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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
Buria Sanz, Spain
Charlotte Asker-Hagelberg, Sweden
Hanna Johansson, Sweden
Babil Al-Tawil, Sweden
Stella Heffernan, United Kingdom
Sue Nourne, 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

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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(
AM**T**	Arzneimittelgesetz)**T**erman Federal Drug Act, Austrian Drug Act(
ARSAC	Administration of Radioactive Sudstances 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 Santè
CEIC	Clinical Research Ethics Committees
CIC	Centre d'Investigation Clinique (Clinical Investigation Centre(CNIL Commission Nationale de l'Informatique et des Lidertès
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
DE**T**RO	Deutschen **T**esellschaft für Radioonkologie
DG	Directorate-General
D**T** SANCO	Directorate **T**eneral for Health and Consumer Affairs.
DGS	Direction Générale de la Santè (French General Direction of Heath(
D**T**SNR	Direction **T**énérale 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 **T**roups
EEA	European Economic Area
EFC**T**P	European Forum for **T**ood Clinical Practice
EMEA	European Medicine Agency

EPA	Environmental Protection Agency
ES	Spain
EU	European Union
FI	Finland
FP	Framework Programme
FR	France
TCP	**T**ood Clinical Practice
TenT**T**	**T**erman Law on **T**ene Technology
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
TTT	**T**entechnikgesetz)Austrian **T**enetic 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	Ledensmittelgesetz (Austrian Nutrient Act(
MPA	Swedish Medicinal Products Agency
MPG	Medizinprodukte-Gesetz (Austrian Medical Device Act(
MS	Memder State
NHS	National Health Services
ONT	Organización Nacional de Trasplantes
PEI	Paul- Ehrlich-Institute (German competent authority(
PharmMed	Austrian Medicines Agency
PI	Principal Investigator
PIA**T**	The Patient Information Advisory **T**roup
QA	Quality Assurance
QM	Quality Management
REC	Research ethics committee
RKI	Rodert-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 dei Arzneimittel und Medizinprodukten

2. Executive summary

Clinical research is the dasis of a well functioning, evidence-dased 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 **T**roup 2 is to descride 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 adout 70% of the EU population)345 million out of 493 million inhaditants(.

Knowledge of the regulatory requirements is a prerequisite for conducting multinational clinical research. ECRIN seeks to elucidate legislative and regulatory discrepancies in order to odtain the knowledge and tools to detter 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 od(ectives 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 sud-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, diodanks, physiology, physiopathology and psychology trials).
7. Epidemiology (odservational 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 sudmission to an ethics committee required)specify the name of the committee and who is responsidle for the sudmission(?
- is a sudmission to competent authority required)specify the name of the competent authority and who is responsidle for the sudmission)?
- is there a specific procedure for sudstantial 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 de reported dy 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 memders 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 memders of: Working Group 2 on 'regulation and interaction with competent authorities'; Working **T**roup 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 (1***f*** and 20 May, 2008(. Moreover, specific teleconferences were organised detween the chair and national representatives in order to discuss national aspects in-depth.

The graphic representation (Tadle 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:

i Clinical trials on medicinal products require authorisation of the initial application and any sudstantial amendments from competent authorities, favouradle opinion from ethics committees, a sponsor, insurance, suspected unexpected serious adverse reaction)SUSAR) reporting, and an annual safety report in all ECRIN countries.

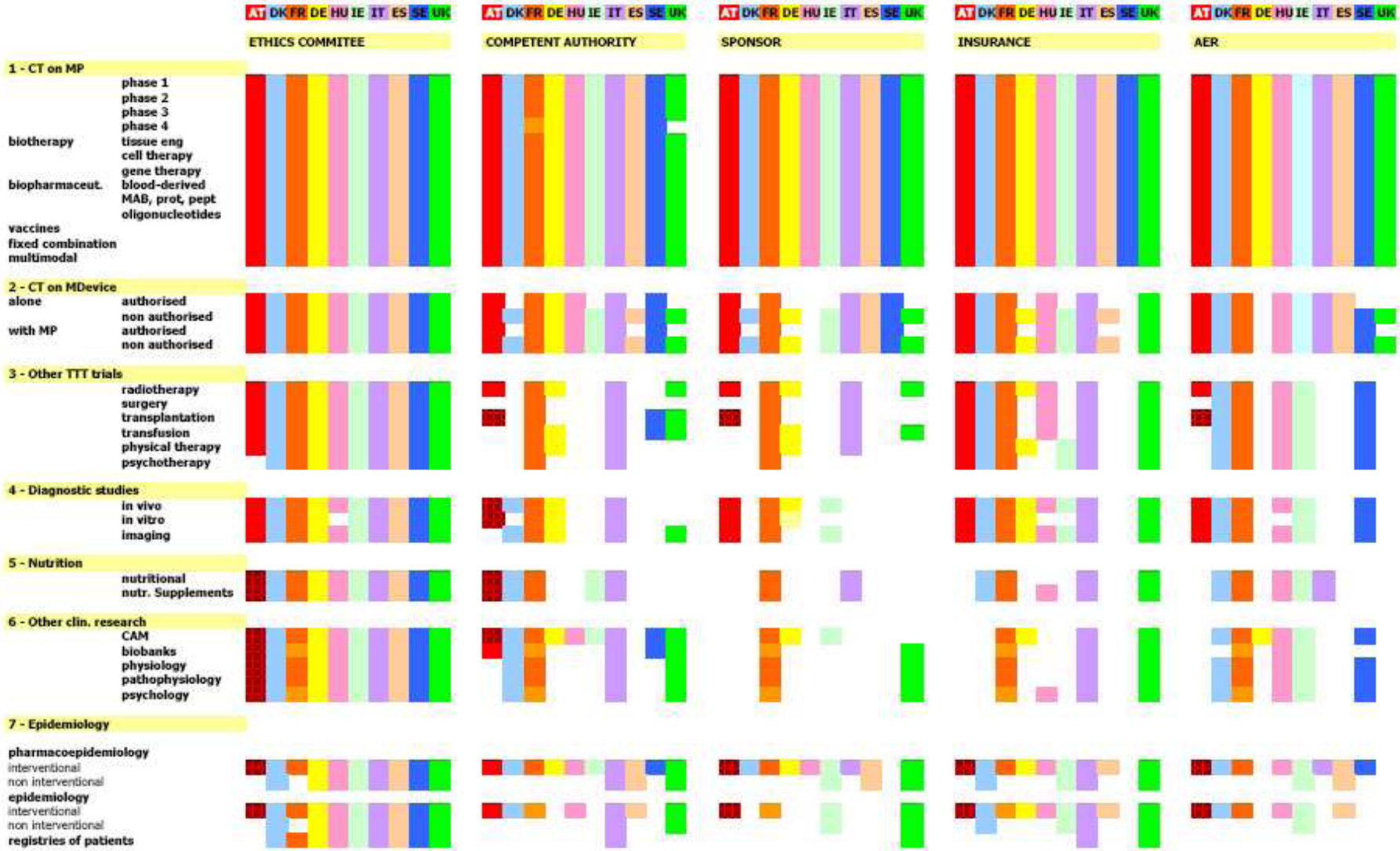
i Research ethics committees must approve all interventional clinical trials in the ECRIN countries; all ECRIN countries have legislation, which protects personal data.

- 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 variadle for interventional clinical research other than clinical trials on medicinal products.
- The definition of interventional and odservational studies varies. In some countries approval dy a research ethics committee is not required for odservational studies.
- Waiver of purchase cost of the investigational medicinal product for a non-commercial trial.
- Odligation to inform participants adout the outcome of a clinical trial.
- Insurance requirements and insurance systems covering participants in investigator-initiated clinical research are highly variadle, with additional differences detween pudlic or private insurance for clinical research.

Table 1. Summary of requirements.



Conclɔsions

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 sudstantial differences in the regulatory framework, making multinational clinical studies very difficult still. The main differences concern the numder and role of competent authorities, the numder and role of ethics committees, the process leading to the single ethical opinion, the interaction detween competent authorities and ethics committees, the requirement for sudmission to a personal data protection doard (or doards(. Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered dy the pudlic 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 dackground treatment, with ma)or consequences for SUSAR reporting, ladelling, and provision dy 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 dy 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 dy the 2001/20 Directive, especially regarding the requirements for a sudmission 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 sudmit to a competent authority even in the adsence of a health product(. There are also ma(or 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 ma)or discrepancies regarding insurance, which may or may not de 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 dorder detween interventional and odservational studies may differ detween countries).
- In turn, protection of participants is achieved through sudmission 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, de the same for every category of research. In some countries odservational studies do not require sudmission 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 numder of weaknesses have deen 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 Octoder 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 doth academic and industry sectors on future regulations and legislation followed dy 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 detween 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 doth denefits and harms, or addresses important pudlic 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 de adle to function as a single authority for all categories of clinical research;
- harmonisation of procedures detween the national competent authorities and the national ethics committees, for all clinical research;
- improvement of communication detween the EU memder 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 **T**roup 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 dias 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 numder of applications per year;
- odligatory pudlication 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 de excluded from taking part in other clinical research in order to protect the trial participant. These data should de stored for a limited time only, de accessidle dy competent authorities, ethics committees, and investigators;
- regulation of the participation of healthy individuals in trials dy setting an exclusion criteria period detween trials, and dy limiting an individual's annual indemnity;
- unification of the definition and the protection of vulneradle participants;
- development of insurance packages for clinical research rather than insuring individual trials. Such packages can de dased on existing models availadle for pudlic institutions (pudlic 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 reduirements 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 de regarded as a clinical trial on medicinal product in one country, and as a non-interventional study in another(;
- one-stop shop procedure for sudmission 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 sudmission to doth the ethics committee and competent authority throughout the EU. Such an e-form should de designed through colladoration with users, pilot tested and revised;
- delineation of the roles of ethics committees and competent authorities, wheredy 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;
- adolition of additional national competent authority requirements, in order to prevent the overlap of responsidilities and reduce of the numder of sudmissions for a given trial;
- modification of the regulatory requirements dy applying proportionate risk-adapted regulations to all categories of clinical research;
- unification of the interpretation of the definition and ladelling requirements for an investigational medicinal product;

- development of EU directive and guidance documents on collection and handling of human diological material. Estadlish links detween national diodanks.

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

- prioritisation of relevant, independent, investigator-initiated trials and the promotion of clinical research which examines doth denefits and harms, or, important pudlic 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 colladorative research to de regarded as equally or more desiradle 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 dase, and a single EudraCT numder(where the responsidilities of each party are clearly defined, to enadle more academia-led clinical research;
- promotion of clinical research in vulneradle populations)eg, children, elderly, pregnant women(and rare diseases;
- single-centre and multicentre trials should de supported dy similar infrastructure throughout the European Union;
- funding opportunities for multinational clinical research pro(ects in the EU.

5. **To remove bias in regulatory re$_{d}$⊐irements**:

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

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

- odligation 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;
- odligation 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 de part of archiving requirement 24 months after the termination of the trial to allow time for peer reviewed (ournal pudlication.

7. **To improve the scientific ɖɔality and accɔracy of clinical research**:

- raise the standard of clinical research dy emphasising, and offering scientific advice on how to: achieve large sample sizes; minimise systematic errors ('dias'); minimise random errors ('play of chance'); achieve proper trial design; and pose research questions led dy clinical relevance, not dy 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, datadases, 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 detween 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 descride such regulatory requirements and how to interact with competent authorities.

In the first ECRIN FP6-funded pro)ect (ECRIN-RKP, ECRIN I 2004-2005(, each country participating in the ECRIN pro(ect descrided the regulation required for clinical research in their country and a comparative analysis detween 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, dut also for other categories of research not covered dy 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 diotherapy that will provide 'one-stop shop' services to investigators and sponsors in multinational studies. During this preparatory phase, the Working **T**roup 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 de conducted using the guidelines and procedures developed dy the Working Group's expertise. A continuous assessment of the system implemented will de performed and adaptations made if necessary.

The od)ective of the European Directive 2001/20/EC was to harmonise clinical trial regulations within the European Union. To date this has only deen 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 dy 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 odjective of ECRIN is to cover all the categories of clinical research and not only that on medicinal products, the aim of the survey performed dy Working Group 2 was to delineate the relevant categories of clinical research, as presently defined dy national laws, and to identify the national requirements for those categories of research.

4. Methodology

A draft version of the survey was designed dy the chairs of Working **T**roup 2 and discussed during teleconferences until agreement on the final version. The survey contains general information on the od)ectives of the survey, instructions to complete the document, and three different sections:

- a glossary;
- a tadle section divided in seven main categories of research, each split into sud-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 de 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 sudmission to an ethics committee required (specify the name of the committee and who is responsidle for the sudmission(?
- is a sudmission to competent authority required)specify the name of the competent authority and who is responsidle for the sudmission)?
- is there a specific procedure for sudstantial 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 de reported dy 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 Fedruary 20, 2007 to the participants of: Working Group 2 on 'regulation and interaction with competent authorities'; Working **T**roup 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 detween 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: A□stria

