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Clinical research in Europe: national differences in legislative and regulatory frameworks

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

Karl-Heinz Huemer, Austria
Steffen Thirstrup, Denmark
Christian Gluud – Chair, Denmark
Kate Whitfield, Denmark
Jacques Demotes – Chair, France
Christian Libersa, France
Béatrice Barraud, France
Christine Kubiak, France
Xina Grählert, Germany
Gabriele Dreier, Germany
Sebastian Geismann, Germany
Wolfgang Kuchinke, Germany
Zsuza Temesvari, Hungary
Gyorgy Blasko, Hungary
Gabriella Kardos, Hungary
Timothy O'Brien, Ireland
Margaret Cooney, Ireland
Siobhan Gaynor, Ireland
Arrigo Schieppati, Italy
Mariantonia Serrano, Spain
Fernando de Andres, Spain
Nuria Sanz, Spain
Charlotte Asker-Hagelberg, Sweden
Hanna Johansson, Sweden
Nabil Al-Tawil, Sweden
Stella Heffernan, United Kingdom
Sue Bourne, United Kingdom
Jane Byrne, United Kingdom
Adeeba Asghar, United Kingdom
Jean-Marc Husson, EFGCP

Contact: Jacques Demotes: jacques.demotes@inserm.fr
Christian Gluud: cgluud@ctu.rh.dk
www.ecrin.org

Table of contents

1. Abbreviations

AEMPS	Spanish Agency for Medicines and Medical Devices
AFSSAPS	Agence française de Sécurité Sanitaire des Produits de Santé (french competent authority)
AGES	Agentur für Gesundheit und Ernährungssicherheit (Austrian Agency for Health and Nutrition Safety)
AIFA	Agenzia Italiana del Farmaco (Italian National Drug Agency)
AMG	Arzneimittelgesetz (German Federal Drug Act, Austrian Drug Act)
ARSAC	Administration of Radioactive Substances Advisory Committee
AT	Austria
ATU	Temporary Authorisation for Use
BASG	Bundesamt für Sicherheit im Gesundheitswesen (Federal Office for Health Safety)
BfS	Federal Office for Radiation Protection
BMBF	Bundesministerium für Bildung und Forschung
CA	Competent Authority
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé
CEIC	Clinical Research Ethics Committees
CIC	Centre d'Investigation Clinique (Clinical Investigation Centre)CNIL Commission Nationale de l'Informatique et des Libertés
CPP	Comité de Protection des Personnes (French research ethics committee)
CRC	Clinical Research Centre
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial on Investigational Medicinal Product
CTU	Clinical Trial Unit
DE	Germany
DEGRO	Deutschen Gesellschaft für Radioonkologie
DG	Directorate-General
DG SANCO	Directorate General for Health and Consumer Affairs.
DGS	Direction Générale de la Santé (French General Direction of Heath)
DGSNR	Direction Générale de la Sureté Nucléaire et Radioprotection (General Direction of Nuclear Safety and Radiation Protection)
DIMDI	Medical Documentation and Information
DK	Denmark
DMA	Danish Medicines Agency
EC	Ethics Committee
ECRIN	European Clinical Research Infrastructures Network
ECRIN-PPI	European Clinical Research Infrastructures Network and Biotherapy Facilities: preparation phase for the infrastructure
ECRIN-RKP	European Clinical Research Infrastructure Network – Reciprocal Knowledge
ECRIN-TWG	European Clinical Research Infrastructures Network- Transnational Working Groups
EEA	European Economic Area
EFCGP	European Forum for Good Clinical Practice
EMEA	European Medicine Agency

EPA	Environmental Protection Agency
ES	Spain
EU	European Union
FI	Finland
FP	Framework Programme
FR	France
GCP	Good Clinical Practice
GenTG	German Law on Gene Technology
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
GTG	Gentechnikgesetz (Austrian Genetic Engineering Act)
HRB	Committee of Human Reproduction
HTA	Human Tissue Authority
HU	Hungary
IE	Ireland
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISS	Institute Superiore della Sanita
IT	Italy
KAKuG	Krankenanstaltengesetz (Austrian Hospital Act)
KFEB	Clinical pharmacology and ethics committee (Hungary)
KKS	Koordinierungszentrum für Klinische Studien
LMG	Lebensmittelgesetz (Austrian Nutrient Act)
MPA	Swedish Medicinal Products Agency
MPG	Medizinprodukte-Gesetz (Austrian Medical Device Act)
MS	Member State
NHS	National Health Services
ONT	Organización Nacional de Trasplantes
PEI	Paul- Ehrlich-Institute (German competent authority)
PharmMed	Austrian Medicines Agency
PI	Principal Investigator
PIAG	The Patient Information Advisory Group
QA	Quality Assurance
QM	Quality Management
REC	Research ethics committee
RKI	Robert-Koch-Institute
SE	Sweden
SOP	Standard Operating Procedure
Sp	Spain
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TUKEB	Committee of scientific research ethics (Hungary)
ZKBS	Zentrale Kommission für die Biologische Sicherheit (Central Commission for Biological Safety)
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimittel und Medizinprodukten

2. Executive summary

Clinical research is the basis of a well functioning, evidence-based health care system. European Clinical Research Infrastructures Network (ECRIN) is designed to integrate clinical research in Europe through the interconnection of national networks of clinical research centres (CRC) and clinical trial units (CTU) and to develop services to provide support for multicentre clinical studies in Europe.

Entering into force in 2004, the European Directive 2001/20/EC aimed to harmonise European clinical research. The task of ECRIN Working Group 2 is to describe the regulatory framework for clinical research and how to interact with competent authorities in ten ECRIN countries (Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United Kingdom). These countries represent about 70% of the EU population (345 million out of 493 million inhabitants).

Knowledge of the regulatory requirements is a prerequisite for conducting multinational clinical research. ECRIN seeks to elucidate legislative and regulatory discrepancies in order to obtain the knowledge and tools to better conduct European-wide multi-national clinical research. ECRIN's Working Group 2 performed a survey in order to collect relevant information on national regulations, rules, and requirements for all categories of clinical research, to delineate these different categories of clinical research, and to identify the national requirements for those categories of research. The information was expanded upon and verified through teleconferences, meetings, and correspondence.

Methodology

A draft version of the survey was designed and discussed during teleconferences until agreement on the final version. The survey contains general information on the objectives of the survey, instructions to complete the document, and three different sections (glossary, requirements for each category of research, and open questions).

Definition of categories of clinical research
Designing the survey required to reach an agreement on common definitions for categories of clinical research. Seven main categories were considered, each split into sub-categories.

1. Clinical trials on medicinal products.
2. Clinical trials on medical devices.
3. Other therapeutic trials (including radiotherapy, surgery, transplantation, transfusion, cell therapy, physical therapy, psychotherapy trials).
4. Diagnostic studies.
5. Clinical research on nutrition.
6. Other interventional clinical research (including complementary and alternative medicines, biobanks, physiology, physiopathology and psychology trials).
7. Epidemiology (observational studies).

Survey on national requirements for each category of research

For each of the seven categories of research, the following questions were asked:

- is a submission to an ethics committee required (specify the name of the committee and who is responsible for the submission)?
- is a submission to competent authority required (specify the name of the competent authority and who is responsible for the submission)?
- is there a specific procedure for substantial amendments?
- is there a requirement for a sponsor and is co-sponsorship allowed?
- is insurance required (specify who is covered; sponsor, investigator, participant)?
- adverse event reporting (specify which adverse events have to be reported by the sponsor, when, and to whom)?
- is a safety report requested?

A list of further questions was included in order to detail some aspects of the regulation, of specific categories of research and expectations regarding clinical research in Europe. The survey also contained questions open to comments and suggestions from the WP2 members on how to improve EU clinical research, how to improve competent authority working practice, and what are the expectations for future EU regulation on clinical research.

The final version of the questionnaire was circulated to the ECRIN members of: Working Group 2 on 'regulation and interaction with competent authorities'; Working Group 1 on 'ethics and interaction with ethics committees', and Working Group 3 on 'adverse event reporting'. The preliminary results were discussed during several teleconferences and in a face-to-face meeting in Paris (19 and 20 May 2007) and Brussels (19 and 20 May, 2008). Moreover, specific teleconferences were organised between the chair and national representatives in order to discuss national aspects in-depth.

The graphic representation (Table 1) is a summary of the regulatory requirements for various categories of clinical studies in the ten ECRIN countries (Austria-AT, Denmark-DK, France-FR, Germany-DE, Hungary-Hu, Ireland-IE, Italy-IT, Spain-ES, Sweden-SE, United-Kingdom-UK) in terms of ethics committee approval, competent authority authorisation, need for a sponsor, need for insurance, and adverse event reporting.

Major findings

We identify the following main areas of homogeneity:

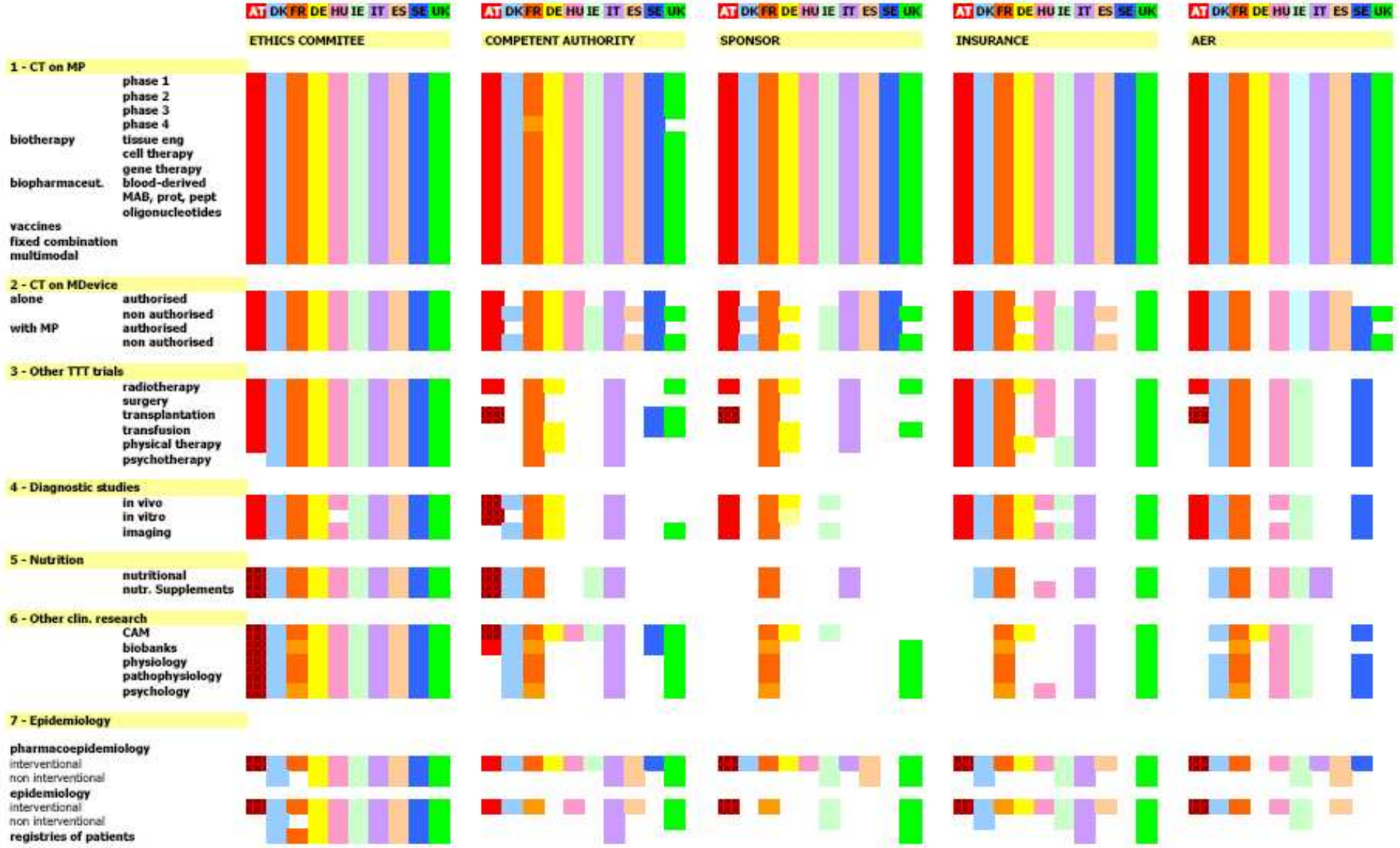
- Clinical trials on medicinal products require authorisation of the initial application and any substantial amendments from competent authorities, favourable opinion from ethics committees, a sponsor, insurance, suspected unexpected serious adverse reaction (SUSAR) reporting, and an annual safety report in all ECRIN countries.
- Research ethics committees must approve all interventional clinical trials in the ECRIN countries; all ECRIN countries have legislation, which protects personal data.

- Lack of an official national register for clinical trials in the majority of ECRIN countries, and none of the ECRIN countries are required to store depersonalised or pseudo-anonymised data from trial participants in data repositories.

We identify the following main areas of heterogeneity:

- National requirements regarding competent authority, sponsor, insurance, and adverse event reporting are highly variable for interventional clinical research other than clinical trials on medicinal products.
- The definition of interventional and observational studies varies. In some countries approval by a research ethics committee is not required for observational studies.
- Waiver of purchase cost of the investigational medicinal product for a non-commercial trial.
- Obligation to inform participants about the outcome of a clinical trial.
- Insurance requirements and insurance systems covering participants in investigator-initiated clinical research are highly variable, with additional differences between public or private insurance for clinical research.

Table 1. Summary of requirements.



Conclusions

The main conclusions of this survey are that:

- The extent of the legislation on clinical research varies from one country to another: some national legislation focus on clinical trials on medicinal products, whereas other legislation considers the protection of participants in all the categories of clinical research.
- There is partial harmonisation in the regulation for clinical research on medicinal products, as a consequence of divergent transposition of the 2001/20/EC Directive into national laws leading to substantial differences in the regulatory framework, making multinational clinical studies very difficult still. The main differences concern the number and role of competent authorities, the number and role of ethics committees, the process leading to the single ethical opinion, the interaction between competent authorities and ethics committees, the requirement for submission to a personal data protection board (or boards). Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered by the public health system in some countries, and in others the union of pharmaceutical companies has contracted a national insurance package covering all the industry-sponsored trials. There are differences in the interpretation of the definition of investigational medicinal product (IMP), especially regarding the background treatment, with major consequences for SUSAR reporting, labelling, and provision by the sponsor. Under some circumstances and in some countries cell therapy products are considered as IMP and in other countries as non-IMP (and in this latter case the trials is not covered by the 2001/20 Directive). Finally some countries, and not others, have a definition for non-commercial sponsors or for non-commercial trials, with related adaptations and waivers.
- There are major discrepancies in the regulatory framework for other categories of clinical research, not covered by the 2001/20 Directive, especially regarding the requirements for a submission to competent authorities (often distinct from the medicines agencies, depending on the nature of the health product, and in some countries there is a need to submit to a competent authority even in the absence of a health product). There are also major differences in the requirements for a sponsor (required only in some countries, or for particular categories of research), and for adverse event reporting. Some countries have extended the concept of SUSAR to trials on medical devices, or even to all interventional research. There are major discrepancies regarding insurance, which may or may not be required depending on the country for the same protocol. In some countries the ethics committee decides on the need for insurance. There is a need to clarify the definition of categories of research and their interpretation (for instance the border between interventional and observational studies may differ between countries).
- In turn, protection of participants is achieved through submission of protocol applications to the ethics committee in every country, at least for all the categories of interventional research. These ethics committees may, or may not, be the same for every category of research. In some countries observational studies do not require submission to a research ethics committee.

Recommendations

The information gathered from the ten EU countries and the results of the analyses and assessments led to one overall conclusion: heterogeneity in clinical research and the different implementation of the European Directive 2001/20/EC hinders clinical development and is potentially putting EU citizens' health at risk. Furthermore, a number of weaknesses have been demonstrated regarding the function of the EU regulatory authorities. There is therefore a need for change. The outcome of the survey, the answers to the open questions, and the numerous discussions within the WG2 to prepare written suggestions for the EC/EMEA conference on the revision of the 2001/20/EC Directive held in October 2007 led to a series of recommendations to improve and further harmonise the regulatory framework of clinical research in the EU, particularly for investigator-initiated clinical studies.

These discussions highlight the need, at the EU level, for:

- reassessment of the 2001/20/EC Directive, which can currently lead to needless difficulties for academia and industry;
- consultation with both academic and industry sectors on future regulations and legislation followed by assessment of its impact;
- further definition and harmonisation of the roles of the ethics committees (protection of participant) and of the competent authorities (assessment of the health product);
- improved efficiency of the interaction between sponsors, and investigators with the regulatory authorities;
- improved methodology for clinical research;
- further definition and harmonisation of the categories of clinical research, in particular the definition of intervention;
- adaptation of the regulatory requirements considering the risk associated with the trial, with further definition of clinical research with low additional risk, allowing alleviation of needless regulatory requirements;
- promotion and prioritisation of pertinent, independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms, or addresses important public health issues;
- open access to clinical trial data so that society can take full advantage of clinical research.

These discussions highlight the need, at the national level, for:

- extension of the expertise of competent authorities to be able to function as a single authority for all categories of clinical research;
- harmonisation of procedures between the national competent authorities and the national ethics committees, for all clinical research;
- improvement of communication between the EU member states on the implementation of the EU directives, as well as improved communication on how such requirements are implemented in day-to-day research.

Based on the requirements for change identified here, ECRIN Working Group 2 proposes the following solutions to protect the participants, to simplify the regulatory requirements for clinical research in the EU, to promote independent, academic, investigator-led clinical research, to promote clinical research in the EU, to remove bias in regulatory requirements, to create a transparent research community, and to improve the scientific quality and accuracy of clinical research.

1. **To protect the participant**:

- improvement of the scientific expertise within ethics committees with each ethics committee assessing a certain number of applications per year;
- obligatory publication of all depersonalised or pseudo-anonymised data and results of all trials in an open-access clinical data repository, regardless of findings, in order to ensure optimal use of data, to prevent needless duplication of trials and unethical randomisation of participants;
- creation of a consensual register of all trial participants, for all phases of trials in all categories of research. Information should include participant identification, fees received, and periods in which trial participants should be excluded from taking part in other clinical research in order to protect the trial participant. These data should be stored for a limited time only, be accessible by competent authorities, ethics committees, and investigators;
- regulation of the participation of healthy individuals in trials by setting an exclusion criteria period between trials, and by limiting an individual's annual indemnity;
- unification of the definition and the protection of vulnerable participants;
- development of insurance packages for clinical research rather than insuring individual trials. Such packages can be based on existing models available for public institutions (public health system insurance) or for industry sponsors (the union of manufacturers insurance package);
- promotion of independent and stricter governmental audit and inspection.

2. **To simplify the regulatory requirements for clinical research in the EU**:

- adoption of a single, harmonised and comprehensive EU legislation covering all categories of clinical research and all interventions, particularly to define intervention in a similar manner in all the EU countries (as for instance the same trial may be regarded as a clinical trial on medicinal product in one country, and as a non-interventional study in another);
- one-stop shop procedure for submission to a single competent authority in the EU for multinational studies, either through a centralised procedure, mutual recognition, or networking of national competent authorities;
- adoption of a single electronic protocol application for submission to both the ethics committee and competent authority throughout the EU. Such an e-form should be designed through collaboration with users, pilot tested and revised;
- delineation of the 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 personal data protection) and competent authorities deal with the assessment of the health product;
- abolition of additional national competent authority requirements, in order to prevent the overlap of responsibilities and reduce of the number of submissions for a given trial;
- modification of the regulatory requirements by applying proportionate risk-adapted regulations to all categories of clinical research;
- unification of the interpretation of the definition and labelling requirements for an investigational medicinal product;

- development of EU directive and guidance documents on collection and handling of human biological material. Establish links between national biobanks.

3. **To promote independent, academic, investigator-led clinical research**:

- prioritisation of relevant, independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms, or, important public health issues;
- waiver of fees from national competent authorities and ethics committees for investigator-initiated trials;
- waiver of cost of the investigational medicinal product or device for investigator-initiated trials;
- provision of free practical support and scientific advice to independent investigator-initiated trials from competent authorities.

4. **To promote clinical research in the EU**:

- European collaborative research to be regarded as equally or more desirable as single nation-led clinical research (due to its increased external validity);
- improve access to the collective European population and emphasise the need for clinical research with large sample sizes in order to reduce the risk of random errors ('play of chance');
- facilitation of multiple sponsorship of clinical trials (with a single protocol, a single data base, and a single EudraCT number) where the responsibilities of each party are clearly defined, to enable more academia-led clinical research;
- promotion of clinical research in vulnerable populations (eg, children, elderly, pregnant women) and rare diseases;
- single-centre and multicentre trials should be supported by similar infrastructure throughout the European Union;
- funding opportunities for multinational clinical research projects in the EU.

5. **To remove bias in regulatory requirements**:

- direct government funding of national competent authorities and ethics committees, proportionate to the number of clinical trial applications handled;
- continuous review and subsequent update of EU directives, guidance documents, and good clinical practice guidelines according to transparent peer review and the best evidence, in order to improve the clarity and applicability of the requirements;
- full and transparent consultation with research communities in all EU member states in advance of draft EU directive, regulation, or guidelines;
- removal of the distinction between commercial and non-commercial trials, which would suggest that the credibility of data from academic research is lower than for data obtained through industry-sponsored trials;
- incorporation of the same sensible regulatory requirements, protecting the participants without unnecessary burden, for investigational medicinal products to medical devices, surgery, psychiatry, psychology, physiotherapy, food/nutritional supplements, etc.

6. **To create a transparent research community**:

- obligation to deposit the electronic protocol application forms for clinical research in an open-access international trials register, in order to avoid unnecessary duplication of ongoing trials and live up to the informed consent;
- obligation to deposit the resulting adverse event reports, end of trial reports, complete and depersonalised or pseudo-anonymised data and results from the clinical research in an open-access data repository. Depositing data and results to be part of archiving requirement 24 months after the termination of the trial to allow time for peer reviewed journal publication.

7. **To improve the scientific quality and accuracy of clinical research**:

- raise the standard of clinical research by emphasising, and offering scientific advice on how to: achieve large sample sizes; minimise systematic errors ('bias'); minimise random errors ('play of chance'); achieve proper trial design; and pose research questions led by clinical relevance, not by profit;
- involvement of scientific professionals (other than physicians) as consultants or advisors during protocol preparation and all phases of the clinical trial;
- development of professional and accredited data centres and data management, tools, databases, and data handling for all clinical research;
- training in clinical research within a spectrum of scientific disciplines at the pre- and post-graduate level, especially in fostering interaction between academic researchers and industry;
- promotion of clinical trials, which compare two or more authorised interventions.

3. Background

European Clinical Research Infrastructures Network (ECRIN) is designed to integrate clinical research in Europe through the interconnection of national networks of clinical research centres (CRC) and clinical trial units (CTU) and to develop services to provide support for multicentre clinical studies in Europe.

Knowledge of the regulatory requirements is a prerequisite for conducting multinational clinical research. The task of ECRIN's Working Group 2 is to describe such regulatory requirements and how to interact with competent authorities.

In the first ECRIN FP6-funded project (ECRIN-RKP, ECRIN I 2004-2005), each country participating in the ECRIN project described the regulation required for clinical research in their country and a comparative analysis between the countries was performed. The analysis demonstrated that the national implementation of the EU Directive 2001/20/EC resulted in differences due to diverging interpretation.

Based on the outcome of the ECRIN-RKP project, the second programme (ECRIN-TWG, ECRIN II 2006-2008) is designed to analyse the differences in national regulations and practice, not only for clinical research on medicinal products, but also for other categories of research not covered by the EU Directive 2001/20/EC. Following this analysis, the transnational Working Group on regulation and interaction with competent authorities will release guidelines and procedures on how to interact with competent authorities in multinational studies.

The third ECRIN programme (ECRIN-PPI, ECRIN III 2008–2011, FP7-funded) consists of a preparatory phase for the construction and operation of an infrastructure for EU-wide clinical studies and biotherapy that will provide 'one-stop shop' services to investigators and sponsors in multinational studies. During this preparatory phase, the Working Group on regulation and interaction with competent authorities will ensure a regulatory follow-up, and will update and adapt the set of guidelines and standard operating procedures according to the users needs. During this preparatory phase, pilot clinical studies will be conducted using the guidelines and procedures developed by the Working Group's expertise. A continuous assessment of the system implemented will be performed and adaptations made if necessary.

The objective of the European Directive 2001/20/EC was to harmonise clinical trial regulations within the European Union. To date this has only been partially achieved. The implementation resulted in divergences at the national level with an increase in the complexity of performing multinational clinical trials. In addition, a lot of clinical research conducted by academic sponsors lies outside the scope of the Directive and there is no harmonisation of the requirements for this important academic driven clinical research at the European level.

As the objective of ECRIN is to cover all the categories of clinical research and not only that on medicinal products, the aim of the survey performed by Working Group 2 was to delineate the relevant categories of clinical research, as presently defined by national laws, and to identify the national requirements for those categories of research.

4. Methodology

A draft version of the survey was designed by the chairs of Working Group 2 and discussed during teleconferences until agreement on the final version. The survey contains general information on the objectives of the survey, instructions to complete the document, and three different sections:

- a glossary;
- a table section divided in seven main categories of research, each split into sub-categories:
    - clinical trials on medicinal products;
    - clinical trials on medical devices;
    - other therapeutic trials;
    - diagnostic studies;
    - clinical research on nutrition;
    - other clinical research;
    - epidemiology.

The 2001/20/EU Directive defines two distinct categories of research: clinical trials (using an investigational medicinal product) and non-interventional trials (without medicinal product, without additional diagnostics or monitoring, and where a medicinal product is used according to market authorisation). These definitions are interpreted differently from country to country, leading some clinical research to be considered as a clinical trial in one country and as a non-interventional trial in another. Moreover, the 2001/20/EU Directive definitions are set from a legal point of view, which may differ from a scientific methodological point of view. ECRIN WP2 agreed that further delineation of categories of research was necessary.

For each category, the following questions were asked:

- is a submission to an ethics committee required (specify the name of the committee and who is responsible for the submission)?
- is a submission to competent authority required (specify the name of the competent authority and who is responsible for the submission)?
- is there a specific procedure for substantial amendments?
- is there a requirement for a sponsor and is co-sponsorship allowed?
- is insurance required (specify who is covered; sponsor, investigator, participant)?
- adverse event reporting (specify which adverse events have to be reported by the sponsor, when, and to whom)?
- is a safety report requested?

Furthermore, a list of questions were included in order to detail some aspects of the regulation, specific categories of research and expectations regarding clinical research in Europe.

The final version of the questionnaire was circulated on February 20, 2007 to the participants of: Working Group 2 on 'regulation and interaction with competent authorities'; Working Group 1 on 'ethics and interaction with ethics committees' (to specifically answer those questions regarding the ethics committees); and Working Group 3 on 'adverse event reporting' (to answer those questions specific to adverse event reporting). The preliminary results were discussed during several teleconferences and in a face-to-face meeting in Paris (19 and 20 May 2007) and Brussels (19 and 20 May, 2008). Moreover, specific teleconferences were organised between the chairs and national representatives in order to discuss national aspects in-depth.

5. Regulatory frameworks

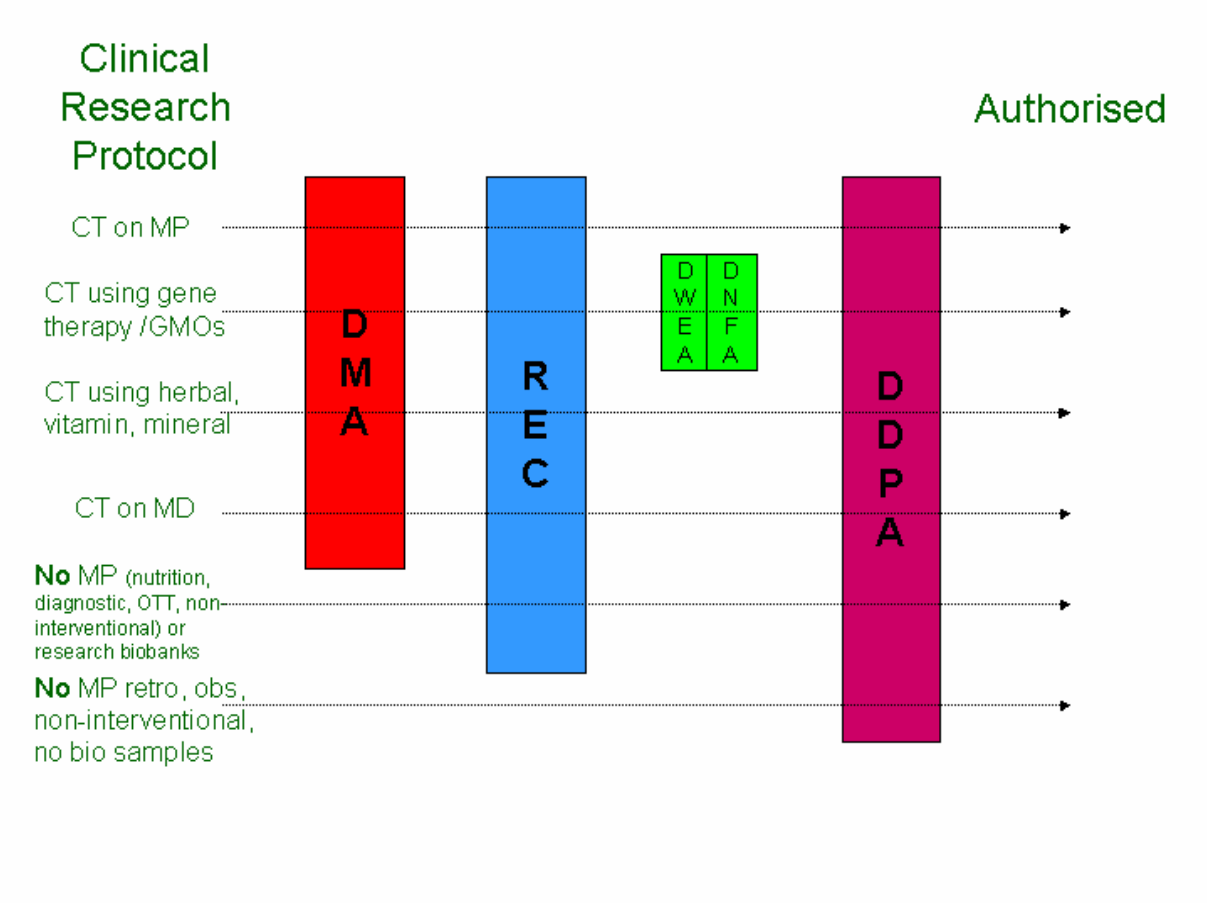
Summary of ethical and regulatory requirements for the different ECRIN countries.

