Retos y oportunidades para los CEIm

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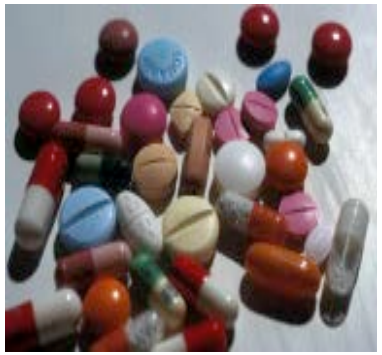
Need for independent clinical trials

- ***Clinical trials :***
  - development of innovative health products: rare diseases, antibiotics, nutrition
  - exploring new indications for existing drugs
  - comparative assessment of efficacy and safety of approved healthcare strategies



- ***Evidence-based medical practice***

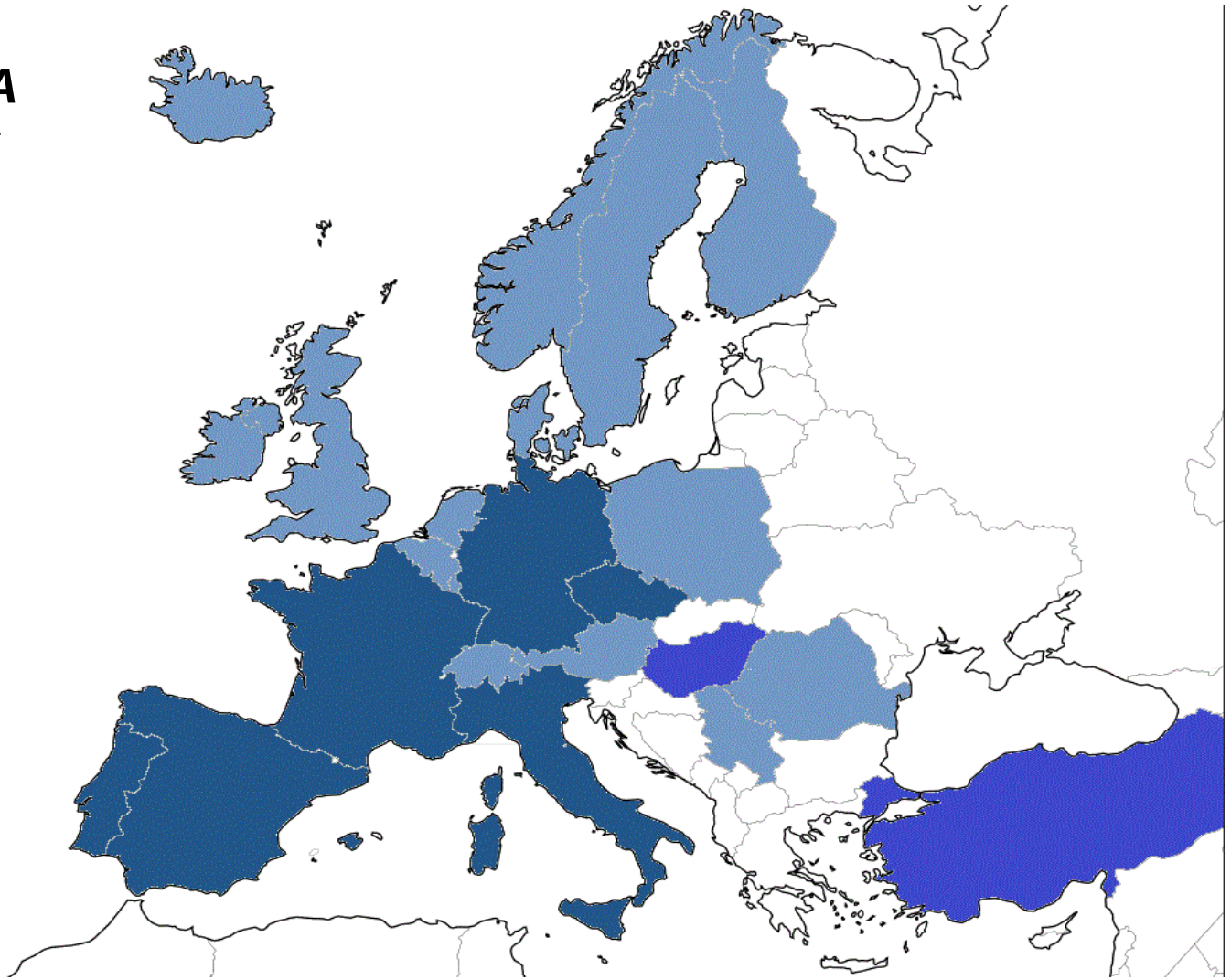
- ***International cooperation required:***
  - cost
  - expertise
  - access to patients

