Suggestions for Modification of the Clinical Trials Directive

ELN Annual Meeting

01 February 2011

European Medical Research Councils

Dr Kirsten Steinhausen

ESF Member Organisations

ESF is an independent association of 79 Member Organisations

- research funding organisations
- research performing organisations
- academies and learned societies

in 30 countries

European Medical Research Councils

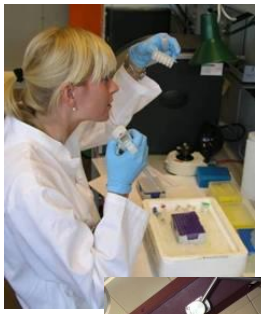
The membership organisation for the medical research councils in Europe under the ESF

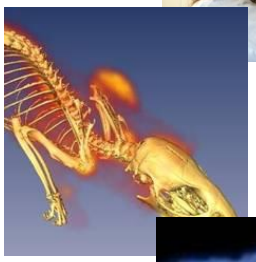
EMRC founded 1971

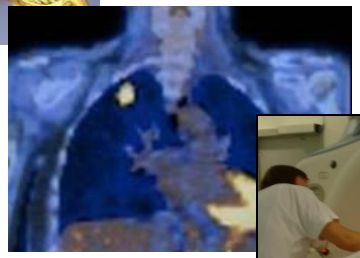
Chair Prof L. Højgaard

Clinical Physiology,
Nuclear Medicine & PET
Rigshospitalet
University of Copenhagen (DK)

EMRC's Mission







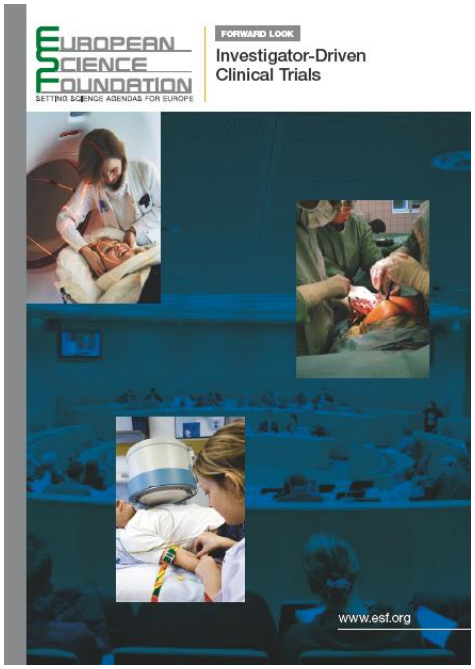
Promote innovative medical research and its clinical application towards improved human health

Medical Research

1. Basic Research
2. Translational Research
3. Clinical Research
4. Epidemiology & Prevention

Forward Looks

Investigator-Driven Clinical Trials



Top 5 recommendations

1. To improve the **education, training and career structure** and opportunities for scientists involved in patient-oriented clinical research

2. To increase levels of **funding** for IDCT

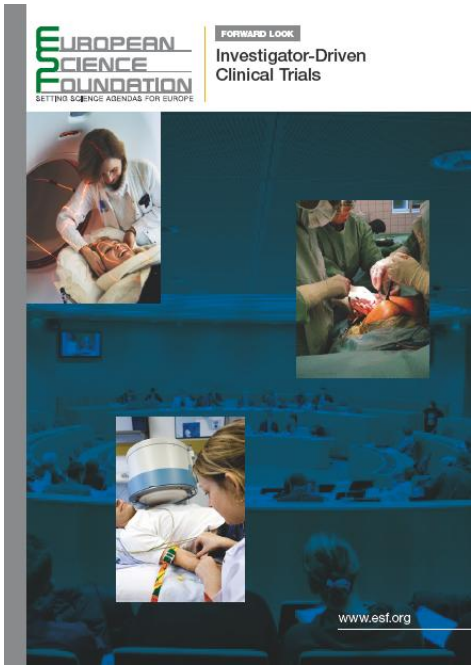
3. To adopt a **'risk-based' approach** to the regulation of IDCT

4. To **streamline procedures** for obtaining authorization for IDCT

5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are '**correctly powered**'

Forward Looks

Investigator-Driven Clinical Trials



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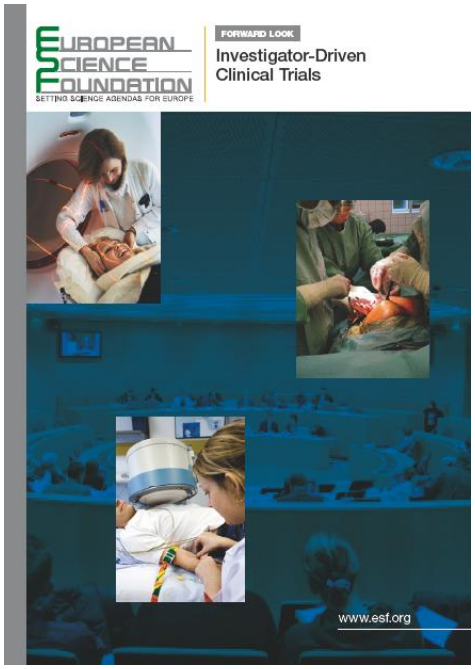