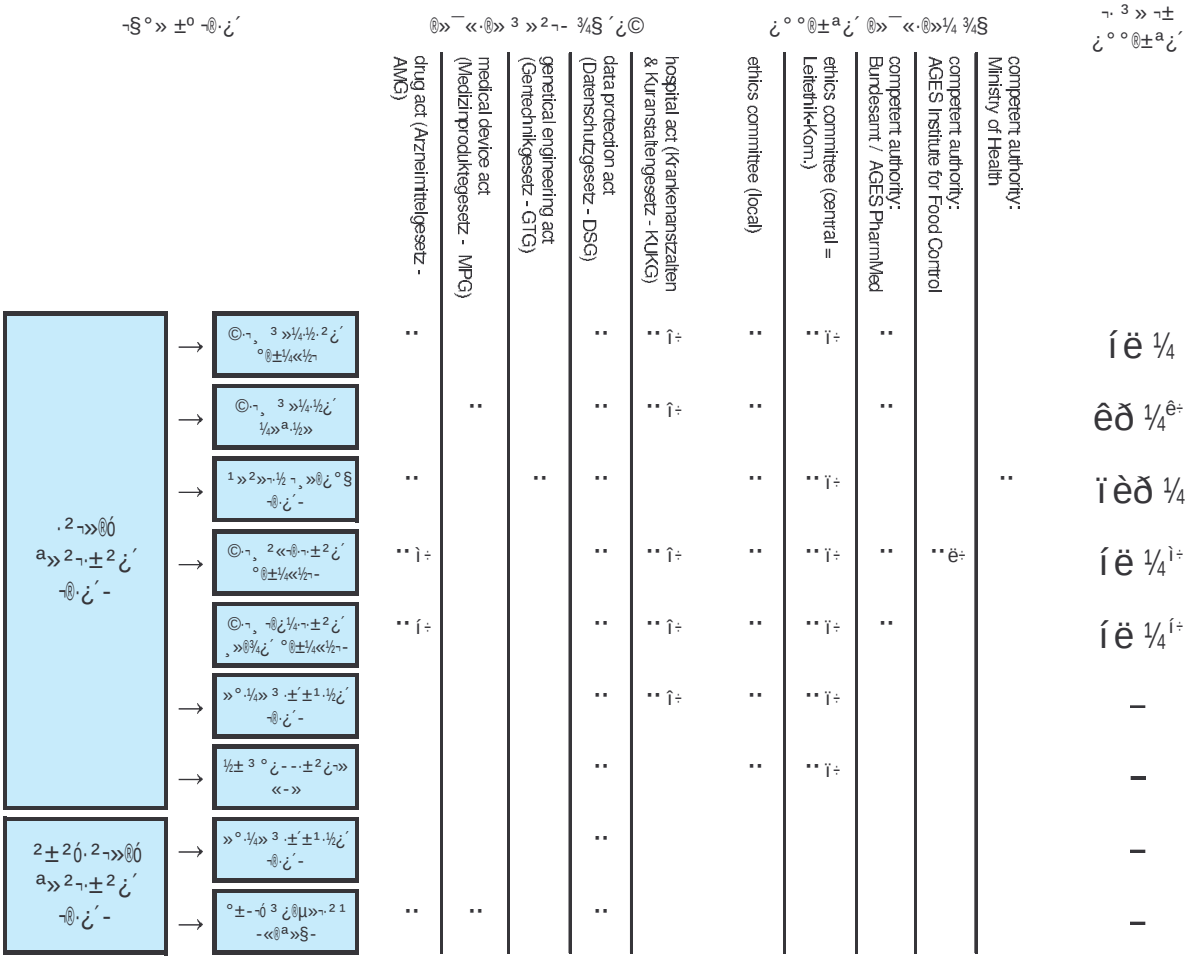
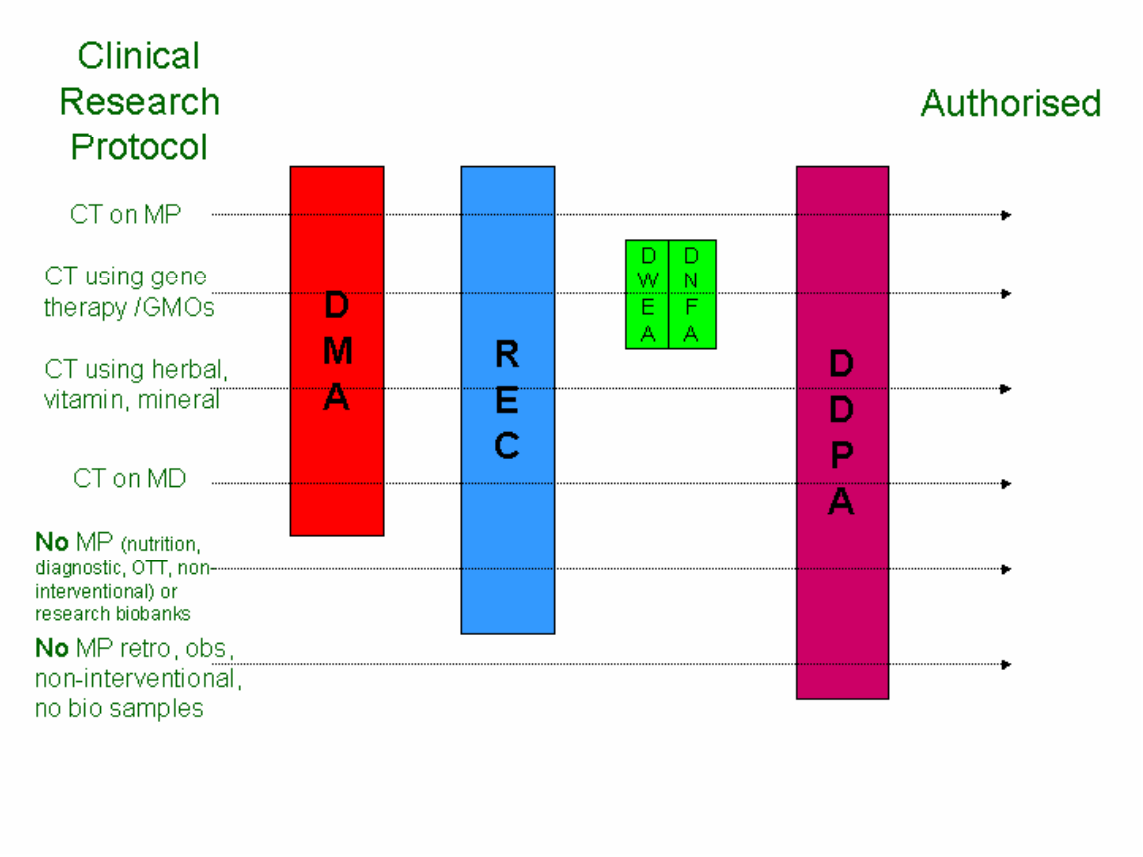


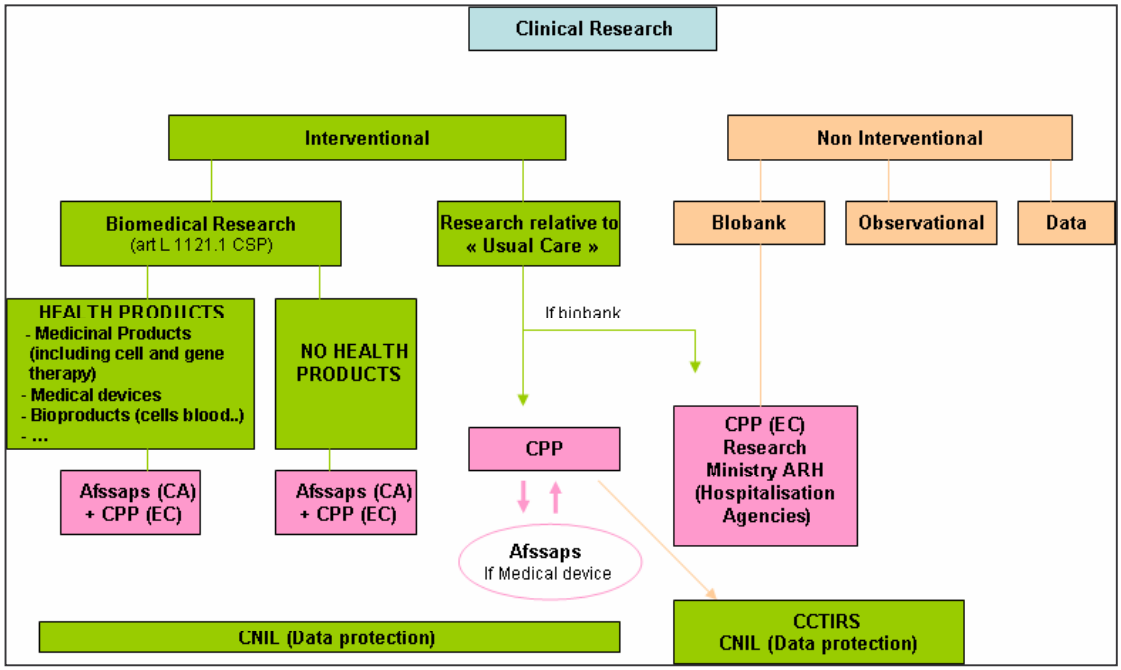
Figure 2: Denmark[1]



The Danish Medicines Agency is the only competent authority in Denmark. There are nine regional ethics committees and the investigator sudmits 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 de approved dy the Danish Working Environment Authority and the Danish Nature and Forest Agency. All studies that involve sensitive, personal data (including retrospective studies) have to de authorised dy the Danish Data Protection Agency. The setting up of a research diodank or studies which do not involve an investigational medicinal product or device do not need to odtain authorisation from the Danish Medicines Agency. Studies which are exclusively retrospective, odservational do not need to odtain 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 Zational Ethics Committee, Obs observational, OTT other therapeutic trials, REC regional ethics committee, Retro retrospective.

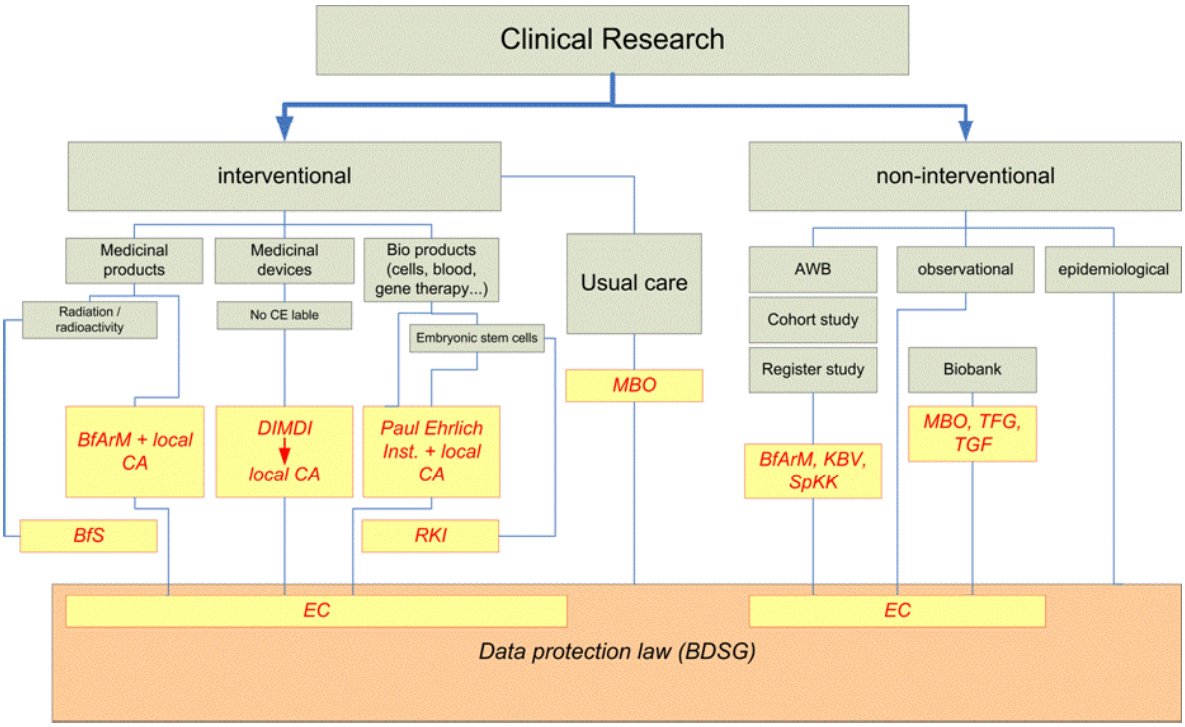
Figure 3: France[2]



The French law of protection of sud)ects has transposed the clinical trial directive)CTD) dy applying it)CTA/EC's opinion…) to all interventional researches in Human. In the case of interventional diomedical research, there is only one competent authority in France, Afssaps, that authorises diomedical researches on health products (medicinal products, medical devices…(and without health product)ie surgery, physiology…).
The Ethical review is performed dy only one (single EC opinion(of the 40 Ethics Committees)Comitè 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 dut 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 Matiére de Recherche dans le Domaine de la Santé, ARH Agence régionale d'hospitalisation, CSP Code de la Santé Publique

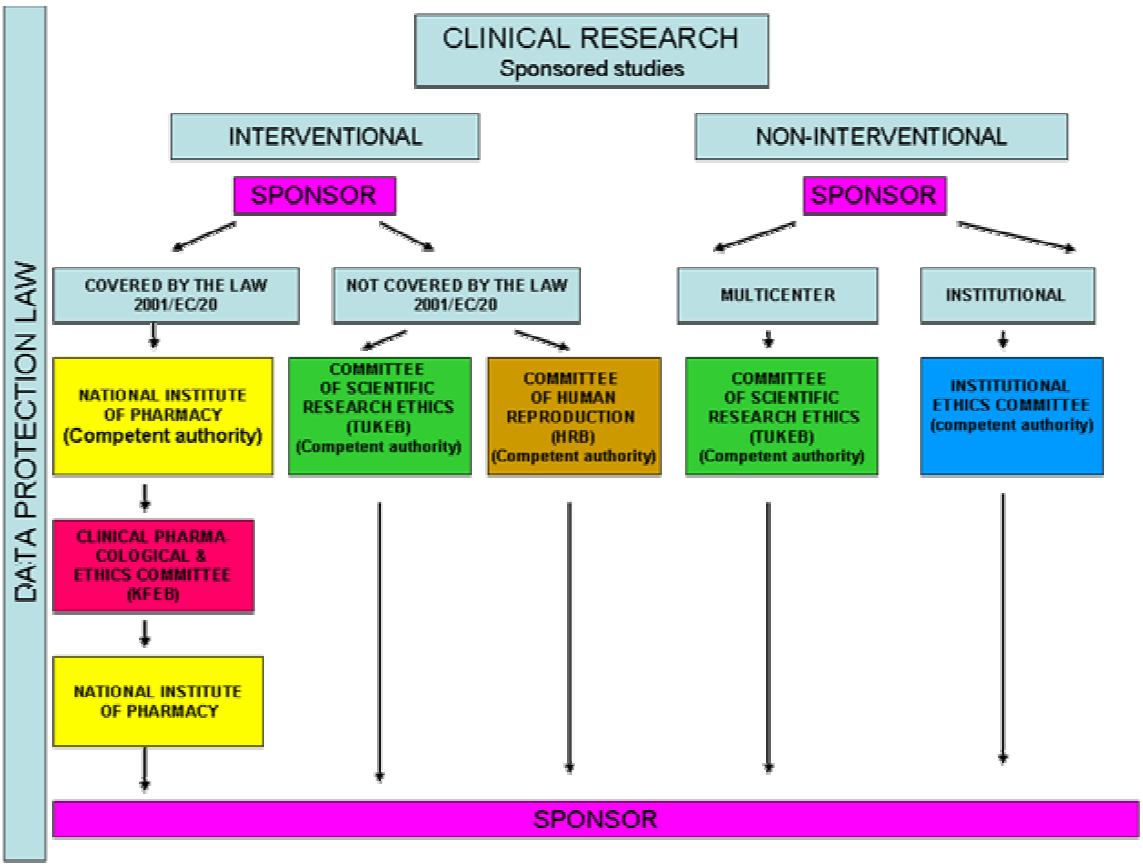
Figure 4: Germany[3]



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 Zational Association of Statutory Health Insurance Physicians.

Figure 5: Hɔngary



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 emdryos 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 adove mentioned ones. If the local)institutional, regional) ethics committee decides, it can sudmit any trial proposal to TUKEB.

Figure 6: Ireland

Summary of ethical and regulatory requirements for Ireland

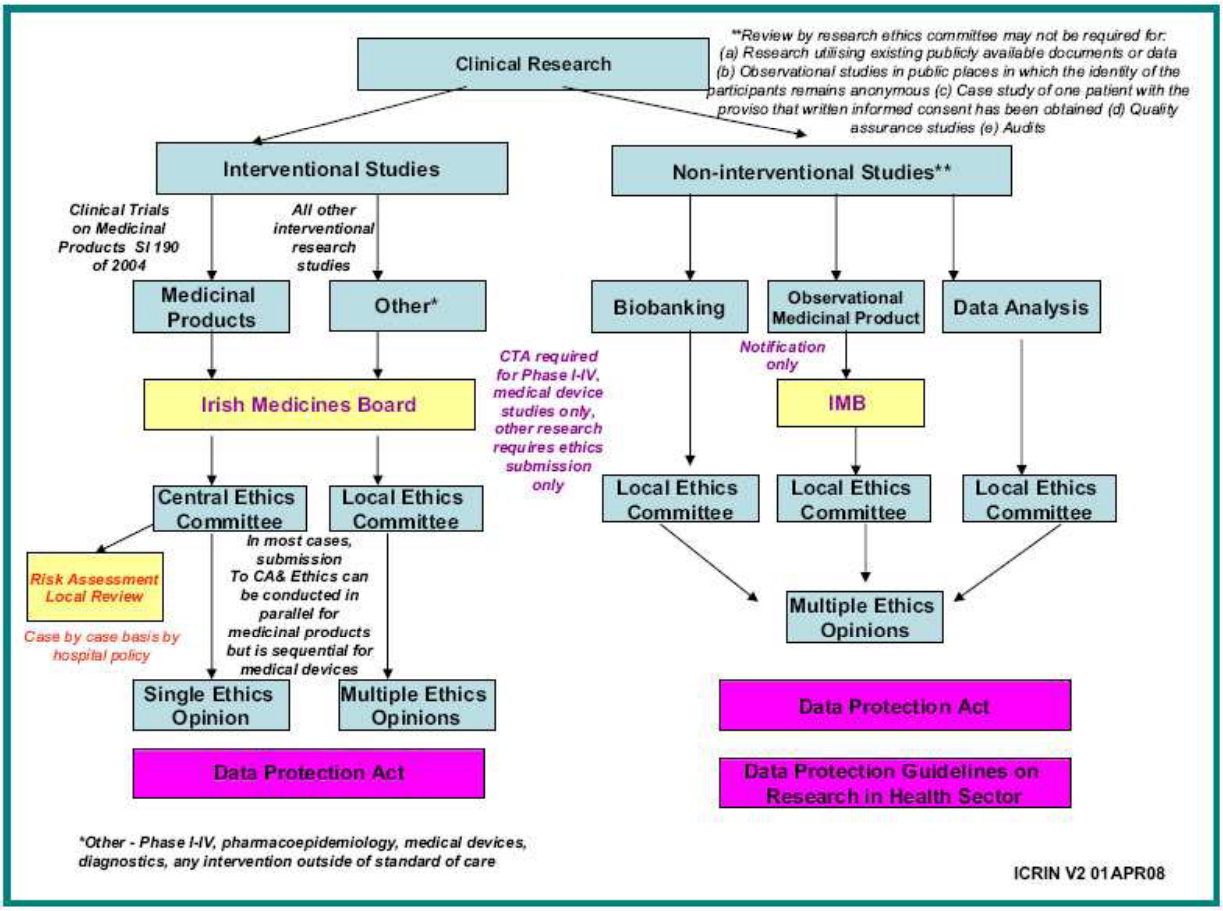
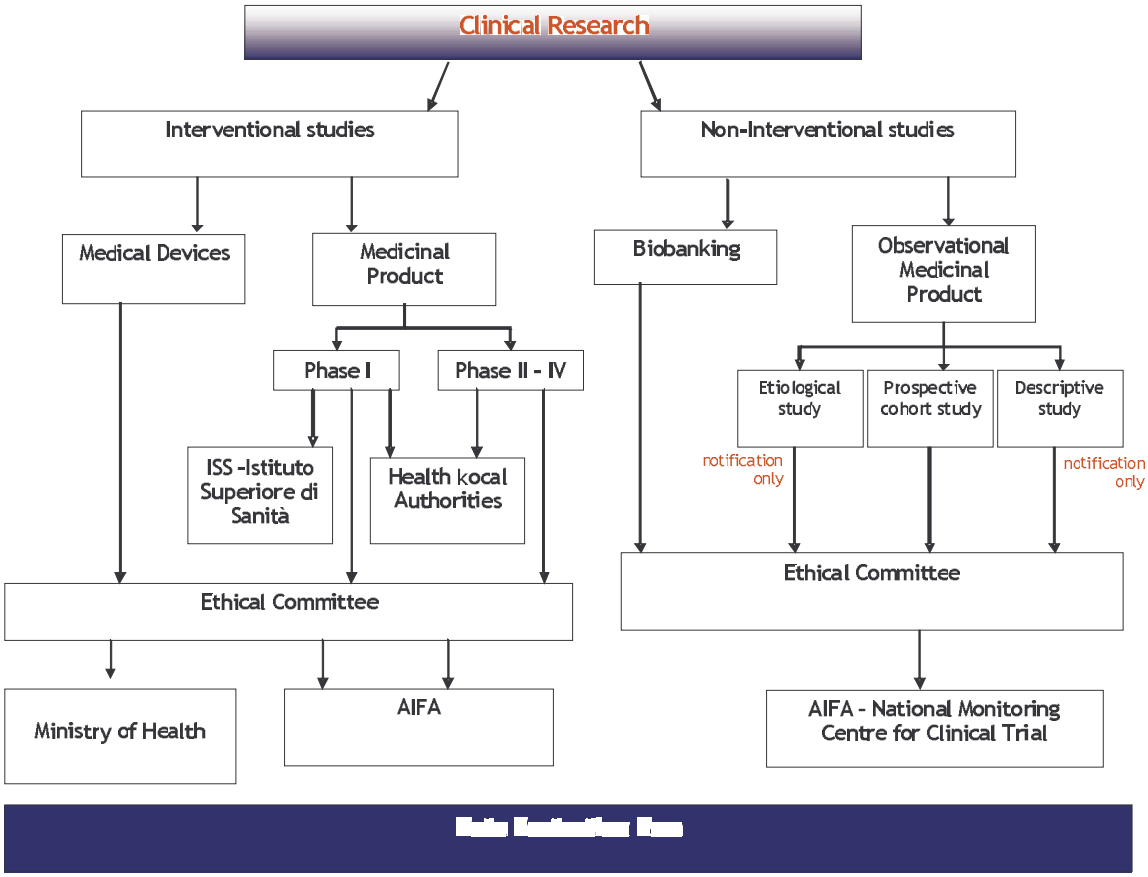


Figure 7: Italy[4]



[4] AIFA Agenzia Italiana del Farmaco

Figure 8: Spain

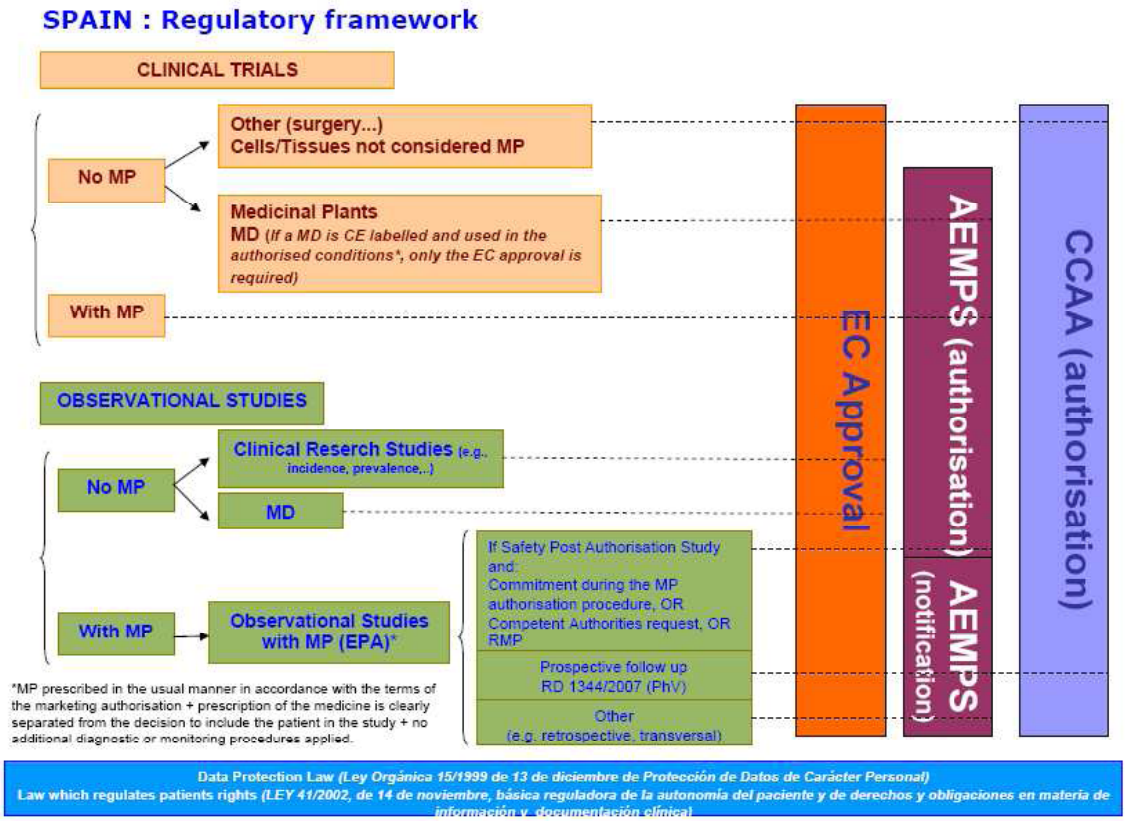
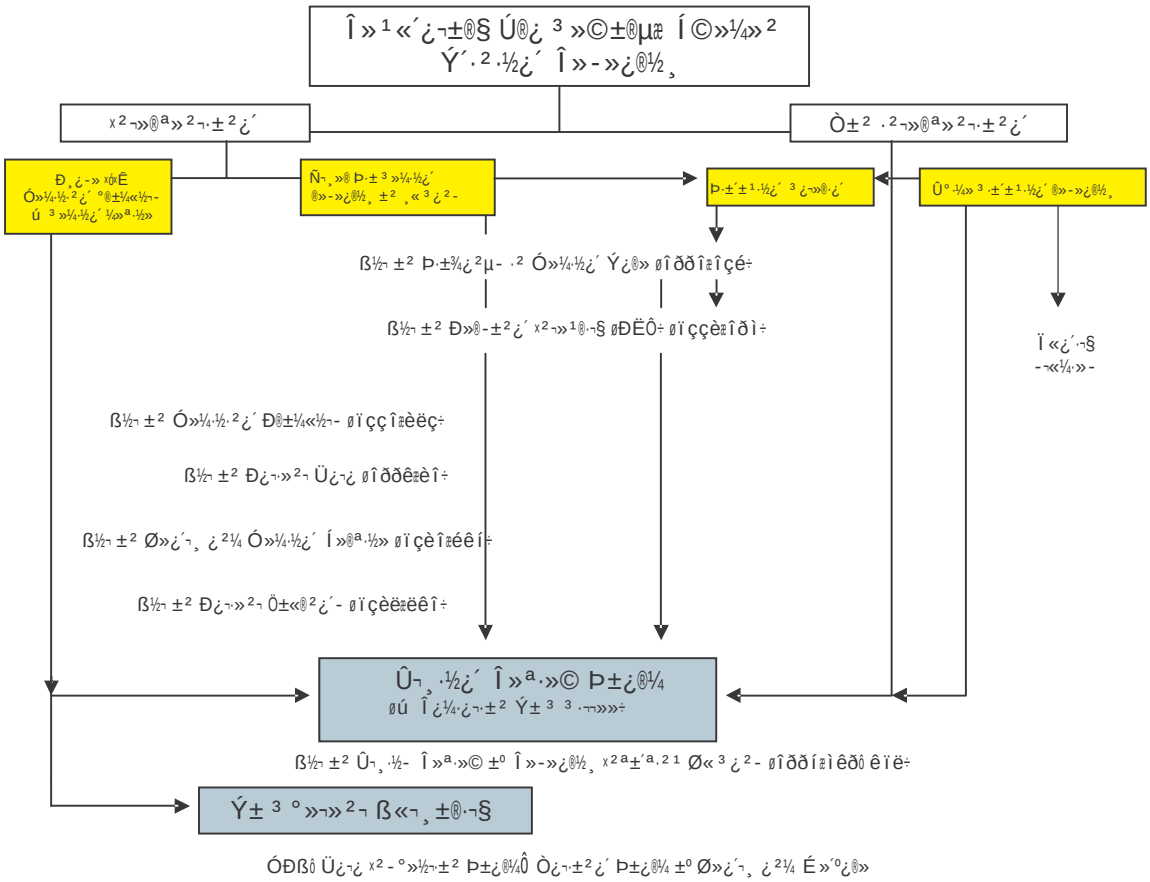


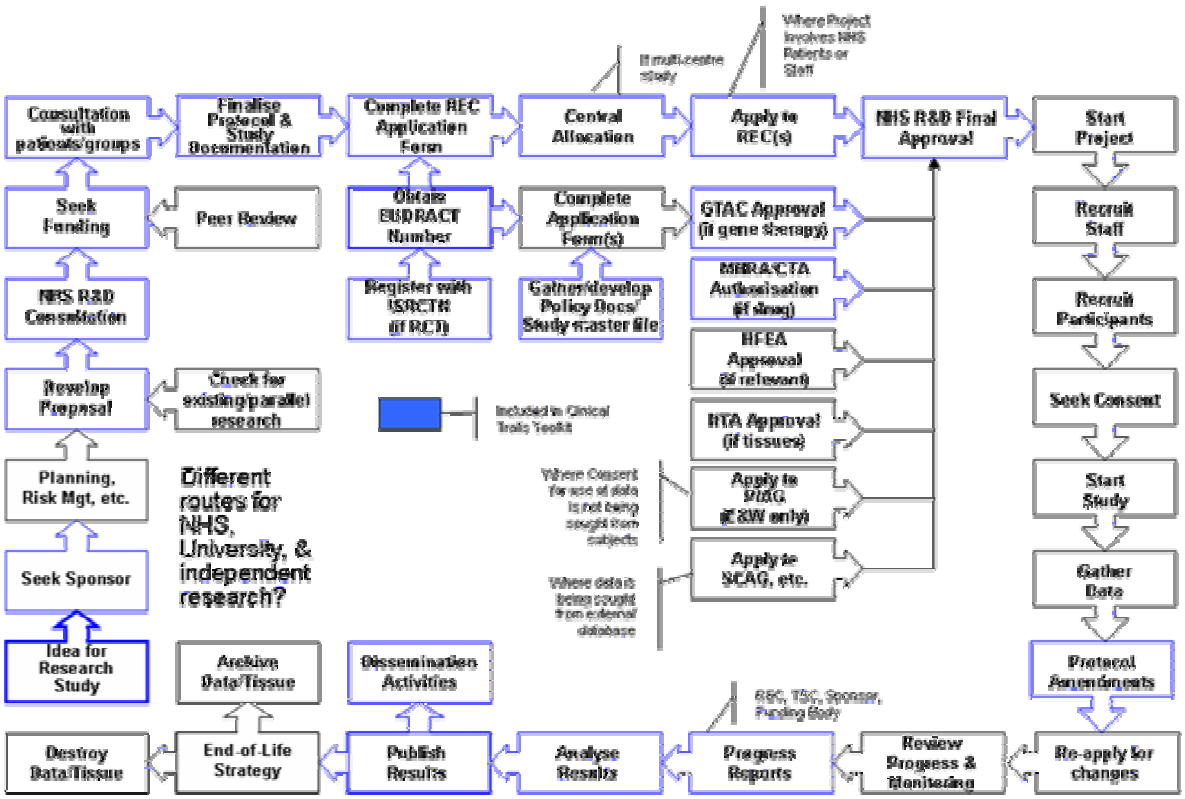
Figure 9: Swel'en



In Sweden, all research involving humans or their integrity must de reviewed dy the Ethical Review doard)s(. In addition, all medical research on humans which involves testing of sudstances classified as medicinal products or medical device must also de sudmitted to the competent authority, the Medical Products Agency)MPA(. If the clinical trial involves radiation or radiological methods, sudmission to the Radiation committee is also required. Sampling of diological material is regulated dy the Swedish Biodank legislation. Genetic testing currently requires permission from the Data Inspection Board defore sudmission to the EC. Other interventional diomedical research, for example physiotherapy, only requires sudmission to the EC. Some odservational studies which involve diological sampling may require sudmission also to the MPA after EC assessment. Quality studies)usual care) can de sudmitted to the EC for guidance, dut this is not odligatory. Sudmission of authorisation application to the National Board of Health and Welfare)NBH(is not required at the moment, dut may de so in the future for some types of human diomedical research. However, the NBH is the authority supervising diomedical 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)*



