published EMRC White Paper *Present Status and Future Strategy for Medical Research in Europe* reveals that the US spends proportionately far more on biomedical research than does Europe. This applies equally to public and private funding. Ten years ago the figures for spending on biomedical research in the EU and US were more comparable; in the last decade US funding has increased dramatically. Europe is therefore lagging behind this major competitor. In the US around half of all funding for research and development is directed at the biomedical sector; in the EU the proportion is about one-sixth. Investments in biomedical research as a percentage of healthcare expenditure is also substantially greater in the US than in the EU. Citation data from scientific publications demonstrate that the US produces more top-quality research papers than the EU. However, there is little data on the level of specific funding for IDCT across Europe.

Levels of Funding for Clinical Research in Europe

Many member states of the EU do not support IDCT and many new members feel they cannot afford them. Because of the relative levels of finance available, there are significant differences between the scientific capabilities of Eastern and Western Europe. Some EU countries, such as the UK, have a tradition of medical research being strongly supported through charities and legacies while in other countries this is not the case. Indeed, in some European countries, a charitable donation to support scientific research is not considered to be 'philanthropic' in the way that, for example, a donation to an art gallery to buy a painting is. As well as a lack of funding for research itself, ethics committees and competent authorities are also underfunded. There are no funding mechanisms to support pan-European trials.

What is needed

- More public funding is required for academic clinical and translational research and more specifically for IDCT. This applies equally to studies related to the prevention and treatment of common disorders as well as to 'orphan' diseases. The value of these trials can be seen in the advances in cancer treatments, where over the years multidisciplinary approaches have been taken to work out the best strategy for treatment, ultimately resulting in much improved survival rates for many cancers. Several reviews have shown a great return on investment generated by such clinical research;
- The financial resources needed for national and especially for pan-European trials need to be secured;

- Funding should also be provided for attractive career development of clinical scientists to perform IDCT;
- Funding should also be organised for specific infrastructure (both physical infrastructure and manpower) to create optimal long-term translational and clinical research;
- Such funding should be based on competitive peer review and scientific and clinical excellence.

Recommendation

We recommend that:

- Innovative clinical trials should be strongly encouraged. This implies that the European Commission (for example through its Framework Programme) should specifically include adequate calls for innovative and scientifically sound IDCT which require international collaboration to generate adequate answers. The funding should be flexible and provide for the full cost of such trials which may be very expensive if large number of subjects recruited to long-term studies are needed to generate the necessary answers. Specific financial support for GMP production of the necessary products should also be part of the this financial support, independent of industry;
- Patient-oriented research funding should be started or increased by governments and philanthropic organisations to allow adequate IDCT that can be organised at a more regional level;
- Where appropriate, joint funding should be sought with a stronger input from the patient representatives and other sources of funding;
- A funding mechanism be established for pan-European clinical studies, including pilots and demonstration projects to show the benefit of the clinical research infrastructure;
- Funding be increased for the training and lifetime careers of the best clinical investigators.

Prioritisation and Mechanism of Funding IDCT

The lack of appropriate funding mechanisms for all aspects of clinical research and IDCT in most European countries is in sharp contrast with the well documented benefits of such research. A coherent strategic development plan is thus needed involving different partners and interest groups.

What is needed

- The medical community and especially clinical researchers need to put their case across strongly and convincingly;
- The lobbying power of patients is becoming increasingly important in helping to shape biomedical

6. Funding and Models of Partnership

research priorities. Researchers seeking funding should make use of this powerful voice. Funding of IDCT should be a strategic priority for all European patient groups;

- Healthcare providers should be better informed about the benefit of such research and should co-sponsor such activities;
- Due to the scale and the complexity of clinical trials, the peer review process is complex and has specific requirements – peer review of clinical trial applications usually involves an iterative process to optimise the trial design. As well as clinical evaluation, biometric evaluation is also needed. Appropriate expertise is needed to assess properly the budget requirements of a trial.

Recommendation

We recommend that:

- A forum at the European level is created to advocate for medical research;
- Specific public funding mechanisms should be established for IDCT and clinical research;
- The different review processes for prioritising funding of trials should be harmonised, for example by using an appropriate peer review system; mechanisms for a dialogue between applicants and peer reviewers have to be part of peer review process of clinical trials. This peer review process involves considerable expert resources and needs to be remunerated accordingly. In some cases evaluators of grant applications should be given incentives.

Models of Partnership

Across Europe there are frequently no or limited opportunities for funding IDCT and clinical research. Where they do exist, such funding mechanisms are heterogeneous and differ according to the nature and stages of the clinical trials and between the fields of research. In general there is no coherence between these funding mechanisms. A coherent funding approach (one which is transparent and fit-for-purpose, not necessarily ‘one-size-fits-all’) across Europe is important because the mechanism through which trials are funded has a marked impact on clinical trials and upon people’s trust in the results.

Funding for trials tends to be at the level of the individual state – there is limited funding at the European level. One consequence of this is that funding often goes to small, under-powered trials.

Some specific areas of research are particularly underfunded by governments. A much higher proportion of spending is from the industrial sector but this spending is usually limited to the a company’s particular

field of interest or its products. Moreover traditional drug companies are now starting to pull out of some areas, and the concern is that this will leave a serious funding vacuum in these areas.

What is needed

- There needs to be greater co-ordination between research centres across Europe that have similar interests, and between research funding agencies and sharing of best practices;
- If there is to be increased co-operation and co-ordination between research centres across Europe, greater harmonisation is needed in many areas, including biobanking, data management and the collation and management of datasets;
- Pharmaceutical companies should be encouraged to provide drugs for non-commercial IDCT. There should be better collaboration between pharmaceutical companies and academic investigators so that drugs can be provided for non-commercial IDCT;
- There is a need for more coherent and innovative funding for IDCT. Lessons could be taken from new models of partnership such as the EU’s Innovative Medicines Initiative, where EU funding is matched in kind by industry, or EATRIS, the European Advanced Translational Research Infrastructure in Medicine. In particular the Framework Programme needs to consider how to support trans-European clinical trials activity and all member states should have strategies and hypothecated funding for IDCT at the national level;
- Another good example of strategic funding partnerships is the Oslo Cancer Cluster, a research institute that is a partnership between industry, government and patient groups, where laboratories and research facilities lie adjacent to a major hospital. Increasingly it is essential to fund both the clinical trial of the intervention and associated biological studies;
- New partnerships need to be constructed with links between academics, industry, learned societies and charitable foundations;
- Industry should consider more educational grants to supporting IDCT within the broad disease area they are interested in, not necessarily just focusing on specific medicinal product within their portfolio;
- In countries where donations to medical research are not considered as ‘philanthropic’, methods need to be found to change this attitude and to make it easier for charities and private individuals to make donations for medical research.

Recommendation

We recommend that:

- Specific funding opportunities for IDCT should be established or, where already existing, be expanded

to allow appropriate funding for all aspects of clinical research and IDCT.

This should include:

- funding for full career development from training through to support for the best clinical scientists;
- funding for infrastructure for clinical research and IDCT (physical infrastructure, manpower and access to the necessary laboratory and function tests and clinical imaging);
- competitive funding for bottom-up or top-down initiatives for clinical research projects.

In addition:

- An implementation plan is drawn up to formulate and drive specific actions (based on the given recommendations) and the people who will take care of this be identified;
- A common European-wide funding mechanism is established for supporting EU-wide IDCT;
- European topics of interest be clearly co-ordinated;
- The funding of all stakeholders involved in patient-oriented research (academia, but also regulatory affairs agencies, ethics committees, charities, etc.) be pooled;
- Networks of disease-specific, patient-oriented research excellence be built;
- Funds are made available not only for clinical trials but also for novel add-on biological studies. Funding streams for clinical trials should cover all types, not just medicines (for example in the past charity money has typically been used for pilot projects, because of the willingness of charities to take risk and the speed with which they make funding decisions);
- Scientists be supported in making their bids to the various funding sources – foundations, banks, venture capitalists, etc – according to the different expectations of these bodies;
- Research synergies in biomarker research between BBMRI, IMI and competent authorities be identified and harnessed.

7. Recommendations

A total of 88 recommendations emerged from the five strategic workshops. These recommendations were considered by the Management Committee at an alignment workshop held on 19 June 2008. A mechanism for processing these recommendations was agreed upon, together with the need to identify the stakeholder group that would be responsible for implementing the recommendations. The Management Committee suggested streamlining and regrouping the 88 recommendations down to about 25. To improve coherence some recommendations were shifted to other strategic themes.

This led to a list of 26 recommendations that were all fully endorsed and refined at a consensus conference held in Strasbourg, France on 29-30 September 2008 under the auspices of the French Presidency of the European Union.

The 26 recommendations are presented below.

Theme: Categories and Design of Investigator-Driven Clinical Trials

- **Recommendation 1:**

- **Categories of patient-oriented research**

Regulators to define categories of clinical trial in a way that is based on the type of study, as follows:

1. Clinical trials on medicinal products
2. Clinical trials on medical devices
3. Other therapeutic trials (e.g. radiotherapy, surgery, transplantation, transfusion, physical therapy, psychotherapy)
4. Diagnostic studies (imaging, other)
5. Nutrition studies
6. Other interventional patient-oriented research (e.g. physiology, physiopathology, biobanks, complementary and alternative methods, psychology)
7. Epidemiological studies (i.e. observational)

- **Recommendation 2:**

- **Interventional versus observational studies**

Regulators to devise a better classification of clinical studies to facilitate the coordination of studies and to prevent problems generated by different national interpretations. This revision needs to better define the border between interventional and observational studies, especially for diagnostic interventions.

- **Recommendation 3:**

- **Phase I-II-III-IV categories**

Regulators to consider the diversity of academic studies and dismantle the 'phase IV' category, which is very heterogeneous with randomised trials on marketed treatments, as well as pharmaco-epidemiology studies in which the treatment is not assigned by the protocol.

- **Recommendation 4:**

- **Commercial versus non-commercial trials**

Regulators not to distinguish between commercial and non-commercial studies but between commercial and non-commercial (i.e. academic) sponsors, and support should be given to academic institutions acting as sponsors. In turn, regulatory requirements should be adapted to reflect the risk associated with the study, not its commercial or non-commercial objective.

- **Recommendation 5:**

- **Paradigm shift by biomedical breakthroughs**

Funding agencies, universities and hospitals to:

- Rethink the model of patient-oriented research further to the -omics paradigm shift (e.g. develop new methodologies, etc.);
- Fully exploit in a more pre-emptive and well planned manner the knowledge produced by new biomedical breakthroughs. This will require the creation of sufficient infrastructure for translational studies (including tissue and sample banks) and harmonisation of regulations for sample storage, sample shipment and use of biobanks;
- Help clinical investigators with good infrastructure and well organised clinical research centres that provide adequate manpower to plan and execute clinical research and IDCT.

- **Recommendation 6: Adequate scale for IDCT**

Funding agencies to allow universities, hospitals and learned societies to conduct solid, multinational, large-scale investigator-driven clinical studies based on the correctly powered scale. This should be facilitated by providing the necessary funding, and also by creating an appropriate environment (such as networks, infrastructure, less bureaucracy) to perform such studies. For smaller scale proof-of-concept studies the funding and structure of organisation of the trials should be adapted appropriately.

Theme: Regulatory and Legal Issues, IPR and Data Sharing

- **Recommendation 7:**

- **Risk-based approach to regulating clinical trials**

Regulators to minimise requirements (submission to ethics committee) for studies whose risk is similar to usual care, and to use a broad risk-based categorisation. For example:

- Level A – low risk (such as non-interventional pathophysiology, imaging)
- Level B – similar to usual care (equivalent to most phase IV clinical trials)
- Level C – moderate risk (most phase III clinical trials)

7. Recommendations

Level D – high risk (most phase I-II drug trials, gene or cell therapy)

and to bear in mind to reduce the administrative burden.

- **Recommendation 8:**

- **Management by a risk-based approach**

- All procedures and requirements be adapted to the appropriate level of risk, include the risk-based approach in the CTD requirements and consider exempting low-risk IMP studies from the CTD requirements;
 - Specific populations (e.g. children) or the use of IMPs outside their licensed indication(s) should not be considered to be automatically ‘Level D – high risk’.

- **Recommendation 9:**

- **Ethics committees**

DG Sanco and national regulators to:

- Define a common mission for the ethics committees;
 - Encourage networking and accreditation of ethics committees;
 - Harmonise national procedures for assessment by Ethics committees that might lead to a real single opinion per country;
 - Increase ethical standards of clinical trials.