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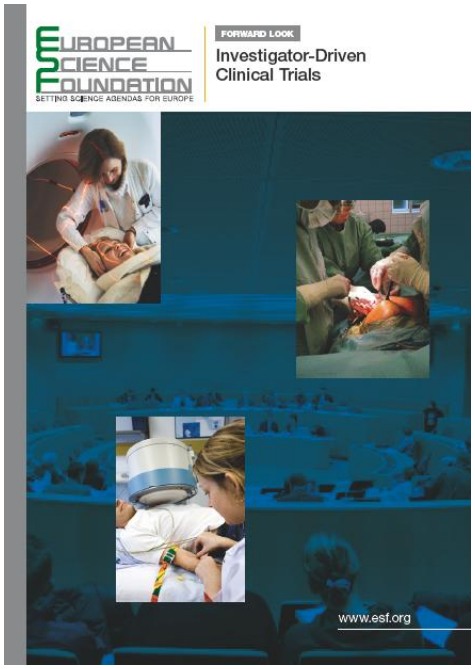

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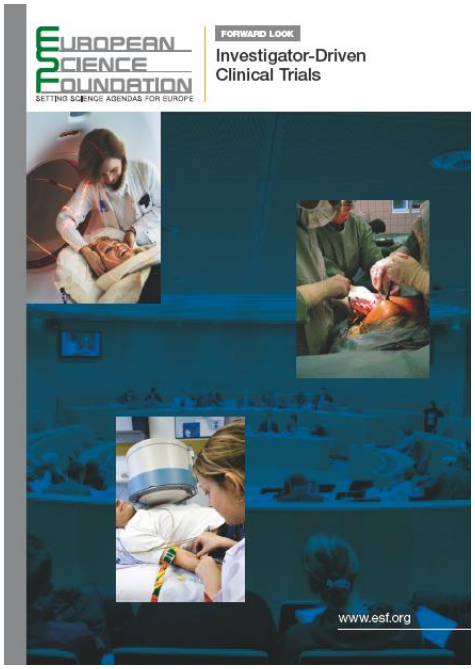

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Position Paper

EMRC proposal for a revision of CTD & recommendations for CT facilitation

1. First meeting in April 2010 Chair, Professor Francoise Meunier, EORTC

2. September 2010: meeting of a technical expert group in Brussels

3. Conclusion:
   In some areas a revision of the directive could be useful , in others local/national or European solutions outside the directive are sufficient.

4. The EMRC position paper will be published in summer 2011

Position Paper CTD

EMRC proposal for a revision of CTD & recommendations for CT facilitation

1. Multiple and divergent assessment of CTs
2. Definitions
3. Safety reporting
4. Substantial amendments
5. Labelling
6. Sponsor issues
7. Emergency in CTs
8. Monitoring
9. General recommendations outside the CTD

Position Paper CTD

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Position Paper CTD

1. Multiple and divergent assessment of Clinical Trials

Issue: multiple different application/assessment processes in different countries - lack of harmonisation.

Recommendation:
single entrance point for national competent authorities (NAC) and ethics committees (EC) for all Member States
Responsibilities for EC and NAC to be defined in the directive.

Revision of CTD: Article 7 and 9

Position Paper CTD

2. Definitions

Need for clearer definitions in the CTD

'Clinical trials' vs. 'Non-interventional trials"

Issue:

Different interpretation in different countries. One trial is quickly "outside definition"

For non interventional trials there is no EU- regulation

Recommendation:

non-interventional: allow interventions with minimal risk.

Revision of CTD: Article 2

Position Paper CTD

3. Safety reporting

Issue:

Current reporting system highly complex
Different reporting requirements and procedures.
Electronic submission is not always possible.

Recommendations:

Define clear and simple electronic forms for reporting of SAEs and SUSARs
Clear definitions what to report
Important information has to be filled in!

Directive: Article 16/17

Position Paper CTD

6. Sponsor issues

Issues:

Single sponsorship: problematic for IDCT

Different interpretation and rules of single sponsorship - lack of harmonisation

Recommendation:

Define Sponsorship

Definition should allow for two or more persons to take on the responsibilities between them.

Define clear allocation of duties. Consistent guidance about how sponsors may allocate their responsibilities.