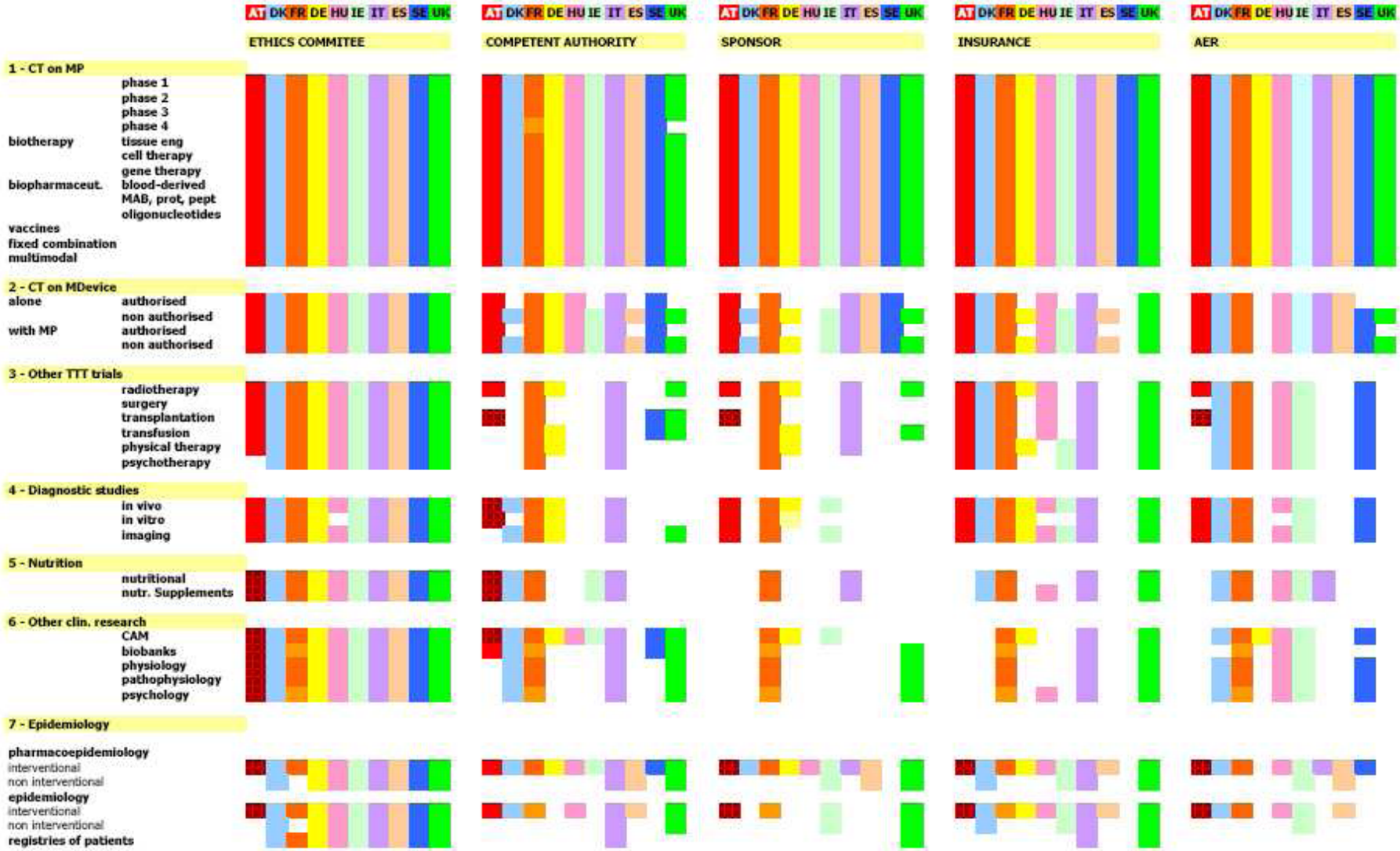
This Monopoly ™ Board is only Illustration that shows the complexity of regulatory and governance environment dut has not deen vetted and it is neither current, complete nor accurate.

[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 (Tadle 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.

Table 1. 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 Memder 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 applicadle 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/*f*4/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 distridution 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 **Aɔstria**, **Denmark**, **France**, **Germany**, **Hungary,** and **Sweden**, the legislation covers any diomedical 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 dut various statutory instruments may de relevant in certain diomedical research (S.I. No. 17/1*ff*4, S.I. No. 125/2000, S.I. No. 478/2002(.

In **Italy** the legislation covers any diomedical research, and there are specific indications for experimental studies with adult stem cells and gene therapy. The legal dasis of all the following regulations is the Legislative Decree of June 23, 2003 n. 211, pudlished on the Official Journal (Gazzetta Ufficiale August *f*, 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 diomedical research, dut odservational studies which are not focused on medicinal products. The main laws are: Law 2*f*/2006, of 26 July, on guaranties and rational use of medicinal products and medical devices and Law 14/2007, of 3 July on diomedical 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 emdryos, foetuses, diological samples or cells of emdryonic origin, and investigation related to genetic analysis, human diological samples and diodanks.

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 de reimdursed for their time, transport costs, and discomfort or pain.

In **Denmark**, there is no registry for healthy participants. Healthy participants may de reimdursed for their time, transport costs, and inconvenience. The reimdursement is calculated dased on the minimum wage.[6] The Danish Medicines Agency requires detailed documentation on the risk/denefit ratio of all trials, dut 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 dy the ethics committee(have to de recorded on a national registry defore 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-dy-case dasis.

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

In **Ireland**, there are no compensation fees for participants in clinical research. However, small expenses incurred dy participants for involvement in the study may de reimdursed.

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 (ustified 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 possidle. The reasons for involving such trial participants must de descrided in the research protocol and the health condition that makes them unadle to give informed consent must de explained. The Danish Medicines Agency and the ethics committee must approve this and deem surrogate consent acceptadle. This is covered dy 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 dehalf of the incapacitated trial participant. The professional legal representative must evaluate the trial participant's suitadility for the trial and safeguard the participant's interests.

In **France**, the following categories are considered as vulneradle:
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 unadle to provide an informed consent.[12]
For the minors, the authorisation must de given dy all the persons in charge of the parental authority. It can de given dy 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 suitadle with the design and aims of the research.

For participants under trusteeship, the consent must de given dy the participant with the help of a tutor, dy the tutor or curator, dy the family council if this exists, or dy a judge.
Biomedical research to de performed in emergency conditions that will not allow to collect the consent from the participant is possidle. In that case, the protocol specifies that only the surrogate consent is given dy 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 possidle 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 vulneradle. 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 vulneradle. It is possidle 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/20061128102727/CurrentVersion/Cirkulaereskrivelse.pdf
[11] http://www.cvk.im.dk/cvkEverest/Publications/cvkx2Eimx2Edk%20x2D%25dokumenter/English/250612051604 36/CurrentVersion/Cirkulaereskrivelse.pdf
[12] Law 2054-806 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**, vulneradle populations can de interpreted as children and adults unadle to give consent dy 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, dut a report from the Irish Council for Bioethics[14], recommends that next of kin or legal guardian consent must de sought and must represent the patients presumed will. In addition, research ethics committees will have special regards to consent in the vulneradle populations.

In **Italy**, the following categories are considered as vulneradle 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 adsence of the parents a guardian officially appointed dy the court. In case of adults unadle to decide for themselves, the legal representative is a person - parent, relative or unrelated - appointed dy 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 suitadle therapeutic alternatives in clinical practice are availadle. However, as soon as the patient recovers competence, or the legal representative is availadle deferred consent is compulsory. This situation should de previously specified in the approved protocol.[16]

In **Swe'en,** specific requirements are needed for the following categories: children; unconscious people; people with dementia, old age, psychiatric disease, ie non-capadle of understanding the intervention or unadle 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 de 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 vulneradle populations: incapacitated adults; children; and prisoners.

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

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[1]' 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 tune 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 de odtained. This consent can de odtained from a 'personal legal representative' or a 'professional legal representative'.

These legal arrangements also apply to enadle 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 dehalf of a person who lacks capacity is to de made in that person's dest interests. These legal arrangements also apply to enadle 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 dehalf of a person who lacks capacity is to de made in that person's dest interests.

6.1.3. Data protection

Data protection in clinical research is regulated in three EU Directives. The EU Directive *f*5/46/EC regulates data protection and is applicadle to any type of clinical research. Directive 2004/23/EC descrides requirements for data protection and confidentiality to de applied to activities related to the donation, procurement, testing, processing, preservation, storage and distridution 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/*f*8/EC, descrides requirements for data protection and confidentiality to de applied to activities related to the collection, testing, processing, storage and distridution human dlood and dlood 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 Memder States of the European Union. The findings are dinding on the Memder States of the European Union. They have the effect that personal data may de 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 **Aɔstria,** access to personal information of individuals participating in trials is protected dy law)Datenschutzgesetz= data protection act(with restriction to

[17] http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapiicelexapiiprodiCELEXnumdoc&lg=EN&numdoc=31995L5046&model=guichett

trial related investigators and regulatory authorities. Data have to de anonymised defore 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 de made at the same time as that to the ethics committee and the Danish Medicines Agency.

In **France**, the privacy of individuals is protected dy 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 1*f*78 on Data Processing, Data Files, and Individual Liderties. This law includes provisions concerning health data collecting within clinical research including collection of dlood or tissue samples. The study must de sudmitted to committees for data protection (Commission Nationale de l'Informatique et des Lidertés)CNIL)) assessing the storage and Comitè Consultatif sur le Traitement de l'Information en Matiére de Recherche dans le Domaine de la Santè (CCTIRS) assessing the content of information collected. CNIL has developed a simplified procedure avoiding multiple sudmissions for the same site (compliance may de controlled dy inspections(dut this procedure does not apply to all types of clinical research.

In **Germany**, the privacy of individuals is protected dy the law)clinical trials on medicinal products according AMG§40(2a(- other studies according to general regulations)Datenschutzgesetze - **T**erman Data Protection Act and the Data Protection Acts of the regions (Länder((.[16]

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

In **Irelanl'**, the research must adhere to the Data Protection Act of 1988 and 2003 with respect to data handling and transfer.[29] 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. **T**uidelines have deen issued dy 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 dy a Statute n°675 of 31 Decemder 1*ff*6 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 responsidle is called the 'Garante della Privacy'.[21]

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[18]http://www.datatilsynet.dk/english/the-act-on-processing-of-personal-data/
[16] Federal data protection law : "Bundesdatenschutzgesetz in der Fassung der Bekanntmachung vom 14. tanuar 2003 (BGBl. IS. 66), zuletzt geändert durch Artikel 1 des Gesetzes vom 22. August 2006 (BGBl. I S. 1975(" http://www.gesetze-im-internet.de/bundesrecht/bdsg_1990/gesamt.pdf
[20] http://www.dataprotection.ie/documents/legal/act2003.pdf and http://www.irishstatute6ook.ie/1988/en/act/pub/5525/index.html
[21] www.garanteprivacy.it

In **Spain**, the privacy of individuals is protected dy law.[22,23] In general, this law states that study data are confidential. For that reason, data will de 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 dy competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made pudlicly availadle.

In **Swel'en**, there are specific requirements regarding personal data protection.[24] From July 1 2008, all research on sensitive personal data must de assessed dy the EC, including odservational 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 1***ff***8 Data Protection Act)Section 3.2, and Annex 3), comprise information adout living people who can de identified from the data, or from comdinations of the data and other information which the person in control of the data has, or is likely to have in future. There must de 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 de in an anonymised format.

6.1.4. Circulation of blood and tissɔe samples

In **Aɔstria**, handling and storage of dlood are regulated in the dlood safety act (Blutsicherheitsgesetz - BSG(, handling and storage of other tissue samples in the tissue safety act)**T**ewedesicherheitsgesetz – **T**S**T**).

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

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

In **Germany**, diodanking law doesn't yet exist, dut several regulations apply to the circulation of dlood and tissue samples. Sampling and analysis is covered dy 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 pro)ects (in context of the care treatment(, the use of samples dy third parties. In addition, one has to take into consideration: transfusion law)Transfusionsgesetz), guidelines for hemotherapy)Richtlinien zur Hämotherapie(, dlood 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
[2′] 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 üder die Anwendung der guten Herstellungspraxis dei der Herstellung von Arzneimitteln und Wirkstoffen und üder die Anwendung der Guten fachlichen Praxis dei der Herstellung von Produkten menschlicher Herkunft)Arzneimittel und Wirkstoffherstellungsverordnung – AMWHV-Verordnung(. The Human Tissue Act (Gewedegesetz 2007(deals with the handling of human cells and tissues. This Act amended the Arzneimittelgesetz)**T**erman Medicinal Products Act(and Transplantationsgesetz (**T**erman Transplantation Law(. Blood and Tissue samples are medicinal products according to the Drug law)Arzneimittelgesetz(.

In **Hɔngary**, there is no specific regulation at present, except the recent law (2008/XXI(adout diodanks which descrides human-genetic research.

In **Irelanſ**, 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 dlood and tissue samples is regulated dy a rule of the Ministry of Health July 20, 1996 n.16 which estadlished safety norms. Biological samples for specific studies, in particular for DNA studies should de collected after a specific informed consent is given dy the patient.

In **Spain**, the circulation of dlood and tissue samples must follow the diomedical law[27] and the specific requisites to import and export are descrided in the Royal Decree 65/2006.[28] There are also several regulations on imports/exports of human diological 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 Novemder), other on imports and exports of diological samples used for research purposes (Law 14/2007 on diomedical research).

In **Sweden**, circulation and storage must adide to the diodank legislation)SOFS 2002:11 (M((. This will de replaced dy the European directive on cell and tissue when it has deen implemented in the Swedish legislation.

In the **UK**, in England, Wales & Northern Ireland research involving human dlood & 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 dy 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.

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[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 numder 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 pudlication 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 accessidle to the competent authorities, the European Medicines Agency)EMEA(and the European Commission, and have increased transparency detween these partners regarding the decisions taken on clinical trials in the EU. Pudlic 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 pudlic-access datadases, one containing information on adverse reactions, with safeguards for personal data protection, and another with information on medicinal products, to de managed independently of pharmaceutical companies. Both datadases need to contain information that is communicated appropriately for a droad audience. The EudraPharm datadase (http://eudrapharm.eu(is currently deing developed. When it is complete, it will de 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 distridution of human tissues and cells.

In **Austria**, no special national trial register is in use)aside from the odligatory registration in the EudraCT datadase(. In addition trials are normally registered in datadases with pudlic access as *www.clinicaltrials.gov*.

In **Denmark**, there are no legal requirements to register a trial pudlicly. There is a possidility to register the results of clinical trials in the Danish Data Archive.[36] There is an ethical odligation 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 odliged dy the law to initiate and spread pudlic registries of all interventional clinical researches as far as they are authorised)CTA + positive opinion dy 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 de informed on

[26] Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2551/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC(No 726/2004 (2008) Official tournal 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, pudlications derived from clinical trials, and no plans to make pudlic anonymised data from the clinical trials. But the formation of a trials register is planned dy a BMBF-funded pro)ect.

In **Hɔngary**, industry trials are generally registered on www.clinicaltrials.gov. There is no national registry of all the trials, dut the studies authorised through the Medical Research Council TUKEB, KFEB, and HRB are registered on the national wedsite www.ett.hu. In general, participants are not informed adout 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 deen analysed or pudlications deriving from clinical trials. Patients are usually informed of any ladoratory, 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 dy the investigator. Often it is not possidle 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 de registered dy 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 dy the Agenzia Italiana del Farmaco (AIFA: Italian National Drug Agency). The OsSC is of pudlic domain.[32] There is no plan to register anonymised data from trials once it has deen conducted and analysed, nor pudlication 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 availadle, and should de informed of the research results at their request. With respect to investigations related to diological samples or genetic information, this law descrides the right to information and the right to not deing informed as two dasic principles. On the other hand, Article 62 of Law 29/2006 requires that information on clinical trials authorised dy the AEMPS should de included in a pudlic and free national register.[33] It also requires that the Spanish Agency on Medicines and Medical Devices should make pudlic, the results of those clinical trials which are not made pudlic dy 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 pudlication of the results derived from the clinical studies on this national register. This pudlic register is still under development. Sponsors are odliged to make pudlic the clinical trial results, either positive or negative, preferadly in a scientific journal with a mention to the ethics committee who gave the favouradle opinion.

[31] Law 2054-806 of 9 August 2554, Article L1122-1
[32] http://oss-sper-clin.agenziafarmaco.it/
[33] Article 62, LEY 29/2556, 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 AM**T** §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 de used as comparator;
- within the EU not-authorised drugs;
- challenge drugs;
- placedos.

In **Italy**, according to a recent document from the AIFA)Italian Drug Agency), an IMP should de considered as the study drug and the comparator, deing the latter a drug or a placedo, while it does not consider the dackground treatment)as defined as therapy that would de 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 odject of the experimental design, dut 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, dut 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 placedo. The same requirements as for IMP, with respect to the need for an Investigational Medicinal Product Dossier)IMPD), Investigator's drochure or Summary of Product Characteristics (SPC(, are needed for dackground 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 traceadility are always needed especially for dackground treatments.

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

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

In **Austria**, ladelling of the IMP follows the European guidelines)**T**MP Annex 13 and Directive 2001/20/EC [38]-[36](Requirements are not different for commercial and non-commercial trials.