- **Recommendation 10:**

- **Adverse event reporting**

We recommend Health authorities to:

- Consider how best to facilitate adverse event detection and reporting;
 - Consider taking advantage of the EU-wide reporting to Clinical Trials of Investigational Medicinal Products (CTIMPs).

- **Recommendation 11:**

- **Insurance requirements**

National funders, ministries of health, insurance companies and relevant government and academic institutions set up a multinational experts taskforce with a clear mandate to:

- Harmonise insurance requirements;
 - Set up a not-for-profit insurance organisation for clinical trials;
 - Explore the possibility to insure studies through the national public health system;
 - Set-up insurance packages.

- **Recommendation 12:**

- **Intellectual property rights (IPR)**

That universities:

- Include a training and specific education in the clinical investigator curriculum on IPR issues;
 - Develop support for technology transfer professional training;

- Endorse the continued development of standard template agreements, such as the ones developed for trials by the UK Clinical Research Collaboration (note: this need to be used with caution by those who have not received any training);
- Encourage specifying in agreements the use of alternatives to litigation in the event of dispute, e.g. alternative dispute resolution, mediation;
- Encourage development of technology transfer professional training and support, and also general education in IP for investigators;
- Explore the potential for a more liberal regime in terms of providing exemption to patent infringement where research is being carried out for marketing approval by competent authorities;
- Promote the creation of an affordable pan-European single language patent system.

- **Recommendation 13:**

- **Data storage capacity**

That the following steps are taken in relation to data sharing, with due respect to the right of investigators to use their data for IP protection and publication within reasonable time:

- Make explicit the policy on data-sharing in each trial protocol and consider data-sharing as part of the audit of the trial;
 - Continue work to improve access to datasets and to build a clinical trial clearing house (providing information about IDCTs);
 - Make available sufficient funding to support data-sharing, to allow, for example, appropriate storage capacity and the installation of relevant architectures;
 - Harmonise data management systems by creating a European standard, e.g. by using ESFRI's European Life Science Infrastructure for Biological Information (ELIXIR) for creating an additional repository for clinical trials data.

- **Recommendation 14:**

- **Publication of clinical trials results**

- Negative results as well as positive results are published;
 - Sponsors, funders and all responsible organisations be obliged to register and publish all clinical trial data regardless of the type of trial or the phase;
 - The WHO recommendations and the WHO clinical trial platform should be implemented through national governments quickly and registration should be free of charge and done rapidly;
 - The quality of data deposited in clinical trials registries be improved;
 - The transfer of results into clinical practice be facilitated.

Theme: Management of IDCT

- **Recommendation 15:**
Clinical trial authorisations (CTA) process
 - Procedures for submission of CTA to the competent authorities are streamlined in a more coherent and efficient way across Europe, ideally requiring only one centralised application or exploring alternative models such as a lead member state with mutual recognition, or specialisation and networking of national competent authorities;
 - A system allowing electronic submission and a shared database be implemented.
- **Recommendation 16:**
Sponsorship
 - Mechanisms are developed to address pan-European sponsorship of IMP trials (e.g. delegating responsibility; shared sponsorship in each EU country, with one leading sponsor collecting the EudraCT number and one single database);
 - The issue of sponsorship of non-IMP trials should be addressed.
- **Recommendation 17:**
Investigational medicinal products (IMP) requirements
 - The possibility be explored for a waiver for drug supply in public- or charity-funded studies and that the EMEA is asked for help to facilitate collaboration between pharma and academic investigators to ensure that adequate post marketing studies are undertaken;
 - The resources currently available in Europe and the level of the demand be explored, building on ECRIN's current initiative on biotherapy;
 - Marketed drugs provided from routine hospital or clinic supplies be exempted from the same requirements for labeling and accountability in the pharmacy as non-marketed IMP (even if not in the licensed indications).
- **Recommendation 18:**
Pharmacovigilance reporting
 - National interpretations of pharmacovigilance requirements are harmonised within Europe and internationally, especially with the US;
 - Effective pharmacovigilance procedures be developed for pan-European non-commercial studies by facilitating electronic reporting via EudraVigilance through the competent authorities with onward transmission to other countries.
- **Recommendation 19:**
Pharmacovigilance notification
 - Immediate SUSAR reporting to ethics committees

and investigators be limited to those reactions which affect the safety of current and future participants;

- The key role of the Independent Data Monitoring Committee (IDMC) be recognised in monitoring the safety of the trial.

- **Recommendation 20:**
Project management
 - Possible licensing application mechanisms are identified before starting the trial;
 - Existing commercial and open source software systems be reviewed with the goal of European level procurement and/or development.
 - Systems are developed that incorporate quality assurance and enable compliance with regulations and protocol.

Theme: Education, Training, Careers and Authorship

- **Recommendation 21:**
Education and training
 - Universities to establish new clinical investigator programmes, strengthen existing ones and include a training and specific education on IPR issues;
 - Universities, healthcare providers, regulators and the pharmaceutical industry to increase international co-operation in education relating to patient-oriented research by building a European Medical Research Academy; there should be harmonisation of European training programmes for clinical investigators and other patient-oriented research professionals by agreeing on a common training syllabus for clinical investigators at all levels (as suggested in the ESF publication *A European Syllabus for Training Clinical Investigators* – see Annex 4);
 - Universities, healthcare providers and regulators to establish quality control mechanism for clinical investigator training and training facilities by giving accreditation (a “driver’s licence”) to clinical investigators, and promote life-long training of clinical investigators by establishing mandatory training courses in appropriate subject areas;
 - Funding agencies to establish programmes supporting visits of clinical investigators to centres of excellence in different countries.
- **Recommendation 22:**
Careers
 - Universities, hospitals and/or funding agencies create full and attractive career opportunities for clinical scientists at all stages throughout their professional development: as young scientists during their clinical research training and finally as independent clinical researchers;

7. Recommendations

- Universities, hospitals and learned societies present patient-oriented research as an attractive career option by providing predictable career paths (with transparent promotion criteria) for clinical investigators and by offering them sufficient time to carry out clinical research and to maintain and update their clinical skills. Innovative models of employment should be tested to attract clinicians into research, to create individual career paths to attract young clinicians and to promote mobility of clinical investigators between academia and industry;
 - Universities and hospitals build clinical research infrastructure such as hospital clinical trial units and provide better administrative support for clinical investigators;
 - Funding agencies and learned societies should sponsor high-level European prizes for patient-oriented research to promote the visibility of such a career path for clinicians as well to highlight the importance of clinical research to the wider public.
- **Recommendation 23:**
Authorship
 - Clinical researchers and medical journal editors to closely follow current recommendations relating to authorship and contributorship. Contribution should be based on the International Committee of the Medical Journals Editors' requirements (see <http://www.icmje.org/sponsor.htm>);
 - Universities, hospitals and funding Agencies to develop strategies to improve listing of academic merits in the CVs of clinical investigators (e.g. by including registration numbers of clinical trials) and recognise the contribution of all who take part in clinical trials, including those who recruit participants.

Theme: Funding and Models of Partnerships

- **Recommendation 24:**
Level of funding for clinical research in Europe
 - Innovative clinical trials should be strongly encouraged. This implies that the European Commission (for example through its Framework Programme) should specifically include adequate calls for innovative and scientifically sound IDCT which require international collaboration to generate adequate answers. The funding should be flexible and provide for the full cost of such trials which may be very expensive if large number of subjects recruited to long-term studies are needed to generate the necessary answers. Specific financial support for GMP production of the necessary products should also be part of the this financial support, independent of industry;
- Patient-oriented research funding should be started or increased by governments and philanthropic organisations to allow adequate IDCT that can be organised at a more regional level;
 - Where appropriate, joint funding should be sought with a stronger input from the patient representatives and other sources of funding;
 - A funding mechanism be established for pan-European clinical studies, including pilots and demonstration projects to show the benefit of the clinical research infrastructure;
 - Funding be increased for the training and life time careers of the best clinical investigators.
- **Recommendation 25:**
Prioritisation and mechanism of funding IDCT
 - A forum at the European level is created to advocate for medical research;
 - Specific public funding mechanisms should be established for IDCT and clinical research;
 - The different review processes for prioritising funding of trials should be harmonised, for example by using an appropriate peer review system; mechanisms for a dialogue between applicants and peer reviewers have to be part of a peer review process of clinical trials. This peer review process involves considerable expert resources and needs to be remunerated accordingly. In some cases evaluators of grant applications should be given incentives.
- **Recommendation 26:**
Models of partnership
 - Specific funding opportunities for IDCT should be established or, where already existing, be expanded to allow appropriate funding for all aspects of clinical research and IDCT.

This should include:

- Funding for full career development from training through to support for the best clinical scientists;
- Funding for infrastructure for clinical research and IDCT (physical infrastructure, manpower and access to the necessary laboratory and function tests and clinical imaging);
- Competitive funding for bottom-up or top-down initiatives for clinical research projects.

In addition:

- An implementation plan is drawn up to formulate and drive specific actions (based on the given recommendations) and the people who will take care of this be identified;
- A common European-wide funding mechanism is established for supporting EU-wide IDCT;
- European topics of interest be clearly co-ordinated;
- The funding of all stakeholders involved in patient-oriented research (academia, but also regulatory

-
- affairs agencies, ethics committees, charities, etc.) be pooled;
- Networks of disease-specific, patient-oriented research excellence be built;
 - Funds are made available not only for clinical trials but also for novel add-on biological studies. Funding streams for clinical trials should cover all types, not just medicines (for example in the past charity money has typically been used for pilot projects, because of the willingness of charities to take risk and the speed with which they make funding decisions);
 - Scientists be supported in making their bids to the various funding sources – foundations, banks, venture capitalists, etc – according to the different expectations of these bodies;
 - Research synergies in biomarker research between BBMRI, IMI and competent authorities be identified and harnessed.

Consensus Conference Recommendations

The consensus conference was attended by delegates invited as representatives of key stakeholder groups (see list of participants). The delegates were asked to rank the recommendations according to priority. These votes were pooled with votes that had been received by mail before the consensus conference from those stakeholders who had been invited but could not participate in the conference. In total 71 ‘voting forms’ were returned, leading to the ranking of the 26 recommendations.

For better coherence a decision was made to merge two recommendations – numbers 21 (education and training) and 22 (careers).

Table 1: Ranking of recommendations according to priority

Rank	Recommendation pertaining to:
1	Education, training and careers
2	Level of funding for clinical research in Europe
3	Risk-based approach to regulating clinical trials
4	Clinical trial authorisation process
5	Adequate scale for IDCT
6	Categories of patient-oriented research
7	Management by risk-based approach
8	Commercial <i>versus</i> non-commercial trials
9	Models of partnership
10	Sponsorship
11	Prioritisation and mechanism of funding IDCT
12	Ethics committees
13	Insurance requirements
14	Paradigm shift by biomedical breakthroughs
15	Publication of clinical trials results
16	Investigational medicinal products (IMP) requirements
17	Pharmacovigilance reporting
18	Project management
19	Data storage capacity
20	Phase I-II-III-IV categories
21	Interventional <i>versus</i> observational studies
22	Pharmacovigilance notification
23	Adverse event reporting
24	Intellectual property rights (IPR)
25	Authorship

8. Status in Central and Eastern European Countries

Due to the lack of strong representation from Central and Eastern European Countries (CEEC) at the consensus conference a specific workshop dedicated to these countries was held in Prague, Czech Republic on December 7 2008 (a list of participants can be found in Chapter 10: Committee Members). The aim of this workshop was for representatives of CEEC to reach a general agreement and to identify any issues specific to CEEC.

General remarks

CEEC are facing the same problems as those faced by their Western European counterparts, but the problems are more acute and extreme. Most clinical trials are run by industry and rarely by academia. Patient-oriented research is lagging behind basic research. There is a strong need to support the paradigm shift towards more application of the -omics into therapeutic and diagnostic innovations and public-private partnerships (PPP) will be necessary to meet these challenges.

Individual countries face specific challenges, as outlined below.

• Bulgaria:

There has been a recent increase in the number of clinical trials run by industry for market authorisation and training support has been made available by these companies. According to existing information there are three main categories of patient-oriented research:

1. Clinical trials that are part of a scientific project (Ministry of Research)
2. Clinical trials that fall within public health (Ministry of Health)
3. Clinical trials that are part of a market authorisation process

For each category the funding mechanism is different. Regulation and training are key priorities and regulatory agencies such as EMEA should be represented in these processes. Clinical trials are global and there is a view that a move towards greater harmonisation of clinical trial authorisations (CTA) between Europe and the US through a collaboration between EMEA and FDA would be desirable.