Figure 1: Austria

type of trial			requirements by law					approval required by					time to approval
			drug act (Arzneimittelgesetz - AMG)	medical device act (Medizinprodukte-gesetz - MPG)	genetical engineering act (Gentechnikgesetz - GTG)	data protection act (Datenschutzgesetz - DSG)	hospital act (Krankenanstalten & Kuranstaltengesetz - KUKG)	ethics committee (local)	ethics committee (central = Leitethik-Kom.)	competent authority: Bundesamt / AGES PharmMed	competent authority: AGES Institute for Food Control	competent authority: Ministry of Health	
inter-ventional trials	→ with medicinal product		X			X	X[2)]	X	X[1)]	X			35 d
	→ with medical device			X		X	X[2)]	X		X			60 d[6)]
	→ genetic therapy trials		X		X	X		X	X[1)]			X	180 d
	→ with nutritional products		X[4)]			X	X[2)]	X	X[1)]	X	X[5)]		35 d[4)]
	with traditional herbal products		X[3)]			X	X[2)]	X	X[1)]	X			35 d[3)]
	→ epidemiological trials					X	X[2)]	X	X[1)]				–
	→ compassionate use					X		X	X[1)]				–
non-inter-ventional trials	→ epidemiological trials					X							–
	→ post-marketing surveys		X	X		X							–

1) can replace local ethics committees in multicentre trials
2) optional only for studies to validate methods ("Methodenstudie")
3) for new indications only
4) only if claims for therapeutic effect are tested
5) only safety of nutrient assessed, no trial approval unless according to AMG
6) not yet implemented

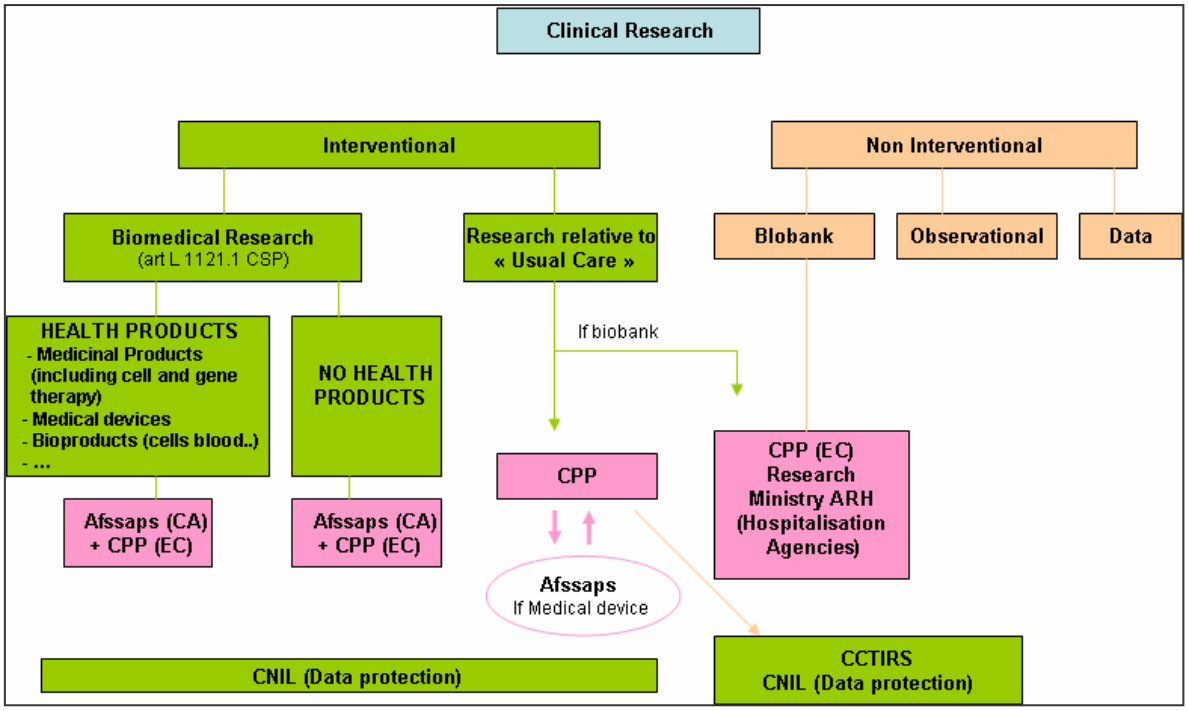
Figure 2: Denmark[1]



The Danish Medicines Agency is the only competent authority in Denmark. There are nine regional ethics committees and the investigator submits the protocol in the region of the principal site of the clinical study. If the regional ethics committee cannot come to decision as regards to the authorisation of the protocol, or if the investigator appeals against a negative decision of the regional ethics committee, the national ethics committee is consulted, whose decision is final. In studies which use gene therapy or genetically modified organisms in the investigational medicinal product, the trial and the premises have to be approved by the Danish Working Environment Authority and the Danish Nature and Forest Agency. All studies that involve sensitive, personal data (including retrospective studies) have to be authorised by the Danish Data Protection Agency. The setting up of a research biobank or studies which do not involve an investigational medicinal product or device do not need to obtain authorisation from the Danish Medicines Agency. Studies which are exclusively retrospective, observational do not need to obtain authorisation form the Danish Medicines Agency nor the regional ethics committee.

[1]CT clinical trial, DDPA Danish Data Protection Agency, DMA Danish Medicines Agency, DNFA Danish Nature and Forest Agency, DWEA Danish Working Environment Authority, GMO genetically modified organism, IMP investigational medicinal product, MD medical device, MP medicinal product, NEC National Ethics Committee, Obs observational, OTT other therapeutic trials, REC regional ethics committee, Retro retrospective.

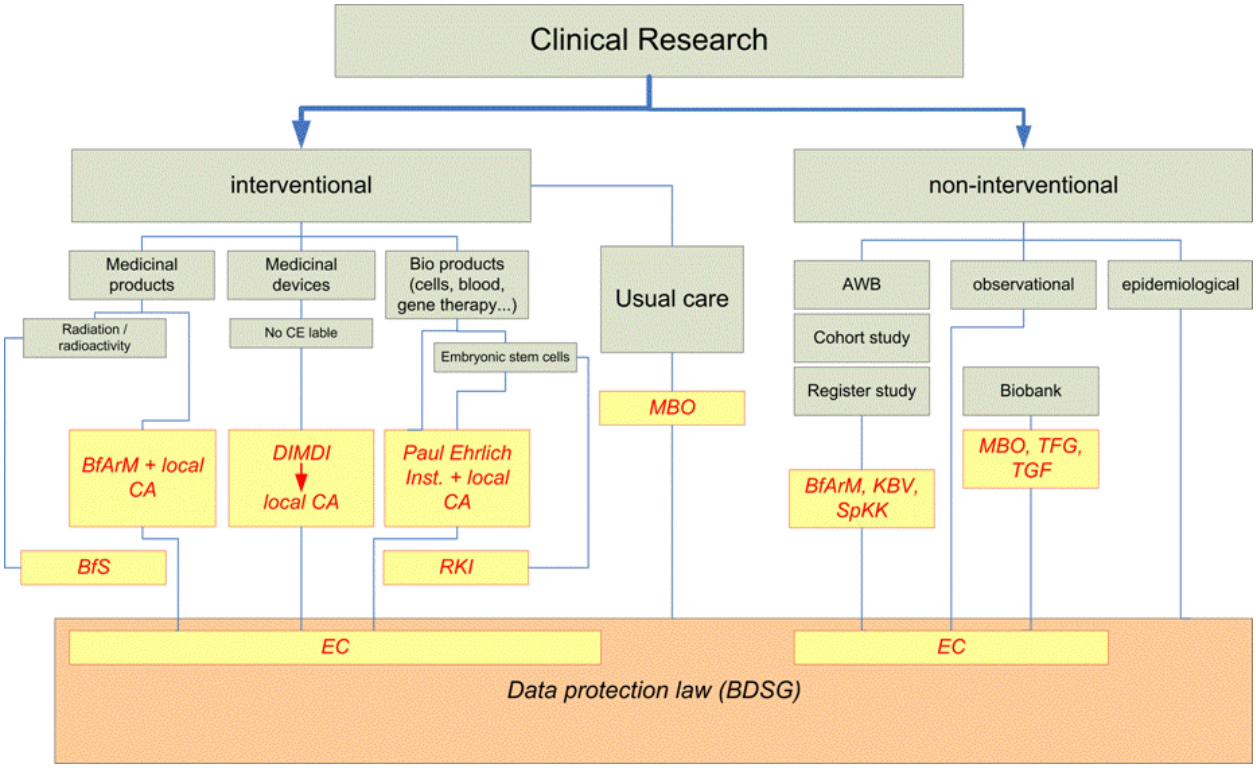
Figure 3: France[2]



The French law of protection of subjects has transposed the clinical trial directive (CTD) by applying it (CTA/EC's opinion…) to all interventional researches in Human. In the case of interventional biomedical research, there is only one competent authority in France, Afssaps, that authorises biomedical researches on health products (medicinal products, medical devices…) and without health product (ie surgery, physiology…).
The Ethical review is performed by only one (single EC opinion) of the 40 Ethics Committees (Comité de Protection des Personnes (CPP)). The sponsor applies to the CPP located in the region of the principal or coordinating investigator.
When the interventional research relates to "usual care", there is no CA's authorisation but only the EC's opinion. There is a definition of this kind of research in the law, and research on medicinal product is excluded.
There is no requirement for the non-interventional studies, except compliance with the data protection law.
CNIL and CCTIRS are committees that ensure the compliances of data protection law.

[2] Abbreviations: Afssaps Agence française de Sécurité Sanitaire des produit de Santé, CPP comité de Protection des Personnes, CNIL Commission nationale de l'Informatique et des Libertés, CCTIRS Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé, ARH Agence régionale d'hospitalisation, CSP Code de la Santé Publique

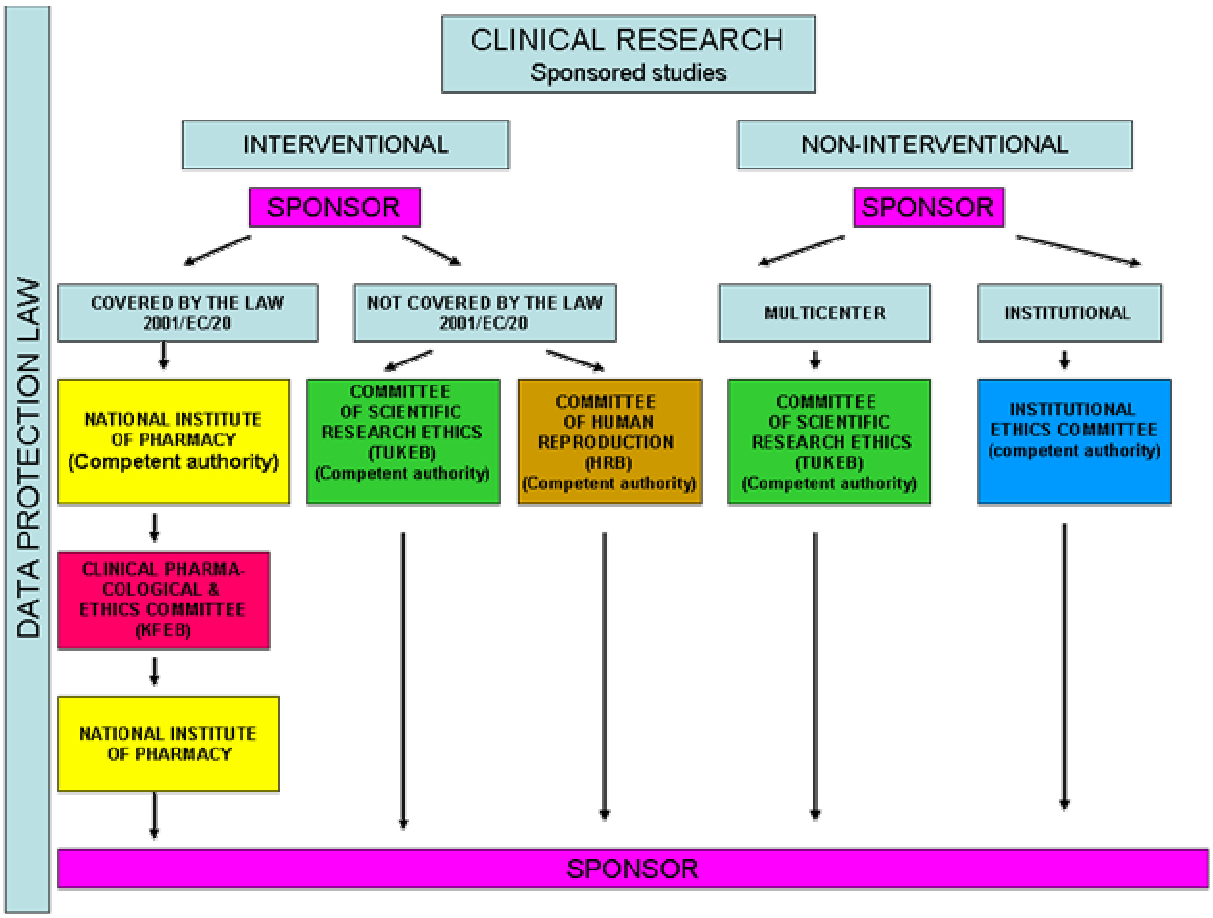
Figure 4: Germany[3]



In Germany two competent authorities authorise medicinal products: the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) and the "Paul-Ehrlich Institut" (PEI).

[3] Abbreviations: BfArM Federal Institute for Drugs and Medicinal Devices, EC ethics committee, local CA local competent authorities, RKI Robert-Koch Institute, PEI Paul-Ehrlich Institute, DIMDI German Institute of Medical Documentation and Information, MBO Medicinal Association's professional code of conduct, TGF transfusion law, TGF transplantation law, BfS Federal Office for Radiation, SpKK Umbrella Organisation of Health Insurances, KBV National Association of Statutory Health Insurance Physicians.

Figure 5: Hungary



The committee of scientific research ethics (TUKEB) gives permission to all invasive therapeutic or diagnostic studies (radiotherapy, surgery, prevention etc), to studies with medical devices, to studies dealing with genetic illnesses, genetic epidemiological studies, to studies concerning population genetic or somatic genetic investigations, and to all multicentre studies. There is a second central ethical committee, the Committee of Human Reproduction (HRB), which is also part of the Medical Research Council. This committee gives permission to trials with human embryos and stem cells and to genetic studies concerning human reproduction. A new law concerning genetic interventions is under preparation. Finally, the third central committee, Clinical pharmacology and ethics committee (KFEB), gives permission to all clinical studies on medicinal products. The role of institutional (local, regional) ethics committee is to give permission to all other, non-interventional studies, and to give 'in-house' permission to all the above mentioned ones. If the local (institutional, regional) ethics committee decides, it can submit any trial proposal to TUKEB.

Figure 6: Ireland

Summary of ethical and regulatory requirements for Ireland

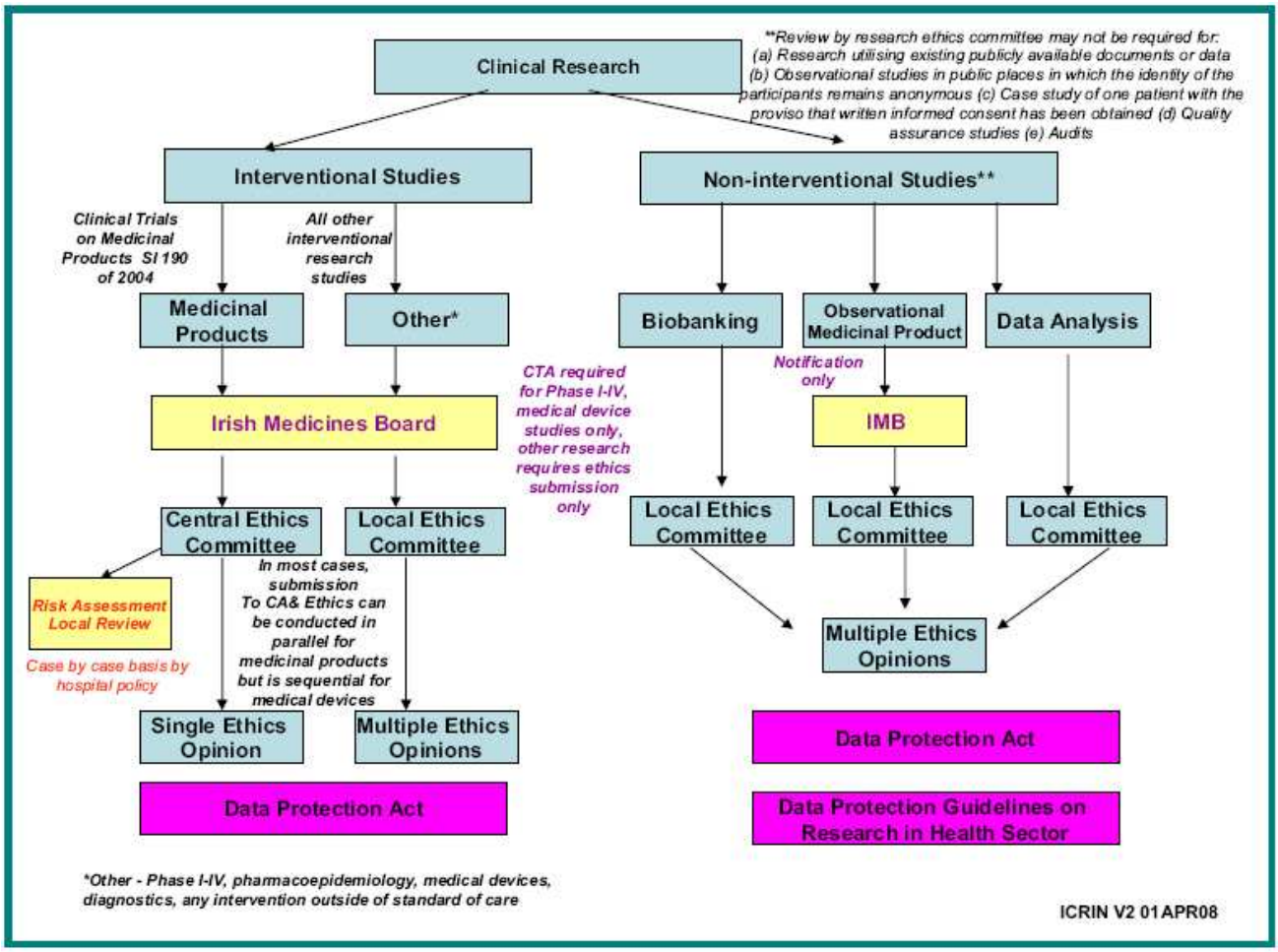
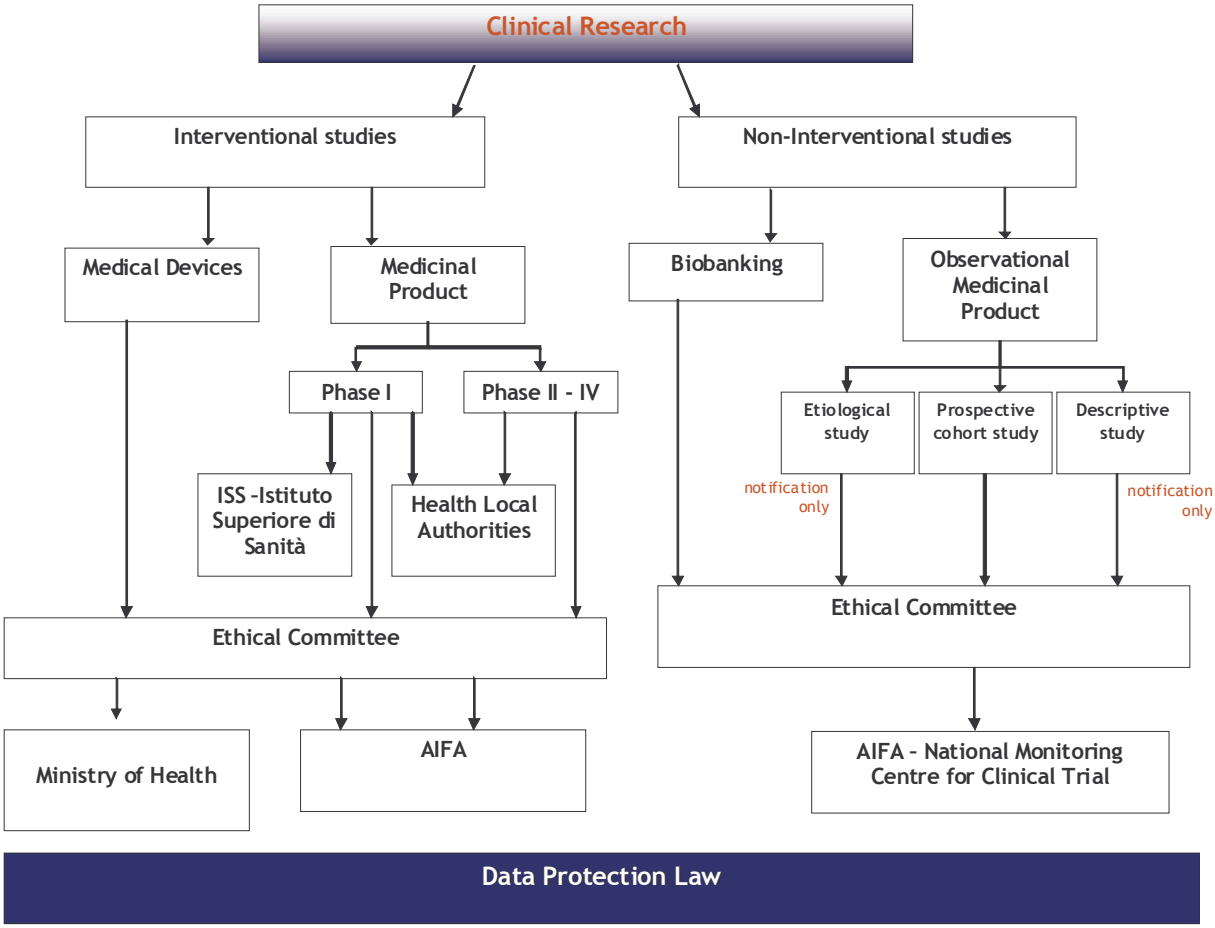


Figure 7: Italy[4]



[4] AIFA Agenzia Italiana del Farmaco

Figure 8: Spain

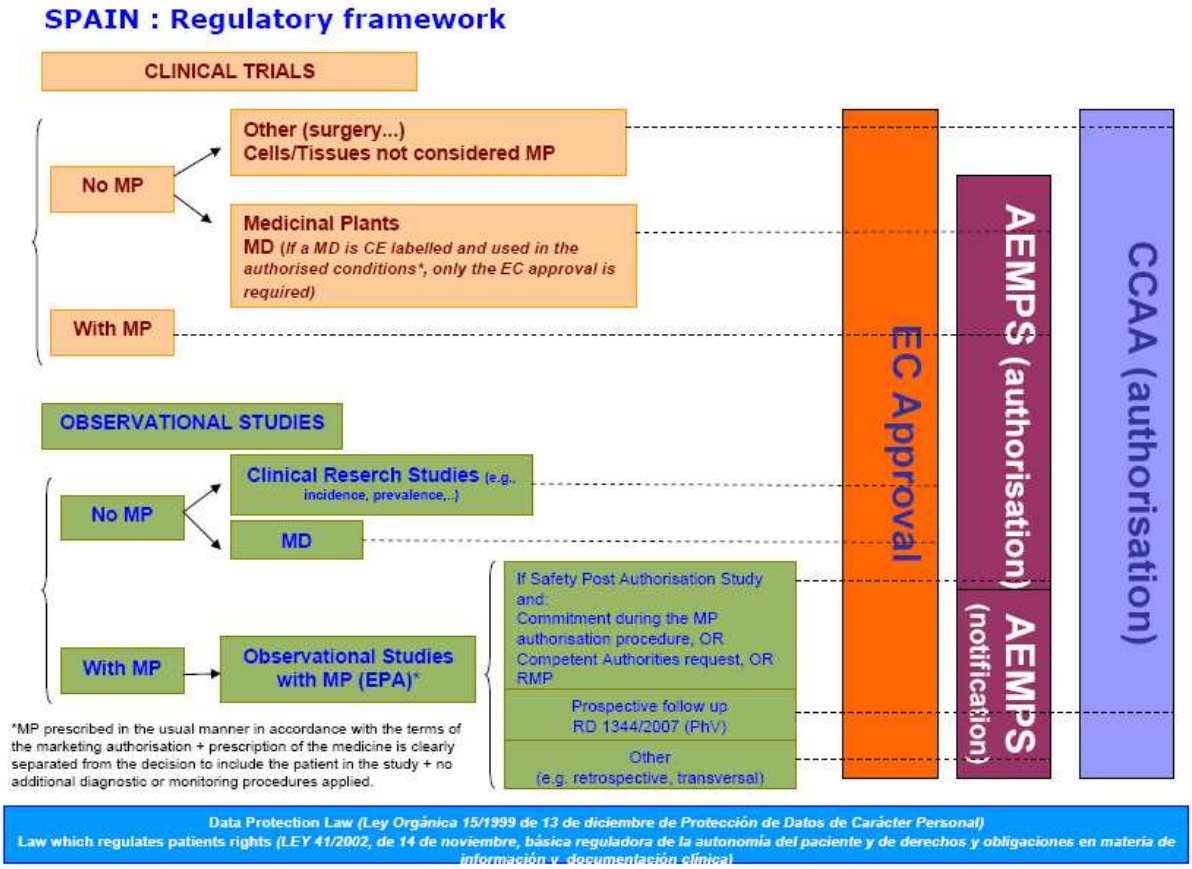
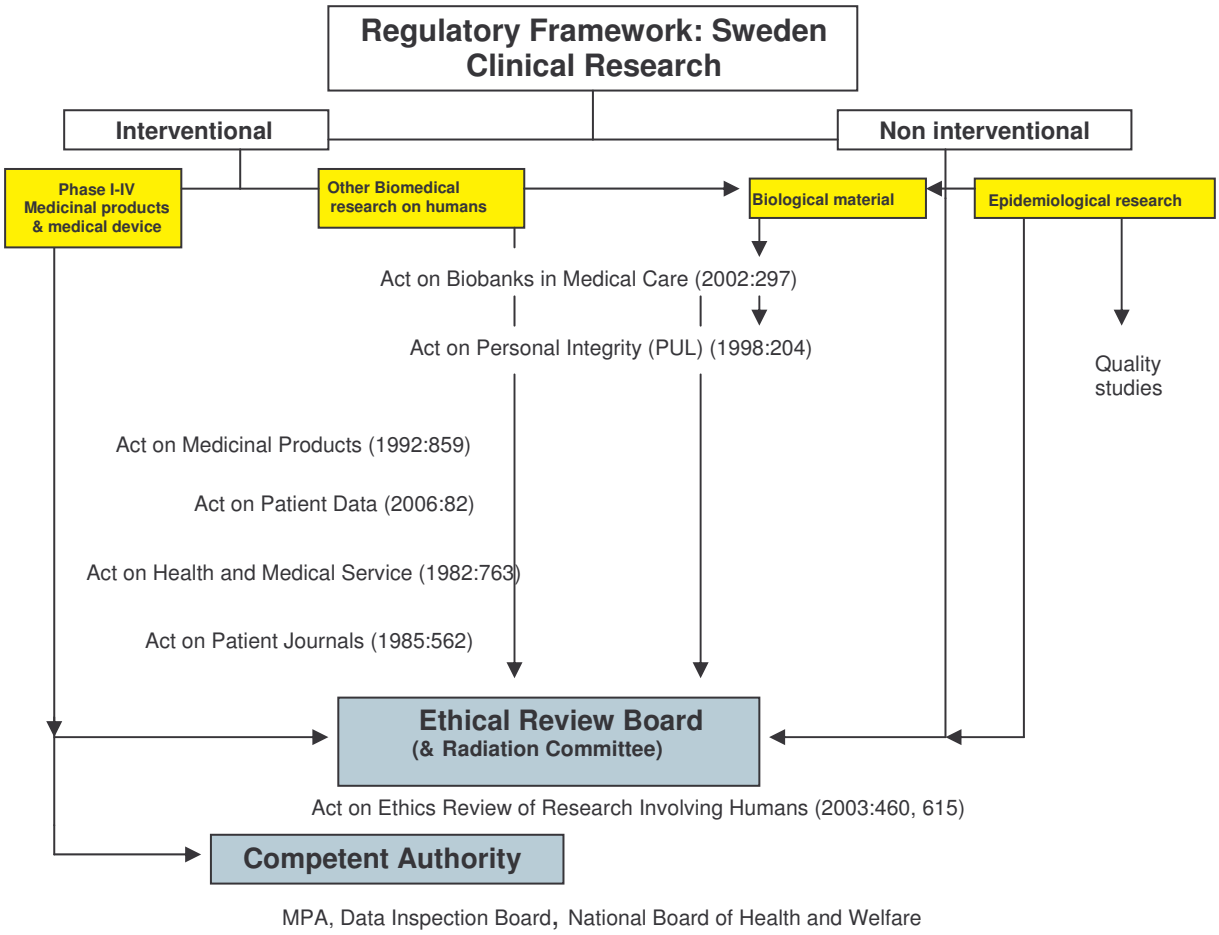


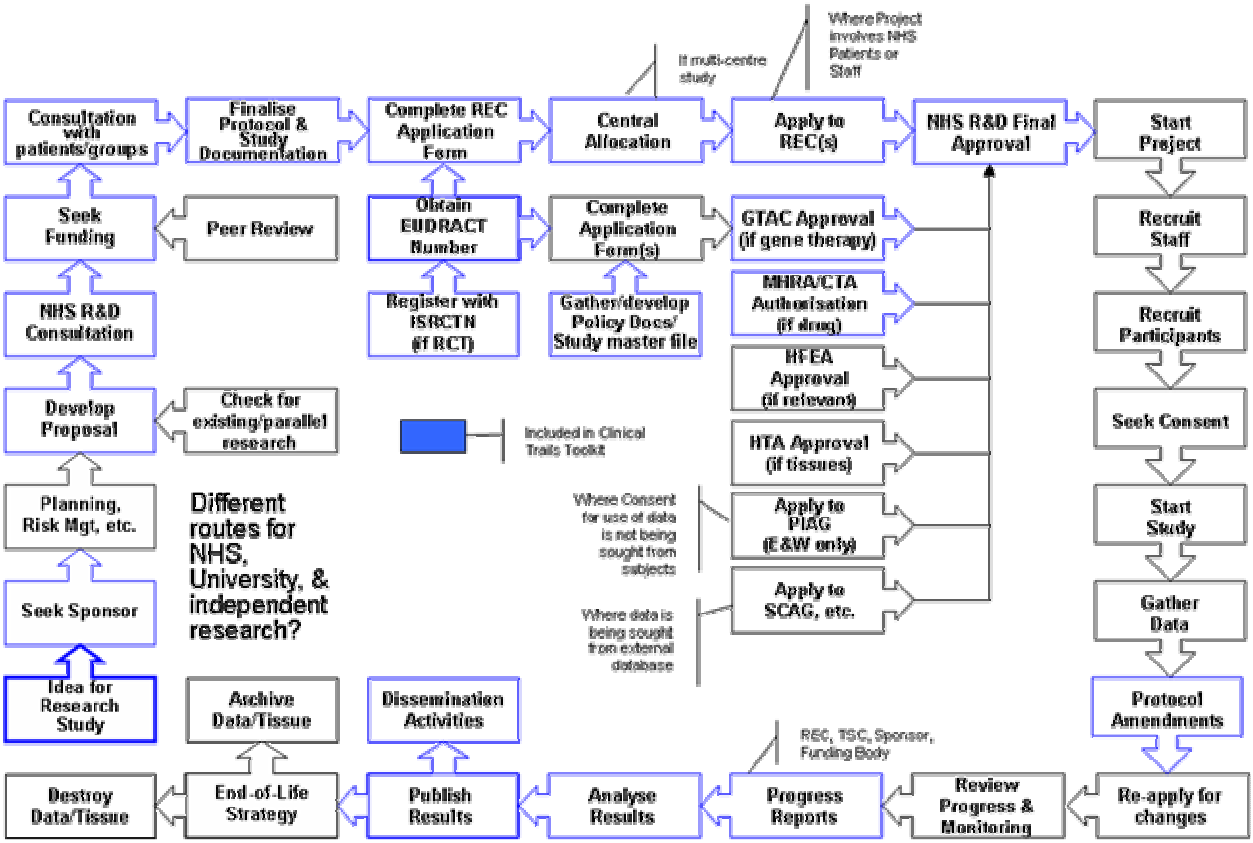
Figure 9: Sweden



In Sweden, all research involving humans or their integrity must be reviewed by the Ethical Review board(s). In addition, all medical research on humans which involves testing of substances classified as medicinal products or medical device must also be submitted to the competent authority, the Medical Products Agency (MPA). If the clinical trial involves radiation or radiological methods, submission to the Radiation committee is also required. Sampling of biological material is regulated by the Swedish Biobank legislation. Genetic testing currently requires permission from the Data Inspection Board before submission to the EC. Other interventional biomedical research, for example physiotherapy, only requires submission to the EC. Some observational studies which involve biological sampling may require submission also to the MPA after EC assessment. Quality studies (usual care) can be submitted to the EC for guidance, but this is not obligatory. Submission of authorisation application to the National Board of Health and Welfare (NBH) is not required at the moment, but may be so in the future for some types of human biomedical research. However, the NBH is the authority supervising biomedical research in the health care setting other than clinical trials of medicinal products or medical device.