ECRIN ERIC 2016

ECRIN IA 2012-16

23 countries
567M citizens

8 countries
360M citizens



Collaboration trend

er

Single–country multi–center

Single–continent multi–country

Multi–continent

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,
Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,
Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D.,
Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D.,
Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D.,
Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D.,
Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D.,
Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D.,
Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D.,
for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

N Engl J Med, June27, 2012, DOI:
10.1056/NEJMoa1204242

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

N Engl J Med, November 17, 2013, DOI:

10.1056/NEJMoa1310519

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

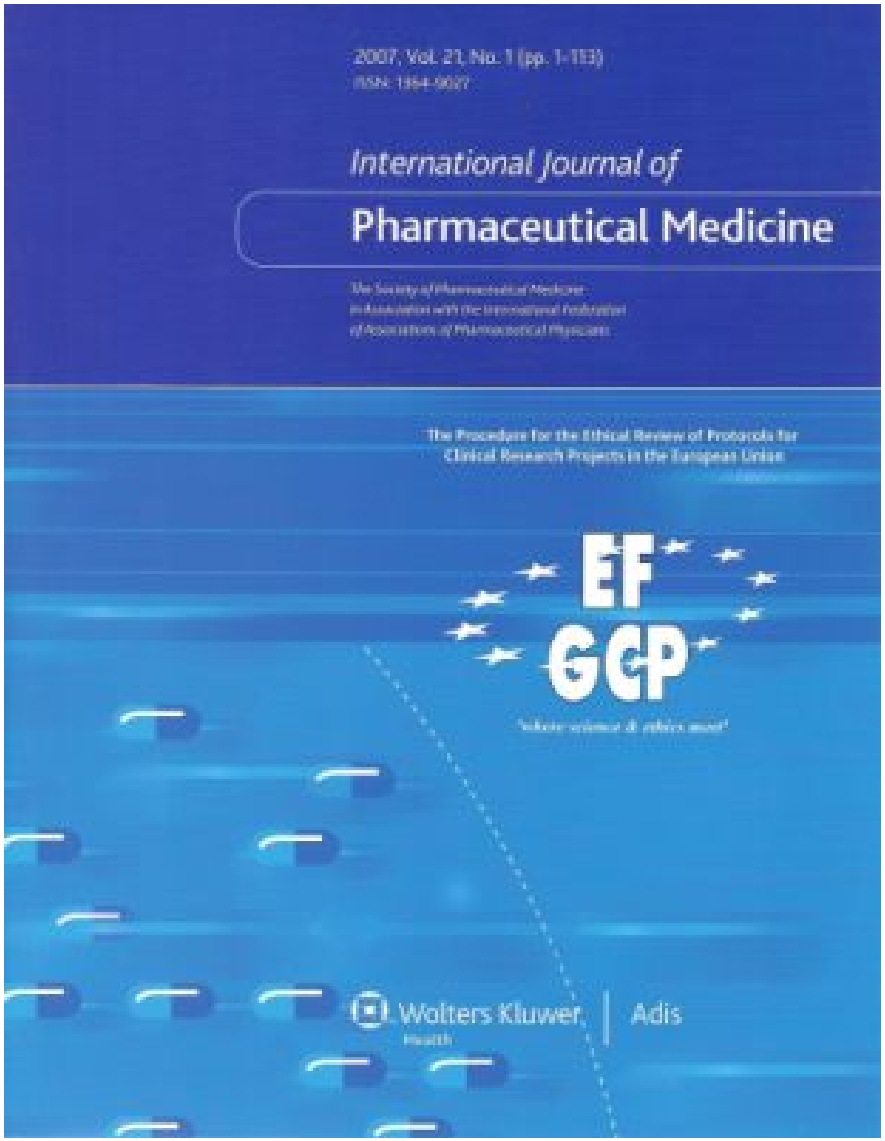
Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen, M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D., Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D., for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group

N Engl J Med, October 2, 2014, DOI:

10.1056/NEJMoa1406617

European Forum for Good Clinical Practice



EFGCP Brussels workshop: GUIDING PRINCIPLES

- Regulatory oversight proportional to risk
- No duplication of review and CA & EC roles clear & uniform
- The best expertise, regardless of country
- Consistency
- Same or zero fees
- Academic sponsors funded for administrative costs
- Single CTA dossier in English (except ICDs)
- Co-sponsorship allowed based on contractual agreements
- Clear definition of IMP, substantial amendment & non-interventional study