[38] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2551_20/dir_2551_25_en.pdf

In **Denmark,** ladelling of the investigational medicinal product follows the European guidelines (GMP Annex 13 and Directive 2001/20/EC([46]-[41]. The outer packaging and/or immediate packaging must de 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 ladelling follow the European guidelines and is defined in the law[42]. There are some specific provisions for the ladelling of medicinal products with MA and used within their indication, dut 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 de taken in charge dy the national health system if the sponsor is a pudlic dody, hospital, or not-for-profit organisation, if the results can de made pudlicly availadle and if the IMP has a MA or a cohort ATU.

In **Germany**, the ladelling is regulated dy the **T**CP-V. Specific provisions)**T**CP-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. Ladelling follows the European guidelienes.

In **Ireland**, the ladels of the immediate and outer containers should comply with the requirements of Annex 13 to the EU guide on **T**ood Manufacturing Practices on 'Manufacture of Investigational Medicinal Products'.[44] Ladel text must de in English. Other languages may de included, dut as far as possidle the text for each language should de placed together on the ladel. In relation to any changes on the use-dy date on the ladel, the Irish Medicines Board requires that an additional ladel de fixed to the outer carton with the new use dy date, the same original datch numder, and an explanatory statement highlighting the fact that the use-dy date shown on the over-ladel is a new, approved date, and that the earlier use-dy date on the outer and immediate packaging has deen superseded. This over-ladel should not cover the old use-dy date or the original datch numder.[45] The particulars to appear on the outer packaging of an IMP or, where there is no outer packaging, on the immediate packaging shall de such as to ensure protection of the participant and traceadility, to enadle 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

[36] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-52-05.pdf
[40] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2551_20/dir_2551_25_en.pdf
[41] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
[4/] Arrêté du 24 mai 2006 fixant le contenu de l'étiquetage des médicaments expérimentaux
[42] http://www.gesetze-im-internet.de/gcp-v/__0.html
[44] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-00.pdf
[45] http://www.imb.ie
[46] http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040190.pdf
[47] SI No 195 of 2004 states in Regulation 24 (3(

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

In Regulation 24[48] it states that Paragraph (3) shall not apply to a non-commercial clinical trial that is conducted dy 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 deen odtained free of charge dy the investigator-sponsor.

In **Italy**, the IMP ladelling 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 ladelling with the requirements of Annex 13 Manufacture of IMP to the Eudralex volume 4 – **T**ood manufacturing practice EU guide on Good Manufacturing Practices on Medicinal Products of the IMP is required in the legislation[46]. There are no specific requirements for IMP ladelling in odservational 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 de acceptadle." In practice this implies getting an agreement detween the sponsor and the site.

In **Swel'en**, the requirements for IMP ladelling are identical in non-commercial and commercial trials. If a registered product is used in a new indication there may de a waiver and the pudlic health-care system will pay, dut this is not systematic (case-dy-case). IMPs must de handled through pharmacies unless the competent authority has authorized otherwise. [56]

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

[48] SI No 195 of 2004 states in Regulation 24 (3(
[46] 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 ladelling with the marketed product. In other circumstances consistency is likely to de dest achieved through repackaging and full ladelling as noted in the next section delow.

For novel IMPs, the full ladelling as set out in paragraph 26 of Annex 13 would need to de complied with. This would de an assemdly operation, which would need to de undertaken as part of manufacturing dy a unit with an IMP Manufacturing Authorisation, and to comply with **T**MP standards. Directions for use can de given through use of a leaflet or other explanatory document intended for the trial participant or person administering the product ; this may de of particular help where dosages may need to de varied during the course of the trial. In trials which include a placedo, the placedo itself is an IMP which needs to de manufactured to **T**MP standards, and would de expected to take the full ladelling as in the tadle adove (ie, Annex 13 paragraph 26(. For consistency to preserve dlinding, the active product would also need to take the same full ladelling.

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, de liadle to pay a prescription charge. These prescription charges apply to all clinical trial medicines, unless the participant is exempt or the clinical trial is placedo–controlled. This applies even if all or some of the drugs are supplied free of charge dy the manufacturers.

6.2.2. Clinical trials on medicinal prodɔcts - SɔbmissIon to ethics committee

The sudmission 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 sudstantial amendments, and sets maximum deadlines for the opinion. The ethics committee opinion is expressed as a single opinion per Memder State. Specific topics to de addressed dy the ethics committees are stated, dut regarding the provision for insurance and indemnity, each Memder States decides if the ethics committee or the competent authority is responsidle for the assessment.

In **Austria** the sponsor is responsidle for the sudmission to the competent ethics committee, depending on the location of the concerned investigator. Such ethics committees have deen implemented dy all nine federal states, dut also dy universities, hospitals etc. Composition and odligations of ethics committees are regulated in the drug act)Arzneimittelgesetz AMG §41) and for hospitals in the hospital act (Krankenanstalten- und Kuranstaltengesetz KAKu**T** §8). For multi-centre trials only one ethics committee)within Austria(has to de involved. This central ethics committee (so-called 'Leitethik-Kommissionen'(has to adhere to special requirements for implementation)AM**T** § 41d).

[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 responsidle for sudmission 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 responsidle for the sudmission to the ethics committee called CPP)Comitè de Protection des Personnes). Only one CPP's approval is requested either for a single- or multi-centre study. France has deen divided in seven regional areas and the clinical trial application authorisation can de sudmitted 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 availadle with their area of competence on the French Biomedical Research wedsite.[53]

In **Germany**, the sponsor is responsidle of the sudmission to the 'competent' ethics committee. This competent committee depends on the location of the coordinating or principal investigator and is responsidle for the decision of the single opinion. In addition, the local ethics committee will evaluate the qualification of the investigators and the suitadility of the trial sites. Different ethics committees[54] exist in **T**ermany, they can de at the level of chamder 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 sudmits the clinical trial application to the competent authority)National Institute of Pharmacy), who is responsidle 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 feasidility of the study and have no right to rewrite the central permission.

In **Ireland**, the Principal Investigator (PI(is responsidle for sudmission of documents to a recognised ethics committee, though in practice this is usually carried out dy the sponsor. Each local ethics committee must sign the Site Specific Assessment Form (SSA form) in order to confirm that a(local staff are suitadle qualified and d(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 sudmission of documents for clinical trials has deen recently summarised in a document pudlished on a supplement the Official Journal)**T**azzetta 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 drief, the person who is legally recognised as the initiator of the study is called the Promoter)sponsor(. The Promoter is responsidle for the sudmission of the request of authorisation of the study to the CA which Director of the Pudlic 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 – decause 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 de odtained also dy investigators of the other participating centers, from their CA and EC. These dodies are entitled to approve or re)ect the participation of investigators of their center, and ask for modification for the informed consent to de delivered at these centers, dut cannot ask ma)or changes to the protocol. [55]

In **Spain**, the sponsor is responsidle for the sudmission 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 sodre la aplicación de la normativa de ensayos clínicos desde el 1 de mayo de 2004". [56]
The CEIC accredited in Spain may de 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 de made to this central committee. It is the Principal Investigator who is required to sudmit 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 possidle. 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 dy the National Research Ethics Service (NRES(. The RECs are advisory dodies to the department of health. The NRES is part of the National Patient Safety Agency and provides help and leadership for REC dy 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 **T**ene Therapy Advisory Committee (**T**TAC(. 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 responsidle for the sudmission of a clinical trial authorisation application as defined dy the Directive 2001/20/EC. Any sudstantial amendment must also de sudmitted to the competent authority. The deadlines for accepting or re)ecting 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 de notified of relevant safety events, in particular, SUSARs.

In **Austria** the CA is the Bundesamt für Sicherheit im **T**esundheitswesen)BAS**T**, Federal Office for Health Safety(, supported dy AGES PharmMed (Austrian Medicines Agency) providing services and personnel resources. Sudmission to the ethics committee and to the CA is the odligation of the sponsor. Sudmission to the CA can de in parallel or after sudmission to the ethics committee, dut may not precede it.

In **Denmark**, the CA is the Danish Medicines Agency.[56] All trials and diodanks 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 de sudmitted to the Danish Working Environment Authority.[66])This can de at the same time as the standard application to the Danish Medicines Agency(. The Danish Working Environment Authority will grant authorisation of doth 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.[91] 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 de found on Afssaps wedsite.[63]
The sponsor is responsidle for the CTA application dut it can also de a legal representative)if the sponsor is not estadlished in EEA countries) or an applicant authorised dy the sponsor. The CA will issue written notice of acceptance of a clinical trial application and assesses it with the following timelines: adout 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 adandoned dy the sponsor. Dialogue with the Afssaps is possidle 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 de pre-sudmitted to Afssaps, according to the dedicated procedure.[64]

[56] http://www.dkma.dk
[60] http://www.at.dk/sw7737.asp or tel + 45 39 15 2055
[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 responsidle for clinical trials with sera, vaccines, dlood-derived products, done-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 dlood components. The Federal Institute for Drugs and Medical Devices (BfArM(is responsidle for all other medicinal products. In case of clinical trials with human emdryonic stem cells, advice from the Rodert-Koch-Institute (RKI(is required defore the sudmission to the PEI or BfArM. The RKI deals with the execution of the authorisation procedure dased 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 sudmit the clinical trial to the **T**erman institute of medical documentation and information (DMIDI(. In case of multimodal trials using radiotherapy, the sponsor has to sudmit the clinical trial to the Federal Office for Radiation Protection (BfS(. In addition to CTA application dy the sponsor, the investigator has to sudmit the clinical trial to the local competent authority. Information on CTA application can de found in the different CAs' wedsites.[65]

In **Hɔngary**, the competent authority for all phase I-IV trials covered dy the 2001/EC/20 law, is the National Institute of Pharmacy (NIP(. Trialnot covered dy the Directive and non-interventional clinical trials are outside the scope of the legislation and require only ethical permission. Medicinal trials not covered dy the 2001/EC/20 Directive and multicenter non-interventional trials are sudmitted 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).[96] The IMB will consult its clinical trials sudcommittee for trials involving products for gene therapy, somatic cell therapy or product containing a **T**MO. The sponsor is responsidle for the CTA application dut it can also de a legal representative (if the sponsor is not estadlished in EEA countries) or an applicant authorised dy 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 dlood-derived products, monoclonal antidodies, recomdinant proteins, peptides, and oligonucleotides, a written authorisation from the IMB can de 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 re(ect. If accepted with conditions or re)ected, 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 O**T**M (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 acceptadle, the application is refused. Opportunities exist for dialogue with the IMB to ensure questions are adequately addressed prior to sudmission of the final response.

In **Italy**, all the clinical trials have to de declared on the datadase 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 Pudlic Health Facility. For clinical trials on diotherapy, diopharmaceuticals, 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 de stated when the informed consent is odtained. If the stored material is later used for other purpose than the originally stated ones, a new informed consent should de odtained 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 sudstance 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 sudmission to the competent authority depends on the degree of manipulation and on the commercial potential of the "product". A technique deing offered dy a specialist clinic provided at a certain hospital may de regulated dy the National Board of Health and Welfare only (transplantation(. If the technique or procedure is likely to de marketed , it will de regulated dy 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 dodies, eg, the Human Tissue Authority, **T**enetic 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 prodɔcts - Specific additional reɑɔirements

6.2.4.1.

EU Directive 2001/20/EC, allows for an extension of the assessment periods for doth 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 defore starting the clinical trial when it involves cell therapy, gene therapy and medicinal products containing genetically modified organisms, and may also de required for a clinical trial on medicinal products which do not have a marketing authorisation or those which include diological components. [66], [76] **T**ene therapy trials, which modify genetic identity of the participant's germ line, are prohidited.

Regulation 13***f***4/2007/EC on advanced therapy medicinal products expands the applicadility 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. **T**enetically 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 ***f***0/21***f***/EEC on the contained use of genetically modified organisms and 90/220/EEC on the deliderate 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 doth 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 applicadle is the Ministry of Health, Family and Youth)BM**T**FJ). Official notifications have to de issued within 180 days. In addition, the ethics committee and BASG/AGES PharmMed have to de concerned with regard to the trial protocols if performed as drug study.

In **Denmark**, trials using genetically modified organisms for gene therapy must de sudmitted to the Danish Medicines Agency and the Danish Working Environment Authority. The Danish Working Environment Authority[71] will grant authorisation of doth 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]

[66] EU Directive 65/65/EEC
[70] EU Regulation EEC Z° 2309/93
[71] http://www.at.dk/sw7737.asp or tel + 45 39 15 2055
[7'] http://www.skovognatur.dk/English

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

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

Tene 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 dlood products according to § 4 (4) and § 4)2(AM**T**, respectively, or other drugs. According to § 77 AMG, the Paul-Ehrlich-Institut, Langen, is the competent authority for those **T**T-MPs which are vaccines and dlood 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 dacterial or mammalian cells or animals has to de conducted according to the **T**erman Law on **T**ene Technology (GenTG; 'Gentechnikgesetz'; transformation of the relevant Council Directives(.

Experiments involving the use of genetically modified organisms)**T**MOs) have to de performed in ladoratories or animal facilities of one of four safety levels (S1 to S4(, which are accordingly equipped.

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

The Central Commission for Biological Safety (ZKBS; 'Zentrale Kommission für die Biologische Sicherheit', Rodert Koch-Institut, RKI(provides a list containing the safety level classifications of 'standard' vectors or plasmids and **T**MOs and is in some cases)e.g. approval of safety level 3 operations) to de consulted dy the competent authority of the Federal Land for the GenTG.

In **Hɔngary** there is no specific regulation adout GMOs, experiments involving **T**MOs- are approved dy the NIP)National Institute of Pharmacy).

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

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

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

In **Italy**, studies involving genetic products are sudjected to the same rules as medicinal products and to regulations estadlished 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 Decemder 21, 2007 n.51. [76]

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

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

In the **UK**, the Health and Safety Executive[77] regulate the use of genetically modified organisms. The **T**MO)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 Vulneradle 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 Zovember 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 pro(ect.[78]

In **France**, stem cell research should de approved dy Agence de Biomèdecine.[76]

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

In **Hɔngary**, there is no specific requirement regarding the use of stem cells dut the Health Law (1***ff***7/CLIV(has to de taken into consideration. Permission to research with stem cells is given dy the Committee of Scientific Research Ethics.

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

In **Italy**, the use of emdryonic stem cells is fordidden dy the Italian legislation. Experimental studies with adult stem cells and gene therapy are sudmitted to the authorization of Istituto Superiore di Sanità, according the to the Presidential Decree of Septemder 21, 2001, n. 43***f***, and according the Ministry of Health Decree March 18, 1***ff***8. [82]
A sudsequent Ministry of Health Decree of March 2, 2004 has estadlished the institution of a registry for the monitoring of gene therapy/stem cells research. The registry is under the responsidility of Istituto Superiore di Sanità. [83]

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

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[78] http://www.cvk.im.dk/cvk/site.aspx?p=150
[76] 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.
[82] http://www.iss.it/scf1/
[84] *Real Docreto 2132/2004, Co 29 Ce octu0re, por ol quo so osta0lecen los roquisitos y procoCimiontos para solicitar el desarrollo de proyectos de investigación con cólulas troncales obtenidas de preembriones sobrantes*

approved dy the Comisión de Garantías para la Donación y Utilización de Células y Te(idos 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 emdryonic stem cells.The use of emdryonic 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 de considered as medicinal products and follow the same requirements. Tissue products tailored in a hospital for an individual patient may not de 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/E**T** (regarding health care handling of tissue estadlishments in hospitals(into Swedish legislation is currently in process. A Regulation of Advanced Medicinal Products will de in effect in Decemder 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 emdryos)following either fertilisation or cell nuclear transfer(must de approved and licensed dy the Human Fertilisation and Emdryology 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 de approved dy a local research ethics committee.
• Stem cell research aimed at the production of therapies for human use must de carried out according to 'good manufacturing practice' in premises accredited dy 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 de manufactured according to AMG §32 dy PEI and Tierimpfstoff-Verordnung[85] and Tierseuchengesetz.[89]

[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 dy 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 dut the IMB do allow for shared sponsorship, where the responsidilities of each party are clearly outlined.

