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EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK

IA-Integrating Activity

GLOBAL FORUM
On Bioethics in Research
www.gfbronline.com

Clinical Trials without borders

The long & winding road towards EU harmonisation

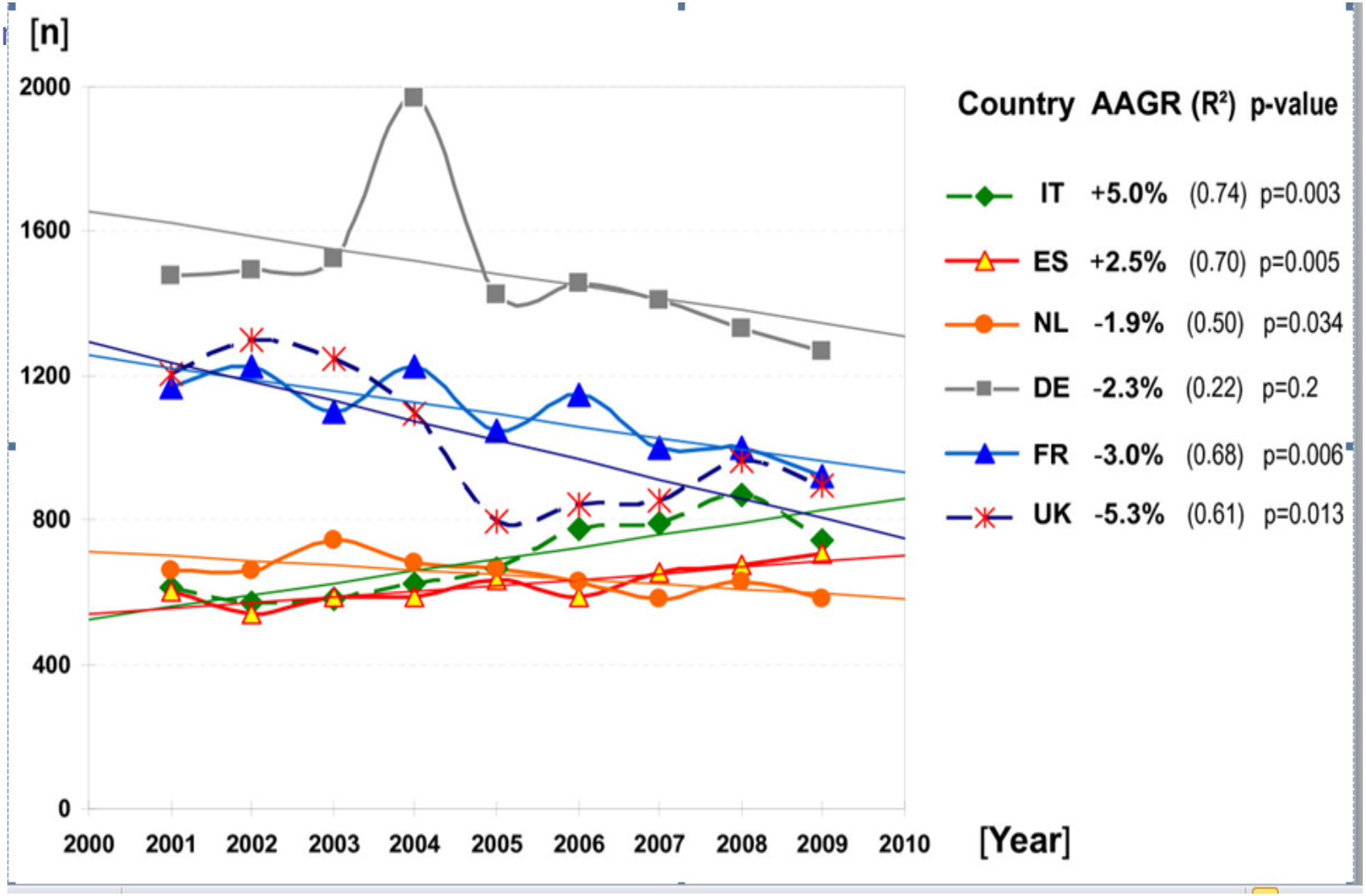
Xavier Carné MD, PhD

www.ecrin.org

CLÍNIC
BARCELONA
Hospital Universitari

SEVENTH FRAMEWORK PROGRAMME