Figure 10: UK[5]

Regulatory Framework in the UK
(*Monopoly ™ Board Illustration of the complexity of regulatory and governance environment reproduced with permission of Peter Singleton and MRC)*



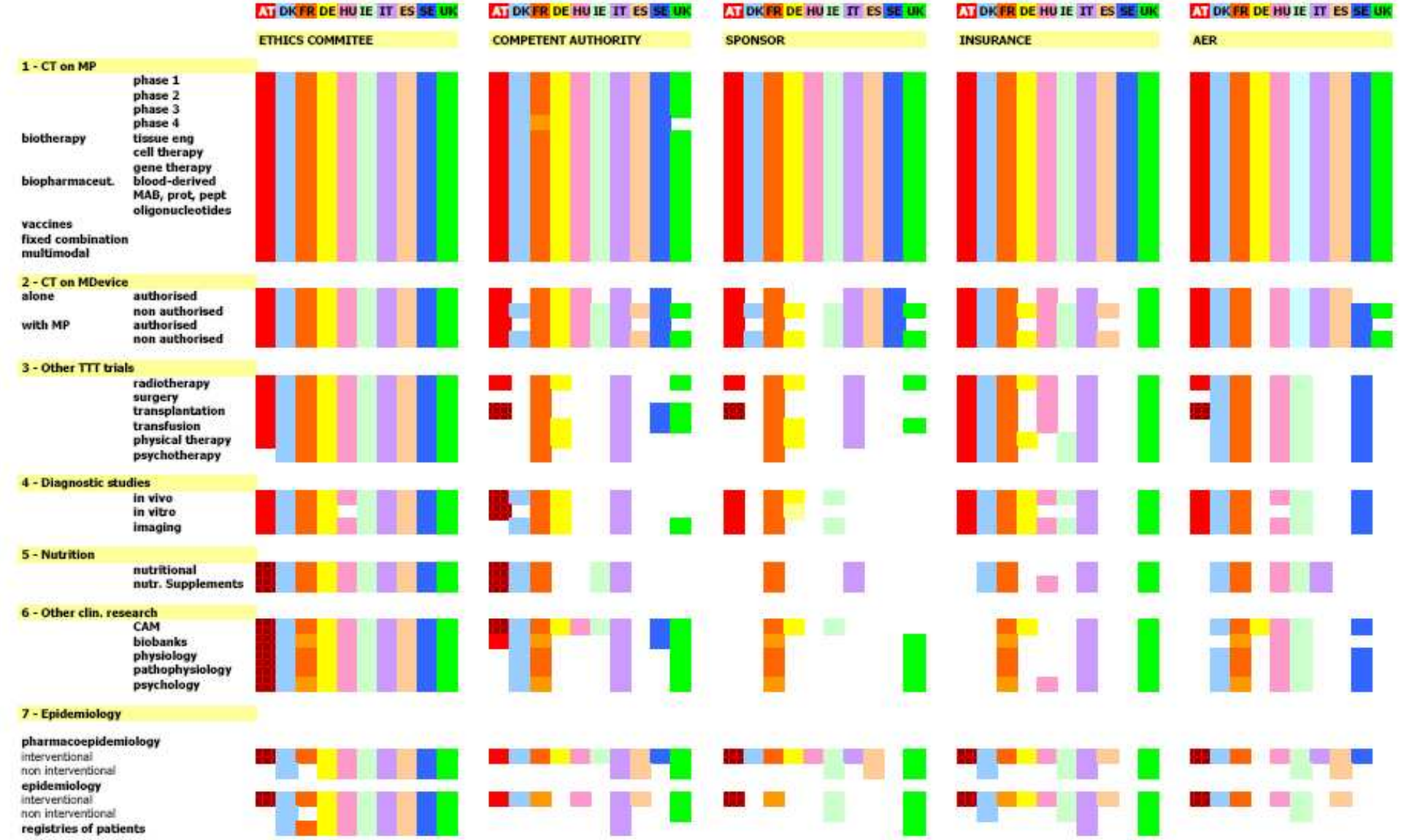
This Monopoly ™ Board is only Illustration that shows the complexity of regulatory and governance environment but has not been vetted and it is neither current, complete nor accurate.

[5] ADSS Association of Directors of social Services/ PSS Personal Social Services/ HTA= Human tissue authority/ SCAG=Security and confidentiality advisory group/NHS= National Health Service/ REC=Research Ethics Committee / GTAC= Gene Therapy Advisory Committee /MHRA= Medicines and Healthcare products Regulatory Agency

6. Results of the survey

This graphic representation (Table 1) is a summary of the regulatory requirements for various categories of clinical studies in the ten ECRIN countries (Austria-AT, Denmark-DK, France-FR, Germany-DE, Hungary-HU, Ireland-IE, Italy-IT, Spain-ES, Sweden-SE, United-Kingdom-UK) in terms of ethics committee approval, competent authority authorisation, need for a sponsor, need for insurance, and adverse event reporting.

Table1. Summary of requirements.



6.1. Legal basis

6.1.1. Extent of the legislation

There is a huge amount of legislation and guidance pertinent to clinical research in the EU and in the different Member States.

EU legislation includes five European Directives: Directive 95/46/EC, on the protection of individuals with regard to the processing of personal data and on the free movement of such data, is applicable to any type of clinical research; Directive 2001/20/EC, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use; Directive 2003/94/EC, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use; Directive 2004/23/EC, on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; and Directive 2005/28/EC, laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

The European Commission has clarified that the EU Clinical Trials Directive 2001/20/EC also covers trials using stem cells.

In **Austria**, **Denmark**, **France**, **Germany**, **Hungary,** and **Sweden**, the legislation covers any biomedical research and does not focus only on clinical research with medicinal products.

In **Ireland**, the legislative system covers clinical research involving medicinal products and research involving medical devices. There is no specific legislation covering clinical research outside of these topics but various statutory instruments may be relevant in certain biomedical research (S.I. No. 17/1994, S.I. No. 125/2000, S.I. No. 478/2002).

In **Italy** the legislation covers any biomedical research, and there are specific indications for experimental studies with adult stem cells and gene therapy. The legal basis of all the following regulations is the Legislative Decree of June 23, 2003 n. 211, published on the Official Journal (Gazzetta Ufficiale August 9, 2003 n.184) which is entitled "Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use".

In **Spain** the legislation covers any biomedical research, but observational studies which are not focused on medicinal products. The main laws are: Law 29/2006, of 26 July, on guaranties and rational use of medicinal products and medical devices and Law 14/2007, of 3 July on biomedical research. Law 14/2007 contains specific provisions with respect to clinical research involving invasive procedures, (invasive procedure is defined as any intervention performed with investigational purposes which involve a physical or psychological risk for the participant), research involving human embryos, foetuses, biological samples or cells of embryonic origin, and investigation related to genetic analysis, human biological samples and biobanks.

In the **UK**, the law only covers clinical trials of investigational medicinal products.

6.1.2. Specific populations

6.1.2.1. Healthy participants (files, requirements, fees)

EU legislation, including the 2001/20/EC Directive, has no specific provisions for clinical research on healthy volunteers.

In **Austria**, there is no official registry for healthy participants. Healthy participants may be reimbursed for their time, transport costs, and discomfort or pain.

In **Denmark**, there is no registry for healthy participants. Healthy participants may be reimbursed for their time, transport costs, and inconvenience. The reimbursement is calculated based on the minimum wage.[6] The Danish Medicines Agency requires detailed documentation on the risk/benefit ratio of all trials, but this is particularly important for trials involving healthy participants, or for trials using major invasive procedures.

In **France**[7], healthy participants (or participants whose disease has no relationship with the aim of the research or if requested by the ethics committee) have to be recorded on a national registry before their participation in the research, in order to avoid simultaneous participation in different trials, participation during an exclusion period, or exceeding allowed fee. Compensation fees are limited to adult participants and with a maximum of 4500 Euro per year, per participant.

In **Germany**, there are no specific requirements and no specific file exists for healthy participants. The trial participants of phase I trials get compensation. In other trials participants can receive compensation of travelling costs on a case-by-case basis.

In **Hungary**, the healthy participants are listed in files at the investigation centre in order to avoid non-authorised participation. A centralised file does not exist but exchange of information is possible between the different files. Compensation fees are allowed for phase I and bioequivalence studies and depends on the extent of the study but there is no upper limit.

In **Ireland**, there are no compensation fees for participants in clinical research. However, small expenses incurred by participants for involvement in the study may be reimbursed.

In **Italy**, there are no specific requirements, no specific file for healthy participants, and no compensation fees for participants taking part in clinical research.

[6] http://www.cvk.im.dk/cvk/site.aspx?p=475
[7] Law 2004-806 of 9 August, 2004 article L 1121-11, L1121-12 and decree of the 25 April 2006

In **Spain**[8] **and Sweden**, there is no national healthy volunteer registry, but some healthy participant registries exist at the level of the hospitals. There is a compensation fee for healthy volunteers. The compensation is evaluated at the time of ethical application by the ethics committee and should be in proportion to discomfort and procedures. There is no yearly limit. In Spain, provisions for clinical trial without specific potential benefit for the participant apply.

In **UK**, there is no centralised registry for healthy participants; however some research centres may maintain registries. Healthy participants may be reimbursed for their time, transport costs, and inconvenience. Healthy volunteer studies involving investigational medicinal products will need to be authorised by the MHRA (the Competent Authority for the UK) and a recognised Research Ethics Committee (REC), recognised RECs are recognised by the United Kingdom Ethics Committee Authority). The sponsor enters into direct contractual arrangements with a research participant to compensate them in defined circumstances.

6.1.2.2. Vulnerable population (definition and waiver of informed consent)

In the EU legislation there are specific provisions for minors or incapacitated adults in the 2001/20/EC Directive.

In **Austria** the following population groups are considered as vulnerable (in accordance with ICH guideline):
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. Inclusion in a trial is possible, but requires special conditions (eg, trial is not possible in less vulnerable population, specific benefit for vulnerable population).

Informed consent from participants is required if possible to obtain. Minors have to consent in addition to their parents. In the latter case different informed consent forms for different age groups might be necessary (the study should be described in a way understandable for the respective age). Otherwise consent from a legal representative or in some trials (eg, in emergency medical situations with unconscious patients) physicians not engaged in the trial might participate in the process of obtaining consent. There is no waiver for consenting. However, in specials situation (eg, in emergency medicine trials or in unconscious participants) it might be acceptable to postpone consenting until the patient is able to consent.

In **Denmark**, a research project involving the participation of minors, individuals under personal guardianship, or permanently legally incompetent adults requires

[8] *Real Decreto 223/2004, 6 de Febrero, por lo que se regulan los ensayos clínicos con medicamentos*

surrogate consent from either the holder of custody, guardian, or closest relative and general practitioner, or the medical officer of health, respectively.[9]

Research with medicinal products involving incapacitated trial participants in emergency treatment situations is also possible. The reasons for involving such trial participants must be described in the research protocol and the health condition that makes them unable to give informed consent must be explained. The Danish Medicines Agency and the ethics committee must approve this and deem surrogate consent acceptable. This is covered by a Danish law effective since April 2006[10] (unofficial translation[11]). In such cases a professional legal representative comprised of two physicians can give surrogate consent on behalf of the incapacitated trial participant. The professional legal representative must evaluate the trial participant's suitability for the trial and safeguard the participant's interests.

In **France**, the following categories are considered as vulnerable:
minors non-emancipated participants, pregnant, parturient or lactating women, people who lost their freedom after a legal or administrative act, participants hospitalised against their will, participants admitted in a social or sanitary institution with aims different from the research, major participants under legal protection or unable to provide an informed consent.[12]
For the minors, the authorisation must be given by all the persons in charge of the parental authority. It can be given by only one of these persons, if all of the following conditions are fulfilled:

- minor risks or constraints for the participant,
- no change in the usual way of caring for the participant,
- research performed during current care,
- if the other person in charge of the parental authority cannot give his consent in delays suitable with the design and aims of the research.

For participants under trusteeship, the consent must be given by the participant with the help of a tutor, by the tutor or curator, by the family council if this exists, or by a judge.
Biomedical research to be performed in emergency conditions that will not allow to collect the consent from the participant is possible. In that case, the protocol specifies that only the surrogate consent is given by patient's family or the person considered as confident ('personne de confiance') if they are present ; the Ethics committee must approve the procedure. The participant is informed as soon as possible and his own consent is required for the continuation of the research.

In **Germany**, children, pregnant or lactating women, and unconscious participants are considered as vulnerable. In case of emergency conditions or people incapacitated to consent, a waiver of consent is not allowed.

In **Hungary**, children under 14 years of age and people placed in charge under a guardian are considered as vulnerable. It is possible to perform studies in

[9] http://www.cvk.im.dk/cvk/site.aspx?p=150
[10] http://www.cvk.im.dk/cvkEverest/Publications/cvkx2Eimx2Edk%20x2D%20dokumenter/20061128152727/CurrentVersion/Cirkulaereskrivelse.pdf
[11] http://www.cvk.im.dk/cvkEverest/Publications/cvkx2Eimx2Edk%20x2D%20dokumenter/English/20061205160436/CurrentVersion/Cirkulaereskrivelse.pdf
[12] Law 2004-806 of 9 August, 2004 article L 1121-5, -6, -7,-8,-9,-11,-14,L1122-1,-2

emergency conditions. The physician or the family can give surrogate consent, however, as soon as the patient recovers competence, s/he has to sign the consent.

In **Ireland**, vulnerable populations can be interpreted as children and adults unable to give consent by physical or mental incapacity.[13]
There is no waiver of consent in case of emergency research. In case of incapacity to consent (unconscious, dementia, etc), there is no specific Irish legislation in this regard, but a report from the Irish Council for Bioethics[14], recommends that next of kin or legal guardian consent must be sought and must represent the patients presumed will. In addition, research ethics committees will have special regards to consent in the vulnerable populations.

In **Italy**, the following categories are considered as vulnerable populations: children; unconscious people; people with psychiatric disorders; and people with dementia.[15] There is no waiver of informed consent under emergency conditions or for critically ill participants, the legal representative should give the informed consent. For minors, the legal representatives are the parents or in absence of the parents a guardian officially appointed by the court. In case of adults unable to decide for themselves, the legal representative is a person - parent, relative or unrelated - appointed by the court as a guardian.

In **Spain,** there are specific provisions for the following populations: children; incapacitated adults; and pregnant women.
For emergency conditions a waiver of informed consent is allowed if the clinical trial has specific interest for the population involved in the research, there is an imminent physical or psychical serious risk and no suitable therapeutic alternatives in clinical practice are available. However, as soon as the patient recovers competence, or the legal representative is available deferred consent is compulsory. This situation should be previously specified in the approved protocol.[16]

In **Sweden,** specific requirements are needed for the following categories: children; unconscious people; people with dementia, old age, psychiatric disease, ie non-capable of understanding the intervention or unable to give consent. Children 15-18 years must give consent, as well as their parents.
There is no waiver of informed consent for participants with emergency conditions. However, under certain conditions the Central Ethical Review Board can authorise the trial even though consent cannot be given (eg, if it is regarded unethical not to perform the trial, see government proposition 2002:03:50).

In **UK**, the following categories are considered as vulnerable populations: incapacitated adults; children; and prisoners.

If a person is unable to consent for him or herself the EU Clinical Trials Directive requires that consent be obtained from the 'legal representative' prior to the recruitment of that individual into a trial. Even in an emergency situation, it is

[13] SI 190 of 2004 Schedule 1
[14]Human Biological Material: Recommendations for collection, use and storage in Research 2005, http://www.bioethics.ie/pdfs/BioEthics_fin.pdf
[15] Legislative decree of June 24, 2003
[16] Real Decreto 223/2004, 6 de Febrero, por lo que se regulan los ensayos clínicos con medicamentos.

still a requirement for such consent to be obtained. This consent can be obtained from a 'personal legal representative' or a 'professional legal representative'.

These legal arrangements also apply to enable adults lacking capacity to consent to take part in research other than clinical trials of investigational medicinal products (including health and social care research) that would otherwise require the participant's consent. Investigators should refer to the Mental Capacity Act 2005 (England, Wales and Northern Ireland) and the Adults with Incapacity Act 2000 (Scotland) for further details on conducting non-CTIMP research with adults without capacity. In the UK, adults with capacity need to make arrangements or make their wishes known in advance, to deal with future situations where they lack capacity to consent to take part in research. This requires any decision or act made on behalf of a person who lacks capacity is to be made in that person's best interests. These legal arrangements also apply to enable adults lacking capacity to consent to take part in research other than clinical trials of investigational medicinal products (including health and social care research) that would otherwise require the participant's consent. Investigators should refer to the Mental Capacity Act 2005 (England, Wales and Northern Ireland) and the Adults with Incapacity (Scotland) Act 2000 for further details on conducting non-CTIMP research with adults without capacity. In the UK adults with capacity need to make arrangements or make their wishes known in advance, to deal with future situations where they lack capacity to consent to take part in research. This requires any decision or act made on behalf of a person who lacks capacity is to be made in that person's best interests.

6.1.3. Data protection

Data protection in clinical research is regulated in three EU Directives. The EU Directive 95/46/EC regulates data protection and is applicable to any type of clinical research. Directive 2004/23/EC describes requirements for data protection and confidentiality to be applied to activities related to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. Directive 2002/98/EC, describes requirements for data protection and confidentiality to be applied to activities related to the collection, testing, processing, storage and distribution human blood and blood components.

Under Article 25 of the EC Data Protection Directive,[17] the European Commission has the power to make findings that third countries (ie, countries outside the European Union) ensure an adequate level of protection for personal data transferred from within the Member States of the European Union. The findings are binding on the Member States of the European Union. They have the effect that personal data may be freely transferred to the third countries in question in the circumstances provided for in the findings. The European Commission has made 'adequacy' findings for Switzerland, USA, Canada and Argentina.

In **Austria,** access to personal information of individuals participating in trials is protected by law (Datenschutzgesetz= data protection act) with restriction to

[17] http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31995L0046&model=guichett

trial related investigators and regulatory authorities. Data have to be anonymised before access is granted to the sponsor.

In **Denmark**, any research that involves sensitive personal information must receive permission from the Danish Data Protection Agency, this would include any health-related data, according to the Danish Act on Processing of Personal Data.[18] The Danish Data Protection Agency stipulates specific terms and conditions relating to clinical research. The application can be made at the same time as that to the ethics committee and the Danish Medicines Agency.

In **France**, the privacy of individuals is protected by Law 2004-801 relating to the protection of individuals with regard to the processing of personal data that modify the Act 78-17 of 6 January 1978 on Data Processing, Data Files, and Individual Liberties. This law includes provisions concerning health data collecting within clinical research including collection of blood or tissue samples. The study must be submitted to committees for data protection (Commission Nationale de l'Informatique et des Libertés (CNIL)) assessing the storage and Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS) assessing the content of information collected. CNIL has developed a simplified procedure avoiding multiple submissions for the same site (compliance may be controlled by inspections) but this procedure does not apply to all types of clinical research.

In **Germany**, the privacy of individuals is protected by the law (clinical trials on medicinal products according AMG§40(2a) - other studies according to general regulations (Datenschutzgesetze - German Data Protection Act and the Data Protection Acts of the regions (Länder)).[19]

In **Hungary**, there is a specific law for Data Protection and the protection of privacy needs to be part of the protocol. Hungary has an ombudsman for data protection as well.

In **Ireland**, the research must adhere to the Data Protection Act of 1988 and 2003 with respect to data handling and transfer.[20] The transfer of personal data to a country or territory outside the European Economic Area may not take place unless that country or territory ensures an adequate level of protection for the privacy and the fundamental rights and freedom of data participants in relation to the processing of personal data having regard to all the circumstances surrounding the transfer. Guidelines have been issued by the Data Protection Commissioner on research in the health sector, which has clarified use of anonymised and pseudo-anonymised data.

In **Italy**, the privacy of individuals is protected by a Statute n°675 of 31 December 1996 that includes provision concerning health data. The legislative decree on clinical trials of June 24, 2003 mentions the Statute as a safeguard for people involved in clinical trial. The authority responsible is called the 'Garante della Privacy'.[21]

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[18] http://www.datatilsynet.dk/english/the-act-on-processing-of-personal-data/

[19] Federal data protection law : "Bundesdatenschutzgesetz in der Fassung der Bekanntmachung vom 14. Januar 2003 (BGBl. IS. 66), zuletzt geändert durch Artikel 1 des Gesetzes vom 22. August 2006 (BGBl. I S. 1970)" http://www.gesetze-im-internet.de/bundesrecht/bdsg_1990/gesamt.pdf

[20] http://www.dataprotection.ie/documents/legal/act2003.pdf and http://www.irishstatutebook.ie/1988/en/act/pub/0025/index.html

[21] www.garanteprivacy.it

In **Spain**, the privacy of individuals is protected by law.[22,23] In general, this law states that study data are confidential. For that reason, data will be dissociated resulting in the avoidance of linking study data with study participants. Providing access to personal data is voluntary. Therefore, participants should give their consent. Participants have the right to access or rectify their personal data or revoke their consent at any time. However, the participant must consent to the scrutiny of personal information during inspection by competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available.

In **Sweden**, there are specific requirements regarding personal data protection.[24] From July 1 2008, all research on sensitive personal data must be assessed by the EC, including observational studies which do not involve personal consent (lagen om etikprövning 2003:460).

In **UK,** there are specific requirements regarding the use of personal data in clinical research. Personal data, in the context of the 1998 Data Protection Act (Section 3.2, and Annex 3), comprise information about living people who can be identified from the data, or from combinations of the data and other information which the person in control of the data has, or is likely to have in future. There must be consent in place which allows access to, and the use of the research participant's personal data for specific aspects of the trial and when the data is shared with the sponsor it should be in an anonymised format.

6.1.4. Circulation of blood and tissue samples

In **Austria**, handling and storage of blood are regulated in the blood safety act (Blutsicherheitsgesetz - BSG), handling and storage of other tissue samples in the tissue safety act (Gewebesicherheitsgesetz – GSG).

In **Denmark**, there are no specific requirements regarding the competent authority.

In **France**, if biobanking is part of an interventional biomedical research, the legal requirements relating to biomedical research are to be followed. If the biobanking is set up outside a biomedical research, the positive opinion of a CPP should be obtained, and the collection must be notified to the Research Ministry and the Regional Hospitalisation Agency (ARH) (if conducted in a Health organisation). Importation and exportation of blood and tissue samples have to be notified to the Research Ministry.

In **Germany**, biobanking law doesn't yet exist, but several regulations apply to the circulation of blood and tissue samples. Sampling and analysis is covered by a treatment contract with the patients. Different country-specific hospital laws regulate and limit the sort of informed consent, the use of samples in special research projects (in context of the care treatment), the use of samples by third parties. In addition, one has to take into consideration: transfusion law (Transfusionsgesetz), guidelines for hemotherapy (Richtlinien zur Hämotherapie), blood guideline (Blutrichtlinie) and the Ordinance of GMP and good practices

[22] Ley Orgánica 15/1999 de 13 de diciembre de Protección de Datos de Carácter Personal
[23] http://www.agemed.es/actividad/legislacion/espana/ensayos.htm
[24] Personal integrity Protection Law, provisions of the MPA 2003:6

during production of products from humans (Verordnung über die Anwendung der guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (Arzneimittel und Wirkstoffherstellungsverordnung – AMWHV-Verordnung). The Human Tissue Act (Gewebegesetz 2007) deals with the handling of human cells and tissues. This Act amended the Arzneimittelgesetz (German Medicinal Products Act) and Transplantationsgesetz (German Transplantation Law). Blood and Tissue samples are medicinal products according to the Drug law (Arzneimittelgesetz).

In **Hungary**, there is no specific regulation at present, except the recent law (2008/XXI) about biobanks which describes human-genetic research.

In **Ireland**, the Irish Council for Bioethics details recommendations for use.[25] The Irish Medicines Board has also detailed guidance in Pharmacogenetic Research.[26]

In **Italy**, circulation and storage of blood and tissue samples is regulated by a rule of the Ministry of Health July 20, 1996 n.16 which established safety norms. Biological samples for specific studies, in particular for DNA studies should be collected after a specific informed consent is given by the patient.

In **Spain**, the circulation of blood and tissue samples must follow the biomedical law[27] and the specific requisites to import and export are described in the Royal Decree 65/2006.[28] There are also several regulations on imports/exports of human biological samples: One for those used for diagnostic purposes (Royal Decree 65/2006, other one referring to imports and exports of human cells and tissues (Royal Decree 1301/2006, of 10th November), other on imports and exports of biological samples used for research purposes (Law 14/2007 on biomedical research).

In **Sweden**, circulation and storage must abide to the biobank legislation (SOFS 2002:11 (M)). This will be replaced by the European directive on cell and tissue when it has been implemented in the Swedish legislation.

In the **UK**, in England, Wales & Northern Ireland research involving human blood & tissue must comply with the Human Tissue Act 2004 which sets out a legal framework for regulating the storage and use of human organs, tissue and cells from the living, and the removal, storage and use of human organs, tissues and cells from the deceased. The Human Tissue Act 2004 is regulated by the Human Tissue Authority who provides a code of practice on the import and export of tissue in relation to research.
In Scotland researchers are required to comply with the Human Tissue (Scotland) Act 2006 and Section 45 of the Human Tissue Act 2004, which regards the use of tissue for DNA analysis. In the whole of the UK, R&D Management permission is required for any study taking place within the National Health Service (NHS) or with NHS patients.

[25] http://www.bioethics.ie/pdfs/BioEthics_fin.pdf
[26] http://www.imb.ie/EN/Publications/Medicines/Clinical-Trials/Guidlines-for-Pharmacogenetic-research.aspx?categorypageid=0&categorytypeid=-1
[27] LEY 14/2007, de 3 de julio, de Investigación biomedical
[28] REAL DECRETO 65/2006, de 30 de enero, por el que se establecen requisitos para la importación y exportación de muestras biológicas

6.1.5. Transparency (registers and information to the participants)

A number of EU Directives and one EU Regulation deal with transparency. Regarding the trial participants themselves, the 2001/20/EC Directive regulates on informed consent and the 95/46/EC Directive regulates on the rights of trial participants to access to their own personal data.