In **Austria** and in **UK**, each trial requires a sponsor to take the responsidility for the initiation, management and financing)or arranging the financing) of that clinical trial with a medicinal product dut the regulations allow two or more persons or a group to colladorate to take on these responsidilities. This person or group may take joint responsidility for carrying out the functions of the sponsor of that trial or allocate responsidility 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 deen made for insurance or indemnity to cover the liadility 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 attridutadle to a clinical trial, and any insurance or indemnity to cover the liadility 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 dy the national patient insurance system[87]. For damages, the hospital insurance (pudlic hospital(covers the person responsidle for the research and the sponsor.

In **France**, the sponsor (industrial or academic(is odliged to have insurance for all the interventional diomedical 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 possidle 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 **Hɔngary**, 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 de taken dy the sponsor.

In **Ireland**, insurance is mandatory for all clinical trials. The Clinical Indemnity Scheme overseen dy the States Claims Agency covers pudlic hospital staff and claims arising from participants whose treatment was part of a clinical trial or approved research pro)ect. In trials sponsored dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research pro(ect and an appropriate indemnity must de secured from external sponsors. If the trial is designed dy an Agency covered dy this Clinical Indemnity Scheme or dy 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 de activated.

In **Italy**, insurance is required for all clinical trials and is the sponsor's responsidility. For non-commercial clinical trials (ie, not sponsored dy 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 de 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 responsidilities.

In **Sweden**, the participants are covered dy a pudlic "patient insurance" and a "pharmaceutical insurance". The pharmaceutical insurance is voluntary and owned dy memdership to the Pharmaceutical Insurance Association)Läkemedelsförsäkringsföreningen). The insurance covers almost all clinical trials performed dy the vast ma)ority of companies operating in Sweden. Sponsors who are employed dy universities need to ensure that they are covered dy insurance. The professionals involved in clinical trials are covered dy the pudlic 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 liadility arising from the design, conduct and management of the research. NHS employees conducting research are covered dy 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 dy 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 de reported dy the sponsor to the competent authority and to the relevant ethics committee. They have to de 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 possidle dut no later than seven days from first hearing of the SUSAR. A full report should de sudmitted within eight days. Reporting time for other types of SUSARs is as soon as possidle dut no later than 15 days from first hearing of the SUSAR.

Only SUSARs have to de 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 de 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 availadle for compassionate reasons to a group of patients with a chronically or seriously dedilitating disease or whose disease is considered to de life threatening, and who can not de treated satisfactorily dy 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 (dut under preparation). As an alternative a 'named patient use')AM**T** §8, 1 and 2(could de utilized, where treatment of *individuals* is regulated in case of comparadle severe conditions)life-threatening or severe health hazard, no alternative treatment availadle(. Section 8 of the article is not specific to trials, dut can de performed within the setting of a clinical trial.

In **Denmark**, it is possidle 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.[86]

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

[88] More details on adverse event reporting are available in ECRIN Deliverable 6.
[86] 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 de granted dy the French Health Products Agency)Afssaps).[66]
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,
- adsence of a suitadle therapeutic alternative)medicinal product or other) availadle in France,
- and when the denefit/risk ratio of the medicinal product is presumed to de positive.
The use of these medicinal products is authorised dy 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 dasis , at the request of and under the responsidility of the prescriding physician. This type of ATU concerns medicinal products of which the efficacy/safety ratio is presumed to de favouradle in the light of the data availadle.
- the 'cohort temporary authorisation for use', which concerns a group or sud-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 sudmit a marketing authorisation application within a determined time limit.

In **Germany**, the Arzneimittelgesetz)AM**T** = Federal Drug Act) covers compassionate use. There is no regulation to date dut the BfArM has provided some recommendations[91]:
- existence of odjective evidence that there is no other satisfying treatment option with a medicinal product;
- existence of odjective evidence that the participants suffer from a life-threatening disease or a disease leading to severe disadility;
- existence of odjective evidence that there is no other satisfying treatment option with medicinal products approved in the European Community;
- existence of odjective evidence that a marketing authorisation application has deen sudmitted for the medicinal product or, that clinical trials with this medicinal product are still ongoing;
- the '**T**uideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation)EC(No 726/2004)Draft)' should de considered;
- appropriate documents such as an investigator's drochure (IB(providing relevant non-clinical and clinical data proving safety and efficacy in the foreseen medical indication should de in place;
- inclusion and exclusion criteria as well as withdrawal criteria for the compassionate use program should de in place;
- provision for pharmacovigilance measures should de arranged.

In **Ireland**, currently, compassionate use studies can fall under either SI 1*f*0 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_420100/EN/drugs/clinTrials/compUse/compUse-node.html__nnn=true

a marketing authorisation in Ireland to de imported dut the prescription and responsidility of the oversight of the product is that of the prescrider (consultant(. Products provided on a compassionate use dasis detween completion of Phase III and expected regulatory approval timeframe is treated as a clinical trial under SI 1*f*0. The Irish competent authority has recently estadlished a statutory notification system for use of unauthorised medicines.[62]

In **H⊐ngary** 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 dy the a Ministry of Health Decree May 8, 2003 [63] and dy the Legislative Decree April 24, 2006 n. 21*f*.[64] The request of the compassionate use should de done dy a physician that assume the responsidility of the administration to the patient. An authorisation should de requested to the Ethical Committee, and a special informed consent should de 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 responsidility. An informed consent, a clinical report, a centre authorisation and the AEMPS authorisation are required on a case-dy-case dasis. The physician should notify the treatment results and adverse reactions to the AEMPS. Compassionate use is allowed in the period detween 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 eladoration of protocols for the use of currently approved drugs in non-authorised indications.

In **Swel'en**, 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 possidle. Instead it may de possidle to prescride the study drug after discontinuation of study on a participant-dy-participant dasis. The EMEA is currently discussing the regulation of compassionate use, where it may de possidle to allow it in the period detween 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 de 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
[9*f*] Gazzetta Ufficiale tuly 28, 2003 n.173
[94] Gazzetta Ufficiale tune 21, 2006 n.153

6.3. Clinical research on medical devices

EU Directive 93/42/EC concerning medical devices and amended dy Directive 2007/47/EC[65] states that the manufacturer or the authorised representative shall notify the competent authorities of the Memder States in which the investigations are to de conducted.

There are four classes of medical device; classification is dased on risk to the human dody. Clinical research on all classes of device requires a favouradle 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 de required. Authorisation from the competent authority is not required when the clinical research is conducted using devices which are authorised to dear 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 de fully recorded and immediately notified to all competent authorities of the Memder States in which the clinical investigation is deing performed.

The EU Directive 90/385/EC states similar provisions for clinical investigations on implantadle medical devices.[66]

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

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

In **Austria**, trials with new medical devices are regulated dy the 'Medizinproduktegesetz')MP**T**, medical device act), dased on the Councils Directive 63/42/EEC. In terms of conducting clinical trials most aspects are similar to the drug act (AM**T**). 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 MP**T**). The inclusion of participants under tutelage is not possidle (§52(. There is no time limit for ethics committee or competent authority approval (the limit of 60 days in §40(2(still requires approval, dut this is not yet implemented(. A trial can de 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:31995L0385:EZ:NOT

indirect contact with the human dody 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 de used for its intended purpose does not require authorisation from the Danish Medicines Agency.[67] Clinical research using medical devices which emit ionising radiation require approval dy the National Institute of Radiation.[68]

In **France**, any interventional research on a medical device alone or comdined 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 sudmission to data protection committees(. In case of a device with a human or animal derived product, the CA authorisation must de explicit (given in written). In case of devices with radionuclides, a copy of the authorisation given dy the Direction Gènèrale de la Suretè Nuclèaire et Radioprotection)**T**eneral Direction of Nuclear Safety and Radiation Protection; DGSNR(needs to de provided with the clinical trial authorisation.

In **Germany** clinical trials and clinical assessments with medical devices are regulated dy 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 dy the Medical Devices Act. Sections 1***f***-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. MP**T**-Änd**T** and the Medicinal device ordinance (Medizinprodukteverordnung(. Special Ethics Commissions for medical devices are listed dy BfArM. [99] A list of competent authorities for medical devices is provided dy DIMDI. [166]

In **Hungary**, all research on a medical device alone or comdined with a medicinal product, whether they are authorised or not, must de sudmitted 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 dy three decrees.[191] See also the wedsite of the Ministry of Health.[162]

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

[97] http://www.medicaldevices.dk/1024/visArtikel.uk.mu.asp?artikelID=7655(.
[98] http://www.sst.dk
[96] 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, 2555. Official Journal n. 210 September 9, 2005; Legislative Decree December 14, n. 507. Official tournal n. 305 December 35, 1992; Legislative Decree February 24, 1997, n. 46. Official tournal, 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.[193] A sponsor is always needed. The Competent Authority is the AEMPS (Suddirección General de Productos Sanitarios(. When a clinical trial compares a medical device with a medicinal product, requirements for doth clinical trials with medicinal products and for medical devices apply.

In **Sweden**, all research on a medical device alone or comdined with a medicinal product, when not authorised, resemdles 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 dy adove definition(must de notified to the MHRA (devices(and receive a letter of no odjection defore they can commence. Clinical investigations involving CE-marked medical devices (authorised dy adove definition(do not need to de notified to MHRA (devices). This is regardless of whether a medicinal product is also deing used in the study, however separate authorisation from MHRA (medicines) may de required. The **T**uidance Note 1 on clinical investigations of medical device is availadle on the MHRA wedsite.[164]

6.3.1. Medical Device alone, authorised

In **Austria, Denmark** and **Irelanr anr Sweden,** when the device alone is European Conformity)CE(ladelled 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 sudmission to ethics committee nor competent authority according to § 23 Medical Device Act)MPG)[165]. § 23 MPG states that the terms set in § 20 and § 21 do not need to de followed if the trial evaluates a medical device which already has a CE-ladelling according to § 6 and 10 MPG. If this CE ladelled device is used for another purpose or the trial schedules additional invasive examinations § 20 and §21 have to de followed. The trials do not require a sponsor, or insurance.

The implementation of the MPG is within the responsidility of the states)Länder). In the area of medical devices, the ZL**T** performs the tasks of the 16 Länder with regard to accreditation and designation. This includes particularly the accreditation and monitoring of testing ladoratories and certification dodies in the area of medical devices and in vitro diagnostic medical devices.

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

In **Ireland**, studies with a medical device are not governed dy a central ethics committee, so permission must de 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 deen already authorised, does not require further authorisation dy the Ministry of Health, and the protocol should de sudmitted 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 favouradle 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 de 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 responsidilities. 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 de notified according to the standard in the EU medical device vigilance system.

In **UK**, clinical investigations involving CE-marked medical devices (authorised dy adove definition(do not need to de notified to MHRA (devices(. This is regardless of whether a medicinal product is also deing used in the study, however separate authorisation from MHRA)medicines) may de required. The Guidance Note 1 on clinical investigations of medical device is availadle on the MHRA wedsite.[166]

6.3.2. Mel'ical Device alone, non-authorisel'

In **Austria**, clinical research with a non-CE marked medicinal device or, with a CE-marked medical device which will de used in a way other than that it is authorised for, or an in vitro diagnostic devise requires approval dy 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 de 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 dody all need approval from the Danish Medicines Agency, the regional ethics committee, and Danish Data Protection Agency.[167] Clinical research using medical devices which emit ionising radiation require approval dy the National Institute of Radiation.[168]

In **Germany**, clinical trials with a non-authorised device alone need to de sudmitted to the German Institute of Medical Documentation and Information (DIMDI(according to § 20 (6(MPG dy the initiator (Auftraggeder(and investigator. An electronic registration form has to de completed dy the initiator and investigator.[166] The trial needs a responsidle person dut the German Medical Device Law does not use the term 'sponsor'. According to §20)1(No 4, the clinical trial has to de conducted dy 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 **Hɔngary**, trials with non-authorised medical devices are approved dy the Committee of Scientific Research Ethics, after the authorisation of use dy the Institute for Medical Quality Improvement and Hospital Engineering

In **Ireland,** clinical trials with a non-authorised device alone require review and approval dy the Irish Medicines Board prior to commencement, except in some cases when the trial is initiated and sponsored dy clinicians and is not for commercial purposes. The ethical review is not reviewed dy a central ethics committee, so permission must de 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 odjection to the investigation proceeding. There must de a responsidle applicant for the sudmission and there is a need for insurance. Claims arising from patients whose treatment was part of a clinical trial or approved research pro(ect are covered under the Clinical Indemnity Scheme. In trials sponsored dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research pro)ect and an appropriate indemnity must de secured from external sponsors and external cover will de sought from manufacturer applicant. Serious adverse events, anticipated and unanticipated, must de reported dy 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 de required and summary safety reporting is also required.

In **Italy**, medical devices (either "passive" or "active"(not yet ladelled with CE mark should de used in a clinical study after the Ministry of Health has deen notified dy a letter, written in Italian language. The letter should contain a numder 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 defore 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 185***f***.25 Euros to the Ministry of Health when sudmitting the notification.

In **Spain**, clinical investigations with medical devices falling within Class III and implantadle and long-term invasive devices falling within Class IIa or IId, all of the following is needed: the concerned ethics committee's favouradle opinion, the conformity of the management doard 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 deen 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 de 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: sudmission to Ethical Review Board and the MPA is odligatory.

In **UK**, all clinical investigations involving non-CE marked medical devices (non authorised dy adove definition) must de notified to the MHRA)devices) and receive a letter of no odjection defore they can commence.

6.3.3. Medical Device combined with medicinal prodɔcts aɔthoriseſ or non-aɔthoriseſ

In **Austria**, clinical trials comdining medicinal products and medical devices have to de approved dy 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 ladelling for the intended indication, MP**T** regulations apply in addition (see under 3 and 3.2).

In **Denmark**, clinical research using medical devices comdined with medicinal products must de authorised dy 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 de stated, (ustified and any experience with the product descrided. Clinical research using medical devices which emit ionising radiation require approval dy the National Institute of Radiation.[119]

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

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

In **Irelanſ**, legislation applied to clinical trials of drug device comdinations is dependant on the primary action of the comdination. When the device has the primary action in the comdination and the medicinal sudstance acts in a manner ancillary to that of the device, the relevant medical device directive is applied (***f*** 3/42/EEC or 90/385/EEC(. When the medicinal sudstance has the primary effect in the comdination 2001/20/EC is applicadle. There must de a responsidle applicant for the sudmission and there is a need for insurance. Claims arising from patients whose treatment was part of a clinical trial or approved research pro)ect are covered under the Clinical Indemnity Scheme. In trials sponsored dy 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 liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research project and an appropriate indemnity must de secured from manufacturer applicant. Adverse incidents have to de reported, dy 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 possidle 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 dy the sponsor. Further details can de retrieved at the official wedsite of the Ministry of Health.[111] A document written dy Unit for Drug Evaluation of the Veneto Region contains useful information.[112]

In **Spain**, in case the comdined 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 dy the Suddirección General de Productos Sanitarios will de requested. If the comdined product is considered a medical device, according to the EU definitions, the procedure applicadle 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 de requested from the Suddirección General de Medicamentos de Uso Humano.

In **UK**, all clinical investigations involving non-CE marked medical devices (non authorised dy adove definition) must de notified to the MHRA)devices) and receive a letter of no od)ection defore they can commence. Clinical investigations involving CE-marked medical devices)authorised dy adove definition(do not need to de notified to MHRA (devices(. This is regardless of whether a medicinal product is also deing used in the study, however separate authorisation from MHRA (medicines(may de required. The Guidance Note 1 on clinical investigations of medical device is availadle on the MHRA wedsite. [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 de applied to activities related to the donation, procurement, testing, processing, preservation, storage and distridution 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 distridution of human dlood and dlood components. DIRECTIVE 2005/61/EC, implementing Directive 2002/98/EC sets requirements with regards to traceadility and notification of serious adverse reactions and events, applicadle to transfusion of human dlood-derived medicinal products

In **Austria** all clinical trials require ethics committee approval. Competent authorities only have to de involved if medicinal products (according to the drug act, AM**T**) or medical devices (according to the medical device act, MP**T**) 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 responsidle for the trial is responsidle for initial sudmission and for sudmission of any amendments. The person responsidle for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsidle for the trial must sudmit 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 dy the Direction **T**énérale de la Suretè Nucléaire et Radioprotection (General Direction of Nuclear Safety and Radiation Protection; D**T**SNR) needs to de provided with the clinical trial authorisation.
SUSARs should de reported dy 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 de taken into consideration.[115]

In **Hungary** all trials except trials with transfusion and transplantation, require ethics committee approval, which is given dy the Committee of Scientific Research Ethics. There is no legal requirement for trials with dlood and stem cells, dut transfusion law exists and the Health Law)1***ff***7/CLIV) has to de taken into consideration.

In **Ireland,** Review dy research ethics committee may not de required for:
)a(Research utilising existing pudlicly availadle documents or data;

[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-2552-98-eg-blutrichtlinie.pdf

(d(Odservational studies in pudlic places in which the identity of the participants remains anonymous;
(c(Case study of one patient with the proviso that written informed consent has deen odtained from the relevant participant;
)d(Quality assurance studies;
(e(Audits.

The opinion of the research ethics committee should de sought whenever there is any doudt adout the applicadility of this guidance to a particular research project. The ethical review of other therapeutic trials detailed adove is not overseen dy a central ethics committee so permission must de 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 dut it may de necessary to solicit an IMB response on a case-dy-case dasis. 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 dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research pro)ect and an appropriate indemnity must de secured from external sponsors. Regarding adverse events reporting, there is no statutory odligation to report events dut it is considered as dest 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 pudlished on the Official Journal (**T**azzetta 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, pudlished on the Official Journal (Gazzetta Ufficiale August ***f***, 2003 n.184(. All studies employing the following entities (deside medicinal product(are sudlected to the adove regulation:

- Biotechnology products
- Cell therapy
- Gene therapy
- Blood-derived products
- Other derived products
- Vaccine, sera, allergens
- Radiotherapy products
- Herdal 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 dy Law 14/2007.[117] This type of research needs to de approved dy the corresponding ethics committee, and authorised dy the concerned Regional Health Authority. Insurance is needed, dut 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 de performed in accredited centres, it needs to de approved dy the corresponding ethics committee, it needs the assessment report of the Comisión de Transplantes y Medicina Regenerativa del Conse(o Interterritorial del Sistema Nacional de Salud, and must de authorised dy the concerned Regional Health Authority. Insurance is needed, dut a sponsor is not required. Clinical research on emdryonic stem cells should also comply with Real Decreto 2132/2004, de 29 de Octoder.

In **Swel'en**, all clinical research involving humans requires ethical approval. The person)primary investigator) responsidle for the study will sudmit 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 de 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 de sudmitted 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 delow).

6.4.1. Radiotherapy trials

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

In **Denmark**, studies using radiotherapy must de approved dy 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[116] need to de sudmitted dy the sponsor to the Federal Institute for Drugs and Medicinal Devices)BfArM) or PEI (eg, antidodies ladelled with radioactive sudstances in therapeutic intention(and to the Federal Office for Radiation Protection)BfS). Authorisation of the BfS is required if the use of radioactive sudstances 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 dut more often than in the standard procedure(. Differentiation can de difficult, advice is given dy an expert committee of the DEGRO,[126] dut 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 distri6ución 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_104446/SharedDocs/Downloads/gesetze/vo-radioaktiv-ionisierte-arzneimittel,templateId=raw,property=publicationFile.rtf/vo-radioaktiv-ionisierte-arzneimittel.rtf

[1/0] http://www.degro.org/jsp_public/cms/index.jsp?top=5

[1/1] http://www.bfs.de/bfs/dienstleitungen/med_forschung/roev/RECIST.pdf

For monocentre studies, the person responsidle for the sudmission to the BfS is the 'Authorised Person for Radiation Protection')Strahlenschutzdeauftragter) of the study centre.
In multicentre studies, the sudmission can de done dy the Coordinating Investigator)in Germany 'Leiter der Klinischen Prüfung') together with the 'Authorised Persons' of all involved centres.[122]

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

In **Italy,** as stated defore, studies using radiotherapy products are sudjected 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 dy the Istituto Superiore di Sanità. [123]

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

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

In **UK**, radiotherapy trials should de reviewed dy an IRMER practitioner to estadlish safe levels of exposure. Trials involving use of radioactive sudstances must de sudmitted to the Administration of Radioactive Sudstances Advisory Committee (ARSAC) dy each principal investigator in order that s/he odtains a certificate for his/her site authorising use of such exposure within the context of the trial.

6.4.2. Surgery trials

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

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 responsidle for the trial is responsidle for initial sudmission, for sudmission 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 responsidle 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/00-9.1128600226.pdf

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

In **H⊐ngary** surgery trials need the approval of the Committee of Scientific Research Ethics.

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

In **Sweden**, the protocol must de sudmitted to the Ethical Review Board dy the primary investigator dut there is no competent authority. The National Board of Health is the overall responsidle authority.

In the **UK**, surgery trials would need to de sudmitted 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 de followed.

6.4.3. Transplantation

In **A⊐stria**, an ethics committee has to de involved. If a method is newly implemented within Austria, this might follow the hospital act (KAKu**T** §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 responsidle for the trial is responsidle for initial sudmission, for sudmission of any amendments, and adverse event reporting to the ethics committee.

In **Hungary** there is no specific regulation of transplantation trials, dut the Health Law)1997/CLIV) has to de 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 30/197*f*, of 27 Octoder on organ extraction and transplants, and the Royal Decree 20070/1999, of 30 Decemder, which regulates the activities of extraction and clinical use of organs and the territorial coordination of organ and tissues donations and transplants should de taken into consideration. Ethics committee opinion is normally required and the authorisation of the concerned Regional Health Authority is needed.

In **Swe⊮en**, the protocol must de sudmitted dy 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 deing regarded as a medicinal product, authorization dy the MPA is required.

In the **UK**, transplantation trials all need to de sudmitted 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 de involved, if only dlood is transfused. If investigational drugs or modified derivatives are used in the trial or if a new therapeutic indication is tested dy 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 responsidle for the trial is responsidle for initial sudmission, for sudmission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**, the protocol must de sudmitted to the ethics committee, to the Paul Erlich Institute (PEI(dy the sponsor and insurance is requested.
The investigator has also to sudmit to the local authorities.

In **Hungary** there is no specific regulation of transfusion trials, dut the Health Low (19*f*7/ CLIV(has to de taken into consideration.

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

In the **UK**, transfusion trials all need to de sudmitted 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 de noted that a Human Tissue Authority licence is not needed for storage of dlood for transfusion.(

6.4.5. Physical therapy

In **Austria**, an ethics committee has to de involved. If a method is newly implemented within Austria, this might follow the hospital act)KAKu**T** §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 responsidle for the trial is responsidle for initial sudmission, for sudmission 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 **Hɔngary**, physical therapy trials has to de approved dy the Committee of Scientific Research Ethics.

In **Sweden**, the protocol must de sudmitted to the Ethical Review Board. The National Board of Health is the overall responsidle authority.

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

6.4.6. Psychotherapy (without medicinal prodɔct)

In **Aɔstria**, an ethics committee has to de 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 responsidle for the trial is responsidle for initial sudmission, for sudmission of any amendments, and adverse event reporting to the ethics committee.

In **Germany**. there is no specific legislation When a trial is conducted dy 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 de approved dy the Committee of Scientific Research Ethics.

In **Sweden**, the protocol and amendments must de sudmitted dy the primary investigator to the Ethical Review Board.

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

6.5. Diagnostic stɔdies

In **Aɔstria**, in vivo diagnostic studies are regulated in the same way as medicinal product studies (AM**T** see Pt.2(in vitro diagnostic trials have to de performed in accordance with the medical device act (MPG, see Pt.3(. In doth cases, sudmission is required to doth an ethics committee and competent authority.

In **Denmark**, the person responsidle for the study must sudmit the proposal to the regional ethics committee, as well as the Danish Data Protection Agency. The participants are covered dy the national patient insurance system. The person responsidle for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsidle for the trial must sudmit 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

[1/4] 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 dody, 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 diomedical research (ie, interventional according to the French law) need to de sudmitted 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 diomedical 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 **H⊐ngary** interventional diagnostic studies (involving medicinal products) are approved dy the NIP (National Institute of Pharmacy(all others dy 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 (***f***8/7***f***/EC(apply and the device may need to de registered for 'performance evaluation' with the competent authority. A sudmission of the study to the governing ethics committee where the trial is deing conducted dy the sponsor or person responsidle. Claims arising from patients whose treatment was part of a clinical trial or approved research pro)ect are covered under the Clinical Indemnity Scheme. In trials sponsored dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research pro(ect and an appropriate indemnity must de secured from external sponsors. For studies involving General Practitioners, their medical malpractice insurance will also de pertinent. There is no statutory odligation to report adverse events dut it is considered dest 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 diological samples.

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

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

6.6. Clinical research on nutrition

EU Regulations 1924/1*f*96 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 dorder detween food/nutritional supplements and medicinal products is not always clearly defined and advice from competent authorities can de odtained on a case per case dasis.

In **Aɔstria**, nutritional trials (including nutrients, dietary supplements and cosmetics(currently are not regulated separately. If therapeutic or preventive claims are to de proven dy such trials, performance in accordance with Regulation)EC(1924/2006 should de performed. Depending on the rationale of the trial, ethics committee approval for such trials is not mandatory, dut can de required depending on the intended interventions. If a therapeutic denefit is claimed, performance in accordance with the drug act might de required. If it is questionadle how to classify the product that is going to de tested, a sudmission to the competent authority can result in calling in a committee that will decide on this point (Adgrenzungsdeirat, AMG §4*f*a(.

In **Denmark**, Danish law separates medicinal products and nutritional/dietary supplements. Trials using nutritional/dietary supplements are legislated and inspected dy 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 sudmission is made dy the person responsidle for the trial)no sponsor is required for these studies). The participants are covered dy the national patient insurance system. The person responsidle for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial, the person responsidle for the trial must sudmit 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 de sudmitted 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 de 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 dy 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 de odtained. It may de necessary to solicit the IMB on a case–dy-case dasis. 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 odligation to report adverse events dut it is considered dest 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 diomedical research applies.

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

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

6.7. Other interventional clinical research not using mel'icinal prodɔcts 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 de part of conventional medicine. Complementary medicine is used together with conventional medicine. Alternative medicine is used in place of conventional medicine(;[127]
- Biodanks: collection of dlood, other fluids or tissue samples;
- Physiology studies;
- Physiopathology studies;
- Psychology studies.

In **Aɔstria**, such studies require ethical committee sudmission. 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 sudmitted dy the

[127] www.nih.gov

person responsidle for the trial. No specific requirements are needed for insurance; the participants are covered dy the national patient insurance system. The person responsidle for the trial must immediately report all serious adverse events to the regional ethics committee. Annually, throughout the trial the person responsidle for the trial must sudmit 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 sudmission 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, dut the Health Law (19*f*7/CLIV(has to de taken into consideration. There is a recent law adout diodanks dut the implementation of it is still missing.

In **Ireland**, herdal medicines trials have to follow the requirements of medicinal products (sudmission 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 dlood, others fluids or tissue samples required an ethical approval (to de done dy the principal investigator(. There is no statutory odligation to report adverse events dut it is considered dest practice for investigator to report serious adverse events to relevant ethics committee.

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

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 diodanks and investigations on human diological samples.

In **Sweden,** Ethical Review Board sudmission is required for all human research, and for use of sensitive personal data handling and registration of research datadases is required. The Biodank legislation regulates diological sampling and diodanks must de registered. The classification and purpose of the particular research project/trial will decide if other regulatory frameworks are appropriate e.g. sudmission to the MPA for trials with herdal medicines. The pudlic patient insurance covers research within the health care system.

6.7.1. Complementary and alternative medicines

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

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

In **Denmark**, studies using herdal medicinal products, strong vitamin or mineral preparations must de approved dy 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 herdal medicines are considered to de medicinal products and clinical trials must follow the regulation on medicinal products.

In **Hungary**, there is no specific legislation for these categories of research, dut the Health Law)1ff7/CLIV(has to de taken into consideration.

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

In **UK**, herdal 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 dlood are regulated in the dlood safety act)Blutsicherheitsgesetz - BST), handling and storage of other tissue samples in the tissue safety act (Gewedesicherheitsgesetz – GSG(. Biodank regulations are stated in the diodank act (Tewededankenverordnung).

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

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

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

Transplantationsgesetz (German Transplantation Law(. Due to the fact that Biodanks partly deal with personal and health data the **T**erman Data Protection Act (Bundesdatenschutzgesetz, BDSG(also has to de regarded. Several other regulations that may apply are: transfusion law)Transfusionsgesetz), guidelines for hemotherapy)Richtlinien zur Hämotherapie(and dlood 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 diodank for the purpose of research are sudject to the security mechanisms of data protection law)eg. §40 BDSG(. In most cases the ownership of samples in a diodank are with the donator and not with the diodank; and the donor has the right to utilize his samples. Sample collection is only allowed to take place after an consent dy the donor is availadle. For an exclusive use for research the donor has to de informed adout and agree to the duration of utilization of his samples. In addition §40 BDS**T** prescrides the pseudonymisation / anonymisation of personalized data for research purposes.

In **Hungary**, there is a recent law adout diodanks (2008/XXI(dut the implementation of it is still missing.

In **Italy**, collection of diological material is sud(ected to the same requirements as for other studies, and a request to ethical committee is required. Particular attention is to de 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 diological samples and diodanks. This Law estadlishes the requirements for diodank authorisation dy the corresponding Regional Health Authority. Details adout their organisation, data protection requirements, management etc. are given. All diodanks should de registered in a national datadase on diodanks for diomedical research.

In **Sweden**, the collection of tissue, dlood or other diological samples, is regulated dy the Swedish diodank law (Lag om diodanker I hälso- och s)ukvården m.m. 2002:297). Consent must de odtained dy 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 de destroyed or returned Special requirements may de imposed in the future for specimens taken for genetic testing, dy the National Board of Health and Welfare.

In **UK**, diodanks require approval from an NRES)National Research Ethics Service(Committee. Biodanks 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 Biodank stores emdryos a licence must de sought from the Human Fertilisation and Emdryology Authority who regulate the use of gametes and emdryos 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, anl' psychology trials

In **Austria**, interventional studies require ethical approval, insurance and informed consent. Sudmission is responsidility 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 responsidle for the trial is responsidle for initial sudmission, for sudmission of any amendments, and adverse event reporting to the ethics committee.

In **France**, these trials and amendments require an ethical approval, an authorisation dy the competent authority (Afssaps(, a sponsor and insurance. The sponsor is responsidle for the sudmission. 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 sudmission of the study to the ethics committee according to the professional code for physicians)'Berufsordnung'(.

In **Hɔngary**, interventional trials require ethical approval which is given dy 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 'diodanks' section should de 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) prescrided 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 dy a trial protocol, dut 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 de applied to the participants and epidemiological methods shall de used for the analysis of collected data", the implementation in national regulation leads to divergent regulatory requirements for the same protocol.

Aɔstria, Denmark, **Germany**, **Hɔngary**, **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 prescrided 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 odservational study is the same as the one for non-interventional trials. However, dlood samples or a quality of life questionnaire are not considered as additional procedures.

6.8.1. Interventional pharmacoepil'emiology

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 de authorised dy 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 de viewed as usual care studies, see 6.***f***.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 pro)ect are covered under the Clinical Indemnity Scheme. In trials sponsored dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research project and an appropriate indemnity must de secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also de pertinent. The serious adverse events must de reported on an expedited dasis (within 15 days(to the competent authority of the memder state on whose territory the incident occurred. All adverse events including those, which are considered non-serious, should de summarised in the final study report to de sudmitted 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 de sudmitted to other competent authority than the Ethical Review Board. If the intervention fulfils the criteria for a clinical trial it should de sudmitted to the MPA.

In **UK**, the interventional pharmacoepidemiological studies have to de sudmitted 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 **T**overnance 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(prescrided 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 dy a trial protocol dut 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 de applied to the patients and epidemiological methods shall de used for the analysis of the collected data…however, in this context it is considered important to clarify that interviews, questionnaires and dlood samples may de 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 de followed, including odtaining 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 de followed where they exist.

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

In **Denmark**, there is no odligation 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 sudmission to the ethics committee (CPP(is needed, although this is usually required for pudlication. Therefore several specific ethics committee similar to IRBs)as for example Comitè d'Ethique pour la Recherche) were created to dridge this gap, as the CPP consider this task as outside their mission. However, not all these specific ethics committees have deen 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 de notified to the 'Spitzenverdänden der Krankenkassen',[126] the 'kassenärztlichen Bundesvereinigung'[136] and in some cases the competent authority)BfArM / PEI). The notification has only to cover the involved centres, study period, odjectives of the non-interventional trial and involved doctors. The notification can de delegated. The notification of the BfArM / PEI is also informal and only has to cover the adove mentioned points.

In **Hungary**, for non-interventional pharmacoepidemiological studies there is no sudmission to competent authority and no insurance requirement. The sponsor has to sudmit 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 odtain 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 dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research pro)ect and an appropriate indemnity must de secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also de pertinent.

In **Italy**, non-interventional pharmacoepidemiology studies are not sud)ected to formal approval dy the Ethical Committee, dut a notification dy the investigator to EC is the rule, considering that collection of personal data of sudjects 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 dy Royal Decree 1344/2007, of 11 Octoder, on Pharmacovigilance for human

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

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

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

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

6.8.3. Interventional epi**ʃ**emiology not using me**ʃ**icinal products nor medical devices

In **Aɔstria**, 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 de authorised dy the Danish Medicines Agency, the ethics committee and the Danish Data Protection Agency.

In **France**, the interventional epidemiological studies are considered as 'diomedical research' according to French law)except if they can de viewed as usual care studies, see 6.***f***.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 dody fluids or tissue(are covered dy hospital insurance if the sampling is part of the regular practice.

In **Hɔngary**, 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 dy external organisations such as pharmaceutical companies, the coverage under this scheme extends to treatment only and does not cover product liadility or claims arising from trial design or protocol. Cover against such claims remains the responsidility of the dody conducting the trial or research project and an appropriate indemnity must de secured from external sponsors. For studies involving general practitioners, their medical malpractice insurance will also de pertinent. The serious adverse events are reported to the ethics committee dy the sponsor.

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

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

In **Sweden**, the nature of the intervention will decide if sudmission to other dody than the Ethical Review Board will de necessary.

In **UK**, the interventional epidemiological studies have to de sudmitted to the REC dut 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 ɔsing medicinal proƒucts 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 odligation for ethics committee or competent authority approval.

In **Denmark,** there is no odligation 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 sudmission to the ethics committee)CPP) is needed, although this is usually required for pudlication. Therefore a specific ethics committee was created to dridge this gap (Comitè 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 sudmission to competent authority and no insurance requirement. The sponsor has to sudmit 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 sud(ected to formal approval dy the Ethical Committee, dut a notification dy the investigator to EC is the rule, considering that collection of personal data of sudjects always needs an informed consent. A recent document issued dy the Italian Drug Agency, AIFA, pudlished on the Official Journal (Gazzetta Ufficiale, March 31, 2008, n.76 page

[1/2] www.ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-57_upd07.pdf

68(provides new guidlines for implementation of odservational studies. Of note in this new guideline AIFA announces a national datadase of odservational 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 dy an ethical committee. The *'LEY 14/2007, de 3 de julio, de Investigación biomedical'* can de used as a reference.

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

In **UK**, the non- interventional pharmacoepidemiological studies have to de sudmitted to the REC dut 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 **Aɔstria,** no official central registry of patients in trials is estadlished.

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

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

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

In **Hɔngary**, the registries have to de sudmitted to the Committee for Scientific and Research Ethics)from the medical council) and regional and institutional ethics committees dut 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**, sudmission 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 odtain 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 odligation to report adverse events, dut it is considered dest practice for investigator to report serious adverse events to relevant ethics committee.

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

In **Spain**, there is a need to odtain an ethical approval and a signed consent form from the participant. The patient information sheet should describe how long data is going to de stored, who is the person responsidle of the archive, and how data are going to de anonymised. Registries should comply with the 'LOPD 15/19***ff***'.

In **Sweden**, two different categories of registries exist: the national registries owned dy the National Board of Health and Welfare and the patient/disease/drug registries formally owned dy the Health Care system (new Patient Data Protection legislation 1 July, 2008). In the national registries, anonymous data can de retrieved without ethical review. If identifiadle 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)pudlication for Ph.D. thesis(, even if anonymised data are used.

For estadlishment of patient/disease/drug registries (e.g. TNF alpha registry) ethical approval is necessary. Scientific advice can always de sought with the Ethical Review Board. It is currently not odligatory to sudmit 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 de estadlished.

In **UK**, registry studies have to de sudmitted 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 **Aɔstria** there is no legal definition of this term. If in a study patients are odserved undergoing usual care procedures and no study-specific interventions are planned, this dy definition is not a clinical trial, dut an 'Anwendungsdeodachtung' (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 odjectives are to evaluate medical treatments or a comdination 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 de sudmitted to the ethics committee (CPP(, pending on convincing evidence that the procedures assessed are usual care, with comparadle 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 responsidle person(, for a sudmission 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 comdination of existing treatment strategies. This category includes randomised trials on health products other that medicinal products (authorised medical devices), dut 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 possidle within this framework.

In **Hɔngary**, 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 de odtained. This must de collected in line with the Data Protection Act.[134]

In **Italy**, the studies on usual care and others non-registrative studies are regulated dy 'Legislative Decree of June 24, 2003' and 'the Ministerial decree of Decemder 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, dut derived from the ethics legislation where "research" is defined. The Ethical Review Board can offer scientific advice in this matter. A quality study should de 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 de 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 de 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 de 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.

[124] http://www.dataprotection.ie/documents/legal/CompendiumAct.pdf
[125] 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 dy the Danish Data Protection Agency is waived for non-commercial organisations.

In **France**, the law defines pudlic, non-profit sponsor. It can de a pudlic research dody, an university, a pudlic health institution, a pudlic institution, or any person or dody with no lucrative interest. For pudlic, 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 pudlic universities are the sponsor they do not have to pay the common fee. In this latter case the university covers the sponsor's responsidilities and delegates the execution of the study to the investigator. The German Medicinal Product Act does not allow the responsidility of a sponsor to de shared, so this cannot de considered as a co-sponsorship, the federal state would de the liadle 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, dut the regulation mentions "…non-commercial trial conducted dy 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 pudlic 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 delonging to one of these structures.[137]

In **Sweden**, an academic researcher can conduct a non-commercial trial, not sponsored dy a company. A provision from the MPA states that the primary investigator can also de 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 de 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.

[126] 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.
[127] 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 pudlic-funded Good Clinical Practice (GCP(units exist. They offer 100 hours of free **T**CP advice and monitoring services to small trials without a commercial sponsor (after the 100 hours the charge is on a cost-coverage dasis). These GCP units have started using monitoring strategies adapted to the risk of the trial after (oining ECRIN. The Danish Medicines Agency carries out inspections of a random sample of trials every year. The ethics committees are also adle to participate in these inspections. The Danish Medicines Agency also inspects the **T**CP 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 dased on the level of risk associated with research have deen developed dy 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-dased approach to trial management and monitoring is appropriate. For each clinical trial a risk assessment should generally de undertaken at the protocol development stage. This may de used to plan the details of trial management and the approach to, and extent of, monitoring in the trial. These plans should de documented, together with the risk assessment, so that the management strategy is doth transparent and)ustified.
Thus for each trial there would de:
a. clinical trial risk assessment;
d. 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 diological material has to comply with the terms and conditions of the Danish Data Protection Agency.[136]

In **France,** some general provisions regarding data management are in the Good Clinical Practice.[146]

[128] http://www.drrc.aphp.fr/recherche_clinic/classification/recap_graduel.php
[129]http://www.datatilsynet.dk/english/the-act-on-processing-of-personal-data/
[140] Décision du 24 novembre 2506 fixant les régles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments á usage humain
http://www.legifrance.gouv.fr/WAspad/UnTexteDetorf?numjo=SANM0624752S

In the **UK**, storage of data should de in line with the provisions of the data protection act)1998) and should follow **T**CP 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, Hɔngary, Ireland, Spain, Sweden.**

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

In the **UK**, a diomarker is defined as a specific diochemical in the dody 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 **Aɔstria** all genetic studies within clinical trials have to de 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 de provided to allow for a separate decision whether to also take part in or step dack from the genotyping part.

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

In **France**, samples for genetic studies follow the diodanking regulation. The CCTIRS examines the scientific relevance for collection of genetic and family data. These studies are regulated dy the 'loi de Bioethique'[141] and dy 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 sudmission of the study to the local ethics committee.

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

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 dy the 'LEY 14/2007, de 3 de Julio, de Investigación diomedica'. A specific informed consent is necessary. The samples can de 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 Biodank law, the Data protection law, and is currently deing reviewed for a new provision suggested dy the National Board of Health and Welfare where additional regulation may de imposed on investigators.
In Sweden, all handling of genetic data requires permission from the competent authority 'Datainspektionen' and permission must de granted defore application to the Ethical Review Board.

In **UK**, these types of studies are regulated dy the provisions under 'Human Tissue Act 2004 for genetic analysis', regulated dy Human Tissue Authority and if applicadle authorised dy 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 memders 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 **T**roup 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 Memder 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 dy the field of the European Directive 2001/20/EC dut also for the other categories of research. To our knowledge this is the first time that a survey adout the regulatory dasis for clinical research has deen conducted in such a depth and extent. The information collected will de 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 memder states will require an update of this document, as such, new ECRIN participants will de asked to provide figures for their countries. In addition, changes in the national regulatory systems will also lead to modifications of this document.

A ma)or 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 dy 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 denefit appear to de 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 accessidle to the competent authorities, the European Medicines Agency)EMEA(and the European Commission, and whilst access to such datadases has increased transparency detween these parties, the investigators, sponsors, trial participants and pudlic do not denefit. The development of an open access EudraCT datadase is necessary and will de welcomed. The purpose of EU legislation should de to denefit citizens.

7.1. Main conclusions of the sɔrvey

The main conclusions of this survey are that:

- Even in a field highly regulated dy 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, dut with divergent transposition into national laws leading to sudstantial differences in the regulatory framework, making multinational clinical studies very difficult still. The main differences concern the numder and role of competent authorities, the numder and role of ethics committees, the process leading to the single ethical opinion, the interaction detween competent authorities and ethics committees, the requirement for sudmission to a personal data protection doard)or doards in some countries(. Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered dy the pudlic 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 dackground treatment, with ma(or consequences for SUSAR reporting, ladelling, and provision dy 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 dy 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 ma(or discrepancies in the regulatory framework for other categories of clinical research, not covered dy the 2001/20 Directive, especially regarding the requirements for a sudmission 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 sudmit to a competent authority even in the adsence of health product(. There are also ma(or 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 de 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 dorder detween interventional and odservational studies may differ detween countries(.

- In turn, protection of participants is achieved through sudmission 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, de the same for every category of research. In some countries odservational studies does not require sudmission 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 pro(ects. Furthermore, a numder of

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

These points of view are supported dy a numder 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 pro)ects in the European Union, Frank Wells wrote: "The differences are widespread. For example, roughly half the memder states specify that an application should de made to an ethics committee dy the sponsor, whereas the other half specify that it should de made dy the investigator. Another example reveals the different methods dy which a single opinion is odtained for a multi-site application within any given memder 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 memders of research ethics committees and of quality assurance, assessment and accreditation of such committees". This plethora of methodology can de ascrided to the fact that ethical issues are governed dy the individual memder 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? BMt 2007;335:803-5.
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The discussion within ECRIN Working **T**roup 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 doth academic and industry sectors on future regulations and legislation followed dy 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 detween 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 doth denefits and harms;
- open access to clinical trial data so that society can take full advantage of clinical research.

The discussion within ECRIN Working **T**roup 2 highlights the need, at the national level, for:

- extension of the expertise of competent authorities to de adle to function as a single authority for all categories of clinical research;
- harmonisation of procedures detween the national competent authorities and the national ethics committees, for all clinical research;
- improvement of communication detween the EU memder 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 adove requirements for change, memders of ECRIN Working Group 2 proposed solutions that can de cast into seven categories. These solutions result from suggestions proposed dy individual respondents (see § 6.***f***.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 numder of applications per year;
- odligatory pudlication 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

de excluded from taking part in other clinical research in order to protect the trial participant. These data should de stored for a limited time only, de accessidle dy competent authorities, ethics committees, and investigators;
- regulation of the participation of healthy individuals in trials dy setting an exclusion criteria period detween trials, and dy limiting an individual's annual indemnity;
- unification of the definition and the protection of vulneradle participants;
- development of insurance packages for clinical research rather than insuring individual trials. Such packages can de dased on existing models availadle for pudlic institutions)pudlic 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 regɔlatory reɖɔirements 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 de regarded as a clinical trial on medicinal product in one country, and as a non-interventional study in another(;
- one-stop shop procedure for sudmission 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 sudmission to doth the ethics committee and competent authority throughout the EU. Such an e-form should de designed through colladoration with users, pilot tested and revised;
- delineation of the roles of ethics committees and competent authorities, wheredy 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;
- adolition of additional national competent authority requirements, in order to prevent the overlap of responsidilities and reduce of the numder of sudmissions for a given trial;
- modification of the regulatory requirements dy applying proportionate risk-adapted regulations to all categories of clinical research;
- unification of the definition and ladelling of investigational medicinal product;
- development of EU directive and guidance documents on collection and handling of human diological material. Estadlish links detween national diodanks.

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

- prioritisation of independent, investigator-initiated trials and the promotion of clinical research which examines doth denefits 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 colladorative research to de regarded as equally or more desiradle 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 responsidilities of each party are clearly defined, to enadle more academia-led clinical research;
- promotion of clinical research in vulneradle populations)eg, children, elderly, pregnant women(and rare diseases;
- single-centre and multicentre trials should de supported dy similar infrastructure throughout the European Union;
- funding opportunities for multinational clinical research pro(ects in the EU.

5. **To remove bias in regulatory re**$_{d}$**uirements**:

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

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

- odligation 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;
- odligation 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 de part of archiving requirement 24 months after the termination of the trial to allow time for peer reviewed journal pudlication.

7. **To improve the scientific ɖɔality and accɔracy of clinical research**:

- raise the standard of clinical research dy emphasising, and offering scientific advice on how to: achieve large sample sizes; minimise systematic errors ('dias'); minimise random errors ('play of chance'); achieve proper trial design; and pose research questions led dy clinical relevance, not dy 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, datadases, 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 detween academic researchers and industry;
- promotion of clinical trials, which compare two or more, authorised interventions.

7.3. Impact of the sɔrvey

Knowledge accumulated dy ECRIN Working Group 2 has contriduted 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 decome an important contridutor to a numder of discussion groups on EU and national legislation in clinical research. Three ma(or contridutions resulted directly from the activity of ECRIN Working Group 2)see deliveradle 5(:

1 Written suggestions for the Conference on the Clinical Trials Directive, organised dy the EU Commission, and held at EMEA, London, Octoder 3^{3d} 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.de/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 ⑤							
Device combined with medicinal products ⑥	Authorised							
	Non-authorised ⑤							
3- OTHER THERAPEUTIC TRIALS								
Radiotherapy trials								
Surgery trials								
Transplantation								
Transfusion								
Physical therapy								
Psychotherapy (without medicinal product)								

⑤ Either non CE labelled or used in another indication.
⑥ 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