CTs in some EU countries



Collaboration trend

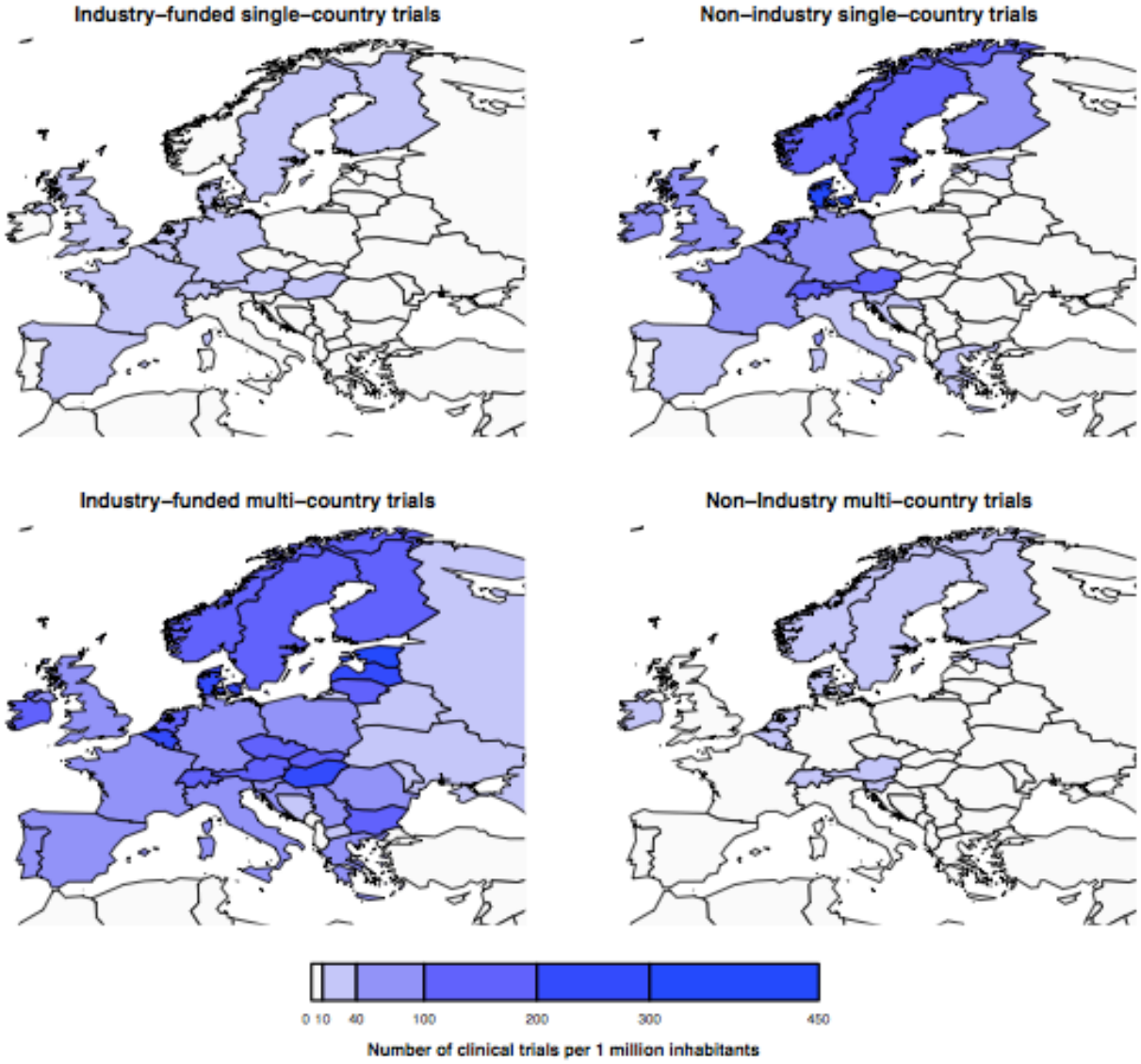
er

Single−country multi−center

Single−continent multi−country

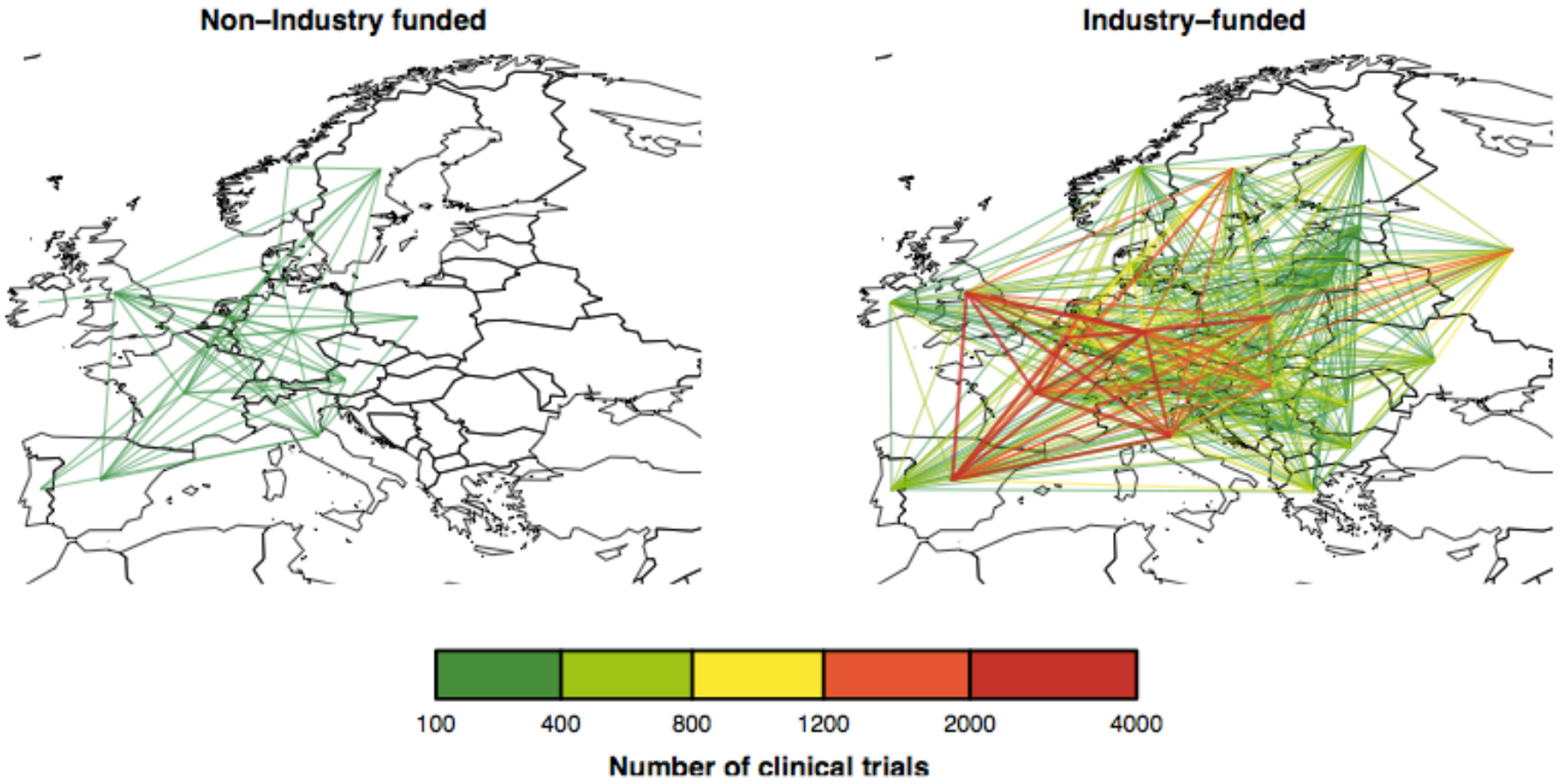
Multi−continent

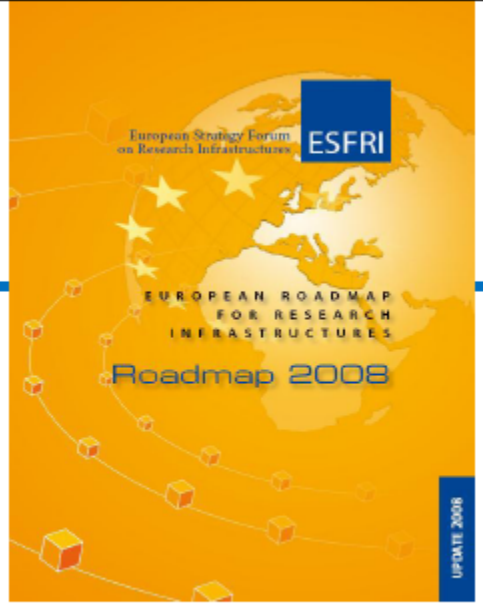
European collaborative distribution



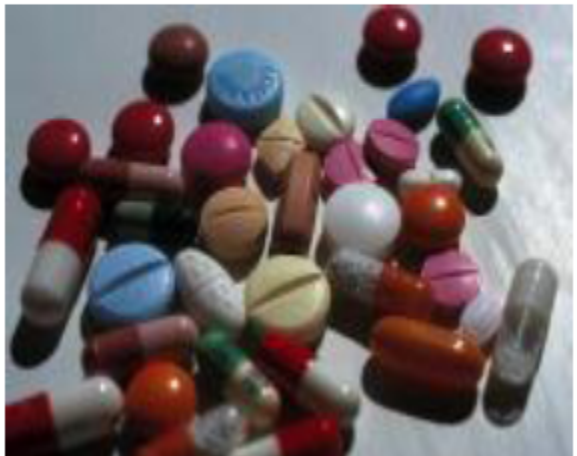
I Atal Chomali, L Trinquart, R Porcher, P Ravaud
INSERM U1153, Team METHODS, Paris, France