- System that allows (CTs with IMP & MD) :
  - Local evaluation, for protocols with 1 site
  - Real 'single opinion per MS', for protocols with > 1 site in a single MS
  - A real 'European single opinion', for protocols with > 1 site in > 1 country

  + Local evaluation (local ECs) for all other types of clinical research

CTD has divergent implementation in different MS

It's specially true in relation to EC practices

1. Application dossier to be provided to different EC is different in different MS
   - In national languages
   - Many paper copies to all involved EC
   - Different requirements in: content, insurance, site assessment
2. Single opinion for multi-centre CT not achieved in all MS
   - EC divergent opinions in the same protocol
3. Duplication of CA & EC roles in the evaluation of the dossier

Avoiding duplications

- Roles
  - CAs: Overall Benefit-Risk assessment of IMP dossiers
  - rECs: (multicenter trials with IMPs) Methodological, Ethical & Protocol BR assessment (if Multinational..... European single opinion)
  - Local ECs
    - (multicenter trials with IMPs): ICD, IP, Site & logistics
    - (in all other trials): ICD, IP, Site & logistics + Methodological & Ethical

Avoiding duplications

- However, this procedure needs a regular updated and fast communication system between CAs, rECs & local ECs in place

- ECs role in Protocol B&R assessment in CT with IMP in order to categorize a given protocol (3 levels)
  - Registered drug according to current labelling
  - Registered drug outside current labelling
  - Unregistered drug

  This could help to define its requirements for insurance & monitoring

4. EC do not have the tools & capacity to judge the actual risk-benefit ratio of a CT, based only in received SUSAR
   - SUSAR reporting to EC seen as a bureaucratic task with no added value to the participants' safety
5. Education, training & capacities of EC members not ensured by the current system
   - Specially true for advanced therapies (stem cells, genetic therapy or bioengineering)

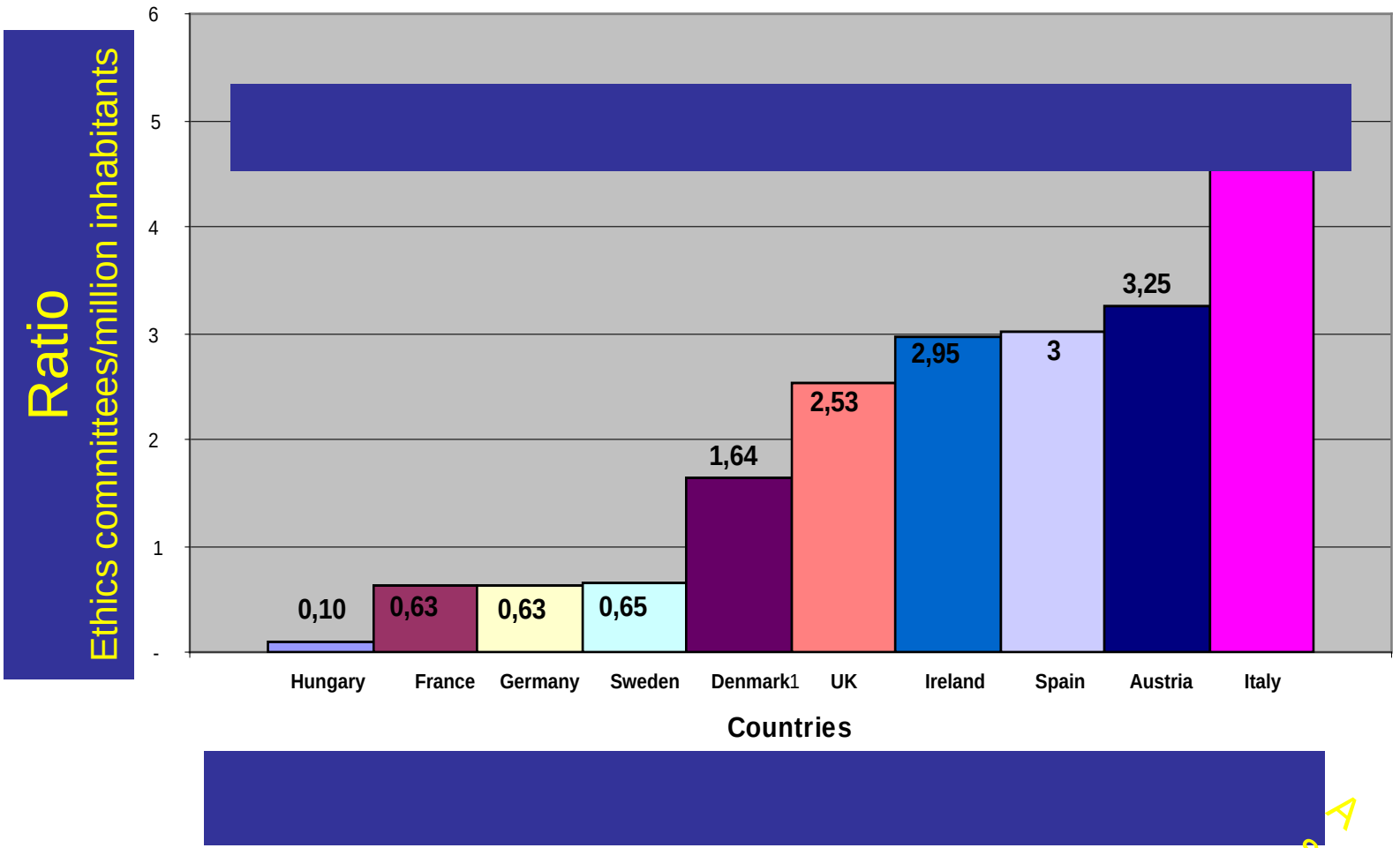
J Med Ethics 2009;35:696–700.