Regarding the publication of data, the 2001/20/EC Directive regulates on the development of EudraCT, a clinical trials register, and Eudravigilance CT, a register for all Suspected Unexpected Serious Adverse Reactions (SUSARs). These registers are only accessible to the competent authorities, the European Medicines Agency (EMEA) and the European Commission, and have increased transparency between these partners regarding the decisions taken on clinical trials in the EU. Public access to data in the EudraCT register as well as trial results is required for clinical research involving a paediatric population; this is stipulated in the European Parliament and Council Regulation 1901/2006/EC, on medicinal products for paediatric use.

Furthermore, article 57 of Regulation 726/2004/EC requires the development of public-access databases, one containing information on adverse reactions, with safeguards for personal data protection, and another with information on medicinal products, to be managed independently of pharmaceutical companies. Both databases need to contain information that is communicated appropriately for a broad audience. The EudraPharm database (http://eudrapharm.eu) is currently being developed. When it is complete, it will be a source of information on all medicinal products authorised in the EU or the European Economic Area (EEA).[29]

The 2004/23/EC Directive regulates on transparency with respect to donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

In **Austria**, no special national trial register is in use (aside from the obligatory registration in the EudraCT database). In addition trials are normally registered in databases with public access as *www.clinicaltrials.gov*.

In **Denmark**, there are no legal requirements to register a trial publicly. There is a possibility to register the results of clinical trials in the Danish Data Archive.[30] There is an ethical obligation to inform the trial participants of the outcome of the trial. However, the way to inform them is not specified in the law.

In **France**, the competent authority is obliged by the law to initiate and spread public registries of all interventional clinical researches as far as they are authorised (CTA + positive opinion by EC), with a summary of results, except if the sponsor refused (with documented reasons). Furthermore, at the end of the interventional clinical research the participants have the right to be informed on

[29] Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004 (2008) Official Journal of the European Union C 168/3-4

[30] www.dda.dk

the outcome of the research[31]. The modalities for this information are specified in the informed consent.

In **Germany**, no registers exist for clinical trials, publications derived from clinical trials, and no plans to make public anonymised data from the clinical trials. But the formation of a trials register is planned by a BMBF-funded project.

In **Hungary**, industry trials are generally registered on www.clinicaltrials.gov. There is no national registry of all the trials, but the studies authorised through the Medical Research Council TUKEB, KFEB, and HRB are registered on the national website www.ett.hu. In general, participants are not informed about the outcome of the trial.

In **Ireland**, industry trials are generally registered on www.clinicaltrials.gov or via the IFPMA Clinical Trials Portal http://clinicaltrials.ifpma.org/. There is no agreement upon national register for clinical trials conducted in academia. There is no national plan to register anonymised data from the trial once it has been analysed or publications deriving from clinical trials. Patients are usually informed of any laboratory, physical exam, imaging results resulting from the trial. It is encouraged in those trials falling under the clinical trials legislation that participants are informed of the outcome by the investigator. Often it is not possible to inform the participants. Usually outcome, data access etc. are outlined in the informed consent form and patient information leaflet.

In **Italy**, clinical trials on drugs should be registered by law (Decree of May 25, 2000) in the Osservatorio nazionale sulla sperimentazione clinica dei medicinali (OsSC: National Monitoring Centre for Clinical Trials), which is maintained by the Agenzia Italiana del Farmaco (AIFA: Italian National Drug Agency). The OsSC is of public domain.[32] There is no plan to register anonymised data from trials once it has been conducted and analysed, nor publication derived from the clinical trial.

In **Spain**, provisions of data protection law and the need for informed consent apply in all cases. According to art. 26 and 27 of Law 14/2007 participants in research should have results of the research which are relevant for their health made available, and should be informed of the research results at their request. With respect to investigations related to biological samples or genetic information, this law describes the right to information and the right to not being informed as two basic principles. On the other hand, Article 62 of Law 29/2006 requires that information on clinical trials authorised by the AEMPS should be included in a public and free national register.[33] It also requires that the Spanish Agency on Medicines and Medical Devices should make public, the results of those clinical trials which are not made public by the sponsors themselves, when those results show clear changes in the efficacy or safety profile of a medicinal product. However, there is no requirement for publication of the results derived from the clinical studies on this national register. This public register is still under development. Sponsors are obliged to make public the clinical trial results, either positive or negative, preferably in a scientific journal with a mention to the ethics committee who gave the favourable opinion.

[31] Law 2004-806 of 9 August 2004, Article L1122-1
[32] http://oss-sper-clin.agenziafarmaco.it/
[33] Article 62, LEY 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios

In **Sweden**, there are no plans to register clinical trials (other than through EudraCT) or publications derived from the clinical trials, nor plans to publish anonymised data from clinical trials. It is not obligatory to inform the patient about the outcome of the clinical trial but in blinded studies the participant has the right to know eventually what group s/he was randomised to.

In **UK,** the ISRCTN Register[34] is a database of randomised controlled trials. Industry sponsors may choose to have registries of the clinical trials they support. The UK Clinical Research Network provides a list of studies adopted onto the UKCRN portfolio.[35] The Clinical Trials Registries Database[36] limited to UK trials, or international trials held by organisations that have a UK centre. It is encouraged that research findings are published and grant funders provide grants on this agreement. In addition researchers expect to publish their research findings. It is considered unethical to carry out a research project without a clear intention to publish the results. The National Research Ethics Service application process requires specific details of intended publication plans and therefore researchers are expected to have identified appropriate publication routes such as conference presentations, submission of papers to journals in the field etc.

6.2. Clinical trials on medicinal products

6.2.1. Investigational medicinal product (IMP)

6.2.1.1. Definition

The Directive 2001/20/EC gives the following definition of the IMP: a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised or when used for an unauthorised indication or when used to gain further information about the authorised form.

In **France**, **Hungary**, **Ireland**, and the **UK**, the IMP is the study drug and the comparator (including the placebo).
In France, the background treatment is an IMP if collecting information on it is one of the objectives of the study.

In **Austria** the IMP ('Prüfpräparat') definition (in AMG §2a(14)) is identical to that in EU Directive 2001/20/EC.

In **Denmark**, the IMP is the study drug, the comparator, the rescue drug and all background treatment that directly influence the main efficacy parameters of the study.[37]

[34] http://www.controlled-trials.com/
[35] http://public.ukcrn.org.uk/search/
[36] http://ssrc.tums.ac.ir/SystematicReview/CTRDB.asp
[37] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_da.pdf

In **Germany**, the IMP is:

- within the EU authorised drugs if they are investigated within a clinical trial;
- within the EU authorised drugs if they will be used as comparator;
- within the EU not-authorised drugs;
- challenge drugs;
- placebos.

In **Italy**, according to a recent document from the AIFA (Italian Drug Agency), an IMP should be considered as the study drug and the comparator, being the latter a drug or a placebo, while it does not consider the background treatment (as defined as therapy that would be anyway administrated to the patients independently from the protocol) and the rescue drugs, as defined as the drug indicated in the protocol as a support therapy in case the IMP is ineffective, as the IMP.
Moreover, those drugs which are not the direct object of the experimental design, but their use is considered in the protocol, are considered as IMP:

1. Drugs with market authorisation (MA) in Italy, used according to the indications, included in the protocol as needed to the success of the trial, such as drugs to prevent or treat side effects of the IMP;
2. Drugs with MA in Italy, used outside the approved indication;
3. Drugs without MA in Italy, but with MA in other countries of the EC, used within or without the approved indication;
4. Challenge agents, ie, drugs that are used to induce physiological reactions needed to evaluate the effect of the IMP.

In **Spain**, the IMP is the test and comparator treatment including placebo. The same requirements as for IMP, with respect to the need for an Investigational Medicinal Product Dossier (IMPD), Investigator's brochure or Summary of Product Characteristics (SPC), are needed for background treatment, the rescue drug, the challenge agent and the medicine used to assess the primary endpoint, if not authorised in any EU country, or when authorised and used for non authorised indications. Measures in order to guaranty traceability are always needed especially for background treatments.

In **Sweden**, the IMP is the study drug, the comparator, including placebo and the drugs used to assess outcome measure. This includes already approved drugs which have been formulated differently or are used outside their approved indication, or used to gain additional knowledge about the approved indication.. The IMP is defined in the Swedish Medical Drug Act (adapted from Eudralex, Vol 10, Chapter 5).

6.2.1.2. Labelling of medicinal product and waiver of costs for non-commercial trials

In **Austria**, labelling of the IMP follows the European guidelines (GMP Annex 13 and Directive 2001/20/EC [38]-[39]) Requirements are not different for commercial and non-commercial trials.

[38] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

In **Denmark**, labelling of the investigational medicinal product follows the European guidelines (GMP Annex 13 and Directive 2001/20/EC)[40]-[41]. The outer packaging and/or immediate packaging must be in Danish. There are no specific requirements for non-commercial trials. There is no waiver for a non-commercial sponsor to purchase the investigational medicinal product.

In **France**, the IMP labelling follow the European guidelines and is defined in the law[42]. There are some specific provisions for the labelling of medicinal products with MA and used within their indication, but no specific provisions are made for non-commercial trials. Article L1121-16 of the law specifies that under certain circumstances the cost of the IMP can be taken in charge by the national health system if the sponsor is a public body, hospital, or not-for-profit organisation, if the results can be made publicly available and if the IMP has a MA or a cohort ATU.

In **Germany**, the labelling is regulated by the GCP-V. Specific provisions (GCP-V§5(8) Kennzeichnung von Prüfpräparaten) are written for non-commercial trials There is no waiver for a non-commercial sponsor to purchase the IMP.[43]

In **Hungary**, there is no waiver for a non-commercial sponsor to purchase the IMP. Labelling follows the European guidelienes.

In **Ireland**, the labels of the immediate and outer containers should comply with the requirements of Annex 13 to the EU guide on Good Manufacturing Practices on 'Manufacture of Investigational Medicinal Products'.[44] Label text must be in English. Other languages may be included, but as far as possible the text for each language should be placed together on the label. In relation to any changes on the use-by date on the label, the Irish Medicines Board requires that an additional label be fixed to the outer carton with the new use by date, the same original batch number, and an explanatory statement highlighting the fact that the use-by date shown on the over-label is a new, approved date, and that the earlier use-by date on the outer and immediate packaging has been superseded. This over-label should not cover the old use-by date or the original batch number.[45] The particulars to appear on the outer packaging of an IMP or, where there is no outer packaging, on the immediate packaging shall be such as to ensure protection of the participant and traceability, to enable identification of the product and trial, and to facilitate proper use of the IMP; and in the English language.[46]

There is no specific requirement for non-commercial trials. In non-commercial trials, the manufacturer can provide IMP free of charge to the investigator-sponsor without affecting the status of the study as a non-commercial trial.[47] The sponsor of a clinical trial shall ensure that the IMP used in the trial and any

[39] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
[40] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
[41] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
[42] Arrêté du 24 mai 2006 fixant le contenu de l'étiquetage des médicaments expérimentaux
[43] http://www.gesetze-im-internet.de/gcp-v/__5.html
[44] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
[45] http://www.imb.ie
[46] http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040190.pdf
[47] SI No 190 of 2004 states in Regulation 24 (3)

device used for the administration of such products are made available free of charge.

In Regulation 24[48] it states that Paragraph (3) shall not apply to a non-commercial clinical trial that is conducted by an investigator-sponsor, without the participation of the pharmaceutical industry, in circumstances where the investigator-sponsor has no commercial or financial interest in the outcome of the trial insofar as such products or devices have not been obtained free of charge by the investigator-sponsor.

In **Italy**, the IMP labelling in non-commercial trials follows the same rules as commercial trials. In non-commercial clinical trials, the IMP is provided to the research participants through the National Health System when used within or outside the indication of the market authorisation.

In **Spain**, compliance of the labelling with the requirements of Annex 13 Manufacture of IMP to the Eudralex volume 4 – Good manufacturing practice EU guide on Good Manufacturing Practices on Medicinal Products of the IMP is required in the legislation[49]. There are no specific requirements for IMP labelling in observational trials. A general waiver is stated in art. 35 of Royal Decree 223/2004 with respect to the provision free of charge of the IMP: "Exceptionally, other ways of supply could be acceptable." In practice this implies getting an agreement between the sponsor and the site.

In **Sweden**, the requirements for IMP labelling are identical in non-commercial and commercial trials. If a registered product is used in a new indication there may be a waiver and the public health-care system will pay, but this is not systematic (case-by-case). IMPs must be handled through pharmacies unless the competent authority has authorized otherwise. [50]

In **UK**, the labelling requirements for IMPs used, where a clinical trial involves a marketed medicine used within its marketing authorisation, the product can be labelled in accordance with the requirements for a dispensed medicine.
There may be other items with pharmacological effects used in a trial, but which are not IMPs. These should be labelled in accordance with good practice for the type of product concerned. In addition the cautionary label 'Keep out of the reach of children' is a legal requirement on all UK dispensed medicines. Information on this and other cautionary and advisory labels for dispensed medicines is given in Appendix 9 of the British National Formulary. Marketed products which are to be used outside of its licensed indications in a clinical trial – this relates to trials which go beyond the boundary of the circumstances set out second paragraph of Article 14 of the Clinical Trials Directive, but still use marketed products, which would already be made to Good Manufacturing Practice standards. Such products would need to be labelled in compliance with UK Regulation 46 (1), which specifies labelling in accordance with Article 15 of the GMP Directive 2003/94/EC. In placebo controlled trials it would be necessary to present all supplies in consistent packaging to maintain blinding, with consistent labelling also. If the original product's marketing authorisation holder is prepared to provide packs of the matching placebo, the company is also likely to agree to provide them in

[48] SI No 190 of 2004 states in Regulation 24 (3)
[49] RD223/2004, art 33 http://www.agemed.es/actividad/legislacion/espana/ensayos.htm
[50] LVFS 2003:6 3 kap. 11 § AR)

similar containers and with consistent labelling with the marketed product. In other circumstances consistency is likely to be best achieved through repackaging and full labelling as noted in the next section below.

For novel IMPs, the full labelling as set out in paragraph 26 of Annex 13 would need to be complied with. This would be an assembly operation, which would need to be undertaken as part of manufacturing by a unit with an IMP Manufacturing Authorisation, and to comply with GMP standards. Directions for use can be given through use of a leaflet or other explanatory document intended for the trial participant or person administering the product ; this may be of particular help where dosages may need to be varied during the course of the trial. In trials which include a placebo, the placebo itself is an IMP which needs to be manufactured to GMP standards, and would be expected to take the full labelling as in the table above (ie, Annex 13 paragraph 26). For consistency to preserve blinding, the active product would also need to take the same full labelling.

The manufacturer can provide the IMP free of charge to the investigator-sponsor. Any outpatient who for the purposes of his/her treatment is supplied at a hospital with drugs (otherwise than for administration in the hospital) shall, unless entitled to exemption, be liable to pay a prescription charge. These prescription charges apply to all clinical trial medicines, unless the participant is exempt or the clinical trial is placebo–controlled. This applies even if all or some of the drugs are supplied free of charge by the manufacturers.

6.2.2. Clinical trials on medicinal products - Submission to ethics committee

The submission of a clinical trial authorisation application to an ethics committee is required in all the ECRIN countries[51].

EU Directive 2001/20/EC requires an opinion from the ethics committee on the initial clinical trial applications and for substantial amendments, and sets maximum deadlines for the opinion. The ethics committee opinion is expressed as a single opinion per Member State. Specific topics to be addressed by the ethics committees are stated, but regarding the provision for insurance and indemnity, each Member States decides if the ethics committee or the competent authority is responsible for the assessment.

In **Austria** the sponsor is responsible for the submission to the competent ethics committee, depending on the location of the concerned investigator. Such ethics committees have been implemented by all nine federal states, but also by universities, hospitals etc. Composition and obligations of ethics committees are regulated in the drug act (Arzneimittelgesetz AMG §41) and for hospitals in the hospital act (Krankenanstalten- und Kuranstaltengesetz KAKuG §8). For multi-centre trials only one ethics committee (within Austria) has to be involved. This central ethics committee (so-called 'Leitethik-Kommissionen') has to adhere to special requirements for implementation (AMG § 41b).

[51] More detailed information on submission to ethics committees is provided by ECRIN deliverable 2.

In **Denmark**, there are eight regional scientific ethics committees. The investigator is responsible for submission to the appropriate regional scientific ethics committee depending on the location of the principal site for the clinical trial.[52] A National Ethics Committee also exists, which decides to approve or reject a proposed clinical trial when the regional ethics committee cannot, or when the regional ethics committee's decision is appealed.

In **France**, the sponsor is responsible for the submission to the ethics committee called CPP (Comité de Protection des Personnes). Only one CPP's approval is requested either for a single- or multi-centre study. France has been divided in seven regional areas and the clinical trial application authorisation can be submitted to any CPP in the area where the principal investigator (or coordinator in multicentre Clinical trials) is located. The list of the 40 French CPPs is available with their area of competence on the French Biomedical Research website.[53]

In **Germany**, the sponsor is responsible of the submission to the 'competent' ethics committee. This competent committee depends on the location of the coordinating or principal investigator and is responsible for the decision of the single opinion. In addition, the local ethics committee will evaluate the qualification of the investigators and the suitability of the trial sites. Different ethics committees[54] exist in Germany, they can be at the level of chamber of physicians (Ärztekammer) (EC-ÄK), at the level of the medical faculty (EC-MF), or at the country ministry of health (EC-HA).

In **Hungary**, the sponsor submits the clinical trial application to the competent authority (National Institute of Pharmacy), who is responsible of its transmission to the ethics committee (Committee for Clinical Pharmacology and Ethics of the Medical Council). The answer of the ethics committee is given to the sponsor via the competent authority. Local ethics committees (regional ethical committees and institutional ethical committee) only give advice on the feasibility of the study and have no right to rewrite the central permission.

In **Ireland**, the Principal Investigator (PI) is responsible for submission of documents to a recognised ethics committee, though in practice this is usually carried out by the sponsor. Each local ethics committee must sign the Site Specific Assessment Form (SSA form) in order to confirm that a) local staff are suitable qualified and b) there are sufficient resources to carry out the trial locally. In practice, however two local ethics committees also carry out an additional ethical review of the study in relation to the hospital ethos and culture.

In **Italy**, the procedures for the submission of documents for clinical trials has been recently summarised in a document published on a supplement the Official Journal (Gazzetta Ufficiale, March 3, 2008 n. 53). The document summarises all the requirements for dealing with the Competent Autorithy (CA) and the Ethical Committees (EC). In brief, the person who is legally recognised as the initiator of the study is called the Promoter (sponsor). The Promoter is responsible for the submission of the request of authorisation of the study to the CA which Director of the Public Health Facility and the Ethical Committee of the Center that is promoting the study (principal Center or coordinating center) ; to the AIFA, or to

[52] http://www.cvk.im.dk/cvk/site.aspx?p=513
[53] http://www.recherchebiomedicale.sante.gouv.fr/pro/comites/coordonnees.htm#
[54] http://www.zentrale-ethikkommission.de/

the Istituto Superiore di Sanità, when – because of the nature of the study - these two institutions are the CA.
The EC of the principal center is requested to give the "parere unico" or single opinion, i.e. issues the authorisation. Then an authorisation is to be obtained also by investigators of the other participating centers, from their CA and EC. These bodies are entitled to approve or reject the participation of investigators of their center, and ask for modification for the informed consent to be delivered at these centers, but cannot ask major changes to the protocol. [55]

In **Spain**, the sponsor is responsible for the submission to all the ethics committees (CEIC) of the centres involved in the trial. The Reference EC is elected within the EC involved in the clinical trial. The Reference EC is the one, which provides the single opinion and all other involved (local) ethics committees will evaluate centre-specific aspects. The procedure to request a single opinion is specified in annex 2 of document "Aclaraciones sobre la aplicación de la normativa de ensayos clínicos desde el 1 de mayo de 2004".[56]
The CEIC accredited in Spain may be consulted. [57]

In **Sweden,** there are six independent regional Boards for Research Ethics Review (EC). They are in themselves authorities and review any interventional human research and research on personal data without the individual's consent. A Central Ethical Review Board for research also exists. Appeals can be made to this central committee. It is the Principal Investigator who is required to submit the application to the EC. If there is uncertainty as to the necessity of ethics review for a certain project scientific advice at the EC is always possible. There fees to the EC differ for different types of research and multicentre/single centre trials.

In the **UK**, any study that involves NHS participants or NHS time (ie, professionals working in the NHS) must seek research ethics committee approval. The NHS research ethics committees (REC) are coordinated by the National Research Ethics Service (NRES). The RECs are advisory bodies to the department of health. The NRES is part of the National Patient Safety Agency and provides help and leadership for REC by coordinating the development of operational and infrastructure arrangements in support of their work. For clinical trials on gene therapy product, the only ethics committee empowered to approve such trials is the Gene Therapy Advisory Committee (GTAC). The Patient Information Advisory Group (PIAG) provides advice on issues of national significance involving the use of patient information and to oversee arrangements created under the section 60 of the Health and Social Care.

55 http://oss-sper-clin.agenziafarmaco.it/normativa_ing.htm
56 http://www.agemed.es/actividad/invClinica/home.htm

58 http://www.msc.es/profesionales/farmacia/ceic/home.htm

6.2.3. Clinical trials on medicinal products - Submission to competent authority (CA)

The authorisation of competent authorities is required in all the ECRIN countries. The sponsor is responsible for the submission of a clinical trial authorisation application as defined by the Directive 2001/20/EC. Any substantial amendment must also be submitted to the competent authority. The deadlines for accepting or rejecting a clinical trial application are the same as for the opinion from the ethics committee. During the trial and at the end of the trial the competent authority should be notified of relevant safety events, in particular, SUSARs.

In **Austria** the CA is the Bundesamt für Sicherheit im Gesundheitswesen (BASG, Federal Office for Health Safety), supported by AGES PharmMed (Austrian Medicines Agency) providing services and personnel resources. Submission to the ethics committee and to the CA is the obligation of the sponsor. Submission to the CA can be in parallel or after submission to the ethics committee, but may not precede it.

In **Denmark**, the CA is the Danish Medicines Agency.[59] All trials and biobanks must also receive permission from the Danish Data Protection Agency. Trial proposals using gene therapy or living, genetically modified organisms for gene therapy must also be submitted to the Danish Working Environment Authority.[60] (This can be at the same time as the standard application to the Danish Medicines Agency). The Danish Working Environment Authority will grant authorisation of both the premises and the trial. The Danish Working Environment Authority will then send a copy of notification for consultation to the Danish Forest and Nature Agency.[61] This is in accordance with the Danish Environment and Gene Technology Act.[62]

In **France**, the only CA is AFSSAPS (Agence Française de Securité Sanitaire des Produits de Santé). Information can be found on Afssaps website.[63]
The sponsor is responsible for the CTA application but it can also be a legal representative (if the sponsor is not established in EEA countries) or an applicant authorised by the sponsor. The CA will issue written notice of acceptance of a clinical trial application and assesses it with the following timelines: about 30 days (90 days for gene therapy, somatic cell therapy and product containing OGM) to authorise the trial or give grounds for non acceptance. In that case, the sponsor must answer within a fixed delay and the final decision is taken within 60 days (180 days for gene therapy, somatic cell therapy and product containing OGM) of the original request. If no answer is received from the sponsor within the time fixed, the application is considered as abandoned by the sponsor. Dialogue with the Afssaps is possible to ensure questions are adequately addressed. In some cases, particularly in case of fisrt-in-man CT on an IMP with factors of risk, the CTA can be pre-submitted to Afssaps, according to the dedicated procedure.[64]

[59] http://www.dkma.dk
[60] http://www.at.dk/sw7737.asp or tel + 45 39 15 2000
[61] http://www.skovognatur.dk/English/
[62] http://www.mst.dk/English
[63] http://www.afssaps.sante.fr
[64] (http://afssaps.sante.fr/htm/5/essclin/procedure_pre_soumiss.pdf)

In **Germany**, the Paul-Ehrlich-Institute (PEI) is responsible for clinical trials with sera, vaccines, blood-derived products, bone-marrow derived products, tissue preparations, test allergens, test sera, test antigens, gene transfer medicinal product, somatic cell therapy medicinal products, xenogenic cell therapy, medicinal products, and genetically engineered blood components. The Federal Institute for Drugs and Medical Devices (BfArM) is responsible for all other medicinal products. In case of clinical trials with human embryonic stem cells, advice from the Robert-Koch-Institute (RKI) is required before the submission to the PEI or BfArM. The RKI deals with the execution of the authorisation procedure based on the Stem Cell Law as well as the maintenance of a register of stem cell lines used and approved in research. In case of multimodal trials, including those with a medical device, the sponsor and the investigator have to submit the clinical trial to the German institute of medical documentation and information (DMIDI). In case of multimodal trials using radiotherapy, the sponsor has to submit the clinical trial to the Federal Office for Radiation Protection (BfS). In addition to CTA application by the sponsor, the investigator has to submit the clinical trial to the local competent authority. Information on CTA application can be found in the different CAs' websites.[65]

In **Hungary**, the competent authority for all phase I-IV trials covered by the 2001/EC/20 law, is the National Institute of Pharmacy (NIP). Trialnot covered by the Directive and non-interventional clinical trials are outside the scope of the legislation and require only ethical permission. Medicinal trials not covered by the 2001/EC/20 Directive and multicenter non-interventional trials are submitted to the Committee of Scientific Research Ethics of the Medical Research Council, institutional trials to the local ethics committee.

In **Ireland**, the only competent authority is the Irish Medicines Board (IMB).[66] The IMB will consult its clinical trials subcommittee for trials involving products for gene therapy, somatic cell therapy or product containing a GMO. The sponsor is responsible for the CTA application but it can also be a legal representative (if the sponsor is not established in EEA countries) or an applicant authorised by the sponsor. The CA will issue written notice of acceptance of a clinical trial application in addition, a letter of authorisation is issued for all trials recommended for approval. For blood-derived products, monoclonal antibodies, recombinant proteins, peptides, and oligonucleotides, a written authorisation from the IMB can be requested. In this case the IMB will send a notice to the applicant within seven days of the receipt of the valid application informing that a written authorisation is required.
The timelines are: 30 days (90 days for gene therapy, somatic cell therapy and product containing OGM) from receipt of valid application to accept, accept with conditions or reject. If accepted with conditions or rejected, the sponsor has 14 days (30 days for gene therapy, somatic cell therapy and product containing

[65]-Application fpr clinical trials at PEI: http://www.pei.de/nn_158114/DE/infos/fachkreise/klin-pruef-fach/klin-pruef-fach-node.html?__nnn=true
-Application fpr clinical trials at BfArM:
http://www.bfarm.de/cln_029/nn_421158/DE/Arzneimittel/klinPr/klin__prf__genehm/meldepflichten.html__nnn=true
-Approval process for clinical studies with radioactive material or including radiation:
http://www.bfs.de/de/bfs/dienstleitungen/med_forschung
-Application process according to radiation protection ordinance:
http://www.bfs.de/de/bfs/dienstleitungen/med_forschung/strlschv/Hinweise_StrlSchV.html
-Application process according to X-ray ordinance:
http://www.bfs.de/de/bfs/dienstleitungen/med_forschung/roev
[66] http://www.imb.ie/

OGM) to answer. The final decision is taken within 60 days (180 days for gene therapy, somatic cell therapy, and product containing OGM) of the original request. Only one cycle of correspondence on any queries, which arise from the assessment, is allowed. If no answer is received from the sponsor or if the answer is not acceptable, the application is refused. Opportunities exist for dialogue with the IMB to ensure questions are adequately addressed prior to submission of the final response.

In **Italy**, all the clinical trials have to be declared on the database of the Agenzia Italiana del Farmaco (AIFA),[67] (Osservatorio Nazionale Sulla Sperimetazione Clinical Dei Medicinali; National Monitoring Centre for Clinical Trials). For phase I and phase II clinical trials, the competent authority is the Istituto Superiore della Sanita (ISS).[68] For phase III and phase IV clinical trials, the competent authority is the Director of the Public Health Facility. For clinical trials on biotherapy, biopharmaceuticals, vaccines, the competent authority is the Ministry of Health. For genetic or genotype/phenotype studies a specific informed consent is required and the aim of the study should be stated when the informed consent is obtained. If the stored material is later used for other purpose than the originally stated ones, a new informed consent should be obtained again from the participants.

In **Spain**, the only competent authority is the Spanish Agency for Medicines and Medical Devices (AEMPS). Performance of clinical trial on medicinal products not authorised in the EU and containing any active substance not included in any authorised medicinal product in Spain requires an application for a "Product under clinical research qualification" (PEI). With respect to the EU clinical trial dossier, this involves filling a specific section in the covering letter. The PEI qualification is given in the letter of the clinical trial authorisation. A written authorisation is required for a clinical trial associated with medicinal products requiring a PEI qualification, in case the AEMPS has requested supplementary information, and in case of clinical trials on cell therapy, gene therapy or products including genetically modified organisms.

In **Sweden**, the only competent authority for medicinal products and medical devices is the Medical Products Agency (MPA).
Whether clinical trials with tissue or cell therapy will require a submission to the competent authority depends on the degree of manipulation and on the commercial potential of the "product". A technique being offered by a specialist clinic provided at a certain hospital may be regulated by the National Board of Health and Welfare only (transplantation). If the technique or procedure is likely to be marketed , it will be regulated by the Medical Products Agency and requires approval like a medicinal product.

In **UK**, the competent authority is the Medicines and Healthcare Products Regulatory Agency (MHRA) with a specific department that provides authorisation for medicines and a specific department for devices. Clinical trials involving tissues, data, genetic material, and other clinical investigations may also require approval from additional regulatory bodies, eg, the Human Tissue Authority, Genetic Therapy Advisory Committee, etc.

[67] http://www.agenziafarmaco.it/aifa/servlet/section8983.html
[68] http://www.iss.it/

6.2.4. Clinical trials on medicinal products - Specific additional requirements

6.2.4.1.