Directive: Article 2 (e)

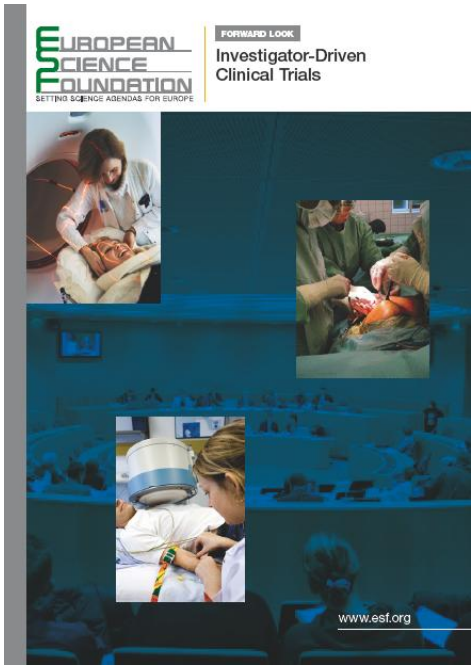
Position Paper CTD

9. General recommendations outside CTD

- Education & training!
- Make it *more simple to set up* a clinical trial
- *Provide simple tools*, templates
- Use *friendly electronic systems* (to follow the regulations 'automatically')
- *Best practice example:* the Netherlands with for instance template research protocol, template IMPD, etc. (see www.ccmo.nl)
- Make it *simple for clinicians to use medicinal products with marketing authorisations* in clinical trials
- If *authorized drugs* are used they *should be reimbursed* by the health care system

Forward Looks

Investigator-Driven Clinical Trials



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Global Setting

National Institute of Allergy and Infectious Diseases

Study	Treatment	Location	Target Enroll-ment	NIH Experiences
START Trial Strategic timing of ARV treatment 2008	Start ARV therapy: CD4>500 or CD4<350 cells/mm^3 17 FDA-approved drugs	22 countries 23 EU sites in: •Germany •Denmark •Poland •Finland •Spain •Italy •UK •Greece	4,000	Indemnification: Merck was willing to indemnify, but didn't want to set precedent. Sponsorship: Grantee agrees to sponsor NIH study. Disparate MS determination of IMP status, application and review processes, and safety reporting requirements. **Outcome:** Study delayed by at least one year.
Immune tolerance network 2010	Abatacept to treat Multiple Sclerosis	Initially proposed for US and EU sites	123	Disparate interpretations among MS of insurance, indemnity requirements and their implications on being trial sponsor. **Outcome:** All EU sites dropped.

Global Setting

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD Global Science Forum

"Towards international recommendations to facilitate cooperation in international non-commercial clinical trials"

- **ESF-EMRC implementation workshop** (Paris, June 2009)
- **German and Spanish** governments support
- **OECD GSF proposal** approved (April 2010)
- **First GSF meeting** (Madrid, May 2010)
- **Second GSF meeting** (Washington, November 2010)
- **Final GSF meeting** (Berlin, May 2011)
- **Participants**: European Commission, ESF, FDA, WHO, Germany, Spain, France, UK, Poland, Denmark, Norway, New Zealand, USA, Canada, Japan, South Africa, etc.

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Survey (Done)

- Regulatory differences
- Current situation for education, training & infrastructure

Working Groups (in progress, finalisation May 2011)

- Risk-based approach to CTs
- Regulatory frameworks & harmonisation
- Infrastructure, education & training practices

Report including recommendations (October 2011)

Thank you

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Global Setting

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Study	Treatment	Location	Target Enrollment	NIH Experiences
Type I Diabetes Consortium New onset type I diabetes. 2004	FDA approved drugs. Compare mycophenolate mofetil +/- daclizumab vs. placebo	Germany Italy	120	GMP/QP: 3rd country mfg. Roche w/ plants in the EU, but unwilling to produce. NIDDK hired a CRO ($750, 000/year). Indemnification: CRO agreed to take on the drug liability (at additional cost) because Roche would not. **Outcome**: Study completed at additional cost.

Global Setting

NIH research funding investments in E.U.

- $284 million through grants, contracts, and components of domestic awards
- 2100 total projects

Global Setting

National Heart Lung and Blood Institute

Study	Treatment	Location	Target Enroll-ment	NIH Experiences
Thalassemia patients with heart dysfunction and iron overload. 2005	Desferal +/- L1-deferiprone	5 sites U.S. and Canada Italy 1 UK 2 Turkey Egypt	87	Indemnification Single sponsor/legal representative Disparate MS application process GMP: third country issues **Outcome**: EU sites never opened to enrollment. Trial stopped in 2008.

Global Setting

Treatment Of Preserved Cardiac function heart failure with an Aldosterone an Tagonist

TOPCAT

Funded by the NHLBI

Study	Treatment	Location	Target Enrollment	NIH Experiences
TOPCAT trial Treatment of Preserved Cardiac function with an aldosterone antagonist. 2004	Spironolactone New formulation vs. current licensed product	US, Canada, Argentina, Brazil, Russia, Republic of Georgia EU sites: •Germany •France •Netherland	Target 3,315 Recruitment is ongoing	Indemnification. CRO unwilling to cover liability. GMP/QP requirements were challenging; costs for documenting compliance with EU provisions and rules cost prohibitive. Disparate safety reporting requirements. **Outcome**: EU sites dropped.