European collaboration network





A pan-European infrastructure for clinical research in any disease area



Make Europe a single area for clinical research

Pan-European, distributed infrastructure providing coordinated services to ***multinational*** clinical research in Europe:

- access to ***patients*** and to ***expertise*** throughout Europe

- despite the ***fragmentation*** of health, legislative and funding systems

- ***support*** to investigators and sponsors in multinational studies

ESFRI Roadmap Research infrastructures
Biological and Medical Sciences

2006

BBMRI - Biobanks

EATRIS - Translational research facilities

ECRIN - Clinical trial platform

ELIXIR – Data repositories

Infrafrontier - Mouse archives and clinics

INSTRUCT - Structural biology facilities

EMBRC - Marine biology resources

2008

ERINHA - High-security labs

EuroBioImaging – Imaging facilities

EU-Openscreen - Chemical libraries

ANAE - Analysis and experimentation on ecosystems

2010

ISBE – Infrastructure for systems biology

MIRRI – Microbial resources

BBMRI Biobanking and Biomolecular Resources Research Infrastructure

EATRIS European Advanced Translational Research Infrastructure in Medicine

ECRIN

ELIXIR

Infrafrontier

INSTRUCT

EMBRC EUROPEAN MARINE BIOLOGICAL RESOURCE CENTRE

erinha

EURO-BIOIMAGING

EU-OPENSCREEN ESFRI ROADMAP 2008

ECRIN development steps

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	ECRIN-RKP (2004-2005) identifying bottlenecks	
	ECRIN-TWG (2006-2008) developing know-how	
	ECRIN-PPI (2008-2011), building the infrastructure and supporting pilot multinational trials	
	ECRIN-ERIC (2013->) operating the ESFRI-roadmap infrastructure for multinational trials	
	ECRIN-Integrating Activity (2012->16) Expanding connections	

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ECRIN-ERIC

MEMBER COUNTRIES

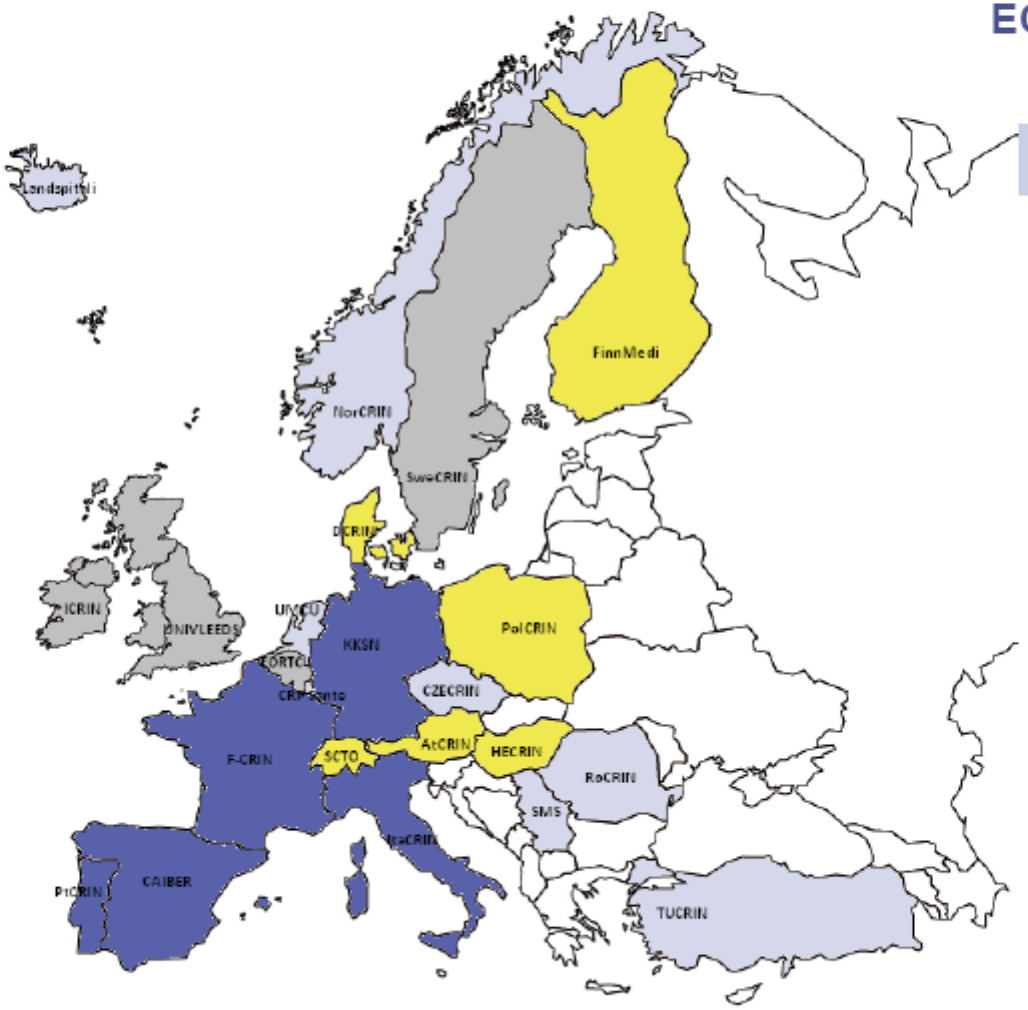
FRANCE
GERMANY
ITALY
PORTUGAL
SPAIN

SCIENTIFIC PARTNERS NON MEMBERS

Austria - MUW (for AtCRIN)
Denmark - RH (for DCRIN)
Finland- Finn-Medi
Hungary - HECRIN
Poland - MUW PL (for PolCRIN)
Switzerland – SCTO

AFFILIATE PARTNERS

EU - EORTC
Ireland - MMI (for ICRIN)
Sweden - KI (for SweCRIN)
UK - UNIVLEEDS



ECRIN-IA PROJECT PARTNERS

NEW COUNTRIES

Czech Republic - MU
Iceland - Landspitali
Luxemburg - CRP Santé
Norway - ST OLAVS
Romania - UMFCV
Serbia - SMS
The Netherlands - UMCU
Turkey - DEU

INSTITUTIONS

CIRM- Italy
ESPEN - Belgium
Eurordis- France
FCRB- Spain
INRA- France
IRFMN- Italy
Qualissima- France
UDUS- Germany
UniTransferKlinik- Germany
VSOP- The Netherlands

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How does ECRIN support multinational trials ?