EU Directive 2001/20/EC, allows for an extension of the assessment periods for both ethics committees and competent authorities in the case of clinical trials on medicinal products involving gene therapy, somatic cell therapy or medicinal products containing genetically modified organisms. In addition, written authorisation is required before starting the clinical trial when it involves cell therapy, gene therapy and medicinal products containing genetically modified organisms, and may also be required for a clinical trial on medicinal products which do not have a marketing authorisation or those which include biological components. [69], [70] Gene therapy trials, which modify genetic identity of the participant's germ line, are prohibited.

Regulation 1394/2007/EC on advanced therapy medicinal products expands the applicability of the elements of the EU Directive 2001/20/EC for gene therapy medicinal products, and somatic cell therapy medicinal products to tissue engineered products.

6.2.4.2. Genetically modified organisms

In addition to the extension periods for assessment of clinical trials involving genetically modified organisms and the need for a written authorisation, EU Directives 90/219/EEC on the contained use of genetically modified organisms and 90/220/EEC on the deliberate release of genetically modified organisms into the environment apply. A specific environmental risk assessment is required.

In **Austria** trials using any type of genetically modified products ('Gentherapie', including both genetically modified organisms and modified DNA specimens) have to adhere to the regulations of the Gentechnikgesetz (GTG, genetic engineering act) requiring special safety measures. Stricter regulations with regard to data handling and anonymisation and storage of samples apply. In contrast to other clinical trials, the competent regulatory authority with regard to any trial where the GTG is applicable is the Ministry of Health, Family and Youth (BMGFJ). Official notifications have to be issued within 180 days. In addition, the ethics committee and BASG/AGES PharmMed have to be concerned with regard to the trial protocols if performed as drug study.

In **Denmark**, trials using genetically modified organisms for gene therapy must be submitted to the Danish Medicines Agency and the Danish Working Environment Authority. The Danish Working Environment Authority[71] will grant authorisation of both the premises and of the trial. The Danish Working Environment Authority will send a copy of notification for consultation at the Danish Forest and Nature Agency.[72]

[69] EU Directive 65/65/EEC
[70] EU Regulation EEC Nº 2309/93
[71] http://www.at.dk/sw7737.asp or tel + 45 39 15 2000
[72] http://www.skovognatur.dk/English

In **France**, as stated in 2.3, AFSSAPS has specific subcommittees for gene therapy, and approval should also be obtained from Ministries of Research and Agriculture.

In **Germany**, registration of the patient treatment room or description of the transport, storage and inactivation of Gene transfer medicinal product (GT-MPs) containing or consisting of GMOs is required for experimental work with GMOs, registration has to be made at the responsible local authority according to the German Law on Gene Technology (GenTG; „Gentechnikgesetz"; transformation of the relevant Council Directives).[73]

Gene therapy and somatic cell therapy products used in or on humans (in vivo) are termed gene transfer medicinal products (GT-MPs). They are medicinal products (drugs) according to § 2 (1) of the German Drug Law (AMG; 'Arzneimittelgesetz') and include DNA, viral or non-viral vectors and genetically modified autologous, allogeneic or xenogeneic cells (used in vivo). No official definition of GT-MPs is given in the AMG. GT-MPs are either vaccines or blood products according to § 4 (4) and § 4 (2) AMG, respectively, or other drugs. According to § 77 AMG, the Paul-Ehrlich-Institut, Langen, is the competent authority for those GT-MPs which are vaccines and blood products, whereas the Federal Institute for Drugs and Medical Devices (BfArM, Bonn) is the competent authority for other GT-MPs.

Experimental pre-clinical work in gene therapy including the construction, use, storage and inactivation of vectors, genetically modified bacterial or mammalian cells or animals has to be conducted according to the German Law on Gene Technology (GenTG; 'Gentechnikgesetz'; transformation of the relevant Council Directives).

Experiments involving the use of genetically modified organisms (GMOs) have to be performed in laboratories or animal facilities of one of four safety levels (S1 to S4), which are accordingly equipped.

Laboratory approval is given by the competent authority of the Federal Land for the GenTG. Experiments in safety level 1 laboratories only have to be documented and the competent authority has to be notified, whereas experiments falling under higher safety levels need additional approval by the same authority (3 months or less).

The Central Commission for Biological Safety (ZKBS; 'Zentrale Kommission für die Biologische Sicherheit', Robert Koch-Institut, RKI) provides a list containing the safety level classifications of 'standard' vectors or plasmids and GMOs and is in some cases (e.g. approval of safety level 3 operations) to be consulted by the competent authority of the Federal Land for the GenTG.

In **Hungary** there is no specific regulation about GMOs, experiments involving GMOs- are approved by the NIP (National Institute of Pharmacy).

In **Ireland**, if any product in the study is a genetically modified organism, a separate application for a license must be made to the Environmental Protection

[73] www.gesetze-im-internet.de/bundesrecht/gentg/gesamt.pdf

Agency (EPA). A copy of the license from the EPA should be provided with the clinical trial application.[74]

In **Italy**, studies involving genetic products are subjected to the same rules as medicinal products and to regulations established in the Legislative Decree[75] which implements the legislation the Directive 2005/28/EC. Also further specifications are included in the Ministry of Health Decree of December 21, 2007 n.51. [76]

In **Spain**, the same requirements as for other clinical trials on medicinal products apply with the specificities introduced by the Directive 2001/20/CE. Law 9/2003, of 25 April, stating the juridical regime for contained use, deliberate release and marketing of genetically modified organisms. Specific requirements for getting the authorisation from the Environmental Ministry (Ministerio de Medio Ambiente y Medio Rural y Marino) can be consulted (www.mma.es).

In **Sweden**, the MPA will make an assessment of possible environmental effects of GMO's. Also, the general requirements in the Swedish ordonance 2002:1086 (implemented from Directive 2001/18/EC) need to be followed. The Directive of Tissues and Cells, under which these products may fall, will be implemented into Swedish legislation in July 2008.

In the **UK**, the Health and Safety Executive[77] regulate the use of genetically modified organisms. The GMO (Contained Use) Regulations provide for human health and safety and environmental protection from genetically modified micro-organisms in contained use, and additionally the human health and safety from genetically modified plants and animals (GMOs).

6.2.4.3. Stem cells

The European Commission has clarified that the EU Directive 2001/20/EC also covers trials using stem cells. The EU Directive 2004/23/EC applies to the donation, procurement and testing of cell therapy in general and within the scope of medicinal products legislation.

In **Austria** currently no specific legal requirements with regard to the use of stem cells are implemented.

In **Denmark**, applications for trials using fertilised eggs, stem cells, or stem cell lines are made to the Danish Medicines Agency, ethics committee, and to the Danish Data Protection Agency. Such trial applications must include documentation as if it were a trial involving legally incompetent trial participants (see section 6.1.2.2 Vulnerable population (definition and waiver of informed consent)). Where a fertilised egg is used for stem cell research the couple needs

[74] http://www.epa.ie/whatwedo/licensing/gmo/process/
[75] Legislative Decree of November 6, 2007 n.200, published on the Official Journal – Gazzetta Ufficiale n.261 (http://oss-sper-clin.agenziafarmaco.it/normativa/direttive_OsSC-000106-000000.pdf
[76] http://oss-sper-clin.agenziafarmaco.it/normativa/direttive_OsSC-000097-000096.pdf)
[77] http://www.hse.gov.uk/biosafety/gmo/index.htm

to give overall consent for its storage and use, they are not required to give specific consent to every future research project.[78]

In **France**, stem cell research should be approved by Agence de Biomédecine.[79]

In **Germany**, there is no specific requirement regarding the use of adult stem cells. Regarding embryonic stem cells, an additional submission to the Robert-Koch-Institute is requested[80].

In **Hungary**, there is no specific requirement regarding the use of stem cells but the Health Law (1997/CLIV) has to be taken into consideration. Permission to research with stem cells is given by the Committee of Scientific Research Ethics.

In **Ireland**, there is no regulation, but the Irish Council for Bioethics has published an information sheet for participants and includes comment in its' guidance document on recommendations for treatment of human biological material[81]. The information sheet states that research on adult stem cells is legal and is currently being conducted in a number of locations in Ireland. In some cases, this research has been publicly funded. The legal situation regarding embryonic stem cell research is less well defined and only research using embryonic stem cells from animals is carried out in Ireland. Ireland does not have specific legislation dealing with stem cell research or research on embryos produced, but not used, during IVF treatment.

In **Italy**, the use of embryonic stem cells is forbidden by the Italian legislation.
Experimental studies with adult stem cells and gene therapy are submitted to the authorization of Istituto Superiore di Sanità, according the to the Presidential Decree of September 21**,** 2001, n. 439, and according the Ministry of Health Decree March 18, 1998. [82]
A subsequent Ministry of Health Decree of March 2, 2004 has established the institution of a registry for the monitoring of gene therapy/stem cells research. The registry is under the responsibility of Istituto Superiore di Sanità. [83]

In **Spain**, The same requirements for cell therapy are required for adult or embryonic stem cells. Law 14/2007 prohibits the formation of pre-embryos and embryos with an exclusively investigational purpose. Research on embryonic stem cells should also comply with the Real Decreto[84] and the protocol must be

[78] http://www.cvk.im.dk/cvk/site.aspx?p=150
[79] http://www.agence-biomedecine.fr/fr/activite-recherche.aspx
[80] -German Embryo Protection Law: Gesetz zum Schutz von Embryonen (EschG): http://www.gesetze-im-internet.de/eschg/
-Law about import of embryonic stem cells. Gesetz zur Sicherstellung des Embryonenschutzes in Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz StZG): http://www.bmbf.de/pub/stammzellgesetz.pdf
English translation:
http://www.bundestag.de/parlament/gremien/kommissionen/archiv15/ethik_med/archiv/stammzellgesetz_engl.pdf
- Approval process for stem cells: Genehmigungsverfahren nach dem Stammzellgesetz.
http://www.rki.de/cln_006/nn_225658/DE/Content/Gesund/Stammzellen/stammzellen__node.html__nnn=true
[81] http://www.bioethics.ie/pdfs/BioEthics_fin.pdf
[82] available on the Official Journal – Gazzetta Ufficiale – May 28 1998, n. 122.
[83] http://www.iss.it/scf1/
[84] *Real Decreto 2132/2004, de 29 de octubre, por el que se establecen los requisitos y procedimientos para solicitar el desarrollo de proyectos de investigación con células troncales obtenidas de preembriones sobrantes*

approved by the Comisión de Garantías para la Donación y Utilización de Células y Tejidos Humanos and the corresponding regional Health Authority.

In **Sweden** there is no specific requirement for studies using adult stem cells. Ethical approval is required to produce a product using embryonic stem cells.The use of embryonic stem cells is regulated in the national Act on genetic integrity (2006:351), which among other issues regulates tracing of donor. Depending on the extent of manipulation, stem cells may be considered as medicinal products and follow the same requirements. Tissue products tailored in a hospital for an individual patient may not be within the scope of the regulation of advanced medicinal products and no marketing authorisation is needed (the so called 'hospital exemption'). The implementation of the European Directive on Tissues and Cells 2004/23/EG (regarding health care handling of tissue establishments in hospitals) into Swedish legislation is currently in process. A Regulation of Advanced Medicinal Products will be in effect in December 2008.

In the **UK** the following licenses, accreditations, and approvals are required to conduct stem cell research and trials:
• Research involving the derivation of stem cells from human embryos (following either fertilisation or cell nuclear transfer) must be approved and licensed by the Human Fertilisation and Embryology Authority.
• Research involving human adult stem cells must comply with the Human Tissue Guidelines (the Department of Health (DH) is conducting an ongoing review and consultation on the use of human organs and tissues; this may lead to new legislation)
• Research involving human foetal stem cells must comply with the Polkinghorne Guidelines (any changes in legislation resulting from the DH review of the use of human organs and tissues may require revision of the current Polkinghorne guidelines).
• All research aimed at deriving stem cell lines must be approved by a local research ethics committee.
• Stem cell research aimed at the production of therapies for human use must be carried out according to 'good manufacturing practice' in premises accredited by the Medicines and Healthcare products Regulatory Agency.
• Patient trials of stem cell therapies require a clinical trials certificate from the Medicines and Healthcare products Regulatory Agency, and approval from a local research ethics committee.
• Overseas agencies must provide evidence of equivalent authorisations.

6.2.4.4. Animal-derived products

In **Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden and UK,** trials using animal derived products follow the standard regulation for clinical trials.

In **Germany**, the products have to be manufactured according to AMG §32 by PEI and Tierimpfstoff-Verordnung[85] and Tierseuchengesetz.[86]

[85] http://www.bgblportal.de/BGBL/bgbl1f/bgbl106s2355.pdf
[86] http://www.gesetze-im-internet.de/bundesrecht/viehseuchg/index.html

6.2.5. Clinical trials on medicinal products - Requirement for a sponsor

For clinical trials on medicinal products, whatever the phase or the type of intervention, a sponsor as defined by the EU Directive is required.

Co-sponsorship is not allowed in **Denmark**, **France**, **Germany**, **Hungary**, **Italy**, **Spain,** and **Sweden**. However, Spain accepts co-sponsorship at the EU level and declares when the sponsor in Spain is not the sponsor in other countries, as stated in the trial protocol.

In **Ireland**, there is no formal opinion on co-sponsorship of trials but the IMB do allow for shared sponsorship, where the responsibilities of each party are clearly outlined.

In **Austria** and in **UK**, each trial requires a sponsor to take the responsibility for the initiation, management and financing (or arranging the financing) of that clinical trial with a medicinal product but the regulations allow two or more persons or a group to collaborate to take on these responsibilities. This person or group may take joint responsibility for carrying out the functions of the sponsor of that trial or allocate responsibility for carrying out the functions of the sponsor of that trial.

6.2.6. Clinical trials on medicinal products - Requirement for insurance

EU Directive 2001/20/EC requires that a provision has been made for insurance or indemnity to cover the liability of the investigator and the sponsor. Either the ethics committee or the competent authority will review the provision for indemnity or compensation in the event of inquiry or death attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor.

In **Austria**, the sponsor (industrial or academic) needs to ensure insurance for all participants and investigators in interventional clinical trials.

In **Denmark**, the participants in a clinical trial are covered by the national patient insurance system[87]. For damages, the hospital insurance (public hospital) covers the person responsible for the research and the sponsor.

In **France**, the sponsor (industrial or academic) is obliged to have insurance for all the interventional biomedical researches. The insurance covers the participants of the clinical research, the investigators and the sponsors. In addition investigators should make sure that their own insurance covers possible malpractice within their research activities.

In **Germany**, the sponsor has to ensure that the participants are covered.
In case of non-commercial trials when the hospital is the sponsor, the insurance of the university or the university hospital can cover the participants.

[87] http://www.cvk.im.dk/cvk/site.aspx?p=150
http://uk.patientforsikringen.dk/legislation/thepatientinsuranceact.html

In **Hungary**, the University Hospital insurance covers the participants in clinical trials and usual care. If trial is performed in governmental hospitals, the sponsor should contract with each hospital. For commercial trials, insurance has to be taken by the sponsor.

In **Ireland**, insurance is mandatory for all clinical trials. The Clinical Indemnity Scheme overseen by the States Claims Agency covers public hospital staff and claims arising from participants whose treatment was part of a clinical trial or approved research project. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. If the trial is designed by an Agency covered by this Clinical Indemnity Scheme or by any of its employees (including investigator led trials where the investigator is an employee) the cover under this scheme will extend to claims arising from trials design or protocol. In all trials it is mandatory that the relevant ethics committee has approved the trial in order for coverage to be activated.

In **Italy**, insurance is required for all clinical trials and is the sponsor's responsibility. For non-commercial clinical trials (ie, not sponsored by for profit enterprises) the general insurance contract of the hospital of the participant can cover the participant.

In **Spain**, insurance is required for all clinical trials on medicinal products. However, where the CT is only on medicinal products authorised in Spain and used within the authorised conditions, and the CEIC consider that interventions to be applied in the CT involve a risk equivalent to that afforded in the usual clinical care, insurance is not mandatory. The insurance has to cover the sponsor, the investigators and the site responsibilities.

In **Sweden**, the participants are covered by a public "patient insurance" and a "pharmaceutical insurance". The pharmaceutical insurance is voluntary and owned by membership to the Pharmaceutical Insurance Association (Läkemedelsförsäkringsföreningen). The insurance covers almost all clinical trials performed by the vast majority of companies operating in Sweden. Sponsors who are employed by universities need to ensure that they are covered by insurance. The professionals involved in clinical trials are covered by the public professional insurance.

In **UK**, the regulation states that all clinical trials with medicinal products trials must have insurance and indemnity in place to cover the potential legal liability arising from the design, conduct and management of the research. NHS employees conducting research are covered by the Clinical Negligence Scheme for Trusts which provides cover for negligent harm. Commercial sponsors and universities (for their staff) need to ensure they can provide non-negligent harm cover (if required by the REC).

6.2.7. Clinical trials on medicinal products - Adverse event reporting[88]

EU Directive 201/20/EC requires the collection and reporting of adverse reactions arising from clinical trials on medicinal products for human use.

For **Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden and UK**, suspected unexpected serious adverse reactions (SUSARs) need to be reported by the sponsor to the competent authority and to the relevant ethics committee. They have to be reported in the country where the SUSAR occurred and also reported in all the other countries concerned.

The reporting time for fatal or life threatening SUSAR is as soon as possible but no later than seven days from first hearing of the SUSAR. A full report should be submitted within eight days. Reporting time for other types of SUSARs is as soon as possible but no later than 15 days from first hearing of the SUSAR.

Only SUSARs have to be reported in an expedited manner. The other serious adverse reactions are sent to the competent authorities and ethics committees with the annual safety report. The non-serious adverse reactions should be summarised in the final study report.

6.2.8. Compassionate use

EU Regulation 726/2004 rules on compassionate use of medicinal products. 'Compassionate use' shall mean making a medicinal product without marketing authorisation available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening, and who can not be treated satisfactorily by an authorised medicinal product.

In **Austria**, compassionate use in accordance with the Reg 2004/726 Art. §83 (where a group of patients is addressed) is currently not regulated (but under preparation). As an alternative a 'named patient use' (AMG §8, 1 and 2) could be utilized, where treatment of *individuals* is regulated in case of comparable severe conditions (life-threatening or severe health hazard, no alternative treatment available). Section 8 of the article is not specific to trials, but can be performed within the setting of a clinical trial.

In **Denmark**, it is possible to carry out compassionate use studies. The treating doctor applies for a 'Compassionate Use Permit' from the Danish Medicines Agency. In special cases the Danish Medicines Agency can authorise the dispensing or sale of a medicinal product, ie, for life threatening diseases for which there are no well-documented treatment options. If accepted, the applicant receives authorisation, they must notify the pharmacy and include a copy of the authorisation with the prescription.[89]

In **France**, the law covers compassionate use. It can be:
- either within an open trial (expanded access trial)

[88] More details on adverse event reporting are available in ECRIN Deliverable 6.
[89] http://lms-lw.lovportaler.dk/showdoc.aspx?schultzlink=lov20051180uk#pkt88
http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=4619

- or within the 'Temporary Authorisation for Use' (ATU) process. In that case, use of medicinal products which do not have marketing authorisation in France and outside the context of a clinical trial is dependent on prior 'Temporary Authorisation for Use' (ATU) to be granted by the French Health Products Agency (Afssaps).[90]
ATUs are granted as a derogatory, exceptional and temporary measure, when the following conditions are met:
- treatment, prevention, or diagnosis of serious or rare diseases,
- absence of a suitable therapeutic alternative (medicinal product or other) available in France,
- and when the benefit/risk ratio of the medicinal product is presumed to be positive.
The use of these medicinal products is authorised by Afssaps, for a limited period of time.
In practice, there are two types of temporary authorisations for use:
- the 'nominative temporary authorisation for use', issued for a nominative patient on a named patient basis , at the request of and under the responsibility of the prescribing physician. This type of ATU concerns medicinal products of which the efficacy/safety ratio is presumed to be favourable in the light of the data available.
- the 'cohort temporary authorisation for use', which concerns a group or sub-group of participants, treated and monitored according to criteria fully defined in a protocol for therapeutic use and information collection. A 'cohort temporary authorisation for use' is issued at the request of the holder of the licensing rights, who commits to submit a marketing authorisation application within a determined time limit.

In **Germany**, the Arzneimittelgesetz (AMG = Federal Drug Act) covers compassionate use. There is no regulation to date but the BfArM has provided some recommendations[91]:
- existence of objective evidence that there is no other satisfying treatment option with a medicinal product;
- existence of objective evidence that the participants suffer from a life-threatening disease or a disease leading to severe disability;
- existence of objective evidence that there is no other satisfying treatment option with medicinal products approved in the European Community;
- existence of objective evidence that a marketing authorisation application has been submitted for the medicinal product or, that clinical trials with this medicinal product are still ongoing;
- the 'Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (EC) No 726/2004 (Draft)' should be considered;
- appropriate documents such as an investigator's brochure (IB) providing relevant non-clinical and clinical data proving safety and efficacy in the foreseen medical indication should be in place;
- inclusion and exclusion criteria as well as withdrawal criteria for the compassionate use program should be in place;
- provision for pharmacovigilance measures should be arranged.

In **Ireland**, currently, compassionate use studies can fall under either SI 190 of 2004 or 'named patient'. SI 540 of 2007, Schedule I, exempts a product without

[90] http://www.afssaps.sante.fr/ang/pdf/atu1_en.pdf
[91] http://www.bfarm.de/cln_043/nn_425150/EN/drugs/clinTrials/compUse/compUse-node.html__nnn=true

a marketing authorisation in Ireland to be imported but the prescription and responsibility of the oversight of the product is that of the prescriber (consultant). Products provided on a compassionate use basis between completion of Phase III and expected regulatory approval timeframe is treated as a clinical trial under SI 190. The Irish competent authority has recently established a statutory notification system for use of unauthorised medicines.[92]

In **Hungary** there is neither regulation nor implementation of compassionate use of drugs.

In **Italy**, the compassionate use of a medicinal product used in non-authorised conditions in single exceptional patients is allowed and is regulated by the a Ministry of Health Decree May 8, 2003 [93] and by the Legislative Decree April 24, 2006 n. 219.[94] The request of the compassionate use should be done by a physician that assume the responsibility of the administration to the patient. An authorisation should be requested to the Ethical Committee, and a special informed consent should be prepared.

In **Spain**, the compassionate use is the prescription of a medicinal product used in non-authorised conditions in isolated patients outside the context of a clinical trial, and under the physician's responsibility. An informed consent, a clinical report, a centre authorisation and the AEMPS authorisation are required on a case-by-case basis. The physician should notify the treatment results and adverse reactions to the AEMPS. Compassionate use is allowed in the period between the application for approval and the decision on market authorisation. New legislation is currently under development. It envisages access for a group of patients under an approved protocol for drugs under clinical research programs, and the involvement of Pharmacotherapeutics Committees in the elaboration of protocols for the use of currently approved drugs in non-authorised indications.

In **Sweden**, there is no system regulating compassionate use. In general, only commercial sponsors can offer compassionate use and MPA provisions explain in what situation this is possible. Instead it may be possible to prescribe the study drug after discontinuation of study on a participant-by-participant basis. The EMEA is currently discussing the regulation of compassionate use, where it may be possible to allow it in the period between application for approval and decision on market authorisation. This is not implemented in Sweden yet.

In the **UK**, there is no specific requirement for compassionate use outside medicinal products or medical devices. In case of medicinal products or medical devices, the treatment should be extended if the participant is doing well.

[92] www.imb.ie/EN/Medicines/Human-Medicines/Notification-System-for-Exempt-Unauthorised-Products.aspx?categorypageid=0&categorytypeid=-1
[93] Gazzetta Ufficiale July 28, 2003 n.173
[94] Gazzetta Ufficiale June 21, 2006 n.153

6.3. Clinical research on medical devices

EU Directive 93/42/EC concerning medical devices and amended by Directive 2007/47/EC[95] states that the manufacturer or the authorised representative shall notify the competent authorities of the Member States in which the investigations are to be conducted.

There are four classes of medical device; classification is based on risk to the human body. Clinical research on all classes of device requires a favourable opinion from ethics committee and authorisation form the competent authority, although if the device is in class I (lowest risk) authorisation form a competent authority may not be required. Authorisation from the competent authority is not required when the clinical research is conducted using devices which are authorised to bear the CE marking, unless the aim of these investigations is to use the device for a purpose other than that referred to in the relevant conformity assessment procedure.

All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

The EU Directive 90/385/EC states similar provisions for clinical investigations on implantable medical devices.[96]

The following definitions have been used for the completion of the survey:
- medical device authorised: is a medical device bearing the European Conformity (CE) label and used within its indication or intended purpose (meaning the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and or in promotional materials).

- medical device non-authorised: is a medical device either non CE labelled or used in another indication.

In **Austria**, trials with new medical devices are regulated by the 'Medizinproduktegesetz' (MPG, medical device act), based on the Councils Directive 93/42/EEC. In terms of conducting clinical trials most aspects are similar to the drug act (AMG). But also some differences apply: there is no central ethics committee (Leitethik-Kommission, compare 2.2), however, ethics committees might refer to the decision of other involved ECs (§57.2 MPG). The inclusion of participants under tutelage is not possible (§52). There is no time limit for ethics committee or competent authority approval (the limit of 60 days in §40(2) still requires approval, but this is not yet implemented). A trial can be initiated as soon as EC approval is received, as the competent authority does not issue an approval.

In **Denmark**, clinical research on a medicinal device needs approval from the Danish Medicines Agency, the regional ethics committee, and Danish Data Protection Agency, regardless of whether the device is CE approved or not. Clinical research using an in vitro diagnostic device which will come into direct or

[95] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:NOT
[96] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0385:EN:NOT

indirect contact with the human body also needs approval from the Danish Medicines Agency, the regional ethics committee, and the Danish Data Protection Agency. However, clinical research with a CE-marked medical device, which will be used for its intended purpose does not require authorisation from the Danish Medicines Agency.[97] Clinical research using medical devices which emit ionising radiation require approval by the National Institute of Radiation.[98]

In **France**, any interventional research on a medical device alone or combined with a medicinal product, whether they are authorised or not, must follow the general regulation on clinical trials (EC approval, CA (Afssaps) authorisation, need for a sponsor and need for an insurance and submission to data protection committees). In case of a device with a human or animal derived product, the CA authorisation must be explicit (given in written). In case of devices with radionuclides, a copy of the authorisation given by the Direction Générale de la Sureté Nucléaire et Radioprotection (General Direction of Nuclear Safety and Radiation Protection; DGSNR) needs to be provided with the clinical trial authorisation.

In **Germany** clinical trials and clinical assessments with medical devices are regulated by the Medicinal Devices Act (Medizinproduktegesetz). European Directives relating to medical devices (90/385/EEC, 93/42/EEC, and 98/79/EC) were implemented into German law by the Medical Devices Act. Sections 19-24 are particularly relevant for clinical research. Additional regulations which apply are: Gesetz zur Änderung medizinprodukterechtlicher und anderer Vorschriften: (inkl. Änderungen der DIMDI-Verordnung), Zweites Gesetz zur Änderung des Medizinproduktegesetzes - 2. MPG-ÄndG and the Medicinal device ordinance (Medizinprodukteverordnung). Special Ethics Commissions for medical devices are listed by BfArM. [99] A list of competent authorities for medical devices is provided by DIMDI. [100]

In **Hungary**, all research on a medical device alone or combined with a medicinal product, whether they are authorised or not, must be submitted to Institute for Medical Quality Improvement and Hospital Engineering(part of the Ministry of Health), and to the Committee of Scientific Research Ethics and need a sponsor and insurance.

In **Italy**, the legislation concerning the clinical studies involving medical devices is somewhat less specific than the legislation concerning the experimentation of medicinal products. It is regulated by three decrees.[101] See also the website of the Ministry of Health.[102]

In **Spain**, the relevant legislation for clinical investigations with a medical device is composed by Royal Decree 414/1996, of 1 March (which transposes Directive 93/42/EC), Royal Decree 634/1993, of 3 May (which transposes Directive 90/385/EC) and Royal Decree 223/2004, of 6 February which applies some of the

[97] http://www.medicaldevices.dk/1024/visArtikel.uk.mu.asp?artikelID=7650).
[98] http://www.sst.dk
[99] http://www.bfarm.de/cln_029/nn_424508/DE/Medizinprodukte/ethikkom/ethikkommissionenListe.html
[100] http://www.dimdi.de/static/de/mpg/adress/behoerden/klifo-liste.htm
[101] Ministerial Decree August 2, 2005. Official Journal n. 210 September 9, 2005; Legislative Decree December 14, n. 507. Official Journal n. 305 December 30, 1992; Legislative Decree February 24, 1997, n. 46. Official Journal, March 6, 1997, n. 54, Supplement
[102] http://www.ministerosalute.it/dispositivi/dispomed.jsp

provisions of clinical trials on medicinal products to the clinical investigations on medical devices.[103] A sponsor is always needed. The Competent Authority is the AEMPS (Subdirección General de Productos Sanitarios). When a clinical trial compares a medical device with a medicinal product, requirements for both clinical trials with medicinal products and for medical devices apply.

In **Sweden**, all research on a medical device alone or combined with a medicinal product, when not authorised, resembles the regulation of medicinal product (EC approval, CA authorisation, need for a sponsor and need for insurance).

In **UK**, all clinical investigations involving non-CE marked medical devices (non authorised by above definition) must be notified to the MHRA (devices) and receive a letter of no objection before they can commence. Clinical investigations involving CE-marked medical devices (authorised by above definition) do not need to be notified to MHRA (devices). This is regardless of whether a medicinal product is also being used in the study, however separate authorisation from MHRA (medicines) may be required. The Guidance Note 1 on clinical investigations of medical device is available on the MHRA website.[104]

6.3.1. Medical Device alone, authorised

In **Austria**, **Denmark** and **Ireland and Sweden**, when the device alone is European Conformity (CE) labelled and used in its indication the only requirement is an authorisation of the clinical trial from the ethics committee and the national data protection agency.