• Croatia:

Croatia is not eligible for EC funding and therefore appreciates its opportunity to be represented at the ESF. Since no national entity will fund pan-European clinical trials there is a need to get national funding and research infrastructure in place for the national contribution to the research project and European funding for the European aspect. Public opinion in Croatia is not in favour of clinical

trials so there is a need to make a strong case for the benefits of patient-oriented research.

• Czech Republic:

The Czech Science Foundation funds only basic medical research, with clinical trials being funded by the Czech Ministry of Health. There is a need to ensure that there is a continuum in the funding system from basic to translational to clinical and public health research.

• Estonia:

There are 'grey areas' where neither industry nor academia have expressed a strong interest and willingness to support research, including for example rare disorders and cancer research in children. Genome studies represent a huge challenge, with a need for specific regulation to be developed by funders and regulators. CEEC benefit from 'structural funds'⁸ from the EU that could be useful in establishing dedicated clinical research centres. Charity funding sources need to be identified and attracted to join this endeavour. There is a need to build clinical trial management expertise and dedicated capacity from support organisations. Competition between research and care still exists.

• Hungary:

Commercial clinical trials outnumber IDCT, partly due to cheap labour. One advantage is that academic researchers have benefitted from adequate training. Academia does not express interest in child psychiatry, nor does industry. Funding mechanisms are seen as too complicated, and there is a need for a tailored programme dedicated to clinical trials funding.

• Lithuania:

There is an apparent clear divide between patient-oriented research run by industry and by academia. This has led to an absence of strategic scientific alliances. For example in the field of therapeutics on blood-derived products Lithuania is seen as a provider only, without research capacity. This is an issue that needs to be addressed.

• Poland:

Here physicians are generally too involved in commercial clinical trials to dedicate time to academic studies. There is a need to set up a EC programme covering the fees of project managers which would act as an incentive for clinical investigators to carry out IDCT. Strategic alliances (e.g. PPP) with pharmaceutical companies might be one way to benefit the research and public health systems.

8. Structural Funds: http://ec.europa.eu/regional_policy/funds/prord/sf_en.htm

8. Status in Central and Eastern European Countries

• Slovak Republic:

The Slovak Science Foundation Agencies (VEGA – the Scientific Grant Agency of the Ministry of Education of Slovak Republic and the Academy of Sciences, or APVV – the Slovak Research and Development Agency) fund only basic medical research. Clinical trials are funded by the Slovak Ministry of Health, pharmaceutical companies or international organizations (e.g. cancer treatment trials are supported by EORTC).

Conclusions

To complement the key recommendations expressed in this report, it appears that specific issues needs to be considered in CEEC.

1. For Education, Training and Career

In general, education and training in clinical research is provided by the international pharmaceutical companies. There is an almost complete lack of specific education for clinical trials from the academic sector. There are no specific MD-PhD programmes in the CEEC that allow for parallel clinical and research training.

The development of intellectual property management support and technology transfer organisations is not among the top priorities for academic institutions in the CEEC.

2. For the Levels of Funding and Models of Partnership

Attitudes towards patient-oriented research in the CEEC do not appear to be particularly positive and the field is severely under-funded. There is a need to change the political perception about the importance of medical research, especially in the field of clinical medicine.

There is a common lack of “wise money” in the CEEC. This results in lack of charities and philanthropic organisations supporting medical research both in the field of basic and clinical medicine. Medical research would not appear to be among the top priorities for these countries.

The role of local pharmaceutical companies of the CEEC in research and development is rather limited. These companies seem to be more concerned about the marketing of generic drugs in developing countries. By contrast, international pharmaceutical companies are very active in running clinical trials in CEEC and governments could launch initiatives to start strategic alliances through public-private partnerships to address important public health issues taking advantage of the genetic epidemiology approach well developed in CEEC.

National funding organisations in the CEEC do not provide necessary funding for clinical trials.

3. For the management of IDCT

There is a need for development of centres of excellence based on collaboration at the pan-European level. Those countries that have recently joined the EU are eligible for support from structural funds from the European Commission. Moreover research infrastructure identified in the ESFRI roadmap is eligible for EU structural funds. This funding is allocated by the EU to develop infrastructure in European Regions. As ECRIN (the European Clinical Research Infrastructures Network) is the ESFRI⁹ roadmap vehicle for clinical research this means that, pending the agreement of the Region, the development of clinical research infrastructure may be supported by EU structural funds in member states willing to participate in ECRIN. This represents a excellent opportunity for establishing academic clinical research centres in the CEEC in connection with the those that have already been developed in Western Europe.

9. http://ec.europa.eu/regional_policy/atlas2007/index_en.htm

9. Implementation Plan

After the consensus conference on September 29-30, 2008, a workshop was held on November 17, 2008 in Frankfurt to discuss and consolidate ideas and plan the basis for a successful and sustainable implementation of the recommendations from the consensus conference. The panel (described in the list of participants) discussed ideas for implementation of all of the recommendations, and in particular those that had been ranked as the five most important by delegates to the consensus conference. Special consideration was given to the impact of the recommendations on different stakeholders, and to possible solutions for implementing the recommendations.

Stakeholder Groups

For a successful and sustainable implementation of the recommendations, it was decided to target specific groups of stakeholders as follows.

Group 1:

- Academic research
- Learned societies
- Universities
- Healthcare providers/hospitals

Group 2:

- National and EU funders
- National and EU regulators
- Ministries
- Ethics committees

Group 3:

- Patients
- Philanthropic organisations
- General public

Group 4:

- Private sector

The stakeholder group categories cover different activities in health research, and there is a certain overlap between groups. Further, use of language and definitions are not the same across Europe. **Figure 1** illustrates which activities in healthcare each of the groups has an interest in, and which recommendations are relevant to the groups in relation to the specific activities.

The first three stakeholder groups cover the whole chain of activities, while the private sector focuses mostly on the middle section of the chain, i.e. diagnosis, treatment development and evaluation. This is in accordance with their business interests to develop drugs and medical devices. Prevention is clearly underserved by all groups. **Figure 1** further shows the recommendations per stakeholder group according to the ranking.

Possible Solutions and Activities

As a first step, the experts recommended making a list of the principal stakeholder organisations to ensure that the particular recommendations were targeted at the appropriate stakeholders.

The first activity is the widespread dissemination of this Forward Look report, with endorsements and recommendations from all EMRC member organisations. Dissemination will be through press statements, press conferences, articles and so on. This is seen as an essential first step.

The Forward Look should also be sent to key political figures in the EU, including commissioners, members of parliament and national government ministers.

The ESF should give continuous support to the process of dissemination, making clear that the ESF's member organisations have endorsed the recommendations.

In addition to these general activities, a first implementation plan specific for the top five recommendations is proposed.

Ranked 1st – Education, Training and Careers

The key aim of all efforts in this direction should be to attract, train and keep young scientists in clinical research. There have to be incentives to run parallel careers in clinical work and research.

To this end a list of models and best practice of MD-PhD training within the different countries of Europe should be created. This will help to disseminate best practice and strengthen European training programmes for clinical investigators. The experts, however, noted that it is not necessary to aim for a common training syllabus for all European countries, given the variety of funding mechanisms and healthcare systems. However, to strengthen clinical research, more and better career opportunities are needed for clinical scientists and to achieve this aim adequate funding should be made available in all EU countries. It will be important not to duplicate ongoing education initiatives, for example projects currently funded by IMI.

Ranked 2nd – Level of Funding

The level of funding for biomedical research in general and for clinical research and IDCT in particular is by far too low in the EU27 and in most if not all EU member states. There is no simple single remedy applicable to all member states. Increased public funding by EU member states (whether from healthcare or research budgets or both) and from EU budgets should be substantially increased with a multi-year growth path and strategy to address problems that require attention at the regional,

9. Implementation Plan

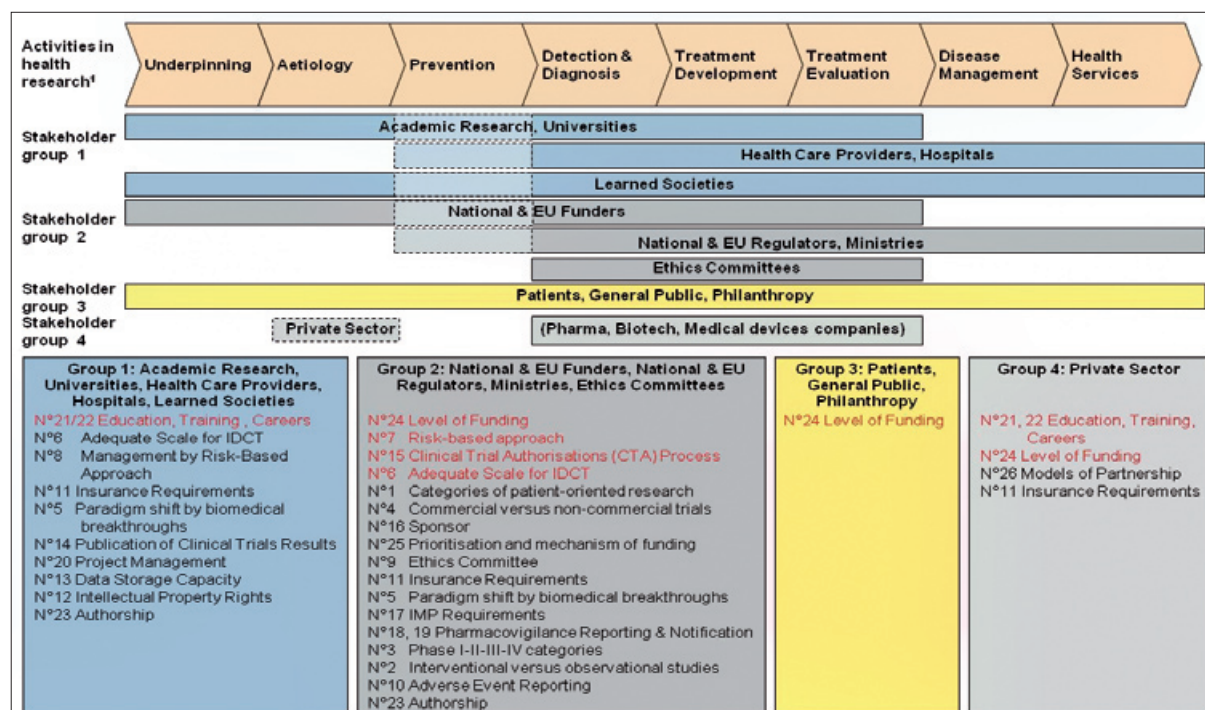


Figure 1. Activities of the stakeholder groups and recommendations relevant to each stakeholder group. The recommendations are listed in the order of their ranking of importance. Recommendations in red are those adjudged to be the top five most important recommendations.

national and European levels. Other funding mechanisms should also be explored.

One possibility to increase funding will be to attract new financial donors to biomedical research. However, there are several obstacles to overcome. One of them is tax law. In the US, for example, tax law promotes such donations; in Europe this is not always the case. One of the first activities for implementation of this recommendation will be to obtain a comprehensive overview of tax regulations for donations in European countries as a basis for further activity in this direction. Such an overview would be useful for academic institutions to lobby for better conditions in their own countries.

In order to increase funding for translational research, a model equivalent to the UK's National Institute for Health Research might work for Europe, and an analysis of these UK examples (more information can be found at <http://www.nihr.ac.uk/> together with Sir David Cooksey's review of UK health research) will serve as a first implementation step. Wider dissemination of this report may also facilitate this goal.

A further implementation activity will be an analysis to ascertain if the EORTC (European Organisation for Research and Treatment of Cancer) model might be transferable to diseases other than cancer.

Another issue is the fact that many trials usually obtain only partial funding initially and the start of the trial is delayed until the rest of the funding is secured. In this respect, an important implementation activity will be an analysis of what is funded at the national level and what is the gap, and then analyse how the gap can be closed with specific EU funding. In any event, it will be important to emphasise that to prevent delays it is vital to provide full funding for clinical trials.

An interesting debate that arose during the workshops was about the possible merits of a European equivalent to the US National Institutes of Health (NIH) for all disease areas. It was ultimately agreed that the NIH model is not transferable to Europe at the moment, but that parts of it may be relevant. In Europe, a "virtual NIH" might be a solution for each disease area, involving relevant learned societies and academies – with bodies such as the EIBIR (European Institute for Biomedical Imaging Institute) comprising the European Society of Radiology, the European Society of Nuclear Medicine, academic hospital departments and university institutes, being possible candidates.

We recommend that the level of funding for IDCT should be increased, and that funding should be better coordinated. A good example of such coordination is the UK Clinical Research Collaboration where the National

Health Service, research funders, industry, regulatory bodies, Royal Colleges, patient groups and academia are working together to develop a coherent approach to funding health related research.