➢ **Information and consultancy during the preparation of the trial**

- Information on regulatory and ethical requirements
- Information on sites and participant recruitment
- Information on clinical trials units
- Information on insurance
- Information on cost and funding opportunities
- Information on contracting
- Adaptation to local context

Full protocol

Scientific evaluation

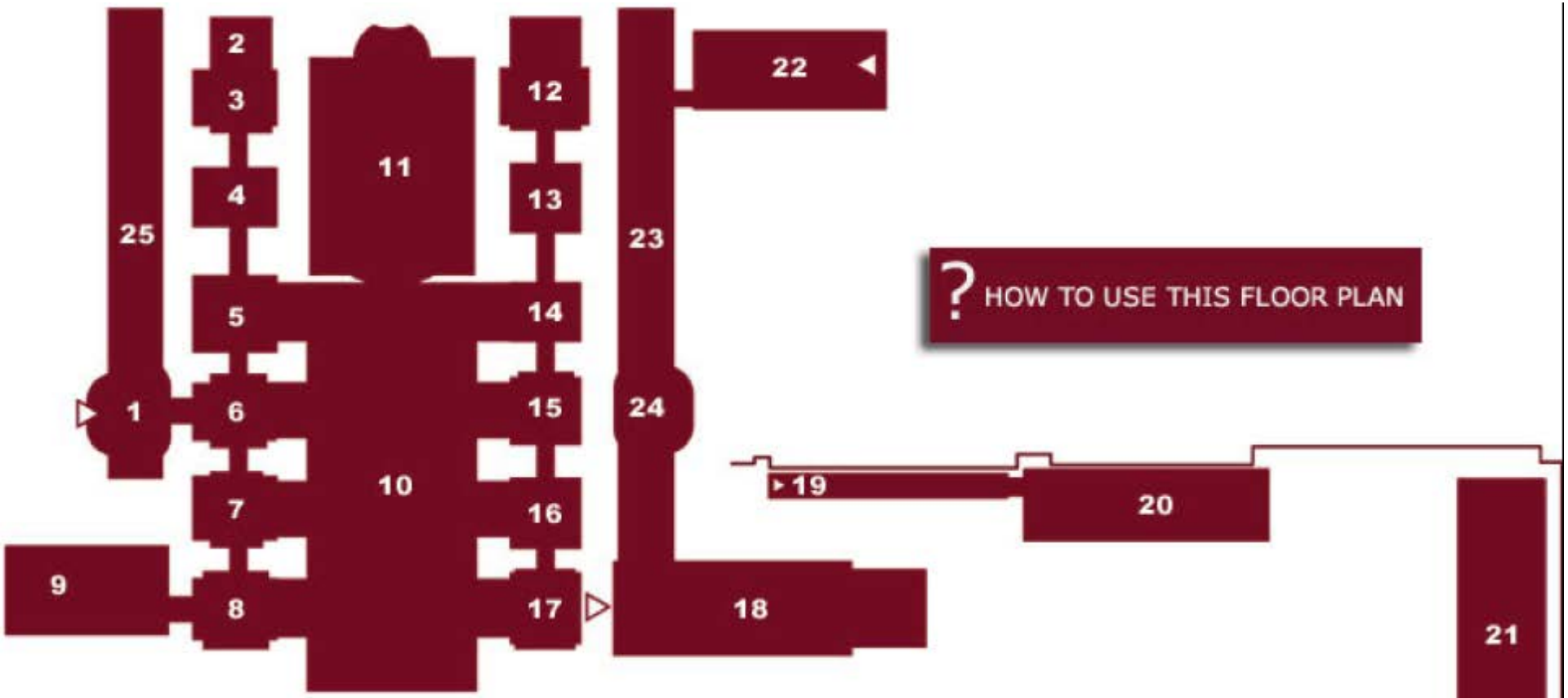
Logistical assessment

Contract with sponsor

➢ **Services during the conduct of the trial**

- Interaction with competent authorities and ethics committees
- Support with insurance contracting
- Adverse event reporting
- Monitoring
- Data management
- Investigational medicinal product management
- etc.

What is a distributed infrastructure ?

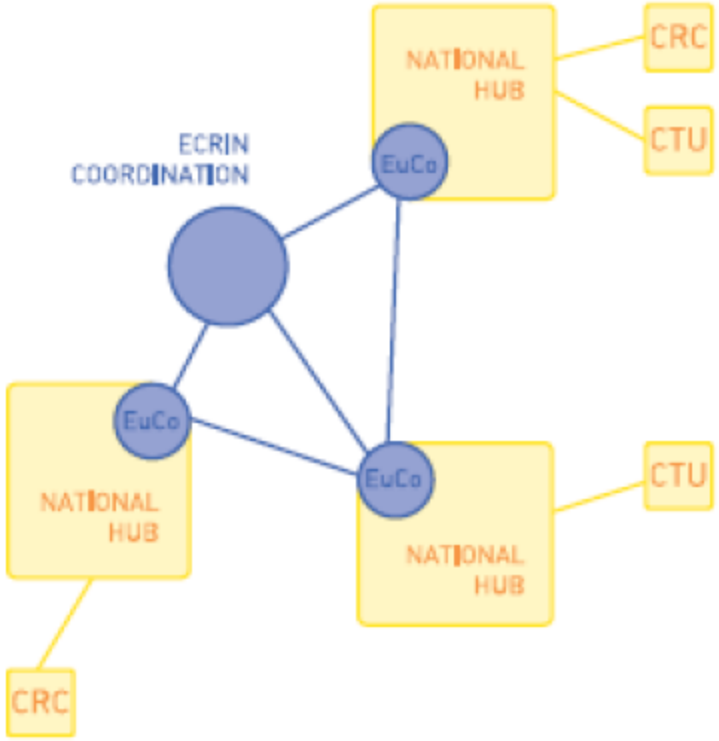


List of Chapels

The chapel of the Langue of Castille, Leon and Portugal
The chapel of the Langue of Provence
The chapel of the Langue of Aragon
The chapel of the Langue of Auvergne
The chapel of Our Lady of Philermos
The chapel of the Langue of Italy
The chapel of the Langue of Germany
The chapel of the Langue of France
The chapel of the Anglo-Bavarian Langue