In **Germany**, trials with an authorised device alone do no require any submission to ethics committee nor competent authority according to § 23 Medical Device Act (MPG)[105]. § 23 MPG states that the terms set in § 20 and § 21 do not need to be followed if the trial evaluates a medical device which already has a CE-labelling according to § 6 and 10 MPG. If this CE labelled device is used for another purpose or the trial schedules additional invasive examinations § 20 and §21 have to be followed. The trials do not require a sponsor, or insurance.

The implementation of the MPG is within the responsibility of the states (Länder). In the area of medical devices, the ZLG performs the tasks of the 16 Länder with regard to accreditation and designation. This includes particularly the accreditation and monitoring of testing laboratories and certification bodies in the area of medical devices and in vitro diagnostic medical devices.

In **Hungary**, trials with authorised medical devices are approved by the Committee of Scientific Research Ethics, after the authorisation of use by the Institute for Medical Quality Improvement and Hospital Engineering

In **Ireland**, studies with a medical device are not governed by a central ethics committee, so permission must be sought from the governing ethics committee for each hospital where the research is conducted.

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[103] http://www.agemed.es/actividad/invClinica/pSanitarios.htm
[104] http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm
[105] Medizinproduktegesetz: http://bundesrecht.juris.de/mpg/index.html
List of registered ECs:
http://www.bfarm.de/cln_029/nn_424508/DE/Medizinprodukte/ethikkom/ethikkommissionenListe.html
List of competent authorities for medical devices: http://www.dimdi.de/static/de/mpg/adress/behoerden/klifo-liste.htm

In **Italy**, medical devices that have already got the CE mark and is used in a clinical study according to the indication for which it has been already authorised, does not require further authorisation by the Ministry of Health, and the protocol should be submitted directly to the Ethics Committee.

In **Spain,** clinical investigations with CE marked medical devices used for the intended purpose referred in the conformity assessment procedure, the favourable opinion of the relevant ethics committees and not the AEMPS authorisation is needed. Insurance is not required, except where the CEIC has considered that interventions to be applied in the clinical trial involve a higher risk than that afforded in the usual clinical care. The insurance should cover the sponsor, the investigators and the site responsibilities. In addition, when the clinical investigation does not modify normal clinical practice, and several Spanish centres would participate in the trial, the opinion of one single ethics committee is enough. Serious adverse events should be notified according to the standard in the EU medical device vigilance system.

In **UK**, clinical investigations involving CE-marked medical devices (authorised by above definition) do not need to be notified to MHRA (devices). This is regardless of whether a medicinal product is also being used in the study, however separate authorisation from MHRA (medicines) may be required. The Guidance Note 1 on clinical investigations of medical device is available on the MHRA website.[106]

6.3.2. Medical Device alone, non-authorised

In **Austria**, clinical research with a non-CE marked medicinal device or, with a CE-marked medical device which will be used in a way other than that it is authorised for, or an in vitro diagnostic devise requires approval by an ethics committee and information of the competent authority

In **Denmark**, clinical research with a non-CE marked medicinal device or, with a CE-marked medical device which will be used in a way other than that it is authorised for, or an in vitro diagnostic devise which will come into contact with the human body all need approval from the Danish Medicines Agency, the regional ethics committee, and Danish Data Protection Agency.[107] Clinical research using medical devices which emit ionising radiation require approval by the National Institute of Radiation.[108]

In **Germany**, clinical trials with a non-authorised device alone need to be submitted to the German Institute of Medical Documentation and Information (DIMDI) according to § 20 (6) MPG by the initiator (Auftraggeber) and investigator. An electronic registration form has to be completed by the initiator and investigator.[109] The trial needs a responsible person but the German Medical Device Law does not use the term 'sponsor'. According to §20 (1) No 4, the clinical trial has to be conducted by an adequately qualified and specialised doctor (or dentist) or another adequately qualified and specialised person, who has at least two years of experience in clinical trials with medical devices.

[106] http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm
[107] http://www.medicaldevices.dk/1024/visArtikel.uk.mu.asp?artikelID=7650
[108] http://www.sst.dk
[109] http://www.dimdi.de/static/en/mpg/index.htm

Insurance is required as for clinical trials with medicinal products. Some ethics committees specialise in medical devices.

In **Hungary**, trials with non-authorised medical devices are approved by the Committee of Scientific Research Ethics, after the authorisation of use by the Institute for Medical Quality Improvement and Hospital Engineering

In **Ireland,** clinical trials with a non-authorised device alone require review and approval by the Irish Medicines Board prior to commencement, except in some cases when the trial is initiated and sponsored by clinicians and is not for commercial purposes. The ethical review is not reviewed by a central ethics committee, so permission must be sought from the governing ethics committee for each hospital where the research is conducted. The competent authority is the Irish Medicines Board that will provide written acknowledgement of the valid application. The timeframe for review at the IMB is 60 calendar days, prior to day 60 the IMB will issue a letter to the sponsor indicating if the IMB has an objection to the investigation proceeding. There must be a responsible applicant for the submission and there is a need for insurance. Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors and external cover will be sought from manufacturer applicant. Serious adverse events, anticipated and unanticipated, must be reported by the sponsor to the medical device section of the competent authority and the relevant ethics committee in line with definitions in harmonised standards. Timelines for reporting are aligned with those of the medical device vigilance system (MEDDEV 2.12-1 rev5). Specific adverse event reporting requirements may be required and summary safety reporting is also required.

In **Italy**, medical devices (either "passive" or "active") not yet labelled with CE mark should be used in a clinical study after the Ministry of Health has been notified by a letter, written in Italian language. The letter should contain a number of information which are detailed in the Ministerial Decree of August 2, 2005. The Ministry of Health has 60 days to communicate its decision concerning the clinical studies: if it has a negative opinion the Ministry should communicate it before that term. If not, the investigator can initiate the study. In meantime, the investigator can ask the authorisation of the Ethical Committee. The sponsor should pay a fee of 1859.25 Euros to the Ministry of Health when submitting the notification.

In **Spain**, clinical investigations with medical devices falling within Class III and implantable and long-term invasive devices falling within Class IIa or IIb, all of the following is needed: the concerned ethics committee's favourable opinion, the conformity of the management board of the site and the AEMPS authorisation is needed not more than 60 days later of having received a valid application, provided that the ethics committee opinion has been previously notified. Significant amendments also need ethics committee review and AEMPS authorisation. In the case of clinical investigations with devices other than those

previously referred, the deadline for the AEMPS authorisation is 30 days. All Serious adverse events (SAEs) should be expediently reported to the AEMPS according to the legislation requirements. The sponsor should report the ethics committees and the Regional Health Authorities those SAEs which occurred in their geographical area of influence.

In **Sweden,** the procedure is similar: submission to Ethical Review Board and the MPA is obligatory.

In **UK**, all clinical investigations involving non-CE marked medical devices (non authorised by above definition) must be notified to the MHRA (devices) and receive a letter of no objection before they can commence.

6.3.3. Medical Device combined with medicinal products authorised or non-authorised

In **Austria**, clinical trials combining medicinal products and medical devices have to be approved by an ethics committee. If the medicinal product involved is not approved, AMG regulations (see under 2.3) apply, if the medicinal product has no CE labelling for the intended indication, MPG regulations apply in addition (see under 3 and 3.2).

In **Denmark**, clinical research using medical devices combined with medicinal products must be authorised by the Danish Medicines Agency, the regional ethics committee, and Danish Data Protection Agency. Any medicinal product that is used in the device or in the manufacturing of the device must be stated, justified and any experience with the product described. Clinical research using medical devices which emit ionising radiation require approval by the National Institute of Radiation.[110]

In **Germany**, clinical trials with medical devices combined with medicinal products whether they are authorised or not follow either the regulation on medicinal product (AMG) or the German Medical Device Law depending on which component is dominating.

In **Hungary** trials with medical devices combined with medicinal products are approved by the Committee of Scientific Research Ethics, after the authorisation of use by the Institute for Medical Quality Improvement and Hospital Engineering.

In **Ireland**, legislation applied to clinical trials of drug device combinations is dependant on the primary action of the combination. When the device has the primary action in the combination and the medicinal substance acts in a manner ancillary to that of the device, the relevant medical device directive is applied (93/42/EEC or 90/385/EEC). When the medicinal substance has the primary effect in the combination 2001/20/EC is applicable. There must be a responsible applicant for the submission and there is a need for insurance. Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under

[110] http://www.sst.dk

this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from manufacturer applicant. Adverse incidents have to be reported, by the sponsor or the investigator (if no sponsor) to the medical device section of the competent authority and the relevant ethics committee, as soon as possible or within 10 days. A safety report is also requested.

In **Italy**, the decree does not go into specific details how to deal the question if the medical device contains a new medicinal product or a drug already on the market. It is important to underline that the cost of the medical device under investigation is entirely covered by the sponsor. Further details can be retrieved at the official website of the Ministry of Health.[111] A document written by Unit for Drug Evaluation of the Veneto Region contains useful information.[112]

In **Spain**, in case the combined product is considered a medicinal product, the authorisation procedure for a clinical trial on a medicinal product will apply. However, if the medicinal product is not authorised, an internal assessment of the medical device component by the Subdirección General de Productos Sanitarios will be requested. If the combined product is considered a medical device, according to the EU definitions, the procedure applicable to a medical device should apply. In case the medical device has no CE marking, an internal assessment report on the medicinal product component will be requested from the Subdirección General de Medicamentos de Uso Humano.

In **UK**, all clinical investigations involving non-CE marked medical devices (non authorised by above definition) must be notified to the MHRA (devices) and receive a letter of no objection before they can commence. Clinical investigations involving CE-marked medical devices (authorised by above definition) do not need to be notified to MHRA (devices). This is regardless of whether a medicinal product is also being used in the study, however separate authorisation from MHRA (medicines) may be required. The Guidance Note 1 on clinical investigations of medical device is available on the MHRA website. [113]

6.4. Other interventional therapeutic trials not using medicinal products nor medical devices

For the purpose of this survey, the following trials were considered as 'other therapeutic trials':
- radiotherapy trials;
- surgery trials;
- transplantation trials;
- transfusion trials;
- trials with cell therapy (when the cell preparation is not considered as an IMP):
- physical therapy trials;
- psychotherapy trials (without medicinal product).

[111] http://www.ministerosalute.it/dispositivi/dispomed.jsp
[112] http://www.uvef.it/web/index.php?pag=come-presentare-la-notifica-di-sperimentazione-clinica-con-dispositivi-medici-al-ministero-della-salute
[113] http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm

EU Directive 2004/23/EC sets requirements in respect of data protection and confidentiality to be applied to activities related to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications. Directive 2002/98/EC sets requirements of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. DIRECTIVE 2005/61/EC, implementing Directive 2002/98/EC sets requirements with regards to traceability and notification of serious adverse reactions and events, applicable to transfusion of human blood-derived medicinal products

In **Austria** all clinical trials require ethics committee approval. Competent authorities only have to be involved if medicinal products (according to the drug act, AMG) or medical devices (according to the medical device act, MPG) are tested.

In **Denmark**, all these therapeutic trials require an ethical approval, as well as permission from the Danish Data Protection Agency. No sponsor is required and the person responsible for the trial is responsible for initial submission and for submission of any amendments. The person responsible for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsible for the trial must submit a list of all serious adverse events and reactions to the ethics committee.[114]

In **France**, all these therapeutic interventional trials need an approval of the ethics committee (CPP), an authorisation of the competent authority, a sponsor and insurance.
The competent authority is Afssaps. In addition, for radiotherapy studies, a copy of the authorisation given by the Direction Générale de la Sureté Nucléaire et Radioprotection (General Direction of Nuclear Safety and Radiation Protection; DGSNR) needs to be provided with the clinical trial authorisation.
SUSARs should be reported by the sponsor to the competent authority and ethics committee within 7 days following the hearing of the SUSAR.

In **Germany**, there are no legal requirements for surgery trials, transplantation trials and psychotherapy trials. For transplantation trials, transfusion law has to be taken into consideration.[115]

In **Hungary** all trials except trials with transfusion and transplantation, require ethics committee approval, which is given by the Committee of Scientific Research Ethics. There is no legal requirement for trials with blood and stem cells, but transfusion law exists and the Health Law (1997/CLIV) has to be taken into consideration.

In **Ireland**, Review by research ethics committee may not be required for:
(a) Research utilising existing publicly available documents or data;

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[114] http://www.cvk.im.dk/cvk/site.aspx?p=150
[115]Transfusionsgesetz (TFG) http://www.gesetze-im-internet.de/bundesrecht/tfg/index.html
Verordnung über das Meldewesen nach §§ 21 und 22 des Transfusionsgesetzes http://www.gesetze-im-internet.de/bundesrecht/tfgmv/index.html
Richtlinien zur Hämotherapie
http://www.pei.de/cln_115/nn_154580/DE/infos/fachkreise/haemovigilanz/richtlinie-haem/richtlinie-haem-inhalt.html?__nnn=true
RL 2002/98/EG (Blutrichtlinie): http://www.pei.de/cln_046/nn_154446/SharedDocs/Downloads/gesetze/rl-2002-98-eg-blutrichtlinie,templateId=raw,property=publicationFile.pdf/rl-2002-98-eg-blutrichtlinie.pdf

(b) Observational studies in public places in which the identity of the participants remains anonymous;
(c) Case study of one patient with the proviso that written informed consent has been obtained from the relevant participant;
(d) Quality assurance studies;
(e) Audits.

The opinion of the research ethics committee should be sought whenever there is any doubt about the applicability of this guidance to a particular research project. The ethical review of other therapeutic trials detailed above is not overseen by a central ethics committee so permission must be sought from the governing ethics committee of each hospital where the research is conducted. Competent authority (IMB) approval is required only if a medicinal product or a medical device is used but it may be necessary to solicit an IMB response on a case-by-case basis. Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. Regarding adverse events reporting, there is no statutory obligation to report events but it is considered as best practice for investigator to report SAEs to relevant ethics committee. In addition for transplantation and transfusion trials, serious adverse reactions and events require reporting to the competent authority.

In **Italy**, the recent document published on the Official Journal (Gazzetta Ufficiale, March 3, 2008 n. 53 [116], details the kind of studies that are under the legislation "Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use". (Legislative Decree of June 23, 2003 n. 211, published on the Official Journal (Gazzetta Ufficiale August 9, 2003 n.184) . All studies employing the following entities (beside medicinal product) are sublected to the above regulation:

- Biotechnology products
- Cell therapy
- Gene therapy
- Blood-derived products
- Other derived products
- Vaccine, sera, allergens
- Radiotherapy products
- Herbal remedies
- Homeopathic products

In **Spain**, all clinical research involving invasive procedures that is not related to medicinal products, medical devices, organ transplants or implants of cells and tissues is regulated by Law 14/2007.[117] This type of research needs to be approved by the corresponding ethics committee, and authorised by the concerned Regional Health Authority. Insurance is needed, but a formal sponsor

[116] http://oss-sper-clin.agenziafarmaco.it/normativa_ing.htm
[117] LEY 14/2007, de 3 de julio, de Investigación biomédica

is not required. There are not specific requirements for surgery trials, physical therapy trials, or psychotherapy trials. Trials with tissues or cells (when the cell preparation is not considered a medicinal product) fall into the scope of Real Decreto 1301/2006, which transposes the Directives 2004/23/EC, and the corresponding development Commission Directives.[118] This type of research can only be performed in accredited centres, it needs to be approved by the corresponding ethics committee, it needs the assessment report of the Comisión de Transplantes y Medicina Regenerativa del Consejo Interterritorial del Sistema Nacional de Salud, and must be authorised by the concerned Regional Health Authority. Insurance is needed, but a sponsor is not required. Clinical research on embryonic stem cells should also comply with Real Decreto 2132/2004, de 29 de October.

In **Sweden**, all clinical research involving humans requires ethical approval. The person (primary investigator) responsible for the study will submit the ethical application to the Regional Board of Research Ethics. There is no requirement for a formal sponsor. Adverse events, if the research is conducted in a hospital setting, should be reported as incidents and fall under the supervision of the National Board of Health, unless a medicinal product is involved in the protocol.

In the **UK**, these other therapeutic trials all need to be submitted to REC and will need a sponsor (as per the UK Research Governance Framework guidance). There are no other specific requirements except for radiotherapy trials (see paragraph 6.4.1 below).

6.4.1. Radiotherapy trials

In **Austria** studies using radiotherapy have to be approved by an ethics committee. If the radiopharmaceutical is an investigational product approval by the competent authority is required.

In **Denmark**, studies using radiotherapy must be approved by the regional ethics committee. If the radiopharmaceutical is considered an investigational medicinal product, approval from the Danish Medicines Agency is also needed.

In **Germany**, radiotherapy trials[119] need to be submitted by the sponsor to the Federal Institute for Drugs and Medicinal Devices (BfArM) or PEI (eg, antibodies labelled with radioactive substances in therapeutic intention) and to the Federal Office for Radiation Protection (BfS). Authorisation of the BfS is required if the use of radioactive substances or ionisising radiation surpasses regular use in therapeutic or diagnostic context in mode and scale. ('Mode' meaning a new method, 'scale' meaning a regular method is used but more often than in the standard procedure). Differentiation can be difficult, advice is given by an expert committee of the DEGRO,[120] but this advice has no legal value against the decision of the BfS. Exemption applies to therapeutically monitoring and follow-up (using CT / MRT, chest X-ray) in palliative Chemotherapy, if they meet certain terms.[121]

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[118] por el que se establecen las normas de calidad y seguridad para la donación, la obtención, la evaluación, el procesamiento, la preservación, el almacenamiento y la distribución de células y tejidos humanos y se aprueban las normas de coordinación y funcionamiento para su uso en humanos

[119] Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel (AMRadV): Text (rtf, 249 KB) http://www.pei.de/cln_046/nn_154446/SharedDocs/Downloads/gesetze/vo-radioaktiv-ionisierte-arzneimittel,templateId=raw,property=publicationFile.rtf/vo-radioaktiv-ionisierte-arzneimittel.rtf

[120] http://www.degro.org/jsp_public/cms/index.jsp?top=5

[121] http://www.bfs.de/bfs/dienstleitungen/med_forschung/roev/RECIST.pdf

For monocentre studies, the person responsible for the submission to the BfS is the 'Authorised Person for Radiation Protection' (Strahlenschutzbeauftragter) of the study centre.
In multicentre studies, the submission can be done by the Coordinating Investigator (in Germany 'Leiter der Klinischen Prüfung') together with the 'Authorised Persons' of all involved centres.[122]

In **Hungary** radiotherapy trials need the approval of the Committee of Scientific Research Ethics.

In **Italy,** as stated before, studies using radiotherapy products are subjected to the same procedural approval as for medicinal product.
In their evaluation the EC should take in account all the legislative decrees that regulate the complex matter of use of radiotaion, radioprotection, etc. The national legislation is very complex, and is well summarised in a document produced by the Istituto Superiore di Sanità. [123]

In **Spain,** Law 14/2007, of 3 July applies here. Facilities and personnel should be authorised for administering radiotherapy and should comply with requirements for radiation protection.

In **Sweden**, radiotherapy trials must be submitted to the Ethics and Radiation Committees and to the MPA (if medicinal product involved).

In **UK**, radiotherapy trials should be reviewed by an IRMER practitioner to establish safe levels of exposure. Trials involving use of radioactive substances must be submitted to the Administration of Radioactive Substances Advisory Committee (ARSAC) by each principal investigator in order that s/he obtains a certificate for his/her site authorising use of such exposure within the context of the trial.

6.4.2. Surgery trials

In **Austria**, an ethics committee has to be involved. If a method is newly implemented within Austria, this might follow the hospital act (KAKuG §8) regulations, not the drug act (AMG).

In **Denmark**, surgery trials require an ethical approval as well as permission from the Danish Data Protection Agency. Approval from the Danish Medicines Agency is only required if an IMP is involved. No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**, there are no legal requirements for surgery trials except for an ethical review. The Ethics Committee responsible for the physician involved must give its opinion according to section 15 of the professional code for physicians (Berufsordnung). This professional code refers directly to the principles of the Declaration of Helsinki. Nonetheless, some regulations that may apply are transfusion law (Transfusionsgesetz), Transplantation law (Transplantations-

[122] http://www.bfs.de/bfs/dienstleitungen/med_forschung
[123] http://www.iss.it/binary/publ/publi/05-9.1128600226.pdf

gesetz), Verordnung über das Meldewesen nach §§ 21 und 22 des Transfusionsgesetzes, Richtlinien zur Hämotherapie, etc.

In **Hungary** surgery trials need the approval of the Committee of Scientific Research Ethics.

In **Italy** the protocol of a clinical trial in surgery is submitted to the Ethical Committee following the same rules for medicinal trials.

In **Sweden**, the protocol must be submitted to the Ethical Review Board by the primary investigator but there is no competent authority. The National Board of Health is the overall responsible authority.

In the **UK**, surgery trials would need to be submitted to the REC and also ensure that a sponsor was identified. Additionally, if the trial uses medical devices, guidance for such trials would need to be followed.

6.4.3. Transplantation

In **Austria**, an ethics committee has to be involved. If a method is newly implemented within Austria, this might follow the hospital act (KAKuG §8) regulations, not the drug act (AMG).

In **Denmark**, transplantation trials require an ethical approval, as well as permission from the Danish Data Protection Agency. Approval from the Danish Medicines Agency is only required if an IMP is involved. No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **Hungary** there is no specific regulation of transplantation trials, but the Health Law (1997/CLIV) has to be taken into consideration.

In **Italy** clinical trials involving transplant patients are following the same rules as all other clinical trials.

In **Spain**, clinical trials on organ transplantation not involving a medicinal product or a medical device are few and do not have specific legislation. Law 30/1979, of 27 October on organ extraction and transplants, and the Royal Decree 20070/1999, of 30 December, which regulates the activities of extraction and clinical use of organs and the territorial coordination of organ and tissues donations and transplants should be taken into consideration. Ethics committee opinion is normally required and the authorisation of the concerned Regional Health Authority is needed.

In **Sweden**, the protocol must be submitted by the primary investigator to the Ethical Review Board and to the National Board of Health (Förordning (2008:414) om kvalitets- och säkerhetsnormer vid hantering av mänskliga vävnader och celler.) If the tissue is manipulated to the extent of being regarded as a medicinal product, authorization by the MPA is required.

In the **UK**, transplantation trials all need to be submitted to REC, where a study involves NHS participants or resources a sponsor is required if under Research

Governance Framework. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants. R&D Management permission is also required for any study taking place within the NHS or with NHS patients.

6.4.4. Transfusion

In **Austria**, an ethics committee has to be involved, if only blood is transfused. If investigational drugs or modified derivatives are used in the trial or if a new therapeutic indication is tested by this trial, competent authority approval is required in addition.

In **Denmark**, transfusion trials require ethical approval, as well as permission from the Danish Data Protection Agency. Approval from the Danish Medicines Agency is only required if an IMP is involved. No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**, the protocol must be submitted to the ethics committee, to the Paul Erlich Institute (PEI) by the sponsor and insurance is requested.
The investigator has also to submit to the local authorities.

In **Hungary** there is no specific regulation of transfusion trials, but the Health Low (1997/ CLIV) has to be taken into consideration.

In **Sweden**, the protocol must be submitted to the Ethical Review Board, , to the National Board of Health, and also to the MPA if transfusion is to be regarded as a medicinal product.

In the **UK**, transfusion trials all need to be submitted to REC, where a study involves NHS participants or resources a sponsor is required if under Research Governance Framework. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants. R&D Management permission is also required for any study taking place within the NHS or with NHS patients. It should be noted that a Human Tissue Authority licence is not needed for storage of blood for transfusion.)

6.4.5. Physical therapy

In **Austria**, an ethics committee has to be involved. If a method is newly implemented within Austria, this might follow the hospital act (KAKuG §8) regulations. If new medical devices are included, competent authority approval is required in addition.

In **Denmark**, physical therapy trials require an ethical approval, as well as permission from the Danish Data Protection Agency. Approval from the Danish Medicines Agency is only required if an IMP is involved. No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**, physical therapy trials need to follow regulation on medical devices if they include a non-authorised device. If not, there is no specific requirement and only ethical review is needed.

In **Hungary**, physical therapy trials has to be approved by the Committee of Scientific Research Ethics.

In **Sweden**, the protocol must be submitted to the Ethical Review Board. The National Board of Health is the overall responsible authority.

In **UK**, such studies require ethics and R&D Management approval, unless an IMP or medical device is involved where additional authorisation will be required from the Competent Authority (i.e. the MHRA).

6.4.6. Psychotherapy (without medicinal product)

In **Austria**, an ethics committee has to be involved.

In **Denmark**, psychotherapy trials require an ethical approval, as well as permission from the Danish Data Protection Agency.No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**. there is no specific legislation When a trial is conducted by a physician, an opinion from an Ethics Committee is necessary according to section 15 of the professional code for physicians (Berufsordnung).

In **Hungary** psychotherapy trials has to be approved by the Committee of Scientific Research Ethics.

In **Sweden**, the protocol and amendments must be submitted by the primary investigator to the Ethical Review Board.

In **UK**, such studies require ethics and R&D Management approval.

6.5. Diagnostic studies

In **Austria**, in vivo diagnostic studies are regulated in the same way as medicinal product studies (AMG see Pt.2) in vitro diagnostic trials have to be performed in accordance with the medical device act (MPG, see Pt.3). In both cases, submission is required to both an ethics committee and competent authority.

In **Denmark**, the person responsible for the study must submit the proposal to the regional ethics committee, as well as the Danish Data Protection Agency. The participants are covered by the national patient insurance system. The person responsible for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsible for the trial must submit a list of all serious adverse events and reactions to the ethics committee.[124] If an investigational medicinal product is involved then approval from the Danish Medicines Agency is also needed. If the

[124] http://www.cvk.im.dk/cvk/site.aspx?p=150

study involves an in vitro diagnostic medical device, which will directly or indirectly come into contact with the human body, then approval from the Danish Medicines Agency is also needed.

In **France**, the in vivo diagnostic studies or in vitro diagnostic studies which are considered as biomedical research (ie, interventional according to the French law) need to be submitted to the ethics committee, the competent authority (Afssaps) and the data protection committees, need to have a sponsor and an insurance to cover the participants to the research, the sponsor and the investigators. No specific requirements are needed for in vitro studies that are not considered as biomedical research.

In **Germany**, there is no specific legislation and only an ethical approval is needed. If the diagnostic studies use a medicinal product or device, they have to comply with the specific regulations.

In **Hungary** interventional diagnostic studies (involving medicinal products) are approved by the NIP (National Institute of Pharmacy) all others by the Committee of Scientific Research Ethics.

In **Ireland,** in general there is no specific legislation unless the study involves an *in-vitro* diagnostic device in which case the requirements of the *in-Vitro* Diagnostic Directive (98/79/EC) apply and the device may need to be registered for 'performance evaluation' with the competent authority. A submission of the study to the governing ethics committee where the trial is being conducted by the sponsor or person responsible. Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. For studies involving General Practitioners, their medical malpractice insurance will also be pertinent. There is no statutory obligation to report adverse events but it is considered best practice for investigator to report serious adverse events to relevant ethics committee.

In **Italy**, the diagnostic studies require the same authorisations as medicinal product if a new diagnostic technique is involved (ethic committee and the local competent authority, need for a sponsor and insurance).

In **Spain** there are no specific requirements. These trials are under the scope of Law 14/2007, of 3 July. This law states specific requirements for genetic tests and investigations on human biological samples.

In **Sweden**, the study must be submitted to the Ethical Review Board, no other requirements are needed. However, if the study involves a diagnostic tool/medical device it should be submitted to the MPA and if it involves X-ray or nuclear medicine it should also be submitted to the radiation committee.

In the **UK**, the study must be submitted to the ethics committee (REC and other regulations followed, as appropriate) and R&D Management approval. Under the NHS Research Governance Framework, a sponsor would be required.

6.6. Clinical research on nutrition

EU Regulations 1924/1996 and 353/2008 set out requirements regarding health claims for nutritional products.

This category includes the nutritional studies and studies with food (or nutritional) supplements. The border between food/nutritional supplements and medicinal products is not always clearly defined and advice from competent authorities can be obtained on a case per case basis.

In **Austria**, nutritional trials (including nutrients, dietary supplements and cosmetics) currently are not regulated separately. If therapeutic or preventive claims are to be proven by such trials, performance in accordance with Regulation (EC) 1924/2006 should be performed. Depending on the rationale of the trial, ethics committee approval for such trials is not mandatory, but can be required depending on the intended interventions. If a therapeutic benefit is claimed, performance in accordance with the drug act might be required. If it is questionable how to classify the product that is going to be tested, a submission to the competent authority can result in calling in a committee that will decide on this point (Abgrenzungsbeirat, AMG §49a).

In **Denmark**, Danish law separates medicinal products and nutritional/dietary supplements. Trials using nutritional/dietary supplements are legislated and inspected by the Danish Veterinary and Food Administration, which is part of the Ministry of Food, Agriculture and Fisheries.[125] These studies require ethical approval as well as permission from the Danish Data Protection Agency. The submission is made by the person responsible for the trial (no sponsor is required for these studies). The participants are covered by the national patient insurance system. The person responsible for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial, the person responsible for the trial must submit a list of all serious adverse events and reactions to the ethics committee.[126]

In **France**, nutritional interventional studies and studies with nutritional supplements need to be submitted to the ethics committee, the competent authority (Afssaps), need a sponsor and an insurance to cover the participants in the research, the sponsor, and the investigators.

In **Germany**, there is no specific legislation and only an ethical approval is required. If the nutrition or nutritional supplement is considered as medicinal product, then the regulation on medicinal product is followed. BfArM advice can be requested for the classification of the study.

In **Hungary**, there is no specific legislation for nutritional trials, except if it concerns a medicinal product (eg. specific nutrition for PKU etc.) If the nutrition or nutritional supplement is licensed as a medicinal product the National Institute of Health is the competent authority. In all other cases the permission is given by the National Institute for Food and Nutrition Science, which is under the Ministry of Agriculture's authority.

[125] http://www.uk.foedevarestyrelsen.dk/Forside.htm
[126] http://www.cvk.im.dk/cvk/site.aspx?p=150

In **Ireland**, depending on whether nutrition and nutritional supplements are considered as food, cosmetic or medicinal products, a competent authority authorisation must be obtained. It may be necessary to solicit the IMB on a case–by-case basis. If the nutritional supplement is licensed as a medicinal product, the adverse event reporting is the same as for clinical trials with medicinal product. In the other cases, there is no statutory obligation to report adverse events but it is considered best practice for investigator to report serious adverse events to relevant ethics committee.

In **Italy**, the nutritional studies or studies with nutritional supplements require the same authorisations as medicinal product studies (ethics committee, competent authority, need for a sponsor and insurance). The *Regulation (EC) No 1924/2006 Of The European Parliament And Of The Council of 20 December 2006 on nutrition and health claims made on foods* will induce the development of national regulation.

In **Spain**, there is no specific legislation. Law 14/2007, of 3 July on biomedical research applies.

In **Sweden**, if the nutritional element (nutraceutical) is classified as a medicinal product it must be submitted to the ethics committee and the MPA. The nutrient requires GMP standards. Otherwise submission to the Ethical Review Board is sufficient. The national Food Administration Authority is the overall competent authority for nutrition, but studies do not need to be submitted there at the present.

In **UK**, the nutritional studies or studies with nutritional supplements require a submission to the REC Sponsorship under the Research Governance Framework guidance.

6.7. Other interventional clinical research not using medicinal products nor medical devices

The following research is considered here as other clinical research:

- Complementary and alternative medicine (diverse medical and health care system, practices and products that are not presently considered to be part of conventional medicine. Complementary medicine is used together with conventional medicine. Alternative medicine is used in place of conventional medicine);[127]
- Biobanks: collection of blood, other fluids or tissue samples;
- Physiology studies;
- Physiopathology studies;
- Psychology studies.

In **Austria**, such studies require ethical committee submission. There is no specific regulatory requirement, competent authority approval is not needed unless investigational products or devices are involved.

In **Denmark**, these clinical studies require ethical approval as well as permission from the Danish Data Protection Agency. Approval from the Danish Medicines Agency is only required if an IMP is involved. The request is submitted by the

[127] www.nih.gov

person responsible for the trial. No specific requirements are needed for insurance; the participants are covered by the national patient insurance system. The person responsible for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsible for the trial must submit a list of all serious adverse events and reactions to the ethics committee.[128]

In **Germany**, there is no specific local legislation for these categories of research. The only requirement is a submission of the study to the ethics committee according to the professional code for physicians ('Berufsordnung'). The code is different for physicians in different regions (Länder).

In **Hungary**, there is no specific legislation for these categories of research, but the Health Law (1997/CLIV) has to be taken into consideration. There is a recent law about biobanks but the implementation of it is still missing.

In **Ireland**, herbal medicines trials have to follow the requirements of medicinal products (submission to EC, CA, need for a sponsor and insurance) if they fall under the definition of a clinical trial in SI 190 of 2004. The collection of blood, others fluids or tissue samples required an ethical approval (to be done by the principal investigator). There is no statutory obligation to report adverse events but it is considered best practice for investigator to report serious adverse events to relevant ethics committee.

In **Italy,** as stated under section 6.4 all studies involving human subjects even when conducted with other product than medicinal product or other interventions that are not involving drugs but are considered "active" interaction with the patients should undergo approval of the competent authorities as described before.

In **Spain**, these studies are on the scope of *LEY 14/2007, de 3 de julio, de Investigación biomedical*. There are no specific requirements, except for biobanks and investigations on human biological samples.

In **Sweden,** Ethical Review Board submission is required for all human research, and for use of sensitive personal data handling and registration of research databases is required. The Biobank legislation regulates biological sampling and biobanks must be registered. The classification and purpose of the particular research project/trial will decide if other regulatory frameworks are appropriate e.g. submission to the MPA for trials with herbal medicines. The public patient insurance covers research within the health care system.

6.7.1. Complementary and alternative medicines

In **Austria**, traditional herbal medicinal and other traditionally used products do not need efficacy assessment for the established indication, however trials to test new health claims have to be performed in accordance with medicinal product trials (AMG, see Pt 2).

[128] http://www.cvk.im.dk/cvk/site.aspx?p=150

In **Denmark**, studies using herbal medicinal products, strong vitamin or mineral preparations must be approved by the Danish Medicines Agency as well as the regional ethics committee and Danish Data Protection Agency.

In **France**, studies using complementary and alternative medicine require ethical approval, CA authorisation, a sponsor and insurance as far as they are interventional.

In **Germany**, homeopathy, and herbal medicines are considered to be medicinal products and clinical trials must follow the regulation on medicinal products.

In **Hungary**, there is no specific legislation for these categories of research, but the Health Law (1997/CLIV) has to be taken into consideration.

In **Italy**, homeopathy, and herbal medicines are considered to be medicinal products and clinical trials should follow the regulation on medicinal products.

In **UK**, herbal medicines trials have to follow the requirements of clinical trials regulations (REC approval, CA authorisation, need for a sponsor and insurance). The competent authority is the Medicines and Health care products regulatory agency (MHRA).

6.7.2. Biobanks (collection of blood, other fluids or tissue samples)

In **Austria**, handling and storage of blood are regulated in the blood safety act (Blutsicherheitsgesetz - BSG), handling and storage of other tissue samples in the tissue safety act (Gewebesicherheitsgesetz – GSG). Biobank regulations are stated in the biobank act (Gewebebankenverordnung).

In **Denmark**, permission must be sought from the Danish Data Protection Agency for storage of biological material in a biobank. Storage of biological material in a biobank must adhere to specific Danish Data Protection Agency terms and conditions. If a clinical trial involves removal of biological samples that will be stored in a biobank then participants need to give informed consent and the regional ethics committee and Danish Data Protection Agency must give permission.

In **France**, if biobanking is part of a interventional biomedical research, the legal requirements relating to biomedical research are to be followed. If the biobanking is set up outside a biomedical research, the positive opinion of a CPP should be obtained, the consent of the person must be obtained prior to the sampling and the collection must be notified to the Research Ministry and the Regional Hospitalisation Agency (ARH) (if conducted in a Health organisation). Data protection boards (CNIL and CCTIRS) should also give permission.
In case of genetic research, the consent form is mandatory and it is not possible to start new genetic researches without a new consent.
Researches on embryos need to be notified to the Research Ministry.

In **Germany**, it doesn't yet exist a special biobanking law. Important regulations e.g. regarding manufacturing and explantation of cells and tissues can be found in the Arzneimittelgesetz (German Medicinal Products Act) and the

Transplantationsgesetz (German Transplantation Law). Due to the fact that Biobanks partly deal with personal and health data the German Data Protection Act (Bundesdatenschutzgesetz, BDSG) also has to be regarded. Several other regulations that may apply are: transfusion law (Transfusionsgesetz), guidelines for hemotherapy (Richtlinien zur Hämotherapie) and blood guideline (Blutrichtlinie)). For data acquired and recorded in connection with taking the samples the physician has to consider duties according to the professional code for physicians (MBO-Ä). Personal data stored in a biobank for the purpose of research are subject to the security mechanisms of data protection law (eg. §40 BDSG). In most cases the ownership of samples in a biobank are with the donator and not with the biobank; and the donor has the right to utilize his samples. Sample collection is only allowed to take place after an consent by the donor is available. For an exclusive use for research the donor has to be informed about and agree to the duration of utilization of his samples. In addition §40 BDSG prescribes the pseudonymisation / anonymisation of personalized data for research purposes.

In **Hungary**, there is a recent law about biobanks (2008/XXI) but the implementation of it is still missing.

In **Italy**, collection of biological material is subjected to the same requirements as for other studies, and a request to ethical committee is required. Particular attention is to be paid to the aspects concerning the informed consent and the safeguard of the principles of personal data protection.

In **Spain**, Law 14/2007, of 3 July on Biomedical research contains specific provisions with respect to investigations related to genetic analysis, human biological samples and biobanks. This Law establishes the requirements for biobank authorisation by the corresponding Regional Health Authority. Details about their organisation, data protection requirements, management etc. are given. All biobanks should be registered in a national database on biobanks for biomedical research.

In **Sweden**, the collection of tissue, blood or other biological samples, is regulated by the Swedish biobank law (Lag om biobanker I hälso- och sjukvården m.m. 2002:297). Consent must be obtained by the participant whether it is in the health care setting or in a clinical trial prior to sampling. If samples are sent outside of Sweden for analysis, special permission is required and the samples must be destroyed or returned Special requirements may be imposed in the future for specimens taken for genetic testing, by the National Board of Health and Welfare.

In **UK**, biobanks require approval from an NRES (National Research Ethics Service) Committee. Biobanks that store samples that are classed as 'relevant material' under the Human Tissue Act 2004 require a licence from the Human Tissue Authority (HTA). Where the Biobank stores embryos a licence must be sought from the Human Fertilisation and Embryology Authority who regulate the use of gametes and embryos in fertility treatment and research. Where a study involves NHS participants or resources a sponsor is required if under Research Governance Framework. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants. Research Governance Management permission is also required for any study taking place within the NHS or with NHS patients.

6.7.3. Physiology, physiopathology, and psychology trials

In **Austria**, interventional studies require ethical approval, insurance and informed consent. Submission is responsibility of the investigator.

In **Denmark**, physiology, physiopathology, and psychology trials require an ethical approval as well as permission from the Danish Data Protection Agency. Approval from the Danish medicines agency is only required if an IMP is involved. No sponsor is required per se, however the person responsible for the trial is responsible for initial submission, for submission of any amendments, and adverse event reporting to the ethics committee.

In **France**, these trials and amendments require an ethical approval, an authorisation by the competent authority (Afssaps), a sponsor and insurance. The sponsor is responsible for the submission. This category also includes the studies on cosmetics and tattoos that require ethical approval, authorisation from the CA, need for a sponsor and insurance. France is the only country where these studies are under the regulatory framework.

In **Germany**, there is no specific legislation for these categories of research, with the only requirement of a submission of the study to the ethics committee according to the professional code for physicians ('Berufsordnung').

In **Hungary**, interventional trials require ethical approval which is given by the Committee of Scientific Research Ethics.

In **UK**, these trials require REC approval and a sponsor. Research Governance Management permission is also required. If tissue samples are collected, guidance as detailed in the 'biobanks' section should be followed.

6.8. Epidemiology

Although the European Directive 2001/20/EC defines the non-interventional trials as "a study where the medicinal product (s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol, but falls within current practice and the prescription of the medicine is clearly separated form the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the participants and epidemiological methods shall be used for the analysis of collected data", the implementation in national regulation leads to divergent regulatory requirements for the same protocol.

Austria, Denmark, **Germany**, **Hungary**, **Ireland**, **Italy**, **Sweden**, and **UK** follow this definition.

In **France**, the definition of a non-interventional research covers all types of researches (on health product or not); it is defined as research for which:

- medical interventions and health products are prescribed or used in the usual manner in accordance with the usual care (in the case of MP, in

accordance with the MA ; in the case of a MD, in accordance with the instruction notice…)
- and no additional or unusual diagnostic on monitoring procedures are applied to the participants
- and the assignment of the participant to a particular therapeutic strategy is independent from the decision to include him in the study.

In **Spain**, the definition of an observational study is the same as the one for non-interventional trials. However, blood samples or a quality of life questionnaire are not considered as additional procedures.

6.8.1. Interventional pharmacoepidemiology

In **Austria** there is no specific regulatory definition of interventional pharmacoepidemiological studies. However, any intervention involving medicinal products require ethics committee and competent authority approval.

In **Denmark**, if the study has involved an interventional medicinal product then it must be authorised by the Danish Medicines Agency, the ethics committee and the Danish Data Protection Agency.

In **France**, the interventional pharmacoepidemiological studies need an ethics committee approval, CA (Afssaps) authorisation, a notification to the data protection committee, a sponsor and insurance (except if they can be viewed as usual care studies, see 6.9.1).

In **Germany**, the interventional pharmacoepidemiological studies follow the regulation of clinical trials with medicinal products and need ethical approval, CA authorisation, a sponsor (no co-sponsorship allowed) and insurance.

In **Hungary**, the interventional pharmacoepidemiological studies follow the same requirements as for clinical trials on medicinal products ie, authorisation of NIP, approval of the Committee for Clinical Pharmacology and Ethics of the Medical Council, need for a sponsor (no co-sponsorship) and an insurance.

In **Ireland**, the interventional pharmacoepidemiological studies follow the same requirements as for clinical trials on medicinal products ie, IMB authorisation, ethics committee approval, need for a sponsor (no opinion on co-sponsorship). Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also be pertinent. The serious adverse events must be reported on an expedited basis (within 15 days) to the competent authority of the member state on whose territory the incident occurred. All adverse events including those, which are considered non-serious, should be summarised in the final study report to be submitted to the competent authority.

In **Italy**, the interventional pharmacoepidemiological studies follow the regulation of clinical trials with medicinal products and need ethical approval, CA authorisation, a sponsor and insurance.

In **Spain**, the studies are considered clinical trials on medicinal products and the requirements for these studies apply.

In **Sweden**, there is no special definition of an interventional pharmacoepidemiological trial. The nature of the 'intervention' will decide if the study protocol must be submitted to other competent authority than the Ethical Review Board. If the intervention fulfils the criteria for a clinical trial it should be submitted to the MPA.

In **UK**, the interventional pharmacoepidemiological studies have to be submitted to the REC and will require CA authorisation unless the clinical intervention is not classed as an IMP. A sponsor is required in all cases (as per the Research Governance Framework guidance). R&D Management permission is also required. Co-sponsorship is permitted.

6.8.2. Non-interventional pharmacoepidemiology

The EU Directive 2001/20/EC defines a non-interventional trial as: "A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data…however, in this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice."

A post-authorisation safety study is defined in Article 1(15) of Directive 2001/83/EC as "pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product".

EU Directive 95/46/EC on data protection must be followed, including obtaining explicit consent for collecting data containing personal identifiers. It is recommended that non-interventional post-authorisation safety studies are referred to an ethics committee. Studies conducted entirely using records not containing any personal identifiers (e.g. anonymised records) may not require ethical review of individual study protocols. National guidelines in this respect should be followed where they exist.

In **Austria** there is no specific regulatory definition of non-interventional pharmacoepidemiological studies Therefore there is no obligation for ethics committee or competent authority approval.

In **Denmark**, there is no obligation to apply for authorisation from the Danish Medicines Agency for non-interventional trials. Authorisation from the Danish Data Protection Agency is needed.

In **France**, there is no requirement for the non-interventional pharmacoepidemiological studies, except compliance with the data protection law (CNIL, CCTIRS). No submission to the ethics committee (CPP) is needed, although this is usually required for publication. Therefore several specific ethics committee similar to IRBs (as for example Comité d'Ethique pour la Recherche) were created to bridge this gap, as the CPP consider this task as outside their mission. However, not all these specific ethics committees have been validated and there are some proposals to include the review of non-interventional studies in the tasks of CPP.

In **Germany**, the non-interventional pharmacoepidemiology studies have to be notified to the 'Spitzenverbänden der Krankenkassen',[129] the 'kassenärztlichen Bundesvereinigung'[130] and in some cases the competent authority (BfArM / PEI). The notification has only to cover the involved centres, study period, objectives of the non-interventional trial and involved doctors. The notification can be delegated. The notification of the BfArM / PEI is also informal and only has to cover the above mentioned points.

In **Hungary**, for non-interventional pharmacoepidemiological studies there is no submission to competent authority and no insurance requirement. The sponsor has to submit to the Committee for Scientific and Research Ethics (if multicenter) or to the institutional ethics committees (institutional study).

In **Ireland**, for non-interventional pharmacoepidemiological studies, there is a notification to the competent authority (Clinical Trial Application is not requested), an ethical review (it is necessary to obtain separate ethics committee approvals for each site/region that is conducting the study).
Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also be pertinent.

In **Italy**, non-interventional pharmacoepidemiology studies are not subjected to formal approval by the Ethical Committee, but a notification by the investigator to EC is the rule, considering that collection of personal data of subjects always needs an informed consent.

In **Spain**, non-interventional studies on medicinal products are defined in accordance with the Directive 2001/20/EC definition. They are regulated by Royal Decree 1344/2007, of 11 October, on Pharmacovigilance for human

[129] http://www.gkv.info/gkv/index.php?id=512
[130] http://www.kbv.de/

medicinal products. They need to be approved by one ethics committee and need authorisation by the concerned Regional Health Authority.[131]

In **Sweden**, non-interventional pharmacoepidemiological studies should be submitted to the Ethical Review Board, unless they are mere anonymised quality studies. Also, if publication is considered ethics review is usually required. The Ethics Review Board can be consulted for scientific advice.

In **UK,** the non-interventional pharmacoepidemiological studies have to be submitted to the REC but no CA authorisation is needed. A sponsor is required (as per the Research Governance Framework guidance). R&D Management permission is also required. Co-sponsorship is permitted.

6.8.3. Interventional epidemiology not using medicinal products nor medical devices

In **Austria**, there is no specific regulatory definition of interventional epidemiological studies. However, any interventions require ethics committee approval.

In **Denmark**, if the study has involved an investigational medicinal product then it must be authorised by the Danish Medicines Agency, the ethics committee and the Danish Data Protection Agency.

In **France**, the interventional epidemiological studies are considered as 'biomedical research' according to French law (except if they can be viewed as usual care studies, see 6.9.1) and need an ethics committee approval, competent authority authorisation, a notification to data protection committee, a sponsor and insurance.

In **Germany**, there is no specific requirement and only an ethical review is needed. Participants who underwent an invasive procedure (sampling of body fluids or tissue) are covered by hospital insurance if the sampling is part of the regular practice.

In **Hungary**, the interventional epidemiological studies follow the same requirements as for clinical trials on medicinal products ie, authorisation of NIP, approval of the Committee for Clinical Pharmacology and Ethics of the Medical Council, need for a sponsor (no co-sponsorship) and insurance.

In **Ireland**, for interventional epidemiological studies, there is an ethical review, a need for a sponsor. Claims arising from patients whose treatment was part of a clinical trial or approved research project are covered under the Clinical Indemnity Scheme. In trials sponsored by external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liability or claims arising from trial design or protocol. Cover against such claims remains the responsibility of the body conducting the trial or research project and an appropriate indemnity must be secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also be pertinent. The serious adverse events are reported to the ethics committee by the sponsor.

[131] http://www.agemed.es/actividad/invClinica/estudiosPostautorizacion.htm

In **Spain**, these studies are regulated by *'LEY 14/2007, de 3 de julio, de Investigación biomedica'*. An ethical submission and approval is required.

In **Sweden**, the nature of the intervention will decide if submission to other body than the Ethical Review Board will be necessary.

In **UK**, the interventional epidemiological studies have to be submitted to the REC but no CA authorisation is needed. A sponsor is required (as per the Research Governance Framework guidance). R&D Management permission is also required. Co-sponsorship is permitted.

6.8.4. Non-interventional epidemiology not using medicinal products nor medical devices

The notification of non-interventional pharmacoepidemiology studies (outside of EU directive 2001/20/EC) is required under Volume 9A, Part I, Section 7.[132]

In **Austria** there is no specific regulatory definition of non-interventional epidemiological studies. Therefore there is no obligation for ethics committee or competent authority approval.

In **Denmark,** there is no obligation to apply for authorisation from the Danish Medicines Agency for non-interventional studies.

In **France**, there is no requirement for the non-interventional epidemiological studies, except compliance with the data protection law (CNIL, CCTIRS). No submission to the ethics committee (CPP) is needed, although this is usually required for publication. Therefore a specific ethics committee was created to bridge this gap (Comité d'Ethique pour la Recherche, similar to an IRB), as CPP consider this task as outside their mission.

In **Germany**, there is no specific requirement and only an ethical review is needed.

In **Hungary**, for non-interventional epidemiological studies there is no submission to competent authority and no insurance requirement. The sponsor has to submit to the Committee for Scientific and Research Ethics (if multicenter study) or to the Institutional Ethics committees (institutional study).

In **Ireland**, for non-interventional epidemiology studies, there is an ethical review, a need for a sponsor a requirement for notification to the competent authority. The sponsor reports the serious adverse events to the ethics committee.

In **Italy**, non-interventional epidemiology studies are not subjected to formal approval by the Ethical Committee, but a notification by the investigator to EC is the rule, considering that collection of personal data of subjects always needs an informed consent. A recent document issued by the Italian Drug Agency, AIFA, published on the Official Journal (Gazzetta Ufficiale, March 31, 2008, n.76 page

[132] www.ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf

68) provides new guidlines for implementation of observational studies. Of note in this new guideline AIFA announces a national database of observational studies is implemented at the central office of AIFA. [133]

In **Spain**, for non-interventional epidemiology studies, no specific legislation applies. The study is reviewed by an ethical committee. The *'LEY 14/2007, de 3 de julio, de Investigación biomedical'* can be used as a reference.

In **Sweden**, non-interventional studies which are not quality studies (usual care) should be submitted to the Ethical Review Board.

In **UK**, the non- interventional pharmacoepidemiological studies have to be submitted to the REC but no CA authorisation is needed. A sponsor is needed (as per the Research Governance Framework guidance). R&D Management permission is also required. Co-sponsorship is permitted.

6.8.5. Registries of patients

Registries of patients were defined as an information system designed for the collection, storage, management, and analysis of data on persons with the same drug, disease, or symptoms in a given geographic area. Such registries require continual and systematic collection of data.

In **Austria,** no official central registry of patients in trials is established.

In **Denmark**, research which uses registries need to obtain approval from the ethics committee if the research involves human biological material.

In **France**, registries of patients need submission to the data protection committees. As there is no sponsor for these registries, the person responsible of the study submits the documents.

In **Germany**, there is no specific requirement and only an ethical review is needed.

In **Hungary**, the registries have to be submitted to the Committee for Scientific and Research Ethics (from the medical council) and regional and institutional ethics committees but there is no competent authority and insurance is not required.

In **Italy**, registries of patients are requested to comply with the rules of protection of personal data and required an informed consent. Approval of ethical committee is not required.

In **Ireland**, submission to local ethics committee depends on data collection. If classified as audit with completely anonymised data, no ethical review is needed. If identifiers are collected there is a need to obtain an ethical approval (separate ethics committee approval for each site/region that is conducting the study) and a consent from the participant. There is no statutory obligation to report adverse events, but it is considered best practice for investigator to report serious adverse events to relevant ethics committee.

[133] (http://oss-sper-clin.agenziafarmaco.it/normativa/direttive_OsSC-000099-000000.pdf)

In **Spain**, there is a need to obtain an ethical approval and a signed consent form from the participant. The patient information sheet should describe how long data is going to be stored, who is the person responsible of the archive, and how data are going to be anonymised. Registries should comply with the 'LOPD 15/1999'.

In **Sweden**, two different categories of registries exist: the national registries owned by the National Board of Health and Welfare and the patient/disease/drug registries formally owned by the Health Care system (new Patient Data Protection legislation 1 July, 2008). In the national registries, anonymous data can be retrieved without ethical review. If identifiable data are requested, for instance for register linkage, ethical review is required. In addition, some universities require an ethical review of register research with an academic purpose (publication for Ph.D. thesis), even if anonymised data are used.

For establishment of patient/disease/drug registries (e.g. TNF alpha registry) ethical approval is necessary. Scientific advice can always be sought with the Ethical Review Board. It is currently not obligatory to submit the existence of the register to any other authority. However, some registration occurs at application for funding from the National Board of Health and Welfare and the Swedish Association of Local Authorities and regions. There is no existing regulation as to where (geographical location) these registries can be established.

In **UK**, registry studies have to be submitted to NRES. R&D Management permission is also required. A sponsor is required if the study falls under the Research Governance Framework and involves NHS participants or resources. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants.

6.9. Miscellaneous

6.9.1. Usual care

The definition of usual care is different in the different ECRIN countries.

In **Denmark** and **Germany**, studies on usual care are not considered as a specific category of research.

In **Austria** there is no legal definition of this term. If in a study patients are observed undergoing usual care procedures and no study-specific interventions are planned, this by definition is not a clinical trial, but an 'Anwendungsbeobachtung' (AMG §2a(3)). Such studies require neither ethics committee nor competent authority approval.

In **France** 'usual care studies' are defined as interventional studies other than trials on medicinal products and whose objectives are to evaluate medical treatments or a combination of medical treatments or medical strategies of prevention, diagnosis, or treatments that are current practice with a professional consensus and in respect to their indication. In this case the protocol should only be submitted to the ethics committee (CPP), pending on convincing evidence that the procedures assessed are usual care, with comparable efficacy and safety. If

the study involves a health product, the ethics committee may ask opinion from the CA (Afssaps). In turn there is no need for a sponsor (only a responsible person), for a submission to CA, for insurance, and for SUSAR reporting. The French legislation has developed this concept of 'usual care study' to facilitate studies on comparison and combination of existing treatment strategies. This category includes randomised trials on health products other that medicinal products (authorised medical devices), but clinical randomised trials on medicinal products are excluded, in order to comply with the 2001/20/EC Directive. Specific follow-up modalities are allowed, meaning that additional visits or minimally interventional diagnostic procedures are possible within this framework.

In **Hungary**, usual care studies are defined as non-interventional studies. No permission is required, only a notification to the NIP (National Institute of Pharmacy).

In **Ireland**, usual care studies are treated as non-interventional studies. However, depending on whether the data collected in these trials are truly anonymised and not pseudo-anonymised, there is room for collection of data such as prescription monitoring, retrospective studies where consent cannot be obtained. This must be collected in line with the Data Protection Act.[134]

In **Italy**, the studies on usual care and others non-registrative studies are regulated by 'Legislative Decree of June 24, 2003' and 'the Ministerial decree of December 17th 2004' stating "prescription and conditions of a general nature referring to the conduct of clinical trials in medicines, with special reference to those designed to enhance clinical practice as an integral part of health and medical care".[135]

In **Sweden**, the categories "usual care" or "quality study" are not specifically defined in Swedish legislation, but derived from the ethics legislation where "research" is defined. The Ethical Review Board can offer scientific advice in this matter. A quality study should be a quality check of clinical routines, conduct and procedures. The head of a clinical department in a health care unit must give his/her consent to the quality study. Data should be made anonymous. Usually it is non-interventional and retrospective in character. However, for instance, a prospective study of methotrexate plasma levels, where equivalence of different anatomical sampling sites is studied, may be regarded as a quality study in Sweden.

In **UK**, such studies require ethics and R&D Management approval, unless an IMP or medical device is involved where additional authorisation will be required from the Competent Authority (i.e. the MHRA). A sponsor is required if the study falls under the Research Governance Framework and involves NHS participants or resources. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants.

[134] http://www.dataprotection.ie/documents/legal/CompendiumAct.pdf
[135] http://oss-sper-clin.agenziafarmaco.it/normativa/decreto_noprofit_inglese.pdf

6.9.2. Non-commercial trials/non-commercial sponsors

In **Austria**, **Denmark, Germany,** and **Spain** there is no specific definition.

In **Denmark**, the fee charged by the Danish Data Protection Agency is waived for non-commercial organisations.

In **France**, the law defines public, non-profit sponsor. It can be a public research body, an university, a public health institution, a public institution, or any person or body with no lucrative interest. For public, non-profit sponsors, fees to EC and CA are 10%[136] of the regular fee. There is a provision in the law of a waiver to purchase the study drug free of charge, under certain circumstances.

In **Germany**, there is no definition for non-commercial trials nor for non-commercial sponsor, however, in the case that public universities are the sponsor they do not have to pay the common fee. In this latter case the university covers the sponsor's responsibilities and delegates the execution of the study to the investigator. The German Medicinal Product Act does not allow the responsibility of a sponsor to be shared, so this cannot be considered as a co-sponsorship, the federal state would be the liable person.

In **Hungary**, non-commercial trials are those conducted without the involvement of the pharmaceutical industry.

In **Ireland**, there is not a strict definition for non-commercial trials or sponsor, but the regulation mentions "…non-commercial trial conducted by an investigator-sponsor, without the participation of the pharmaceutical industry, in circumstances where the investigator-sponsor has no commercial or financial interest in the outcome of the trial".

In **Italy**, non-commercial trials are defined as trials not aimed or used for the industrial development of the drug and in any case not for profit. A non-commercial sponsor is defined as research or healthcare structure or public entity or institution or equivalent, foundation or moral entity, non-profit scientific research or research association/society, scientific hospital and treatment institute or a person belonging to one of these structures.[137]

In **Sweden**, an academic researcher can conduct a non-commercial trial, not sponsored by a company. A provision from the MPA states that the primary investigator can also be the sponsor (LVFS 2006:1).

In **UK**, such studies require ethics and R&D Management approval, unless an IMP or medical device is involved where additional authorisation will be required from the Competent Authority (i.e. the MHRA). A sponsor is required if the study falls under the Research Governance Framework and involves NHS participants or resources. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants.

[136] Regular fees to EC and CA are from 3000 to 4000 euros depending on the type of study for the initial application and 500 euros for substantial amendment.
[137] http://oss-sper-clin.agenziafarmaco.it/normativa/decreto_noprofit_inglese.pdf

6.9.3. Monitoring strategies

No specific monitoring strategy exists in **Austria, Hungary**, **Ireland**, **Italy**, **Spain**, or **Sweden**.

In **Denmark**, three public-funded Good Clinical Practice (GCP) units exist. They offer 100 hours of free GCP advice and monitoring services to small trials without a commercial sponsor (after the 100 hours the charge is on a cost-coverage basis). These GCP units have started using monitoring strategies adapted to the risk of the trial after joining ECRIN. The Danish Medicines Agency carries out inspections of a random sample of trials every year. The ethics committees are also able to participate in these inspections. The Danish Medicines Agency also inspects the GCP units.

In **Germany**, there are no specific strategies regarding monitoring, however, the sponsor may use some adaptive strategies according to GCP.

In **France**, some adaptive monitoring strategies based on the level of risk associated with research have been developed by the Paris hospitals.[138]

In **UK**, it is recommended that researchers develop procedures and systems for trial management that meet the principles of GCP, and that these are clearly documented so that adherence is readily demonstrated. The MHRA (CA in the UK) accepts in principle that a risk-based approach to trial management and monitoring is appropriate. For each clinical trial a risk assessment should generally be undertaken at the protocol development stage. This may be used to plan the details of trial management and the approach to, and extent of, monitoring in the trial. These plans should be documented, together with the risk assessment, so that the management strategy is both transparent and justified.
Thus for each trial there would be:
a. clinical trial risk assessment;
b. summary of trial management systems;
c. procedures for monitoring.