Ranked 3rd – Risk-Based Approach

A first step to implement this straightforward recommendation is to change the EU Clinical Trials Directive from 2001, where the necessary changes are highlighted in the annex of this Forward Look report (see Annex 6). These suggestions for change will be shared with DG Research/Enterprise/Health, EMEA, and national member states, as well as other competent authorities and ethical committees. A resulting amended directive should be based on a risk-based approach and should take into consideration the new paradigm of biomedical research (see recommendation number five, “paradigm shift by biomedical breakthroughs”). For revision of the directive, the EU could set up an *ad hoc* group consisting of national representatives and observers from non-EU countries.

This is a global issue which could usefully be discussed under the auspices of organisations such as the OECD Global Science Forum. This could lead to internationally agreed standards, where ethical codes of conduct are especially relevant.

Ranked 4th – Clinical Trial Authorisations (CTA) Process

This is a straightforward practical recommendation similar to the process that led to the European patent system. The first step is to agree on a set of procedures common to the different countries, to a limited number of languages, and to mutual recognition. Then, in a second step, a centralised European authority could be proposed and set up. Again, the effort should probably be led by an EC *ad hoc* group, with national representatives and non-EU observers.

This recommendation should also be included in the amended Clinical Trials Directive. However, implementation should not wait for new legislation, which will take time. Voluntary harmonisation between member states, building on the excellent foundation of the Clinical Trial Facilitation Group and the Brussels *ad hoc* group on guidance, will be quicker and could achieve the same result. An analysis on how to move forward in this direction will be a first activity for implementation of this recommendation. The EMRC member organisations have a crucial role here.

Another activity already underway is the ICREL (Impact on Clinical Research of European Legislation) project on the impact of the current directive on competent authorities and principal investigators, launched in December 2008.

Ranked 5th – Adequate Scale for IDCT

Dissemination of research results to all European countries may be facilitated if multicentre trials involve many countries, as experience has shown that results are better implemented in countries where trials have taken place and by investigators who have contributed to the trials. However, the lack of recognition of the contribution of individual researchers is an important limiting factor to the launch of large-scale IDCT. It is therefore absolutely imperative to acknowledge all authors of and contributors to large-scale IDCT. Thus, a first activity on the route to implementation of this recommendation will be contact to the ICMJE, the International Committee of Medical Journal Editors, to secure adequate recognition of authorship contributions on multi-author clinical trial papers.

The most important factor for achieving the goal of sufficient number of patients in clinical trials is education and training about how to perform power calculations and how to properly design a clinical trial. ECRIN, EORTC and the ESFRI's infrastructure on translational medical research EATRIS have crucial roles here, along with the editors of the medical journals, the EMEA, academia and learned societies.

Do we need a new organisation?

The EMRC of the ESF represents all the medical research councils in Europe, and as such is an appropriate platform for the co-ordination of the effort to implement the recommendations in this report. However, there is a need to secure cooperation with the above-mentioned stakeholders.

The top five recommendations to strengthen IDCT in Europe as ranked by the consensus conference are targeted towards the following stakeholder groups (see Figure 1):

- 1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research (Groups 1 and 4).**
- 2. To increase levels of funding for IDCT (Groups 2, 3 and 4).**
- 3. To adopt a 'risk-based' approach to the regulation of IDCT (Group 2).**
- 4. To streamline procedures for obtaining authorisation for IDCT (Group 2).**
- 5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered' (Group 2).**

10. Conclusions

Improved patient-oriented research in Europe will benefit European citizens and the European medical industry and facilitate the transfer of scientific discoveries into patient care. For Europe and for the rest of the world this effort will be of great importance for the quality of life of individuals and the wellbeing of society.

This Forward Look focuses on areas where conditions for IDCT in Europe can be improved. The Forward Look is the result of a thorough process which has involved the top experts in the field.

An integrated, EU-wide approach to patient-oriented research is needed, with priorities set by patient needs. Such an approach will reduce fragmentation of research across Europe and allow high-quality research, including multinational clinical studies. Efficient patient-oriented research requires both specialised competences and advanced infrastructure. Non-commercial clinical research is performed in academic medical centres and university hospitals in Europe and could also benefit from collaboration with the pharmaceutical industry. The infrastructure required for high-quality patient-oriented research, with database management, quality assurance, monitoring and support for regulatory affairs, is not sufficient in Europe. The increasing demand for efficiency in clinical work in the hospitals creates difficult conditions for clinical patient-oriented research, a situation which is exacerbated by the increasing burden of red tape.

A coherent and long-term strategic plan is needed to improve clinical research in Europe. This requires the following issues to be addressed.

- 1) Better career opportunities for clinical scientists from training, to junior positions and up to support for senior clinical investigators. It is vital to attract, train and keep young scientists in clinical research. A list of models and best practice for MD-PhD training in different countries in Europe will help to spread best practice.
- 2) A major funding effort is needed for clinical research, preferably based on a competitive model and using a peer review process, with more emphasis given to 'bottom up' proposals for projects and programmes, rather than 'top down' directives. At present, the best approach may be a combination of funding efforts at regional/national and EU-wide levels. The efforts should be substantial with growth planned over at least a decade. Increased funding for IDCT is crucial, from both public and private sources. A comprehensive survey of tax regulations relating to donations to medical research in countries throughout Europe might be useful. Such an overview could be used as a lobbying tool in those countries where tax exemptions for donations to medical research are not as generous as in others. For clinical trials it is especially crucial to

provide full cost funding for the complete trial in order to prevent delays and assure the trial's success and impact.

- 3) Infrastructure for clinical research and IDCT should be substantially improved. This is needed not only to improve the efficacy of existing and future research, but also to make clinical research a much more attractive career choice.
- 4) Regulations governing clinical research are ripe for review. They need to be revised and simplified but without compromising patient protection. A risk-based approach to the categorisation and management of clinical trials should be implemented as part of an overhaul of the EU Clinical Trials Directive of 2001. A common clinical trials authorisation process should be considered and adequate recognition of individual researcher's contributions on multi-author clinical trial papers should be secured. A sufficient number of patients in clinical trials is necessary in order to give the trial statistical credence, and education and training about how to perform clinical trials is central for advancing this area of medical research.

Central and Eastern European Countries are facing the same problems as those faced by their counterparts in Western Europe, but they are more acute and extreme. In these countries most clinical trials are run by industry and rarely by academia. Patient-oriented research is lagging behind basic research. There is a strong need to support the paradigm shift towards more application of the -omics into therapeutic and diagnostic innovations. Public-private partnerships will be necessary to meet these challenges. While across Europe there are many challenges facing clinical research, in Central and Eastern Europe Countries there are some specific issues. There is a lack of donations for clinical research from charities and philanthropic organisations, a lack of specific education on clinical trials within the academic sector, no MD-PhD programmes and research is not a top priority. Infrastructure for IPR management support and technology transfer is lacking, and there is no specific funding mechanism for clinical trials. Structural funds from the EU could represent a good opportunity to fund clinical research infrastructure. There is a need to change the political perception about the importance of medical research. Pharmaceutical companies are active in running clinical trials here and governments could launch initiatives to start strategic alliances to address important public health issues.

The Forward Look ends with a stakeholder analysis and an implementation plan for how to strengthen IDCT Europe. Wide dissemination of this Forward Look is essential, as the message is clear.

10. Conclusions

We are facing real problems in the area of investigator-driven clinical trials in Europe. We suggest these problems can be solved by our recommendations. Action is needed urgently and we recommend that action is taken now.

If we can collaborate on this important issue and improve conditions for clinical research, we can bring better health and prosperity to Europe.

The top five recommendations to strengthen IDCT in Europe as ranked by the consensus conference were as follows:

- 1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.**
- 2. To increase levels of funding for IDCT.**
- 3. To adopt a 'risk-based' approach to the regulation of IDCT.**
- 4. To streamline procedures for obtaining authorisation for IDCT.**
- 5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.**

11. Committee Members

Management Committee

Chair

- Professor Jürgen Schölmerich, DFG and University Medical Center, Regensburg, Germany

Co-Chairs

- Professor Roger Bouillon, FWO and Katholieke Universiteit, Leuven, Belgium
- Professor Håkan Billig, SRC and Göteborg University, Göteborg, Sweden

Other Members

- Dr. Susan Shurin, National Heart, Lung and Blood Institute – NIH, Washington, United States
- Dr. Robert Goldstein, JDRFI, New York, United States
- Professor Marja Makarow, ESF, Strasbourg, France
- Professor Liselotte Højgaard, EMRC, France and University of Copenhagen and DTU, Copenhagen, Denmark

Scientific Committee

- Professor Stefan Bielack, Olga Hospital, Stuttgart, Germany
- Professor Christian Bréchet, Mérieux Alliance, Lyon, France
- Professor Janet Darbyshire, Medical Research Council Clinical Trials Unit and UK Clinical Research Network, London, United Kingdom
- Professor Sally Davies, Department of Health, London, United Kingdom
- Professor Jacques Demotes, ECRIN (European Clinical Research Infrastructures Network), Paris, France
- Professor Harry L.A. Janssen, Erasmus MC, Rotterdam, The Netherlands
- Professor Pierre Lafolie, Karolinska Institutet, Stockholm, Sweden
- Professor Richard Sullivan, London School of Economics & Political Science, London, United Kingdom
- Professor Eero Vuorio, University of Turku, Turku, Finland

Contribution to the Expert Committees

SW1. Categories and Design of Investigator-Driven Clinical Trials

31 March 2008, Strasbourg, France

Chair:

- Professor Harry L.A. Janssen, Erasmus MC, Rotterdam, The Netherlands

Co-Chair:

- Professor Jacques Demotes, ECRIN (European Clinical Research Infrastructures Network), Paris, France

Participants:

- Mr. Nikos Dedes, European AIDS Treatment Group, Brussels, Belgium
- Professor Guy Goodwin, University of Oxford, Warneford Hospital, Oxford, United Kingdom
- Professor François Lemaire, Comité National de Recherche Clinique, Paris, France
- Professor Marja Makarow, European Science Foundation, Strasbourg, France
- Professor Wolfgang Oertel, Philipps University, Marburg, Germany
- Professor Stefaan Van Gool, Pediatric Hemato-oncology and Neuro-oncology, Belgium
- Professor Ulrich Walker, EULAR (European League against Rheumatism), Basel University, Switzerland

SW2. Regulatory and Legal Issues, IPR and Data Sharing

28 May 2008, London (UK)

Chair:

- Professor Sally Davies, Department of Health, London, United Kingdom

Co-Chair:

- Professor Jacques Demotes, ECRIN (European Clinical Research Infrastructures Network), France

Participants:

- Professor Stefan Bielack, Olga Hospital, Stuttgart, Germany
- Mr. Chris Bird, Wellcome Trust, London, United Kingdom
- Professor Hans-Georg Eichler, European Medicines Agency (EMA), London, United Kingdom
- Dr. Catherine Elliott, Medical Research Council, London, United Kingdom
- Professor Gary Ford, Newcastle University and Stroke Research Network, United Kingdom
- Dr. Trish Groves, British Medical Journal, London, United Kingdom
- Dr. Juan Martinez Armesto, Fundación Progreso y Salud, Sevilla, Spain

11. Committee Members

- Dr. Sarah Meredith, Medical Research Council, London, United Kingdom
- Dr. Lana Skirboll, National Institutes of Health, Washington, United States
- Professor Richard Sullivan, London School of Economics & Political Sciences, London, United Kingdom
- Dr. Rémy Von Frencckell, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium
- Professor Til Wykes, Kings College London, United Kingdom

SW3. Management of Investigator-Driven Clinical Trials

29 May 2008, London, United Kingdom

Chair:

- Professor Janet Darbyshire, Medical Research Council Clinical Trials Unit and UK Clinical Research Network, London, United Kingdom

Co-Chair:

- Professor Stefan Bielack, Olga Hospital, Stuttgart, Germany

Participants:

- Professor Jacques Demotes, ECRIN (European Clinical Research Infrastructures Network), Paris, France
- Professor Gary Ford, Newcastle University and Stroke Research Network, United Kingdom
- Dr. Sarah Meredith, Medical Research Council, London, United Kingdom
- Dr. Rémy Von Frencckell, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium

SW4. Education, Training, Career and Authorship

7 April 2008, Strasbourg, France

Chair:

- Professor Eero Vuorio, University of Turku, Turku, Finland

Co-Chair:

- Professor Pierre Lafolie, Karolinska Institutet, Stockholm, Sweden

Participants:

- Professor Fritz Bühler, European Center of Pharmaceutical Medicine (ECPM), Basel, Switzerland
- Mag. Christa Janko, Vienna School of Clinical Research, Vienna, Austria
- Professor Marçal Pastor Anglada, Universitat de Barcelona, Barcelona, Spain
- Professor Daniel Scheidegger, Swiss National Science Foundation, University of Basel, Basel, Switzerland

- Professor Alan Tyndall, University of Basel, Basel, Switzerland
- Professor Doctor Peter Van der Spek, Erasmus University Medical Center, Rotterdam, The Netherlands

SW5. Funding and Models of Partnership

8 April 2008, Strasbourg, France

Chair:

- Professor Christian Bréchet, Mérieux Alliance, Lyon, France

Co-Chair:

- Professor Richard Sullivan, London School of Economics & Political Science, London, United Kingdom

Participants:

- Professor Steinar Aamdal, Norwegian Radium Hospital, Oslo, Norway
- Professor Roger Bouillon, Katholieke Universiteit Leuven, Leuven, Belgium
- Mr. Mathieu Cantegreil, European Foundation Centre-AIBSL, Brussels, Belgium
- Mag. Christa Janko, Vienna School of Clinical Research, Vienna, Austria
- Dr. Rebecca Ludwig, Helmholtz Centre for Infection Research, Braunschweig, Germany
- Professor Françoise Meunier, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium
- Dr. Ian Ragan, EFPIA, Brussels, Belgium
- Dr. Wouter Spek, European Science Foundation, Strasbourg, France
- Professor Alan Tyndall, University of Basel, Basel, Switzerland
- Mr. Guy Vernet, Fondation Mérieux, Lyon, France
- Dr. Ingrid Wüning Tschol, Robert Bosch Stiftung GmbH, Stuttgart, Germany
- Professor Kurt Zatloukal, Medical University of Graz, Graz, Austria

SW6. Business Planning of the Forward Look IDCT

17 November 2008, Frankfurt, Germany

Chair:

- Professor Liselotte Højgaard, EMRC, France and University of Copenhagen and DTU, Copenhagen, Denmark

Participants:

- Professor Hans-Georg Eichler, European Medicines Agency (EMA), London, United Kingdom
- Dr. Ralf Emmerich, Capgemini Consulting, Stuttgart, Germany
- Dr. Robert Goldstein, Juvenile Diabetes Research Foundation International (JDRF), New York, United States

-
- Dr. Markus Hartmann, European Consulting & Contracting in Oncology, Trier, Germany
 - Professor Harry Janssen, Erasmus MC, Rotterdam, The Netherlands
 - Dr. Christine Kubiak, ECRIN, Paris, France
 - Dr. Claire Levy-Marchal, Inserm, France
 - Professor Françoise Meunier, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium
 - Dr. Carole Moquin-Pathey, ESF-EMRC, Strasbourg, France
 - Dr. Oliver Müller, Capgemini Consulting, Stuttgart, Germany
 - Professor Ulf Müller-Ladner, Liebig University, Liebig, Germany
 - Professor Richard Sullivan, London School of Economics & Political Science, London, United Kingdom
 - Professor Peter Van Der Spek, Erasmus MC, Rotterdam, The Netherlands
 - Mr. Julien Weber, ESF-EMRC, Strasbourg, France

SW7. Status in Central and Eastern European Countries

7 December 2008, Prague, Czech Republic

Chair:

- Professor Eero Vasar, University of Tartu, Tartu, Estonia

Participants:

- Professor Anna Czlonkowska, Institute of Psychiatry and Neurology, Warsaw, Poland
- Dr. Marko Jakopovic, Clinical hospital for Lung diseases, Zagreb, Croatia
- Professor Zita Ausrele Kucinskiene, University of Vilnius, Vilnius, Lithuania
- Dr. Tuuli Metsvaht, Tartu University Clinic, Tartu, Estonia
- Professor Bogdan Petrunov, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria
- Dr. Katarína Poláková, Slovak Academy of Sciences, Bratislava, Slovak Republic
- Dr. János Réthelyi, Semmelweis University, Budapest, Hungary
- Professor Josef Syka, The Czech Science Foundation, Prague, Czech Republic
- Dr. Kadri Tamme, Tartu University Clinic, Tartu, Estonia

Support Team

- Mrs. Geneviève Cliquet, DL&P, Paris, France
- Dr. Ralf Emmerich, Capgemini Consulting, Stuttgart, Germany
- Mr. Jean-François Gouzer, Capgemini Consulting, Basel, Switzerland
- Mr. Simon Hadlington, Science Writer, York, United Kingdom
- Dr. Oliver Müller, Capgemini Consulting, Stuttgart, Germany
- Mr. Ozcan Saritas, PREST, Manchester, United Kingdom
- Mr. Julien Weber, ESF-EMRC, Strasbourg, France

Coordination

- Dr. Carole Moquin-Pathey, ESF-EMRC, Strasbourg, France

12. Annexes

Annex 1

Methodology

The Forward Look 07-001 'Investigator-Driven Clinical Trials' initiative is led by members of national funding and research performing organisations and managed by the EMRC. The overall methodology is in compliance with the "Forward Look Design and Implementation Guidelines Design" produced by ESF on 26 June 2007. The specific methodology used for the workshops and the implementation plan was developed by the EMRC together with Capgemini Consulting and validated by PREST (the centre for science and technology policy and management research at the Manchester Business School, UK) to be compliant with foresight guidance. The whole methodology was approved by the management committee.

The topic for a Forward Look on 'Non-Commercial Clinical Trials' was proposed by the EMRC core group members in January 2007 and written by Professor Liselotte Højgaard, EMRC Chair and Dr. Carole Moquin-Pathey, Head of EMRC Unit. The proposal was approved by the ESF Governing Council at its meeting held on 20 April 2007 based on support letters from Professor Jürgen Schölmerich (DFG, Germany), Professor Colin Blakemore (MRC, UK), Professor Gianluigi Condorelli (CNR, Italy) and expert opinion from Dr. Elias A. Zerhouni (NIH, US) and Dr. Robert Goldstein (Juvenile Diabetes Research Foundation International, US).

In a preparatory meeting in Paris on 20 July 2007, Professor Jürgen Schölmerich (DFG, Germany), Professor Håkan Billig (SRC, Sweden) and Professor Roger Bouillon (FWO, Belgium) agreed to respectively chair and co-chair this activity. The outcome of the meeting was to discuss and approve:

- the new title of the Forward Look activity: 'Investigator-Driven Clinical Trials',
- the organisational structure,
- the methodology,
- the time line,
- the five strategic themes,
- the general output format and
- the quality assurance procedure.

The management committee is composed of the chair and two co-chairs of the Forward Look, the ESF Chief Executive, the EMRC Chair and the two external reviewers who assessed the proposal.

A scientific committee was formed to lead the analysis of the five strategic themes, with the aim to shape solutions and recommendations. This committee was made of the chairs and co-chairs of the five strategic workshops (SW), as follows:

- SW1 'Categories & Design of IDCT' chaired by Professor Harry Janssen (Erasmus MC, The Netherlands), and co-chaired by Professor Jacques Demotes (ECRIN, France)

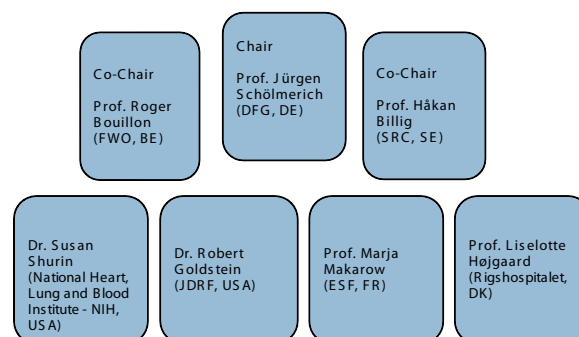


Figure 2. Members of the Management Committee

- SW2 'Regulatory, Legal Issues, IPR and Data Sharing' chaired by Professor Sally Davies (DH, UK), and co-chaired by Professor Jacques Demotes (ECRIN, France)
- SW3 'Management of IDCT' chaired by Professor Janet Darbyshire (UKCRN and MRC CTU, UK), and co-chaired by Professor Stefan Bielack (Olga Hospital Stuttgart, Germany)
- SW4 'Education, Training, Careers and Authorship' chaired by Professor Eero Vuorio (University of Turku, Finland), and co-chaired by Professor Pierre Lafolie (Karolinska Institute, Sweden)
- SW5 'Funding and Models of Partnership' chaired by Professor Christian Bréchet (Mérieux-Alliance, France), and co-chaired by Professor Richard Sullivan (London School of Economics, UK)

Figure 4 describes the analytical approach that was conducted to assess the current problems and needs faced by researchers when initiating investigator-driven clinical trials in Europe, to generate and prioritise recommendations and to plan their implementation. The whole process was carried out in the most transparent way.

The five strategic workshops and the final consensus conference took place from 31 March to 30 September 30 2008. The participants¹ for each were invited based on their high level expertise in IDCT and their affiliation to different stakeholder groups, including:

- Academic research
- Universities
- Healthcare providers and hospitals
- National and EU funders (i.e. ESF member organisations)
- Ministries, i.e., ministries of research and ministries of health
- European Institutions (European Commission, European Parliament, Council of Europe)
- Ethics committees

1. See chapter 'Committee members' and Annex 2

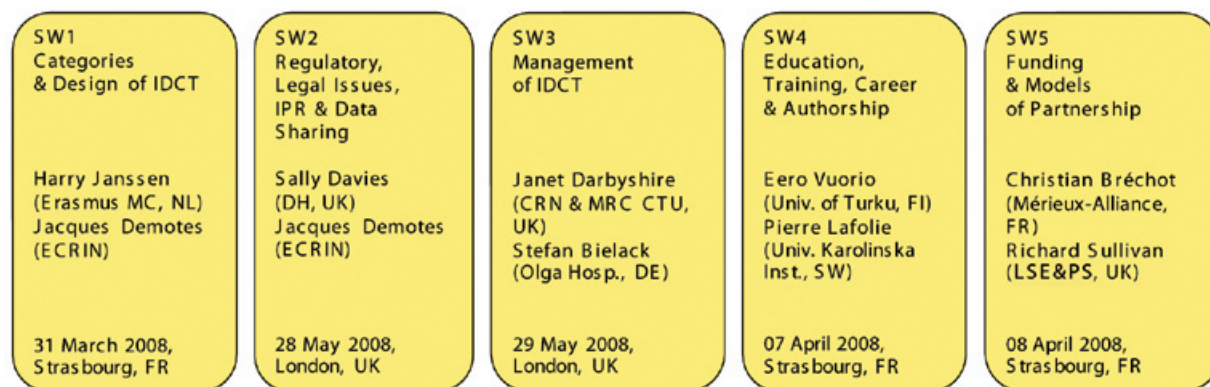


Figure 3. Strategic workshops chaired by the members of the scientific committee

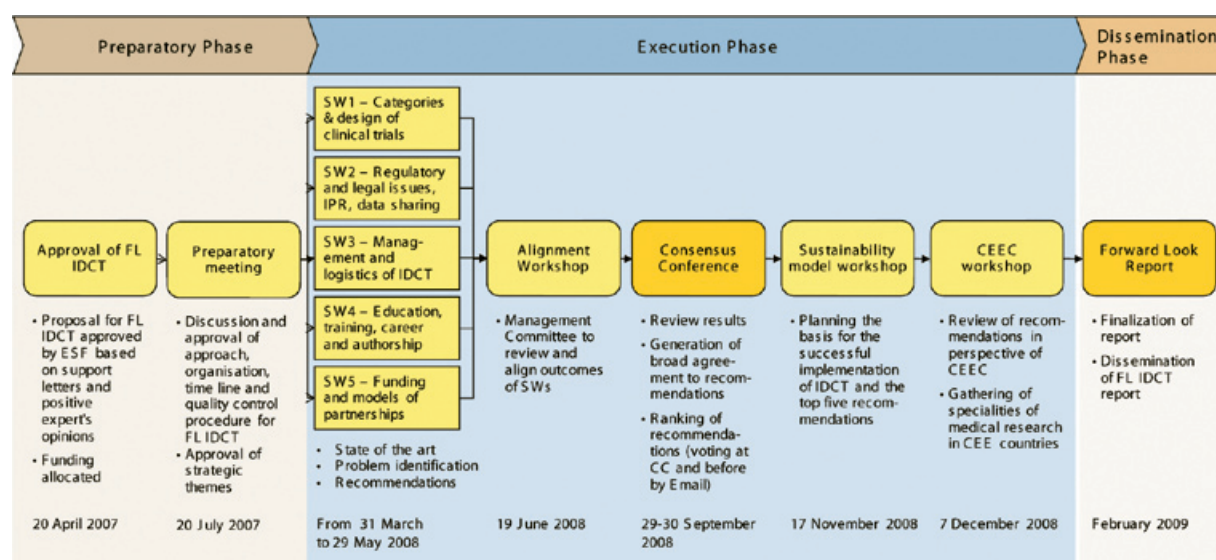


Figure 4. Overall approach and time-line of the Forward Look on IDCT

- Regional politics
- Clinical trial networks
- Patient organisations
- European learned societies in the main disease areas
- National and EU regulators ('competent authorities')
- Charities and philanthropic organisations
- Coordinators of ESFRI and other European research agencies involved in patient-oriented research
- International not-for-profit organisations
- The private sector, including the European Confederation of Medical Devices Associations and the pharmaceutical and diagnosis industry

In each strategic workshop the problems and needs of IDCT in the respective theme were identified and discussed. Each theme was also assessed against the needs across the main health categories currently addressed by the existing initiatives focusing on related issues (e.g., IMI JU, EATRIS, BBMRI²). Then in each strategic workshop, recommendations to overcome these problems and needs were formulated and agreed upon through a collaborative problem solving process.