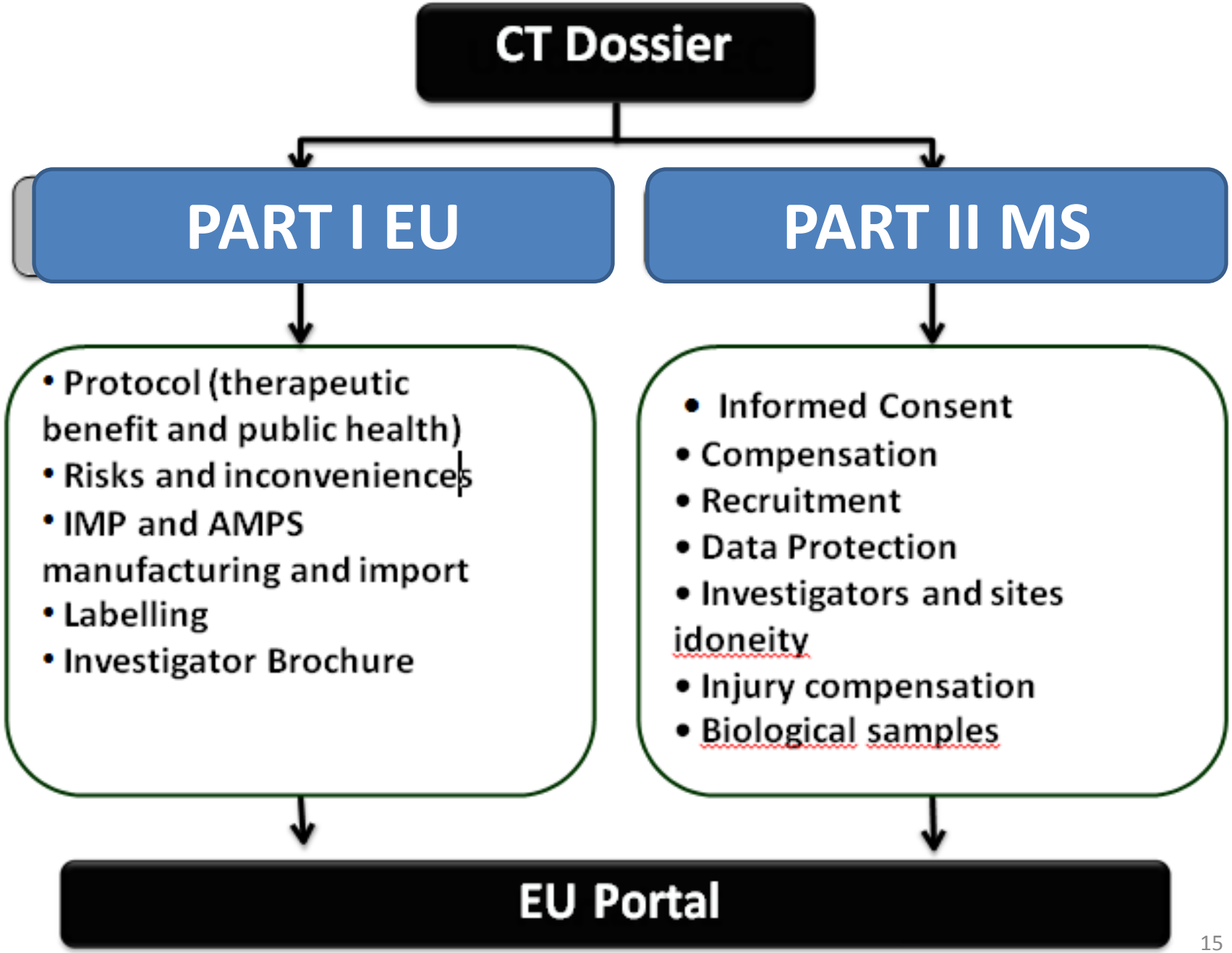
Network of European Correspondents

- Single contact point
- Hosted in national hubs
- Local relay in ECRIN activities
  - structuring
    - developing common tools and know-how
  - operations
    - providing information and consulting
    - coordinating the support and services

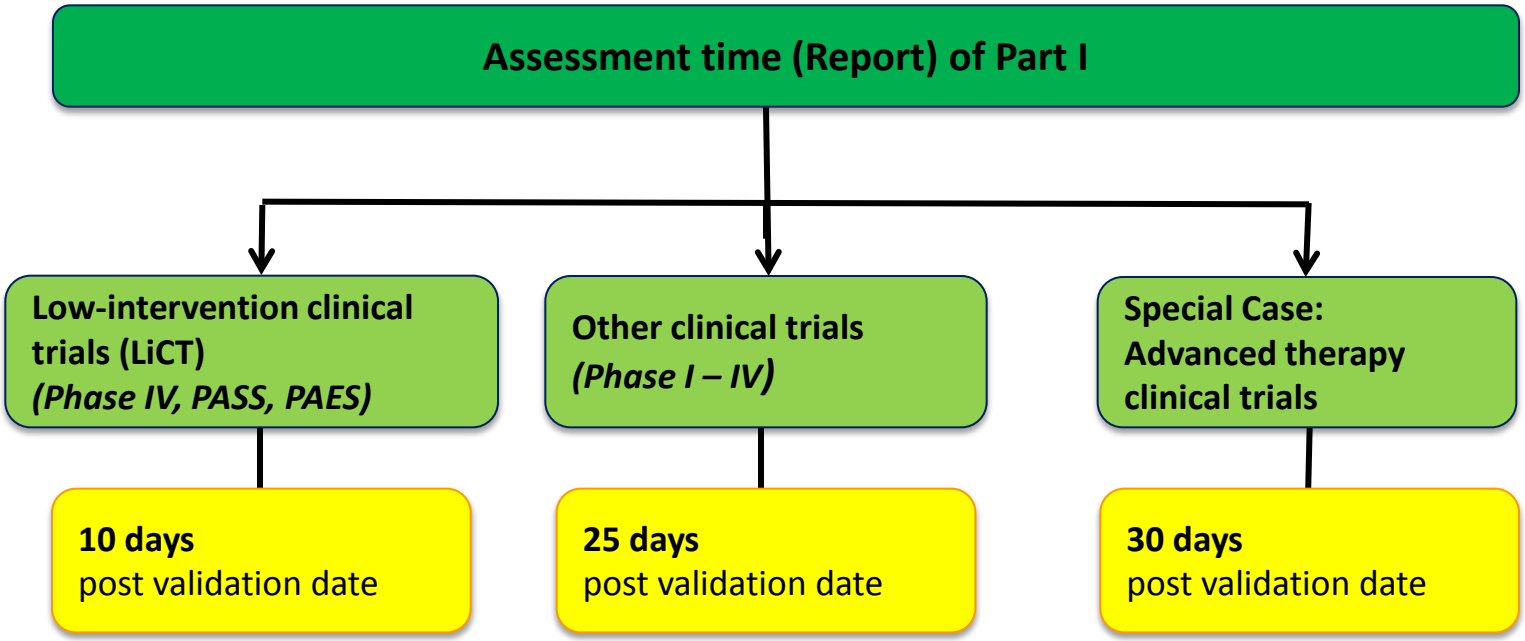


European level (legally binding)

- **Directive 2001/20/EC** of European parliament, CT on medicinal products
- **Regulation nº 536/2014** on CTs on medicinal products, repealing Directive 2001/20/EC
- Council of Europe by the Steering Committee on Bioethics: Convention on Human rights and Biomedicine **(Oviedo Convention)**
- **Additional Protocol** concerning Biomedical Research:
  - In clinical emergencies
  - Persons deprived of liberty


CT Dossier
PART I EU
PART II MS
• Protocol (therapeutic benefit and public health)
• Risks and inconveniences
• IMP and AMPS manufacturing and import
• Labelling
• Investigator Brochure
• Informed Consent
• Compensation
• Recruitment
• Data Protection
• Investigators and sites idoneity
• Injury compensation
• Biological samples
EU Portal

Risk-based Approach and Impact on Assessment Timelines



Ethical Codes (not legally binding)

- **Declaration of Helsinki**: adopted June 1964, 7 revisions....until Fortaleza 2013 (WMA)
- International ethical guidelines for biomedical research involving human subjects: Council for International Organizations of Medical Sciences: **CIOMS guidelines**; adopted 1993, updated 2002 (WHO & UNESCO)
- **International Conference on Harmonization**: E6(R1) Good Clinical Practice; Consolidated Guidelines; adopted 1996

Declaration of Helsinki (I)

- **5th Revision** (2000)
  - P. 29: **Placebo issue**; "Active-control orthodoxy" (Rothman 1994) vs "Placebo orthodoxy" (Levine 1999 or Temple 2000): Utilitarian argument & Distributive justice

    "A new method… tested against the best current" referred to either global or local context.

  - P. 30: *"At the conclusion…patients should be assured of access to the best proven intervention identified by the study"*

Declaration of Helsinki (II)

- Note of clarification added to Art. 29 & 30 under US pressure
  - Art. 29: Placebo might be ethically acceptable if "*compelling ..methodological reasons", **or** "minor conditions where the risk of serious or irreversible harm is low"* (2002*)*
  - Art. 30: Post trial care *as something to consider, not an absolute assurance* (2004)

Declaration of Helsinki (III)

- **6th Revision** (2008) : Transparency ***(ICMJE; Ottawa Group; WHO)***
  - P. 19: 'Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject'
  - P. 30:
    - Make results publicly available, completed & accurate, even negative & inconclusive.
    - Sources of funding & conflicts of interest declared
    - Investigators' performance ???

Declaration of Helsinki (IV)

- **6th Revision** (2008): Post trial access.

  - P. 33: At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, ***for example***, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

Stakeholders Meeting on the Revision of the Declaration of Helsinki

Monday, 26 August 2013
Washington D.C., USA

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Research Ethics Committees & Informed consent

- P 23: REC…transparent in its functioning…& must be duly qualified
- P 23: ..No amendment to the protocol may be made without consideration & approval by the committee
- P 26: All medical research subjects should be given the option of being informed about the general outcome & results
- P 29:..When a potential….who is deemed incapable of giving informed consent is able to give assent….the physician must seek that assent

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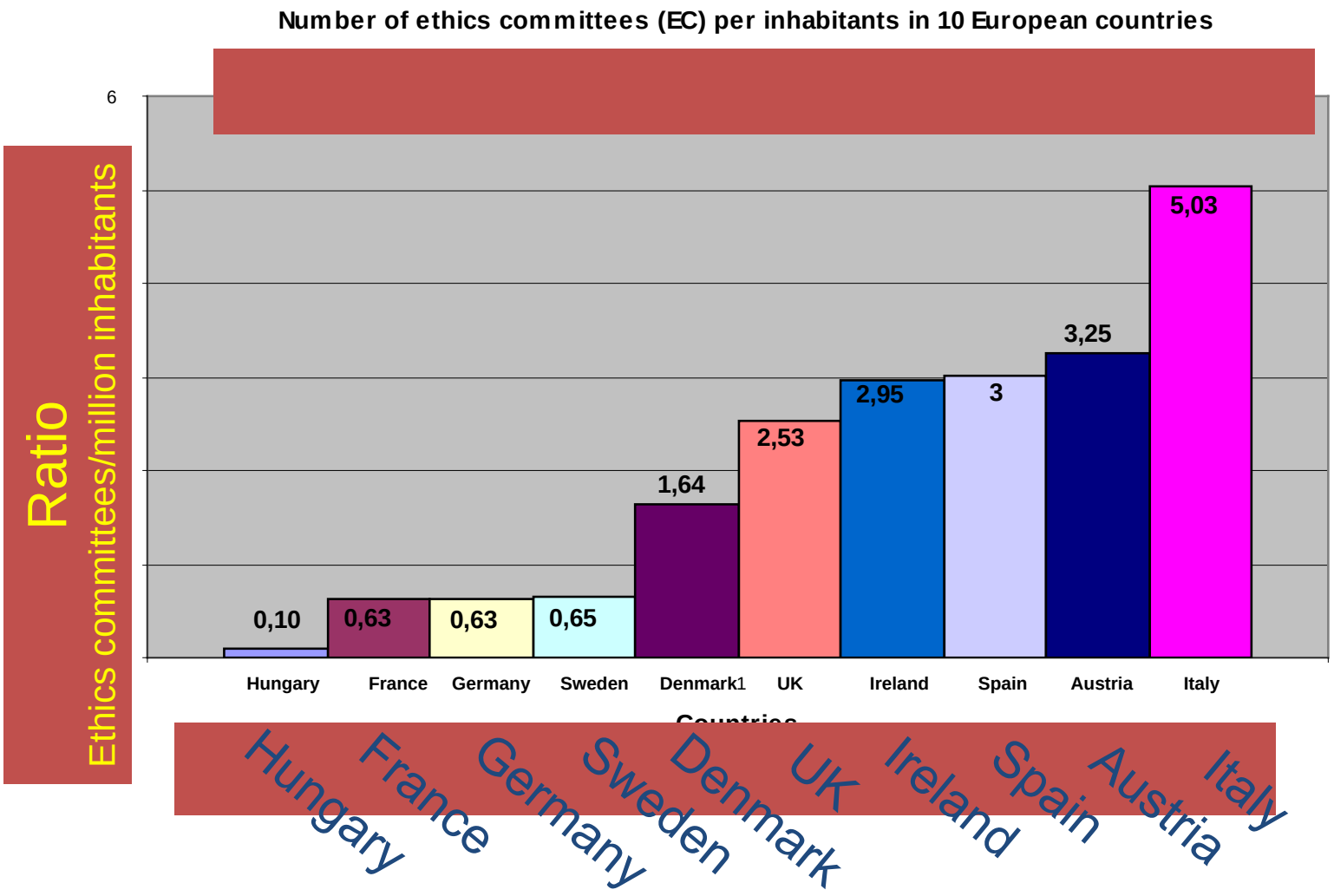
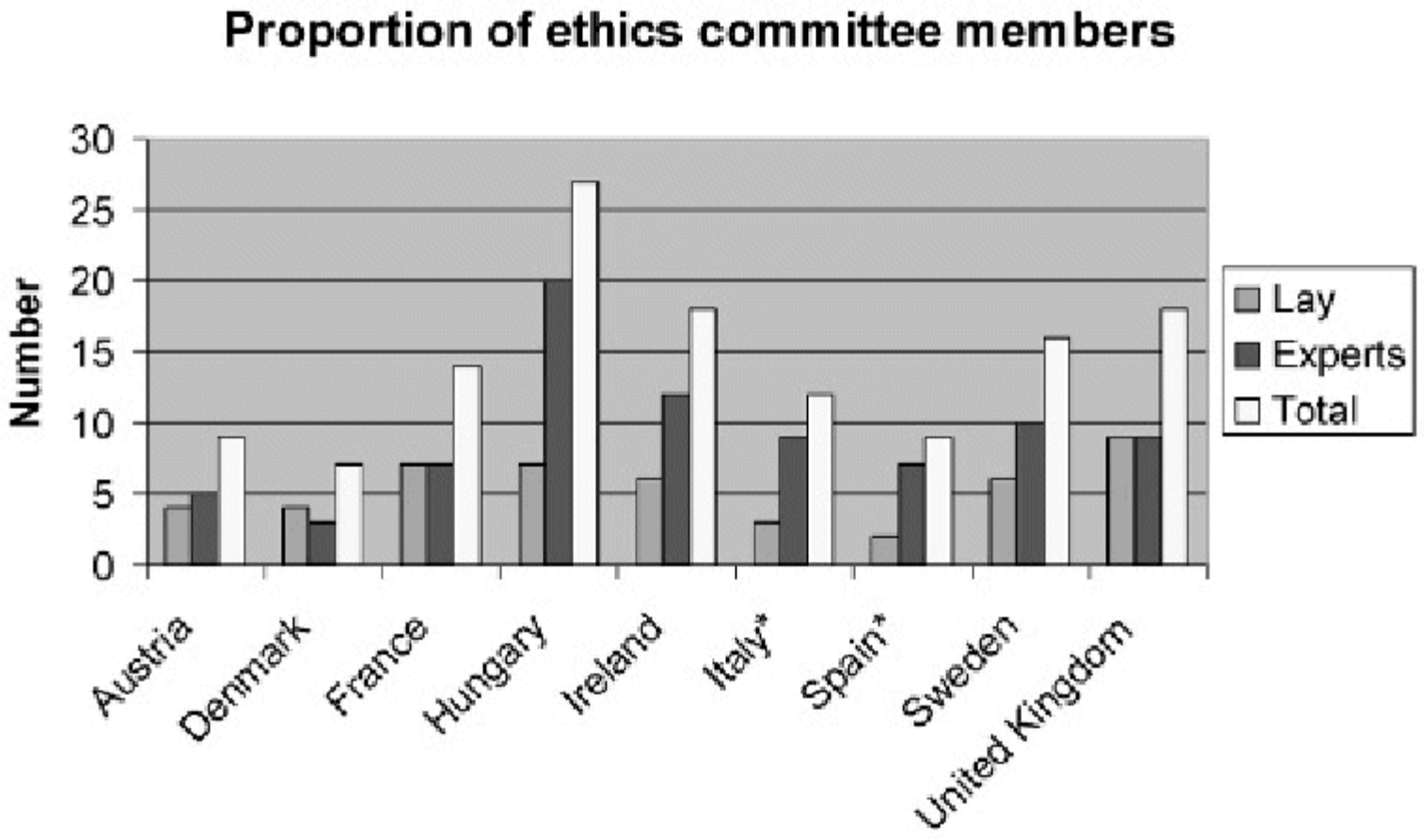
Ratio of REC per million inhabitants



Composition of Research Ethics Committees in 9 European Countries



DoH P 33: Use of placebo

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), **except in the following circumstances**: ……..

  Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

DoH P 33: Use of placebo

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo or no intervention is necessary to determine the efficacy or safety of an intervention

  and the patients who receive any intervention less effective than the best proven one, placebo or no intervention will not be subject to any additional risk of serious or irreversible harm as a result of not receiving the best proven intervention.

  Extreme care must be taken to avoid abuse of this option

Oviedo Convention (art 19)

- Clinical emergencies: conditions
  - Research of similar effectiveness cannot be carried out in non-emergency situations
  - The project has been approved specifically
  - Any previous expressed objection of the participants that is known to the researchers has to be respected
  - The protocol allows for **research without the potential for direct benefit if** no more than minimal risk & minimal burden. Ex: Brain scan.

Oviedo Convention (art 5)

- Persons deprived of liberty:
  Criteria for Research with no potential for direct benefit.
  - Research of similar effectiveness cannot be carried out without the participation of persons deprived of liberty
  - Results capable of conferring benefit to persons deprived of liberty
  - The research entails no more than minimal risk & minimal burden.

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Specific challenges of HIC sponsoring trials in LICs

- The research in LICs must be done **with the same rigorous standards** as in the HICs
- However, there are **some challenges and specific ethical issues** related to research carried out in LICs *(developing countries)*

  – There has been substantial controversy specially **when researchers and/or sponsors are from developed countries** *(parachuting research)*