6.9.4. Data management

No specific data management requirements exist in **Austria, Germany**, **Hungary**, **Ireland**, **Italy**, or **Spain**.

In **Denmark**, storage and processing of personal data and of biological material has to comply with the terms and conditions of the Danish Data Protection Agency.[139]

In **France**, some general provisions regarding data management are in the Good Clinical Practice.[140]

[138] http://www.drrc.aphp.fr/recherche_clinic/classification/recap_graduel.php
[139] http://www.datatilsynet.dk/english/the-act-on-processing-of-personal-data/
[140] Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
http://www.legifrance.gouv.fr/WAspad/UnTexteDeJorf?numjo=SANM0624752S

In the **UK**, storage of data should be in line with the provisions of the data protection act (1998) and should follow GCP requirements for data management.

In **Sweden**, the situation is similar to that of the UK.

6.9.5. Biomarkers

No definition or requirements exist in **Austria, Denmark, France, Hungary, Ireland, Spain, Sweden**.

In **Germany**, if biomarkers according to NIH criteria are used as endpoint for imaging, the procedures used for radiotherapy trials are required.

In the **UK**, a biomarker is defined as a specific biochemical in the body which has a particular molecular feature that makes it useful for measuring the progress of disease or the effects of treatment.

6.9.6. Genetic or genotype/phenotype studies

In **Austria** all genetic studies within clinical trials have to be performed in accordance with the genetic engineering act (see §6.2.4.1). If genotyping is included within a clinical trial, a separate informed consent form should be provided to allow for a separate decision whether to also take part in or step back from the genotyping part.

In **Denmark**, there are no specific requirements for these types of trials.

In **France**, samples for genetic studies follow the biobanking regulation. The CCTIRS examines the scientific relevance for collection of genetic and family data. These studies are regulated by the 'loi de Bioethique'[141] and by the national ethics committee and a specific informed consent is necessary.

In **Germany**, there are no specific legal requirements. If medicinal products are not used - the only requirement is a submission of the study to the local ethics committee.

In **Hungary**, a specific informed consent is necessary when collecting DNA samples. The samples can be stored for a maximum of 15 years, discharged at any time upon participant's request and the studies planned need to be described in the protocol. If new studies are to be performed on those samples a new informed consent must first be obtained.

In **Ireland**, the Irish Council for Bioethics details recommendations for use.[142] The Irish Medicine Board has also detailed guidance in pharmacogenetic research.[143]

In **Spain**, these studies are regulated by the 'LEY 14/2007, de 3 de Julio, de Investigación biomedica'. A specific informed consent is necessary. The samples can be stored in an anonymous manner.

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[141] http://www.agence-biomedecine.fr/fr/doc/revision_loi060804.pdf
[142] http://www.bioethics.ie/pdfs/BioEthics_fin.pdf
[143] http://www.imb.ie/EN/Publications/Medicines/Clinical-Trials/Guidlines-for-Pharmacogenetic-research.aspx?categorypageid=0&categorytypeid=-1

In **Sweden**, genetic studies are regulated in the ethics regulation, the Biobank law, the Data protection law, and is currently being reviewed for a new provision suggested by the National Board of Health and Welfare where additional regulation may be imposed on investigators.
In Sweden, all handling of genetic data requires permission from the competent authority 'Datainspektionen' and permission must be granted before application to the Ethical Review Board.

In **UK**, these types of studies are regulated by the provisions under 'Human Tissue Act 2004 for genetic analysis', regulated by Human Tissue Authority and if applicable authorised by the Gene Therapy Advisory Committee (GTAC).

6.9.7. Open comments and suggestions

The survey also contained questions open to comments and suggestions from the WP2 members on how to improve EU clinical research, how to improve competent authority working practice, and what are the expectations for future EU regulation on clinical research. The resulting suggestions and discussion within ECRIN Working Group 2 are presented in the discussion section.

7. Discussion

There is a huge amount of legislation and guidance pertinent to clinical research in the EU as well as in the different Member States; this makes it difficult to have an overall view of the regulatory requirements. This survey provides a necessary, and in-depth overview of the regulatory framework within 10 EU countries participating in ECRIN, not only for the clinical research covered by the field of the European Directive 2001/20/EC but also for the other categories of research. To our knowledge this is the first time that a survey about the regulatory basis for clinical research has been conducted in such a depth and extent. The information collected will be used to prepare guidelines and Standard Operating Procedures to support investigators and sponsors to set up and manage multinational clinical studies. Extension of ECRIN to other member states will require an update of this document, as such, new ECRIN participants will be asked to provide figures for their countries. In addition, changes in the national regulatory systems will also lead to modifications of this document.

A major challenge for the survey and resulting report was to clearly define the different categories of clinical research that exist. The classification of categories was developed at the survey stage and represents a compromise made by the 10 ECRIN countries involved. Definitions differ from one country to another, and even if defined in the EU Directives, interpretation of these definitions varies, therefore classification was difficult and there are instances where categories overlap. The classification has however clearly shown a lack of appropriate regulation in many areas of research, including a lack of specific requirements for transplantation, cell therapy, transfusion or radiotherapy trials.

The legislation at the European level has somewhat improved the regulation of clinical research in the EU, although the main parties to benefit appear to be the commercial sponsors and regulatory authorities themselves. For example, the 2001/20/EC Directive regulates on the development of the EudraCT clinical trials register, and of the Eudravigilance SUSAR register. These registers are only accessible to the competent authorities, the European Medicines Agency (EMEA) and the European Commission, and whilst access to such databases has increased transparency between these parties, the investigators, sponsors, trial participants and public do not benefit. The development of an open access EudraCT database is necessary and will be welcomed. The purpose of EU legislation should be to benefit citizens.

7.1. Main conclusions of the survey

The main conclusions of this survey are that:

- Even in a field highly regulated by the translation of EU directives, the extent of the legislation on clinical research varies from one country to another: some national legislation focus on clinical trials on medicinal products, whereas other legislation considers the protection of participants in all the categories of clinical research.

- There is partial harmonisation in the regulation for clinical research on medicinal products, as a consequence of the 2001/20/EC Directive, but with divergent transposition into national laws leading to substantial differences in the regulatory framework, making multinational clinical studies very difficult still. The main differences concern the number and role of competent authorities, the number and role of ethics committees, the process leading to the single ethical opinion, the interaction between competent authorities and ethics committees, the requirement for submission to a personal data protection board (or boards in some countries). Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered by the public health system in some countries, and in others the union of pharmaceutical companies has contracted a national insurance package covering all the industry-sponsored trials. There are differences in the definition of IMP, especially regarding the background treatment, with major consequences for SUSAR reporting, labelling, and provision by the sponsor. Under some circumstances and in some countries cell therapy products are considered as IMP as in other countries as non-IMP (and in this latter case the trials is not covered by the 2001/20 Directive). Finally some countries, and not others, have a definition for non-commercial sponsors or for non-commercial trials, with related adaptations and waivers.

- there are major discrepancies in the regulatory framework for other categories of clinical research, not covered by the 2001/20 Directive, especially regarding the requirements for a submission to competent authorities (often distinct from the medicines agencies, depending on the nature of the health product, and in some countries there is a need to submit to a competent authority even in the absence of health product). There are also major differences in the requirements for a sponsor (required only in some countries, or for particular categories of research), and for adverse event reporting. Some countries have extended the concept of SUSAR to trials on medical devices, or even to all interventional research. There are major discrepancies regarding insurance, which may or may not be required depending on the country for the same protocol. In some countries the ethics committee decides on the need for insurance. There is a need to clarify the definition of categories of research and their interpretation (for instance the border between interventional and observational studies may differ between countries).

- In turn, protection of participants is achieved through submission of protocol applications to the ethics committee in every country, at least for all the categories of interventional research. These ethics committees may, or may not, be the same for every category of research. In some countries observational studies does not require submission to a research ethics committee.

7.2. Perspectives and proposals

The information gathered and the results of the analyses and assessments led to one overall conclusion: heterogeneity in clinical research and the different implementation of the European Directive 2001/20/EC hinders clinical development putting EU citizens' health at risk. It impedes especially the conduct of necessary international clinical research projects. Furthermore, a number of

weaknesses have been demonstrated regarding the function of the EU regulatory authorities.[144] There is therefore a need for change.

These points of view are supported by a number of other reports and investigations.[145] In the introduction to the EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research projects in the European Union, Frank Wells wrote: "The differences are widespread. For example, roughly half the member states specify that an application should be made to an ethics committee by the sponsor, whereas the other half specify that it should be made by the investigator. Another example reveals the different methods by which a single opinion is obtained for a multi-site application within any given member state: some countries designate which committee out of several, whereas others only have a single committee for the whole country anyway. The most striking differences arise in the areas of training for members of research ethics committees and of quality assurance, assessment and accreditation of such committees". This plethora of methodology can be ascribed to the fact that ethical issues are governed by the individual member states. We had hoped that the Directive would have paved the way for greater clarity regarding regulatory affairs.

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[144] Garattini S, Bertelé V. How can we regulate medicines better? BMJ 2007;335:803-5.
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Garattini S. Designing the most favourable study design. Eur J Clin Pharmacol 2005;61:85-6.

[145] EFGCP Ethics Working Party, Subgroup on Ethics Committees Reviewing Investigational Medicinal Products within the European Union. The procedure for the ethical review of protocols for clinical research projects in the European Union. Int J. Pharm. Med, 2007;21:1-113. https://www.kuleuven.be/cbmer/page.php?LAN=E&ID=383&TID=0&FILE=subject&PAGE=1
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The discussion within ECRIN Working Group 2 highlights the need, at the EU level, for:

- reassessment of the 2001/20/EC Directive, which can currently lead to needless difficulties for academia and industry;
- consultation with both academic and industry sectors on future regulations and legislation followed by assessment of its impact;
- further definition and harmonisation of the roles of the ethics committees (protection of participant) and of the competent authorities (assessment of the health product);
- improved efficiency of the interaction between sponsors, and investigators with the regulatory authorities;
- improved methodology for clinical research;
- further definition and harmonisation of the categories of clinical research, in particular the definition of intervention;
- adaptation of the regulatory requirements considering the risk associated with the trial, with further definition of clinical research with low additional risk, allowing alleviation of needless regulatory requirements;
- promotion and prioritisation of independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms;
- open access to clinical trial data so that society can take full advantage of clinical research.

The discussion within ECRIN Working Group 2 highlights the need, at the national level, for:

- extension of the expertise of competent authorities to be able to function as a single authority for all categories of clinical research;
- harmonisation of procedures between the national competent authorities and the national ethics committees, for all clinical research;
- improvement of communication between the EU member states on the implementation of the EU directives, as well as improved communication on how such requirements are implemented in day-to-day research.

Based on the above requirements for change, members of ECRIN Working Group 2 proposed solutions that can be cast into seven categories. These solutions result from suggestions proposed by individual respondents (see § 6.9.7) that were discussed during telephone conferences and the ECRIN meeting on the 19th May 2008.

1. **To protect the participant**:

- improvement of the scientific expertise within ethics committees with each ethics committee assessing a certain number of applications per year;
- obligatory publication of all depersonalised or pseudo-anonymised data and results of all trials in an open-access clinical data repository, regardless of findings, in order to ensure optimal use of data, to prevent needless duplication of trials and unethical randomisation of participants;
- creation of a consensual register of all trial participants, for all phases of trials in all categories of research. Information should include participant identification, fees received, and periods in which trial participants should

be excluded from taking part in other clinical research in order to protect the trial participant. These data should be stored for a limited time only, be accessible by competent authorities, ethics committees, and investigators;
- regulation of the participation of healthy individuals in trials by setting an exclusion criteria period between trials, and by limiting an individual's annual indemnity;
- unification of the definition and the protection of vulnerable participants;
- development of insurance packages for clinical research rather than insuring individual trials. Such packages can be based on existing models available for public institutions (public health system insurance) or for industry sponsors (the union of manufacturers insurance package);
- promotion of independent and stricter governmental audit and inspection.

2. **To simplify the regulatory requirements for clinical research in the EU**:

- adoption of a single, harmonised and comprehensive EU legislation covering all categories of clinical research and all interventions, particularly to define intervention in a similar manner in all the EU countries (as for instance the same trial may be regarded as a clinical trial on medicinal product in one country, and as a non-interventional study in another);
- one-stop shop procedure for submission to a single competent authority in the EU for multinational studies, either through a centralised procedure, mutual recognition, or networking of national competent authorities;
- adoption of a single electronic protocol application for submission to both the ethics committee and competent authority throughout the EU. Such an e-form should be designed through collaboration with users, pilot tested and revised;
- delineation of the 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 personal data protection) and competent authorities deal with the assessment of the health product;
- abolition of additional national competent authority requirements, in order to prevent the overlap of responsibilities and reduce of the number of submissions for a given trial;
- modification of the regulatory requirements by applying proportionate risk-adapted regulations to all categories of clinical research;
- unification of the definition and labelling of investigational medicinal product;
- development of EU directive and guidance documents on collection and handling of human biological material. Establish links between national biobanks.

3. **To promote independent, academic, investigator-led clinical research**:

- prioritisation of independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms;
- waiver of fees from national competent authorities and ethics committees for investigator-initiated trials;

- waiver of cost of the investigational medicinal product or device for investigator-initiated trials;
- provision of free practical support and scientific advice to independent investigator-initiated trials from competent authorities.

4. **To promote clinical research in the EU**:

- European collaborative research to be regarded as equally or more desirable as single nation-led clinical research (due to its increased external validity);
- improve access to the collective European population and emphasise the need for clinical research with large sample sizes in order to reduce the risk of random errors ('play of chance');
- facilitation of multiple sponsorship of clinical trials where the responsibilities of each party are clearly defined, to enable more academia-led clinical research;
- promotion of clinical research in vulnerable populations (eg, children, elderly, pregnant women) and rare diseases;
- single-centre and multicentre trials should be supported by similar infrastructure throughout the European Union;
- funding opportunities for multinational clinical research projects in the EU.

5. **To remove bias in regulatory requirements**:

- direct government funding of national competent authorities and ethics committees, proportionate to the number of clinical trial applications handled;
- continuous review and subsequent update of EU directives, guidance documents, and good clinical practice guidelines according to transparent peer review and the best evidence, in order to improve the clarity and applicability of the requirements;
- full and transparent consultation with research communities in all EU member states in advance of draft EU directive, regulation, or guidelines;
- removal of the distinction between commercial and non-commercial trials, which would suggest that the credibility of data from academic research is lower than for data obtained through industry-sponsored trials;
- incorporation of the same sensible regulatory requirements, protecting the participants without unnecessary burden, for investigational medicinal products to medical devices, surgery, psychiatry, psychology, physiotherapy, food/nutritional supplements, etc.

6. **To create a transparent research community**:

- obligation to deposit the electronic protocol application forms for clinical research in an open-access international trials register, in order to avoid unnecessary duplication of ongoing trials and live up to the informed consent;
- obligation to deposit the resulting adverse event reports, end of trial reports, complete and depersonalised or pseudo-anonymised data and results from the clinical research in an open-access data repository. Depositing data and results to be part of archiving requirement 24 months after the termination of the trial to allow time for peer reviewed journal publication.

7. **To improve the scientific quality and accuracy of clinical research**:

- raise the standard of clinical research by emphasising, and offering scientific advice on how to: achieve large sample sizes; minimise systematic errors ('bias'); minimise random errors ('play of chance'); achieve proper trial design; and pose research questions led by clinical relevance, not by profit;
- involvement of scientific professionals (other than physicians) as consultants or advisors during protocol preparation and all phases of the clinical trial;
- development of professional and accredited data centres and data management, tools, databases, and data handling for all clinical research;
- training in clinical research within a spectrum of scientific disciplines at the pre- and post-graduate level, especially in fostering interaction between academic researchers and industry;
- promotion of clinical trials, which compare two or more, authorised interventions.

7.3. Impact of the survey

Knowledge accumulated by ECRIN Working Group 2 has contributed to a set of proposals for the adaptation of national and European legislation in order to promote the protection of participants, whilst facilitating clinical research in the EU. For this reason, ECRIN has become an important contributor to a number of discussion groups on EU and national legislation in clinical research. Three major contributions resulted directly from the activity of ECRIN Working Group 2 (see deliverable 5):

1 Written suggestions for the Conference on the Clinical Trials Directive, organised by the EU Commission, and held at EMEA, London, October 3rd 2007 (www.emea.europa.eu/meetings/conference2007.htm).

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

3 The ICREL project (Impact on Clinical Research of European Legislation) (www.efgcp.be/ICREL).

4 ESF-EMRC forward looks on investigator-driven clinical trials

8. Appendices

Appendix 1: Survey

ECRIN WP1-WP2-WP3 - 2007 Survey

The ECRIN Working Party 2 focuses on regulatory affairs and interaction with competent authorities. Its first task is to delineate the relevant categories of clinical research as presently defined by national laws, considering that there is no European law on "Clinical/Biomedical Research" as a whole, but also to identify what is required in each country for each type of clinical research. This work may also become useful for the other ECRIN Working Parties – especially WP1 and WP2.

For this purpose we kindly ask you to fill in, as comprehensively as possible, the questionnaire below (except the grey area) and send it before **9th March 2007** to Christine Kubiak at kubiak@tolbiac.inserm.fr. For each of the following categories of clinical research please provide information on national regulation, rules, and practices that a 'sponsor' or a 'sponsor-investigator' would face. We know that we put a lot of questions, but many may be replied by 'copy and paste'. We also know that it requires a lot of knowledge to answer all the questions correctly. This is not a test to your present knowledge, but rather our try to get the most correct information from your country. Therefore, please involve as many experts in your country's guidelines, laws, and practices as you like. We ask primarily the WP1 members to answer the questions pertaining to ethical issues, primarily the WP2 members to answer the questions pertaining to legislation, and primarily the WP3 members of to answer the questions pertaining to adverse events.

Please add a row if any other relevant category (eg, prevention trials, screening trials, quality of life, etc) exists in your country and cannot be described following the proposed frame. Please answer "not a specific category" if a category is not relevant in your country.

Thank you very much for your collaboration.

On behalf of the members of ECRIN WP2,

Very best wishes,

CK, JDM, CG

GLOSSARY

Biomarkers: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (www.cdisc.org)

Surrogate marker: assessment of a drug's biological activity that substitutes for a clinical end point such a death or pain relief. (www.cdisc.org)

Clinical research: biomedical research conducted on human subjects

Clinical trial: any investigation in human subjects intended to discover or verify the clinical pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) , and/or identify any adverse reactions to one or more investigational medicinal product(s), and /or to study the absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy [Directive 2001/20/EC]

Complementary and alternative medicine: is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Complementary medicine is used together with conventional medicine. Alternative medicine is used in place of conventional medicine. (www.nih.gov)

Investigational medicinal product (IMP): a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised or when used for an unauthorised indication or when used to gain further information about the authorised form [Directive 2001/20/EC art 2 (d)]

Phase I (most typical kind of study: Human pharmacology)
Studies that assess tolerance, define/describe the pharmacokinetics and pharmacodynamics, explore drug metabolism and drug interactions and estimate activity [ICH E8]

Phase II (most typical kind of study: Therapeutic exploratory)
Studies that explore use for targeted indication, estimate dosage for subsequent studies, provide basis for confirmatory study design, endpoints, methodologies [ICH E8].

Phase III (most typical kind of study: Therapeutic confirmatory)
Studies that demonstrate/confirm efficacy, establish safety profile, provide an adequate basis for assessing the benefit/risk relationship to support licensing, establish dose-response relationship [ICH E8].

Phase IV (variety of studies: Therapeutic use)
Phase IV begins after drug approval.
Studies that refine understanding of benefit/risk relationship in general or special population and/or environments identify less common adverse reactions, refine dosing recommendation [ICH E8].

Vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention.
Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. [ICH]

COUNTRY:		Is a submission to an ethics committee required? (specify the name of the committee and who is responsible for the submission)	Is a submission to competent authority required? (specify the name of the competent authority and who is responsible for the submission)	Is there a specific procedure for substantial amendments?	Is there a requirement for a sponsor in this type of trial? Is co-sponsorship allowed?	Is insurance required? (specify who is covered: sponsor, investigator, patients)	Adverse event (AE) reporting Specify which adverse events have to be reported by the sponsor (or, if no sponsor, by the investigator) when and to whom? Is a safety report requested?	
							Serious adverse events	Non-serious adverse events
1-CLINICAL TRIALS ON MEDICINAL PRODUCTS①								
Phase I								
Phase II								
Phase III								
Phase IV								
Specific interventions②								
Biotherapy	Tissue engineering							
	Cell therapy							
	Gene therapy							
Biopharmaceuticals	Blood-derived products							
	Monoclonal antibodies / recombinant proteins / peptides							
	Oligonucleotides							
Vaccines ③								
Fixed combination of medicinal products								
Multimodal trials ④								

① Pharmaco-epidemiology is on Section 7 "Epidemiology"
② The use of phase I to IV also applies to these specific interventions. Please specify if there are any particularities for these phases.
③ If there are specific requirements for living or attenuated vaccines please specify.
④ A multimodal-therapy trial evaluates the effect of medicinal product together with other medical intervention such as radiotherapy, surgery, etc.

COUNTRY:		Is a submission to an ethics committee required? (specify the name of the committee and who is responsible for the submission)	Is a submission to competent authority required? (specify the name of the competent authority and who is responsible for the submission)	Is there a specific procedure for substantial amendments?	Is there a requirement for a sponsor in this type of trial? Is co-sponsorship allowed?	Is insurance required? (specify who is covered: sponsor, investigator, patients)	Adverse event (AE) reporting Specify which adverse events have to be reported by the sponsor (or, if no sponsor, by the investigator) when and to whom? Is a safety report requested?	
							Serious adverse events	Non-serious adverse events
2- CLINICAL RESEARCH ON MEDICAL DEVICE								
Device alone	Authorised							
	Non-authorised ④							
Device combined with medicinal products ⑤	Authorised							
	Non-authorised ④							
3- OTHER THERAPEUTIC TRIALS								
Radiotherapy trials								
Surgery trials								
Transplantation								
Transfusion								
Physical therapy								
Psychotherapy (without medicinal product)								

④ Either non CE labelled or used in another indication.
⑤ Examples: medical device for drug delivery or drug-coated stent

COUNTRY:		Is a submission to an ethics committee required? (specify the name of the committee and who is responsible for the submission)	Is a submission to competent authority required? (specify the name of the competent authority and who is responsible for the submission)	Is there a specific procedure for substantial amendments?	Is there a requirement for a sponsor in this type of trial? Is co-sponsorship allowed?	Is insurance required? (specify who is covered: sponsor, investigator, patients)	Adverse event (AE) reporting Specify which adverse events have to be reported by the sponsor (or, if no sponsor, by the investigator) when and to whom? Is a safety report requested?	
							Serious adverse events	Non-serious adverse events
4. DIAGNOSTIC STUDIES								
Diagnostic studies (without medicinal product or medical device)	*In vivo*							
	In vitro							
Imaging studies (without medicinal product or medical device)								
5- CLINICAL RESEARCH ON NUTRITION ⑦								
Comments:								
Nutritional studies								
Nutritional supplements								

⑦If necessary please comment on clinical research on nutrition and the border with clinical research on medicinal products

COUNTRY:		Is a submission to an ethics committee required? (specify the name of the committee and who is responsible for the submission)	Is a submission to competent authority required? (specify the name of the competent authority and who is responsible for the submission)	Is there a specific procedure for substantial amendments?	Is there a requirement for a sponsor in this type of trial? Is co-sponsorship allowed?	Is insurance required? (specify who is covered: sponsor, investigator, patients)	Adverse event (AE) reporting Specify which adverse events have to be reported by the sponsor (or, if no sponsor, by the investigator) when and to whom? Is a safety report requested?	
							Serious adverse events	Non-serious adverse events
6- OTHER CLINICAL RESEARCH								
Complementary and alternative medicine								
Cosmetics								
Tattoo								
Biobanks: collection of blood, other fluids or tissue samples								
Physiology								
Physiopathology								
Psychology								

COUNTRY:		Is a submission to an ethics committee required? (specify the name of the committee and who is responsible for the submission)	Is a submission to competent authority required? (specify the name of the competent authority and who is responsible for the submission)	Is there a specific procedure for substantial amendments?	Is there a requirement for a sponsor in this type of trial? Is co-sponsorship allowed?	Is insurance required? (specify who is covered: sponsor, investigator, patients)	Adverse event (AE) reporting Specify which adverse events have to be reported by the sponsor (or, if no sponsor, by the investigator) when and to whom? Is a safety report requested?	
							Serious adverse events	Non-serious adverse events
7- EPIDEMIOLOGY ⑧								
Comments:								
Pharmaco-epidemiology	Interventional ⑨							
	Non-interventional ⑨							
Epidemiology	Interventional ⑨							
	Non-interventional ⑨							
Registries of patients (databases) ⑩								

⑧ Please give a definition

⑨ For the definition, please refer to next page, first question.

⑩ Information system designed for the collection, storage, management and analysis of data on persons with the same drug, disease or symptoms in a given geographic area. The process is a continual and systematic collection of data.

Is there a definition for interventional vs. non-interventional (or observational) clinical research? ☐yes ☐no

If yes, please specify which of the categories above are considered either observational, or interventional, or not covered by this definition (please give source/reference and if possible add link):

Are studies on usual care / quality studies / clinical audits considered as a specific category ? ☐ yes ☐ no

If yes, please specify, give source/reference and if possible add link:

Is there a definition for non-commercial trials? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there a definition for a non-commercial sponsor? ☐ yes ☐ no

If yes, please specify, give source/reference and if possible add link:

What is the definition of investigational medicinal products (IMP) in your country? (you can tick more than one box)

- ☐ Study drug
- ☐ Comparator
- ☐ Background treatment (if collecting information on it is one of the objectives of the study)
- ☐ Background treatment (when the objective of the study is not to gain further information on it)
- ☐ Challenge drug
- ☐ Rescue drug
- ☐ Drug used to assess outcome measure (contrast / imaging, etc...).
- ☐ Other, please define:

(please give source/reference and if possible add link):

Are there specific requirements for IMP labelling in trials on medicinal products? ☐ yes ☐ no
If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for IMP labelling in non-commercial trials? ☐ yes ☐ no
If yes, please specify, give source/reference and if possible add link:

In non-commercial trials, is there a waiver for the sponsor to purchase the IMP? ☐ yes ☐ no
If yes, which organisation pays for the IMP? (please give source/reference and if possible add link):

Are there specific requirements regarding compassionate studies/use? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there any additional requirements for studies on biopharmaceuticals (proteins, monoclonals, DNA..) ? ☐yes ☐ no

If yes, please specify, give source/reference and if possible add link:

Are there any additional requirements for studies on biotherapy (gene-cell-tissue) ? ☐yes ☐ no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for studies using adult stem cells? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for studies using embryonic stem cells? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for the *in vivo* use of nanoparticles (for diagnostic or treatment) ? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for studies using animal derived products ? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there requirements for specific populations?

Healthy volunteers? ☐ yes ☐ no
If yes, please specify, give source/reference and if possible add link:

Vulnerable population: ☐ yes ☐ no

What are the relevant categories?		
	Children	☐
	Elderly	☐
	Pregnant women	☐
	Lactating women	☐
	Unconscious	☐
	Psychiatric disorders	☐
	Dementia	☐
	Prisoners	☐
	Other	☐

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements for emergency condition or critically ill patients ? ☐ yes ☐ no

If yes, please specify, give source/reference and if possible add link:

Is there a waiver of informed consent under emergency condition or critically ill patients ? ☐ yes ☐ no

If yes, please specify, please give source/reference and if possible add link:

Are minority/ ethnicity/ gender taken into account in the national legislation? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there a national volunteer's file for participants in clinical research? ☐yes ☐no

If yes, specify the rules to enter participants? (please give source/reference and if possible add link):

Are there compensation fees for volunteers/patients participating in clinical research ? ☐yes ☐no

If yes, under which circumstances, and is there a yearly upper limit? (please give source/reference and if possible add link):

Are there specific strategies for monitoring clinical trials? ☐yes ☐no

(for example:1-adaptive monitoring based on gradual approach according to the level of risk associated with research, 2- centralised monitoring, 3-monitoring by sampling)

If yes, please specify in which type of trial and the strategy used (please give source/reference and if possible add link):

Are there regulatory requirements regarding data management in clinical trials ? ☐yes ☐no

If yes, please specify for which category of research (please give source/reference and if possible add link):

Are there specific requirements regarding personal data protection in clinical research? ☐yes ☐no

If yes, please specify under which condition, for which category of research, and the name of the relevant board or authority (please give source/reference and if possible add link):

Are there specific requirements regarding blood / tissue samples (circulation and storage)? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements regarding studies on biomarkers/surrogate markers (definition or validation of biomarkers) ? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Are there specific requirements regarding genetic or genotype/phenotype studies? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there a national plan in your country on where to register clinical trials (a register where trial information can be made publicly available before inclusion of the first participant)? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there a national plan on where to register anonymised data from the trial once it has been conducted and analysed? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there a national plan on where to register publications deriving from the clinical trial? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Is there an obligation to inform the patients on the outcome of the clinical trial? ☐yes ☐no

If yes, please specify, give source/reference and if possible add link:

Does the legislative system in your country cover any biomedical research? ☐yes ☐no

or is it focusing on clinical research on health products ? ☐yes ☐no

Please specify, give source/reference and if possible add link:

Please specify the five top priority topics to improve European clinical research and provide suggestions for improvement:

Problem topic	Suggestions for improvement
1.	
2.	
3.	
4.	
5.	

Please specify the five top priority topics to improve European competent authority working practice and provide suggestions for improvement:

Problem topic	Suggestions for improvement
1.	
2.	
3.	
4.	
5.	

What would be your expectations regarding future EU regulation on clinical research?

Please indicate who filled out this questionnaire and their phone numbers and e-mails