Research ethics

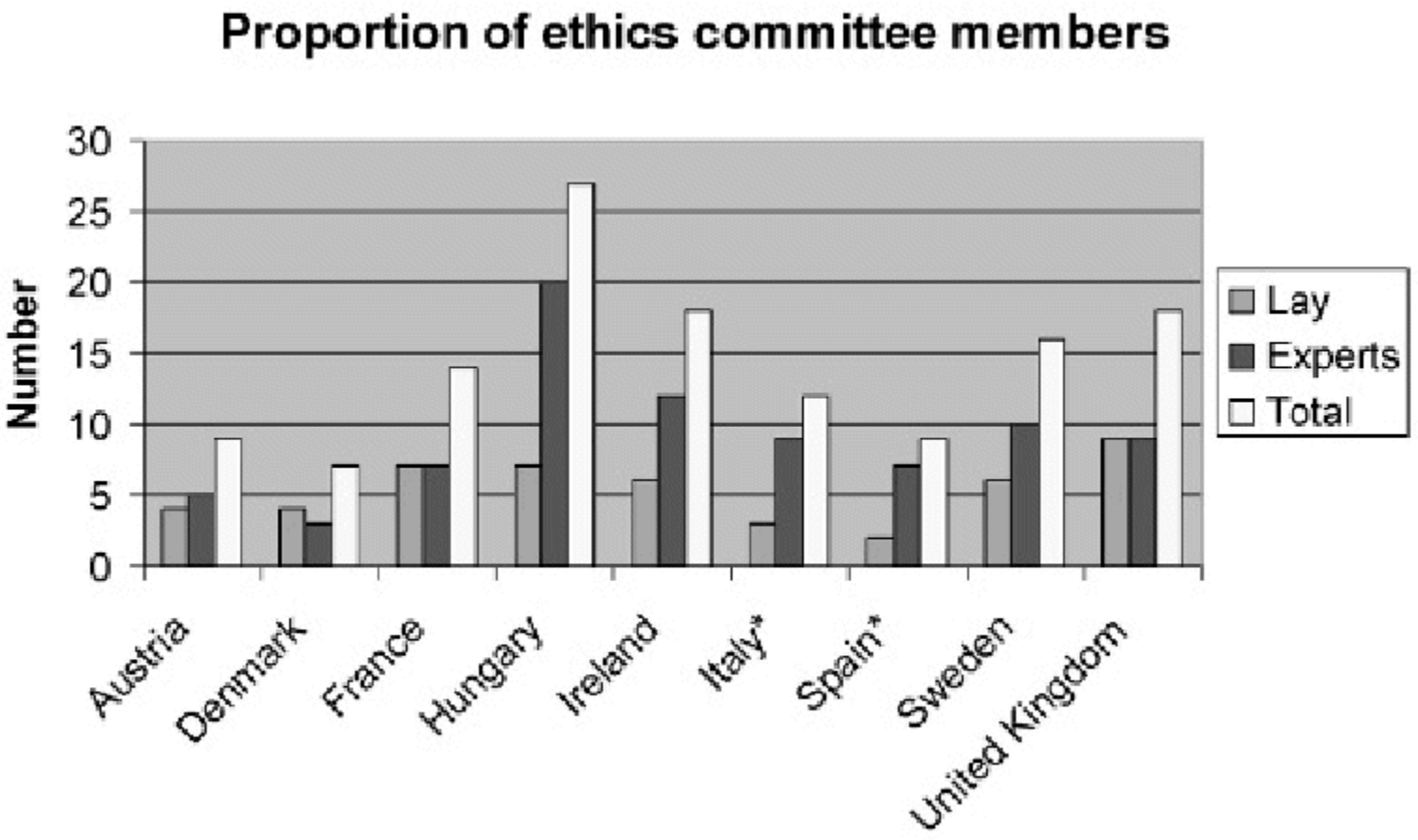
Harmonisation of ethics committees' practice in 10 European countries