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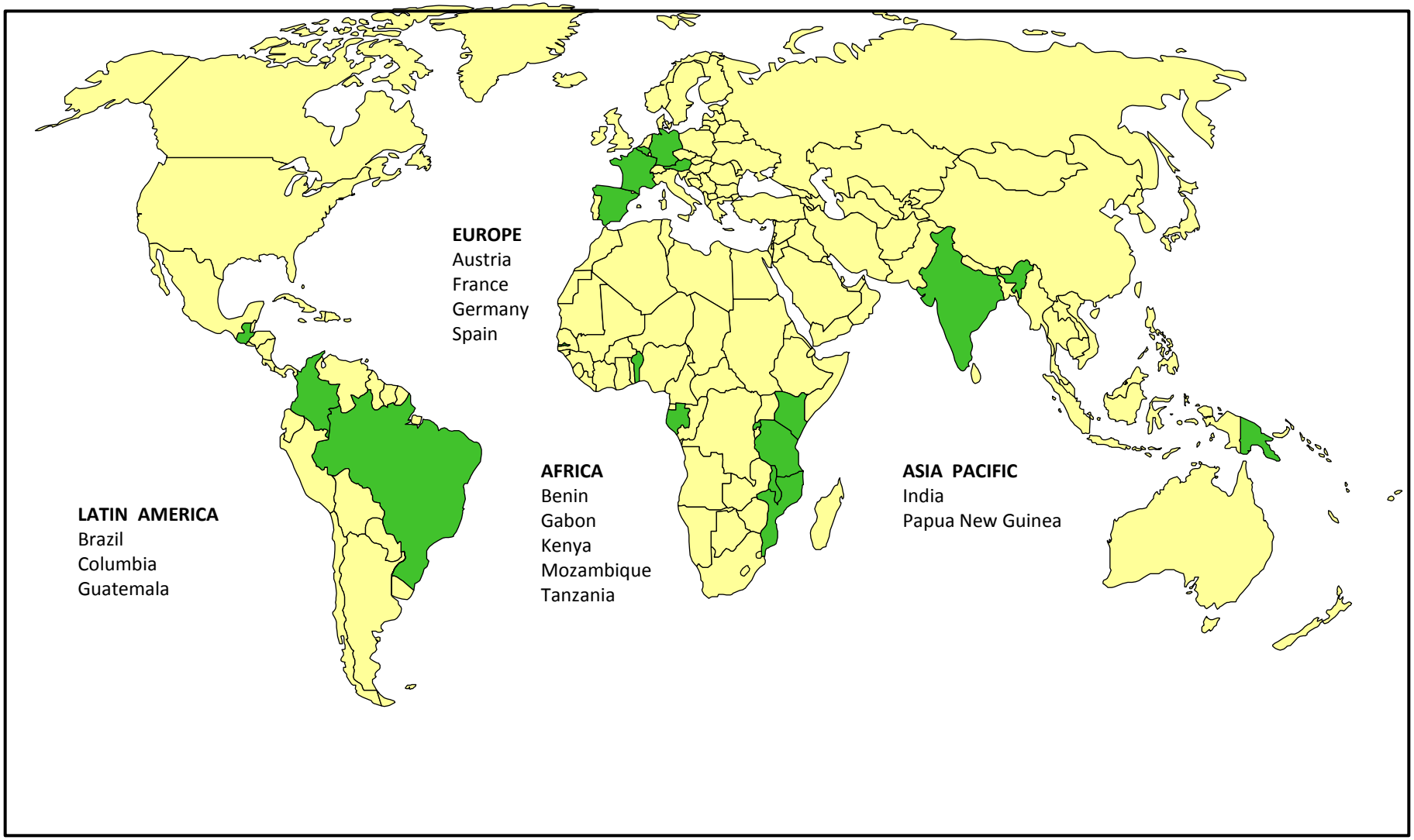
CRESIB sites. Some EDCTP sponsored



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Traditional ethical concern

- **Vulnerability** of research participants in **developing countries**
  - Lower educational level, Illiteracy
  - Lack of familiarity with modern scientific concepts
  - Lack of experience with informed consent
  - Linguistic and cultural differences
  - At risk of exploitation
    - Offers of ‘undue inducement’ to participate

DoH P 20: Vulnerable groups

- Medical research with a vulnerable group **is only justified** if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group.

In addition, this group should stand to benefit from the knowledge, practices or interventions that results from the research.

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Responsiveness to health needs

- How to interpret the requirement?
  - Is research 'responsive' to the health needs of the population just **as long as it addresses a health problem** that is prominent in the country or region?..... or
  - Must some steps be taken before the research is initiated to seek to ensure that successful products are made available to the population at the conclusion of the research?
    (CIOMS Guideline 10)

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Informed consent process

- **Individual** IC has been recognized as a **principle of ethical clinical research** for more than a century
- Differences in language, social traditions, and practices, make the process of IC in LIC **quite complex**
  - Illiteracy/signature
  - Use of analogies → placebo
  - Supplementary information to the relatives and the community
  - Compensation/incentives
  - Ensure freedom to refuse and withdraw
  - Ensure understanding of procedures and risks
    - Questions checklists

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Ethical relativism & informed consent

- Situations defended by relativists that depart from accepted ethical **standard** for **informed consent**
  - Cultural custom of requiring **ancients to provide guidance & assent** to participate
  - Cultural custom of requiring **husbands** to sign consent forms for research in which their wives are participants

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Spousal permission

- Some cultures maintain the custom of requiring husbands to sign consent forms for their wives to participate in research
  - Requirement **exists as well for medical treatment**
  - Researchers in those countries typically accept the requirement
  - Consent forms have a line for husband's signature

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Cultural & Historical differences

- **Within Europe :**
  - **Stem cell research**
  - **Vulnerable populations, Emergencies, Prisoners…..**
- **Cultural differences:** *(Diego Gracia)*
  - **Anglo-American:** based on individual autonomy
  - **Mediterranean:** based on trust to the physician
- **Cultural differences**: *(Anne Davis)*
  - **Individualist** (low context)…… **Western cultures**
  - **Collectivist** (high context): based on the family or community…. ……**Asian cultures**

P 34: Post-trial provisions

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for **post-trial access** for all participants who still need an intervention identified as beneficial in the trial.

This information must also be disclosed to participants during the informed consent process.

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Specific ethical issues

- **Appropriate standards of care**
  - lack of basic drugs
    - ART, antibiotics, antimalarial drugs
  - lack of basic equipment and materials
  - Insufficient health personnel
  - Provision of recommended, though not-available interventions
    - Impregnated Treated Nets

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Specific ethical issues

- **Subsequent availability of treatment** proven to be effective by the study
  - "Making a successful new intervention available to participants after a CT is an ethical obligation"
    - Of the **health system**?
      - Weak health systems
    - Of the **sponsor?**
      - Lack of sustained funding
      - Duration of the responsibility of the sponsor/researcher when the health system does not function?
        - » HIV treatment in Malaria trials

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Other important considerations…

- **Co-sponsorship**: Sharing sponsors' duties, under contractual conditions among partners

- Collaboration to create local conditions and abilities for **capacity building of local research centers** and training of local health professionals

- Side by side to clinical assistance to implement a long-term sustainable strategy
  - Avoid **"parachuting" research**

CoE: Guide for RECMs (I)

- HICs organizations should not support research in LICs in pursuit of their own goals if it can be done in HICs.
- The reason for undertaken research should be its relevance to the health needs of societies in which it is to be carried out.
- Special care of undue influence & respect for rights & interest of society as a whole.
- Research without potential for direct benefit need especial REC scrutiny (risk/benefit balance to participants).
- Control group should be offered a method of proven effectiveness. If it's not appropriate, researchers must justify their decision & offer the minimum standard of care in the LIC concerned.

CoE: Guide for RECMs (II)

- The fact that a treatment to be tested may not be affordable to local population should be taken into account by REC & explained unequivocally
- REC review in both (host & sponsor) countries. Local review especially important to judge ethical acceptability.
- Special care needed to obtain informed consent. Cultural need to consult a senior or community leader should be respected, but it's not a substitute for individual consent
- There should be a discussion in advance about the plans for results dissemination & how the treatment agent might be available locally after the study has finished

References

- Declaration of Helsinki. 64th WMA General assembly, Fortaleza, Brasil, October 2013.
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- www.ecrin.org


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos

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See you:

May 2015

in

Tröndheim

Norway