2. IMI JU: Innovative Medicines Initiative Joint Undertaking; EATRIS: European Advanced Translational Infrastructure in Medicine, BBMRI: Biobanking and Biomolecular Resources Research Infrastructure. See glossary for more information on these initiatives.

Annex 1

Methodology

		Strategic themes				
		Categories and Design of IDCT	Regulatory, Legal issues, IPR, Data sharing	Management of IDCT	Education, Training, Career, Authorship	Funding, Models of partnerships
IDCT needs per health category aligned to EATRIS, BBMRI, IMI JU	Cancer					
	CNS					
	CVD					
	Infectious Diseases					
	Inflammatory Disorders					
	Metabolic Disorders					

Figure 5. Matrix approach to build a comprehensive analysis of strategic themes across the main health categories

Out of the five strategic workshops, 88 recommendations were made. These recommendations were then considered by the Management Committee at an alignment workshop held on 19 June 2008. A mechanism for processing these recommendations was agreed upon, together with the need to identify the stakeholder group that would be responsible for implementing the recommendations. The management committee suggested streamlining and regrouping the 88 recommendations down to about 25. To improve the coherence some recommendations were shifted to other strategic themes.

This led to a list of 26 recommendations that were all fully endorsed and refined by the participants in the consensus conference held in Strasbourg, France on 29-30 September 2008 under the auspices of the French Presidency of the European Union. There, about 90 participants representing the key stakeholder groups were invited to rank all recommendations per theme and to nominate their top five recommendations across whole list of recommendations. These votes were pooled with the votes performed by mail before the consensus conference and amounted to a total of 71 'voting forms' leading to the identification of the top five recommendations.

Due to the lack of strong representation of Central and Eastern European Countries (CEEC) at the consensus conference a dedicated workshop aimed at identifying any particular needs of these countries was held in Prague, Czech Republic on 7 December 2008 (see

participants listed under 'Committee Members' at the beginning of this document). The aim of this workshop was to review the 26 recommendations with the views of CEEC, to reach a general agreement and to identify specific issues to be considered in CEEC.

A workshop aimed at gathering advice on how to best develop an implementation plan for the five top-ranking recommendations was held in Frankfurt, Germany on 17 November 2008. This workshop was attended by members of the Management Committee together with business experts.

The Forward Look report will be publicised and disseminated widely among the various stakeholder groups.

Annex 2

Speakers and Participants in the Consensus Conference, 29-30 September 2008, Strasbourg, France

Chair:

- Professor Jürgen Schölmerich, DFG and University Medical Center, Regensburg, Germany

Co-Chairs:

- Professor Roger Bouillon, FWO and Katholieke Universiteit, Leuven, Belgium
- Professor Håkan Billig, SRC and Göteborg University, Göteborg, Sweden

Speakers:

- Professor Stefan Anker, Charité Hospital, Berlin, Germany
- Professor Stefan Bielack, Olgahospital, Stuttgart, Germany
- Mr. Chris Bird, The Wellcome Trust, London, United Kingdom
- Dr. Philip Budashewitz, National Institutes of Health (NIH), Bethesda, United States
- Professor Jacques Demotes, ECRIN (European Clinical Research Infrastructures Networks), Paris, France
- Dr. Trish Groves, British Medical Journal, London, United Kingdom
- Professor Liselotte Højgaard, EMRC, France and University of Copenhagen and DTU, Copenhagen, Denmark
- Professor Cyril Höschl, Third Faculty of Medicine, Prague, Czech Republic
- Professor Harry Janssen, Erasmus MC, Rotterdam, The Netherlands
- Mrs. Monique Jung, Alsace Region, Strasbourg, France
- Professor Marja Makarow, European Science Foundation (ESF), Strasbourg, France
- Dr. Sarah Meredith, MRC, London, United Kingdom
- Professor Françoise Meunier, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium
- Dr. Carole Moquin-Pathey, ESF-EMRC, Strasbourg, France
- Professor Richard Sullivan, London School of Economics & Political Science, London, United Kingdom
- Professor Eero Vuorio, University of Turku, Turku, Finland
- Dr. Moritz N. Wente, University of Heidelberg, Heidelberg, Germany

Participants:

- Professor Steinar Aamdal, Norwegian Radium Hospital, Oslo, Norway
- Dr. Philippe Arhets, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France
- Dr. Signe Bang, Research Council of Norway, Oslo, Norway
- Dr. Alfonso Bellia, University of Rome “Tor Vergata”, Rome, Italy
- Dr. Chantal Belorgey-Bismut, Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis, France
- Professor Patrick M. M. Bossuyt, Academic Medical Centre, Amsterdam, The Netherlands
- Professor Pascal Bousquet, Faculté de Médecine, Strasbourg, France
- Professor Gérard Bréart, Inserm – Institut Santé Publique, Paris, France
- Mrs. Insa Bruns, KKS-AG (working federation of coordinating centres for clinical trials), Köln, Germany
- Professor Carsten Carlberg, University of Luxembourg, Luxembourg
- Dr. Alfredo Cesario, DG Research, Directorate Health, Brussels, Belgium
- Professor Giancarlo Comi, European Neurological Society, Milano, Italy
- Dr. Natividad Cuende, Andalusian Health Service – Andalusian Transplant Coordinating Office, Seville, Spain
- Dr. Georges Dagher, Inserm, Paris, France
- Miss Inge Danielsen, Danish Agency for Science, Technology and Innovation, Copenhagen, Denmark
- Dr. Rafael De Andres-Medina, Instituto de Salud Carlos III, Madrid, Spain
- Dr. Ralf Emmerich, Capgemini Consulting, Stuttgart, Germany
- Dr. Kristjan Erlendsson, University Hospital of Iceland, Reykjavík, Iceland
- Professor Wolfgang Fleischhacker, Medical University Innsbruck, Innsbruck, Austria
- Dr. Jesus Frias, Hospital Universitario La Paz, Madrid, Spain
- Dr. Rafael Gabriel Sanchez, Hospital Universitario La Paz, Madrid, Spain
- Professor Guy Goodwin, University of Oxford, Oxford, United Kingdom
- Mr. Simon Hadlington, York, United Kingdom

Annex 2

Speakers and Participants in the Consensus Conference, 29-30 September 2008, Strasbourg, France

- Dr. Markus Hartmann, European Consulting and Contracting in Oncology, Trier, Germany
- Dr. Richard Imrich, Slovak Academy of Sciences, Bratislava, Slovak Republic
- Dr. Christa Janko, Vienna School for Clinical Research, Vienna, Austria
- Mrs. Valérie Journot, Université Victor Segalen, Bordeaux cedex 1, France
- Dr. Ingrid Klingmann, European Forum for Good Clinical Practice, Wezembeek-Oppem, Belgium
- Professor Gabriel P. Krestin, Erasmus Medical Center, Rotterdam, The Netherlands
- Dr. Christine Kubiak, Inserm – ECRIN Project, Paris, France
- Professor Zita Ausrele Kucinskiene, University of Vilnius, Vilnius, Lithuania
- Professor Ruth Ladenstein, St Anna Children's Hospital, Vienna, Austria
- Mrs. Michèle Longuet, French Ministry for Research and Higher Education, Paris, France
- Dr. Rebecca Ludwig, Helmholtz Centre for Infection Research, Braunschweig, Germany
- Dr. Laurence Lwoff, Council of Europe, Strasbourg Cedex, France
- Professor Herbert Maier-Lenz, Network of German Academic Clinical Trial Centers KKS-Network, Freiburg, Germany
- Dr. John Marks, European Science Foundation, Strasbourg, France
- Dr. Carlos Manuel Matias Dias, Instituto Nacional de Saúde, Lisboa, Portugal
- Professor Charles Mgone, European and Developing Countries Clinical Trials Partnership, The Hague, The Netherlands
- Dr. Berit Mørland, Oslo, Norway
- Dr. Oliver Müller, Capgemini Consulting, Stuttgart, Germany
- Dr. Georg Munz, Deutsche Forschungsgemeinschaft (DFG), Bonn, Germany
- Professor John Norrie, University of Aberdeen, Aberdeen, United Kingdom
- Professor Kjell Öberg, Uppsala University, Uppsala, Sweden
- Professor Mairead O'Driscoll, The Health Research Board, Dublin, Ireland
- Professor Wolfgang Oertel, Philipps University Marburg, Marburg, Germany
- Dr. Christiane Pauli-Magnus, Basel University Hospital, Basel, Switzerland
- Mr. Eric Postaire, French Ministry for Research and Higher Education, Paris, France
- Dr. János Réthelyi, Semmelweis University, Budapest, Hungary
- Professor Martin Röllinghoff, Erlangen-Nuremberg Universität, Erlangen, Germany
- Professor Henning Sass, Universitätsklinikum Aachen, Aachen, Germany
- Dr. Gabriela Senti, University and University Hospital Zurich, Zurich, Switzerland
- Dr. Frédéric Sgard, OCDE, Forum Mondial de la Science, Paris, France
- Professor Axel Steiger, Max Planck Society, München, Germany
- Professor Olle Stendahl, Linköping University, Linköping, Sweden
- Dr. Hans Stødkilde-Jørgensen, University of Aarhus, Aarhus N, Denmark
- Professor Alan Tyndall, European League Against Rheumatism (EULAR), Basel, Switzerland
- Professor Willem Gerard Van Aken, ZonMw, Amselveen, The Netherlands
- Professor Greet Van Den Berghe, Catholic University of Leuven, Leuven, Belgium
- Professor Peter Van Der Spek, ERASMUS Medical Center, Rotterdam, The Netherlands
- Mr. Evert-Ben Van Veen, MedLawconsult, The Hague, The Netherlands
- Dr. Guy Vernet, Fondation Mérieux, Lyon, France
- Professor Brigitte Volk-Zeiher, University of Freiburg, Freiburg, Germany
- Professor Manfred Westphal, University Hospital Eppendorf, Hamburg, Germany
- Dr. John Williams, The Wellcome Trust, London, United Kingdom
- Professor Kent Woods, Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom
- Dr. Aysim Yilmaz, Swiss National Science Foundation, Bern, Switzerland

Annex 3

Glossary

BBMRI

Biobanking and Biomolecular Resources Research Infrastructure. A pan-European network of existing and new biobanks and biomolecular resources.

Biobank

Also known as a biorepository, a place that collects, stores, processes and distributes biological materials and the data associated with those materials.

Biomarker

A cellular or molecular indicator of exposure, health effects, or susceptibility. Biomarkers can be used to measure internal dose, biologically effective dose, early biological response, altered structure or function, susceptibility.

Clinical research

Patient-oriented research conducted with human subjects or on material of human origin involving interaction with human subjects in order to discover what causes human disease, and how it can be prevented and treated. Clinical research can include: mechanisms of human disease; therapeutic interventions; and clinical trials; or development of new technologies. Epidemiological and behavioural studies, and outcomes research and health services research can also be part of clinical research.

Clinical trial authorisation (CTA)

Permission from the appropriate regulatory authorities to carry out a clinical trial.

EATRIS

European Advanced Translational Infrastructure in Medicine, a strategic EU project that aims to offer a research infrastructure to help overcome bottlenecks hampering the transfer of basic research findings into clinical application and of clinical observations into basic research.

EC Clinical Trials Directive

The European Union published in April 2001 a European Parliament and Council Directive 2001/20/EC regulating clinical trials with medicinal products. By May 2004, all Member States were requested to have the Directive implemented in national regulations.

ECRIN

European Clinical Research Infrastructures Network. A Pan-European Infrastructure for clinical trials providing, high-quality services to multinational clinical research. As a distributed infrastructure linking national networks of clinical research centres and clinical trials units, ECRIN provides integrated 'one-stop shop' services to investigators and sponsors in multinational studies, with the local contribution of staff embedded in each national coordination.

Effectiveness

A measure of the extent to which a specific intervention, procedure, regimen or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population; a measure of the extent to which a health care intervention fulfils its objectives. To be distinguished from efficacy.

Efficacy

The ability of a drug to produce the purported effect as determined by clinical trials.

EMA

The European Medicines Agency, a body of the European Union responsible for the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use.

EudraCT

A database of all clinical trials commencing in the European Community from 1 May 2004 onwards.

EudraVigilance

A data-processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area.

FDA

The US Food and Drug Administration, an agency of the United States Department of Health and Human Services responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products and cosmetics.

Fixed-dose combinations

Two or more drugs combined in one pill or capsule, in specific dosages, to facilitate correct drug intake.

GCP

Good clinical practice: rules for quality conduct of clinical studies.

Generic drug

A pharmaceutical product usually intended to be interchangeable with the original 'innovator' product, which is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights. Generic drugs are marketed either under a non-proprietary or approved name rather than a proprietary or brand name.

Genomics

The study of the genome (the sum total of the genetic material present in a particular organism) and its action.

IMI

Innovative Medicines Initiative, a novel approach for research funding under the European Commission's 7th Framework Programme. It aims to remove bottlenecks hampering the efficiency of the development of new medicines through public-private partnerships.

GLP

Good laboratory practice: rules for quality conduct of laboratory testing.

GMP

Good manufacturing practice: rules for quality manufacturing conduct in producing human drugs.

IMP

Investigational medicinal product. A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with marketing authorisation but formulated or packaged in a way different from the authorised form, or used for a treatment or group of patients different from those for whom authorisation was given.

Meta-analysis

A statistical synthesis of the data from comparable studies, leading to a quantitative summary of the pooled results. The aim is to integrate the findings, pool the data, and identify the overall trends of results.

Neglected diseases

Diseases which are seriously disabling or life-threatening but for which treatment options are inadequate or do not exist and the drug marketing potential is insufficient to readily attract a private sector response.

Orphan diseases

Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.

Pandemic

A widespread disease outbreak affecting the population of an extensive area of the world.

Pharmaco-epidemiology

The study of the use and effects of medicines in large numbers of people.

Pharmaco-economics

The application of the economic framework to the study of medicines use and effectiveness.

Placebo

An inert medication or procedure i.e., one having no pharmacological effect, but that is intended to give patients the perception that they are receiving treatment of their complaint.

Post-marketing surveillance

A procedure implemented after a medicine has been licensed for public use, designed to provide information on the actual use of the medicine for a given indication and on the occurrence of side-effects, adverse effects, etc.

Power

The number of patients enrolled in a study has a large bearing on the ability of the study to reliably detect the size of the effect of the study intervention. This is described as the 'power' of the trial. The larger the sample size or number of participants in the trial, the greater the statistical power.

Priority medicines

Those medicines which are needed to meet the priority health care needs of the population ("essential medicines") but which have not yet been developed. In this report, a "priority" medicine for a priority disease is by definition also a significant improvement over already-marketed products.

Randomised clinical trial

An experiment in which subjects in a population are randomly allocated into groups, usually called *study* and *control* groups, to receive or not to receive an experimental preventive or therapeutic procedure, manoeuvre or intervention. The results are assessed by rigorous comparison of rates of diseases, death, recovery or other appropriate outcome in the study and control groups.

Secondary prevention

Action taken to detect a health problem at an early stage in an individual or a population, so facilitating cure, or reducing or preventing it spreading or reducing or preventing its long-term effects.

SOPs

Standard operating procedures: detailed instructions on what to do to achieve good clinical, laboratory and manufacturing practice.

Sponsor

An individual or organisation which initiates, manages and/or finances a clinical trial and takes the responsibility of the clinical trial.

Translational research

The conversion of basic research advances into products that can be tested on humans.

A European Syllabus for Training Clinical Investigators, ESF July 2003



Clinical Investigator Training

In 2001, as one development of its action in relation to clinical trials, the European Science Foundation (ESF) and its European Medical Research Councils (EMRC) Standing Committee set up an Advisory Group on Clinical Research Training to investigate the opportunity and feasibility of developing a European basic education and training programme on the conduct of clinical trials.

This programme should include all types of intervention in any therapeutic area, in private practice as well as in public sector. It should also be based on the ethical principles stated in the Declaration of Helsinki and the Good Clinical Practice principles as defined by the International Conference on Harmonisation (ICH-GCP) and the EC Clinical Trials Directive (2001/20/EC)).

The ESF Advisory Group decided first to carry out a European survey of training in clinical research to evaluate the current level of teaching and need for further education of clinical investigators.

The responses to the questionnaire, which was sent to ESF Member Organisations, identified a major need for training courses in clinical research. According to the result of this questionnaire, such courses should preferably be organised at the national level and lead ultimately to certification, so that this training can be recognised as an essential step in ensuring qualification of clinical investigators. The optimal duration should be 3 to 5 days.

Taking these findings into account, the Advisory Group decided to move forward in establishing a syllabus for a common basic training course for clinical investigators and ethics committee members, to be promoted by ESF as a guide for its Member Organisations. It also decided to further investigate the e-based learning approach as one powerful tool to provide such training with the ultimate goal to develop a European certification process.

In autumn 2002, the Advisory Group proposed a final draft of an ESF European Syllabus for Clinical Investigator Training that was then approved by the EMRC Standing Committee and the ESF Executive Board. This syllabus covers seven areas. The intention is to define a common ground of ethical values, scientific and quality assurance principles covering all types of clinical trials, from which countries and universities can build individualised courses.

A European Syllabus for Training Clinical Investigators

Section 1

A critical review of the trial concept

- The rationale of the trial
- Stages and milestones
- Clinical / public health importance

The rationale of the trial must be detailed, and the design must address the specific question according to present state of knowledge. The study should be put into a clinical practice context, and its hypothesis carefully defined.

Section 2

Clinical trial design

General issues

- Type of design and rationale
- Protocol and Case Report Form (CRF)
- Use of control groups / active substance and placebo
- Inclusion / exclusion criteria
- Efficacy and choice of endpoints
- Safety outcomes
- Quality of life / health economics, if appropriate

Statistical issues

- Fundamentals of statistical testing
- Power & sample size determination
- Superiority or equivalence

Special populations

- Children / elderly
- Pregnant women / foetuses
- Renal / liver failure
- Ethnic factors
- Gender

The design should be outlined. What control groups are appropriate, what type of statistical testing is planned, and is the sample size adequate? What are the differences between superiority, equivalence and non-inferiority studies? What safety issues should be identified? The course must help the investigator to identify general and specific issues for trial design.

Section 3

Ethical issues

- Values and principles in clinical investigations
- International guidelines
- Patient care in clinical research
- Responsibilities in research
- Conflict of interest
- Ethical review
- Informed consent
- Vulnerable populations
- Biological samples
- Genetic research
- Databases and confidentiality
- Fraud & misconduct

Depending on the population studied and the type of study, the clinical trial may need to address different ethical issues, e.g. in genetic research, when taking / storing biological samples, or in exportation of data outside the EU.

Section 4

Study organisation

- Clinical trial registration
- Selection of investigators
- Organisation and delegation in the investigation team
- Flow chart
- Internal and external communication
- Contracts and agreement
- Liability and insurance
- Essential and other required documents
- Logistics
- Responsibilities for the development of the intervention (medicinal products, medical device, etc.)
- Data management
- Clinical trial committees

The success of a trial is largely dependent on its organisation. There must be an organised flow of information between the principal investigator and the sponsor, the Ethics Committee, the national regulatory authority, if appropriate, other investigators and participants. Logistics including handling of informed consent procedures, eligibility, randomisation, drug accountability and data flow should be established before the study starts. Involvement of other parties (e.g. pharmacies) should be considered.

Section 5

Legal, regulatory and good practice framework

- Regulatory and legal frameworks
- Good Clinical Practice according to ICH and EU Clinical Trials Directive
- National regulations
- Application to Regulatory Agency, if appropriate
- Quality assurance systems
- Standard Operating Procedures (SOPs)
- Audits and inspections

Established quality assurance systems are crucial for the integrity of the study. They should adhere to national and international regulations and cover, when appropriate, GLP – good laboratory practice, GMP – good manufacturing practice, GCP – good clinical practice.

Section 6

Study conduct

- Investigator's brochure or equivalent
- Study monitoring
- Safety monitoring and reporting
- End-of-trial issues

The successful conduct of the study depends on all team members, their competence and understanding of the intervention. An appropriate level of quality assurance and monitoring is essential to ensure high quality of data and procedures in the study. This is based on an on-going and continuous review of the accuracy and completeness of the data.

Section 7

Reporting clinical trials

- Completeness of follow-up
- Data analysis issues
- Primary outcome analysis
- Exploratory analysis
- Clinical study report
- Communication & publication of study results

Reporting of the study must be agreed beforehand in writing with investigators and sponsors. The report should address the question in the primary hypothesis and include exploratory analyses only as hypothesis generating. Missing data and incomplete follow-up should be reported. Negative results should be made public.

Glossary and explanations

These explanations are listed to help the reader of the European Science Foundation Syllabus for Clinical Investigator Training. For a complete glossary list, see e.g. ICH-GCP.

ICH: International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. A set of scientific and regulatory standards in clinical research on medicinal products agreed between EU, Japan and USA.

IB: Investigator's Brochure. A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

CRF: Case Report Form. A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

GCP: Good Clinical Practice. A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

GLP: Good Laboratory Practice. Principles for quality conduct of laboratory testing.

GMP: Good Manufacturing Practice. Principles for quality manufacturing conduct in producing drugs for human use.

SOPs: Standard Operating Procedures. Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sponsor: An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

The EC Clinical Trials Directive:

The European Union published in April 2001 a European Parliament and Council Directive 2001/20/EC regulating clinical trials with medicinal products. By May 2004, all Member States should have the Directive implemented in national regulations.

The Helsinki Declaration:

The basic ethics document which underpins human research. It is upheld by the World Medical Association and derives from the Code of Nuremberg. The last version (Edinburgh) is dated October 2000.

The investigators' responsibilities:

These are outlined in the Helsinki Declaration, the ICH-GCP, the EC Directive and in national regulations.

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Annex 5:

Clinical Trial Authorisations: Legislation and Guidance Documents

Legislation

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

- Directive 2001/20/EC ([external link](#))

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Text with EEA relevance).

- Directive 2003/63/EC ([external link](#))


Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

- Directive 2001/83/EC ([external link](#))

The Medicines for Human Use (Clinical Trials) Regulations 2004.

- The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 ([external link](#))

The MHRA has produced a description, which aims to help those involved in the conduct of clinical trials to follow and understand the Regulations.

- Description of the Medicines for Human use (Clinical Trials) regulations 2004  (236Kb)


The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 – SI 2006/1928 ([external link](#))


The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006.

- The Medicines for Human Use (Clinical Trials) Amendment Regulations (No.2) 2006 – SI 2006/2984 ([external link](#))

The consultation exercise on the Amendment Regulations (MLX 328, see below) ran from November 2005 to February 2006.

- MLX 328: consultation on implementation of the European Commission's Directive on Good Clinical Practice (2005/28/EC)  (548Kb)

A summary of responses to the consultation exercise MLX 328.

- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 – Summary of responses to consultation document MLX 328  (143Kb)

Guidance Documents

EC The rules governing medicinal products in the European Union, Volume 10. Notice to applicants. Clinical Trials.

- EudraLex: The Rules Governing Medicinal Products in the European Union: Volume 10 – Clinical Trials ([external link](#))

EC The rules governing medicinal products in the European Union, Volume 10 Notice to applicants. Questions & Answers. Clinical Trial Documents April 2006.

- EudraLex: The Rules Governing Medicinal products in the European Union: Volume 10- Questions & Answers ([external link](#))

EC The rules governing medicinal products in the European Union, Volume 4. Notice to applicants. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use.

- EudraLex: The Rules Governing Medicinal Products in the European Union: Volume 4 – Good Manufacturing Practice ([external link](#))

EC Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial October 2005.

- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial – October 2005 ([external link](#))

EMA/CHMP/SWP/28367/07.

- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products ([external link](#))

For guidance on EudraCT.

- EudraCT supporting documentation ([external link](#))

HMP/QWP/185401/2004 final.

- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials ([external link](#))

Labelling requirements. EC The rules governing medicinal products in the European Union, Volume 4. Notice to applicants.

- ANNEX 13 Manufacture of investigational medicinal products JULY 2003

Annex 5:

Clinical Trial Authorisations: Legislation and Guidance Documents

Databases

The European Clinical Trials database, EudraCT, established in accordance with Directive 2001/20/EC.

- EudraCT: European Clinical Trials Database (external link)

EudraVigilance, a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

- EudraVigilance (external link)

Information from the MHRA

The Commission on Human Medicines provides advice to the Ministers and the MHRA on human medicinal products: Commission on Human Medicines

- The final report of the expert scientific group (ESG) on phase 1 clinical trials (external link)


Following the publication of the final report of the independent expert working group on phase 1 clinical trials, the MHRA issued the following response.

- TGN1412: MHRA response to final report by independent expert working group on phase 1 clinical trials.


Time based performance measures for licensing.

- Licensing time-based performance measures

The Department of Health and Universities UK have issued a joint statement, 'Responsibilities, liabilities and risk management in clinical trials of medicines'. It recognises the Regulations do not change the underlying allocation of responsibilities in the partnership between universities and the NHS.

- Responsibilities, liabilities and risk management in clinical trials of medicines  (163Kb)

A Memorandum of Understanding being agreed and signed by the MHRA, the Central Office for Research Ethics Committee (COREC) and the Gene Therapy Advisory Committee (GTAC) to allow sharing of information.

- Medicines for Human Use (Clinical Trials) Regulations 2004 – Memorandum of understanding between MHRA, COREC and GTAC  (91Kb)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Good Manufacturing and Distribution Practice

Useful Sites

The Department of Health and the Medical Research Council (MRC) have established a joint project to address a range of important issues raised by the academic trials community about the implementation of the Directive in the UK.

- Clinical Trial toolkit (external link)

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949.

- Council for International Organisations of Medical Sciences (external link)

Gene Therapy Advisory Committee (GTAC) is the UK national research Ethics Committee (REC) for gene therapy clinical research according to the Medicines for Human Use (Clinical Trials) Regulations 2004.

- Gene Therapy Advisory Committee (GTAC) (external link)

The Department of Health provides health and social care policy, guidance and publications.

- Department of Health (external link)

The Research Governance Framework for health and social care defines the broad principles of good research governance.

- Department of Health-Research governance (external link)

The National Research Ethics Service, Central Office.

- Central Office for Research Ethics Committees (COREC) (external link)

Health & Safety Executive (HSE) regulate contained use activities of genetically modified organisms.

- Genetically modified organisms (external link)

The Department for Environment, Food and Rural Affairs (DEFRA) regulate releases of genetically modified organisms into the environment.

- Genetically Modified Organism Regulations (external link)

The Administration of Radioactive Substances Advisory Committee (ARSAC) advises the Department of Health (DH) on matters relating to the granting of certificates to practice nuclear medicine in the UK, and radiological safety issues.

- The Administration of Radioactive Substances Advisory Committee (ARSAC)

The Stationery Office (TSO) publishes UK legislation and guidance documents.

- The Stationery Office (TSO) (external link)

The Office of Public Sector Information (OPSI) provides information on re-use of public sector information.

- Office of Public Sector Information (OPSI) (external link)

Annex 6:

Highlights of ECRIN suggestions for the possible revision of the clinical trials directive (directive 2001/20/EC)

1. Adoption of a single, harmonised and comprehensive EU legislation covering all categories of clinical research and all interventions, 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.

2. Adoption of a common definition for categories of clinical research, with common risk assessment methods

Categories of research should be carefully and unambiguously defined, as well as a common interpretation of the definition for intervention. Common risk assessment methods should support the risk-based regulatory framework.

3. Protection of participants and promotion of high-quality clinical science in the EU through regulatory requirements adapted on the risk associated with the study

Adaptation of the regulatory requirements by applying proportionate risk-adapted regulations to all categories of clinical research, not according to its 'commercial' or 'non-commercial' objective, will reduce the administrative burden for the low-risk clinical research, which represents a significant part of academic clinical research.

4. Provision of support to academic institutions acting as sponsors in clinical research

Rather than regulatory adaptation to 'non-commercial trials', we recommend support to academic institutions in clinical research (regulatory requirements being determined by the level of risk). This support to public institutions acting as sponsors in clinical research should include a regulatory information helpdesk, scientific advice from competent authority, support to adverse event reporting, waiver to pay fees to competent authorities and ethics committees for investigator-initiated trials, waiver to pay the investigational medicinal product or medical device.

5. Single assessment of the health product by a single competent authority

Since the health product is the same for a multinational trial across the EU, assessment of the health intervention should be conducted by a single agency (either centralised at the EMEA, or through networking and specialisation of the national competent authorities, or through mutual recognition).

This would require a clear and common definition of the

respective roles of ethics committees and competent authorities, whereby ethics committees deal with all of the issues related to protection of participants (from methodological assessment to collection of informed consent) whereas competent authorities focus on the assessment of the health product.

6. Accreditation and co-ordination of ethics committees

This requires that the roles and practice of ethics committees become harmonised in the EU. Implementation of a quality assurance and accreditation system, and of a EU coordination under the responsibility of DG SANCO, should be used to harmonise their roles, training and practice. The ethics committee may be asked to assess the risk associated with the study.

7. Multiple sponsorship of clinical trials should be made possible

Using a single protocol, a single data base, and a single EudraCT number, co-sponsorship should be allowed, with an applicant sponsor in charge of the EudraCT application. A contract should define the roles and responsibilities of each party within a country or across the borders.

8. Harmonised insurance requirements and insurance packages

Development of a harmonised framework for insurance coverage of participants in clinical research throughout the EU. Development of insurance packages for clinical research rather than insuring individual trials, and promotion of insurance coverage by the public health system for clinical research conducted by academic institutions.

9. Clinical studies conducted by independent institutions should be part of the development procedure for health products.

Trust, transparency and optimal use of data in clinical research should be promoted through enforcement of open study registration, of study reporting, and data sharing through repositories for anonymised clinical research data.

Annex 7:

References

1. Rationale

- The Academy of Medical Sciences, “Strengthening Clinical Research”, October 2003, London (UK)
<http://www.acmedsci.ac.uk/images/publication/pscr.pdf>
- Kaplan W, Laing R, “Priority Medicines for Europe and the World”, World Health Organization, Department of Essential Drugs and Medicines Policy, November 2004, Geneva (CH)
http://whqlibdoc.who.int/hq/2004/WHO_EDM_PAR_2004.7.pdf
- Microsoft Research, “Towards Science 2020”, 2006, Cambridge (UK)
http://research.microsoft.com/en-us/um/cambridge/projects/towards2020science/downloads/t2020s_reporta4.pdf
- HM treasury, DTI, Department for education and skills, DH, “Science and innovation investment framework 2004-2014: next steps”, March 2006, London (UK)
<http://www.berr.gov.uk/files/file29096.pdf>
- German Health Research Council of the BMBF, “Roadmap for the German Health Research Program of the Federal Government, September 2007, Bonn/Berlin (DE)
http://www.bmbf.de/pub/Roadmap_Summary.pdf
- AERES, “A review of Inserm by the International visiting Committee: Enhancing the Future of Life Sciences and Health Research in France”, November 2008
<http://www.aeres-evaluation.fr/IMG/pdf/AERES-S1-INSERM2008.pdf>
- Griffin GE & al., “UK Research Trials are on verge of extinction”, Timesonline, January 14, 2009
<http://www.timesonline.co.uk/tol/comment/letters/article5511067.ece>

2. Categories and Design of Investigator-Driven Clinical Trials

- Gluud C, Gluud LL, “Education and debate – Evidence based diagnostics”, BMJ 2005;330:724-726 (26 March)
- UK Clinical Research Collaboration, “Health Research Classification System”, 2006, London (UK)
<http://www.ukcrc.org/PDF/Health%20Classification%20system%2014%20June%20.pdf>
- Tyndall A, “Why do we need non-commercial, investigator initiated clinical trials”, Nature Clinical Practice Rheumatology, 2008, 4, 354-355

- Douglas, FL Mitchell L, “Assessing risk and return: personalized medicine development & new innovation paradigm, Ewing Marion Kauffman Foundation, October 2008, Kansas City (US)
<http://www.kauffman.org/Details.aspx?id=4506>
- Rahbari NH, and al., “A concept for trial institutions focusing on randomized controlled trials in Surgery”, Trials, 9:3, 2008
- UK Clinical Research Collaboration, “Health Research Classification System”, January 2009, London (UK)
http://www.hrcsonline.net/hrccs/files/HRCS_Document.pdf

3. Regulatory and Legal Issues, Intellectual Property Rights and Data Sharing

- Smith R, Roberts I (2006) Patient safety requires a new way to publish clinical trials. PLoS Clin Trials 1(1): e6
- Hartmann M, Hartmann-Vareilles F, (2006) The Clinical Trials Directive: How is it affecting Europe's Non-Commercial Research? PLoS Clin Trials 1(2): e13
- EC-EMEA, “Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future, 3 October 2007, London (UK)
<http://www.emea.europa.eu/meetings/conference.htm>
- Miller FG, Ezekiel JE, “Quality-Improvement Research and Informed Consent”, N Engl J Med, 2008;358:8; 765-767
- CORESE Newsletter N°3, Summer 2008 “Recent European Developments in regulation of biomedical & epidemiological research in Europe”
http://www.medisin.ntnu.no/ism/nofe/Diverse/CORESE_3_0808.pdf

4. Management of Investigator-Driven Clinical Trials

- The National Academies, “Improving the quality of cancer clinical trials: workshop summary”, 2008, Washington (US)
<http://www.nap.edu/catalog/12146.html>
- ESFRI, “European Roadmap for Research Infrastructures – Roadmap 2008”, December 2008
<http://www.cordis.europa.eu/esfri>

5. Education, Training, Career Tracks and Authorship

- Follet P, Casassus B, “Revolution or Evolution for French Science”, Science, 2003;301:35-36
- Check E, “More biologists but tenure stays static”, Nature; 2007; 448:848-849 (23 August)
- Groves T, “Stronger European Medical Research”, BMJ 2008;336:341-342 (16 February)
<http://bmj.com/cgi.content/full/336/7640/341>

6. Funding and Models of Partnership

- Alison Young, Improving National Surveys and their international Comparability: Clinical Trials and R&D in Hospitals”, p. 43-48 in OECD, Measuring Expenditure on Health-related R&D, May 2001, Paris (FR)
<http://www.oecdbookshop.org/oecd/display.asp?CID=&LANG=EN&SF1=DI&ST1=5LMQCR2K9H22>
- UK Clinical Research Collaboration, “UK Health Research Analysis”, May 2006
http://www.ukcrc.org/PDF/UKCRC_Health_Research_Analysis_Report.pdf
- Sobocki P & al., “Resource Allocation to Brain Research in Europe – a full report”, European Journal of Neuroscience, 24(10), 1-24, 2006
- Sir David Cooksey, “A Review of UK Health Research Funding”, December 2006
http://www.hm-treasury.gov.uk/d/pbr06_cooksey_final_report_636.pdf
- Eckhouse S, Lewison G, Sullivan R, European Cancer Research Managers Forum, “Investment and Outputs of Cancer Research: from the Public Sector to Industry- The Second Cancer Research Funding Survey”, Summer 2008 “, September 2007
<http://www.ecrmforum.org>
- UK Clinical Research Collaboration, “From Donation to Innovation”, October 2007, London (UK)
<http://www.ukcrc.org/researchcoordination/healthresearchanalysis/charityanalysis.aspx>
- EFPIA, “The Pharmaceutical Industry in Figures”, 2008 Edition
<http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=4883>
- Olle Stendahl, “Åtgärdsplan för den kliniska forskningen”, March 2008, Stockholm (SE)
<http://www.regeringen.se/content/1/c6/09/79/05/3881eb4a.pdf>
- Health Economic Research Group, Office of Health Economics, RAND Europe, “Medical Research: What’s it worth? Estimating the economic benefits from medical research in the UK”. UK Evaluation Forum; For the Medical Research Council, the Wellcome Trust and the Academy of Medical Sciences, November 2008
<http://www.brunel.ac.uk/385/other/TAP825EconomicBenefitsReportFULLWeb.pdf>
- Banati P, Moatti JP, The positive contributions of global health initiatives, Bulletin of the WHO, November 2008, 86(11)
<http://www.who.int/bulletin/volumes/86/11/07-049361/en/index.html>