R Hernandez,[1] M Cooney,[2] C Dualé,[3] M Gálvez,[4] S Gaynor,[2] G Kardos,[5] C Kubiak,[6] S Mihaylov,[7] J Pleiner,[8] G Ruberto,[9] N Sanz,[1] M Skoog,[10] P Souri,[11] C O Stiller,[11] A Strenge-Hesse,[12] A Vas,[13] D Winter,[8] X Carné[1]

Results: Ratios



Results: Composition



Reasons why a protocol could be good & right in Barcelona but not in Helsinki

- Familiarity with modern scientific concepts
- Overall educational level of participants
- Acceptance of the *standard of care*
- Undue inducement (*lack of health care protection*, € in *CTs 'without potential therapeutic benefit'*)
- Overall level of vulnerability of participants
- Diverse **cultural setting (historical)**

Items to be analyzed in a CT protocol

- Methodology
- Ethics..... Universal....vs....*Ethical relativism*

  reference Ethics Committees (rEC)

- Investigator
- Equipment & Site
- Logistics
- Informed Consent documents

  Local issues to be dealt by Local ECs

EC current practice (I).....

- Directive 2001/20/EC defines the role of ECs in CT with Medicinal Products, but ECs deal with many other types of Clinical Research
- ECs have not enough knowledge to deal with Advanced Therapies and other complex areas
- Historically EC & IRB are independent bodies that have evolved from classical peer review committees, incorporating lay & patients` representative members
- They should be truly independent: from researchers from health managers, payers, institutions ??? & appointing bodies ???

EC current practice… (II)

- Currently the protocol rejection rate is very low & quite similar across borders
- The great majority of discrepancies lay not in the protocol itself (E&M) but in the informed consent wording
- Pharmaceutical companies provide long ICs devoted more to protect themselves against lawsuit than to provide patients with grounds for a rational decision

Conclusions & Options (I)

- Need of networking of European EC
- DG SANCO should play a role in an European Regulation on Clinical Research
- Common electronic application dossier for EC & CA
- English as a common language (except Summary, Inform Consent Documents)
- Standardised education & training of EC members
- European accreditation, QA & audits

Conclusions & Options (II)

- A real 'single opinion' for Multi-centre national trials
- For multinational CTs with IMPs a European single opinion
  - One or several Central European EC to review ethical & methodological aspects of the protocol
    - + local evaluation on: ICD, PI, site & logistics
  - Mutual recognition of ethical & methodological aspects by a leading rEC in all MS
    - + local evaluation on: ICD, PI, site & logistics

Conclusions & Options (III)

- Except on very sensitive areas (Historical and/or Cultural reasons)
  - Stem cell research
  - Vulnerable populations
  - .....

Conclusions & Options (IV)

- Expedited SUSAR reporting to responsible local EC only for early phases, single centre, trials
- For the rest, EC should receive periodic Safety reports with aggregate data
- EC should have access to EudraVigilance database
- Role of DSMB on ongoing benefit/risk ratio should be strengthened
- Need of further dialogue and harmonization sensible areas: vulnerable population, stem cells, etc
- Need to foster academic & independent clinical research

International cooperation

Follow-up / implementation phase

- **WG on infrastructure and funding**
- **WG on investigator training and certification**
- **WG on accreditation of ethics committees**
- **WG on patient involvement**
- **WG on comparative effectiveness research**
- **WG on regulation**

www.oecd.org/sti/sci-tech/49344626.pdf

Big challenge for Europe

- It is a long an winding road
- Is it Utopia???

Respecting European diversity.....

to try to improve & unify systems in order to foster advances in clinical research..

ECRIN
EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK