

**Sensible Guidelines for the Conduct of Clinical Trials II**

# **How Can We Resolve the Current Problems with the EU Directive?**

St. Anne's College, Oxford

06.09.2009

**Ingrid Klingmann, MD, PhD**

**European Forum for Good Clinical Practice**

**Brussels**

# How Can We Resolve the Current Problems with the EU Directive?

---

## The Current Situation

- Numerous articles and case studies have postulated that Directive 2001/20/EC, the „Clinical Trials Directive“ (CTD) has failed to promote efficient clinical research in Europe and to better protect the study participants
- However, there are more causes for the decreasing clinical research activity in Europe than the legal framework
- The European Medical Research Council of the European Science Foundation has analysed in a series of workshops the current problems faced in IITs. They developed 26 high-level recommendations to improve patient-oriented research in Europe, presented in „Forward Look: Investigator-Driven Clinical Trials“ (2009)

# How Can We Resolve the Current Problems with the EU Directive?

---

## The Current Situation

- **ESF's EMRC developed 26 recommendations. The top 5 were:**
  - ✓ **Better conditions for education, training and career for clinical researchers**
  - ✓ **Level of funding for clinical research in Europe**
  - ✓ **Risk-based approach to regulating clinical trials**
  - ✓ **Improved clinical trial authorisation process, ideally with a single CTA**
  - ✓ **Adequate scale for IITs: funding infrastructure for correctly powered trials**

# How Can We Resolve the Current Problems with the EU Directive?

---

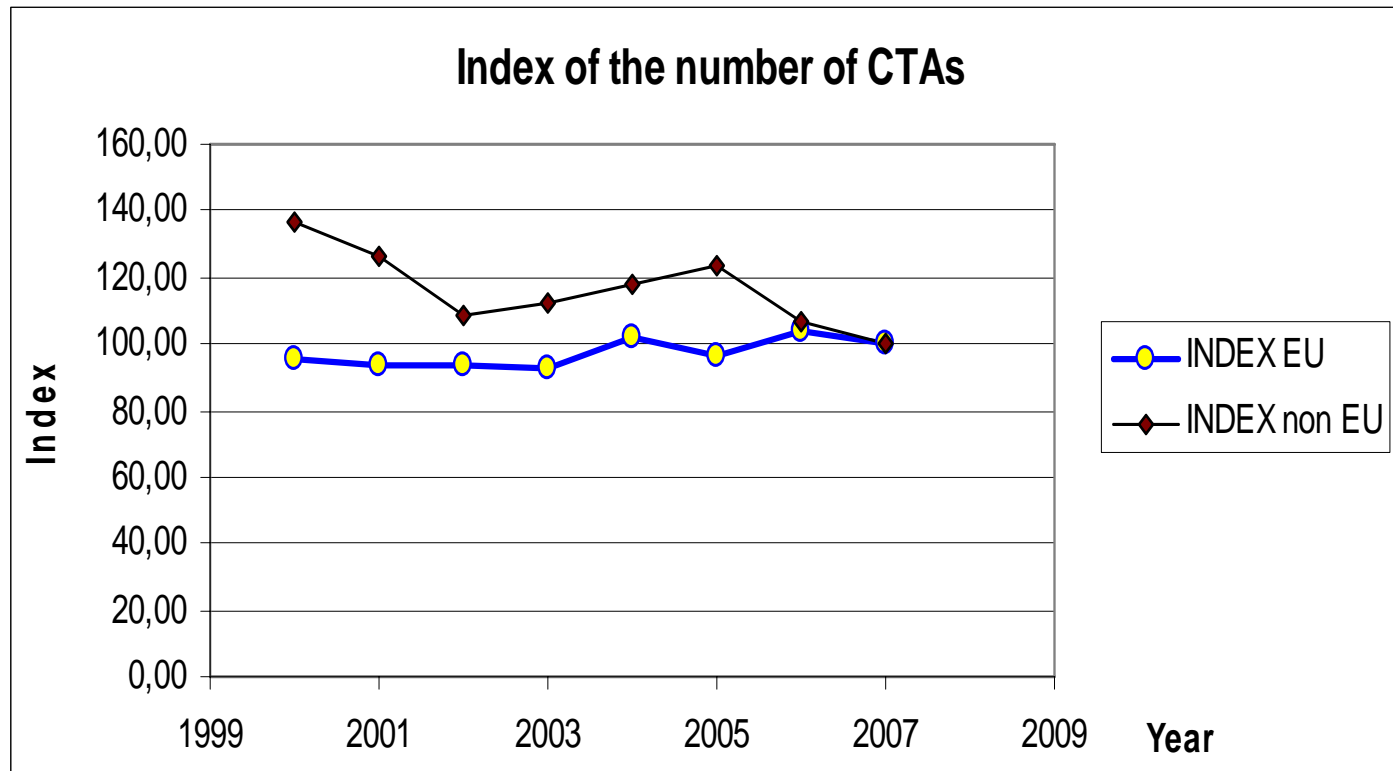
## The Current Situation

- Focusing on the legislative environment as a potential source of hurdles for clinical research, DG Research funded within FP7 the „ICREL Study“ with the aim to generate objective information on the current situation
- ICREL was performed in 2007 and provided evidence that important steps towards more sophisticated study review and harmonisation of clinical trial procedures in all EU Member States (MSs) have been made

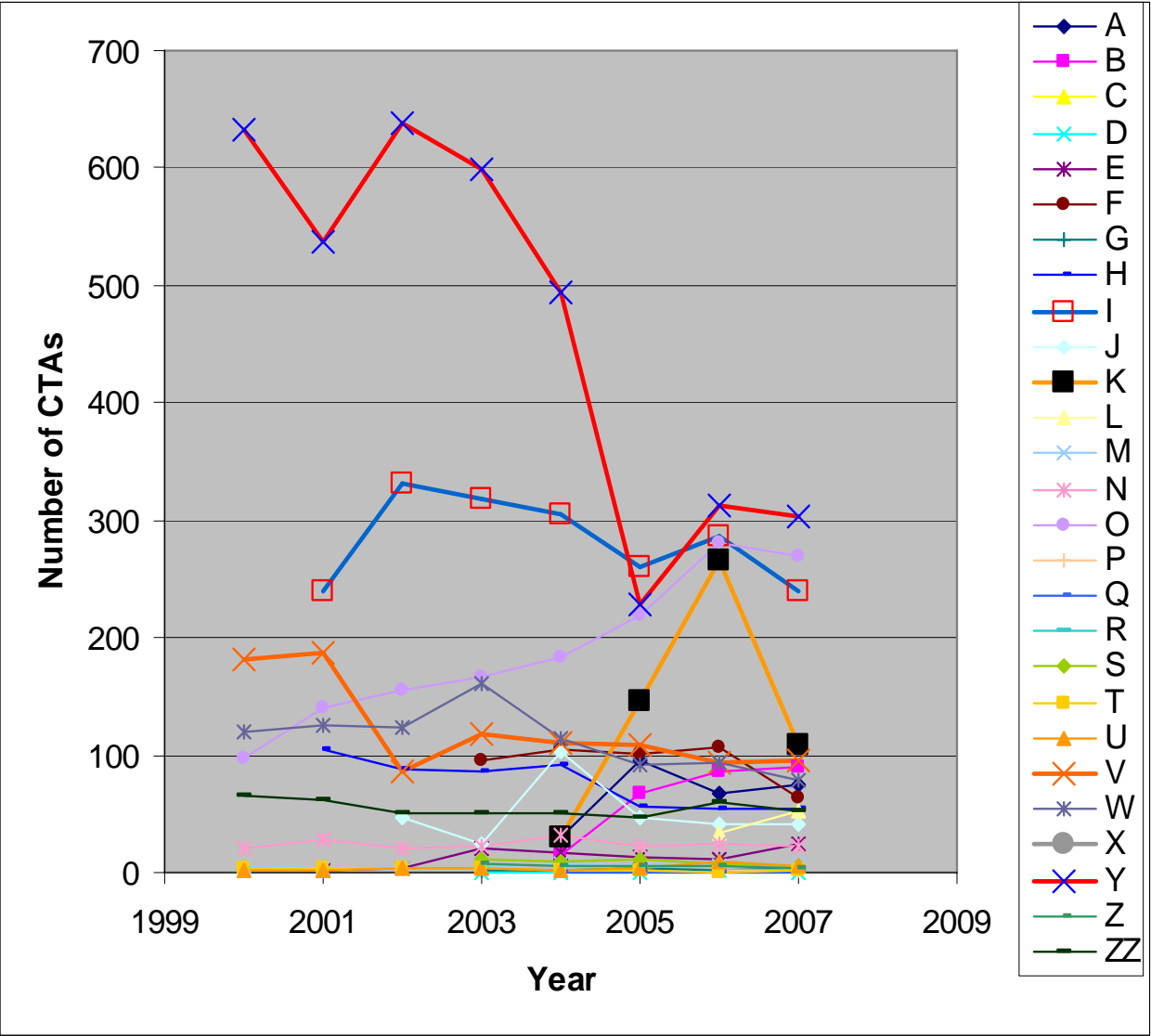
**BUT**

so far the new legislation has made the preparation and performance of clinical trials more complicated and most probably hindered the performance of important research

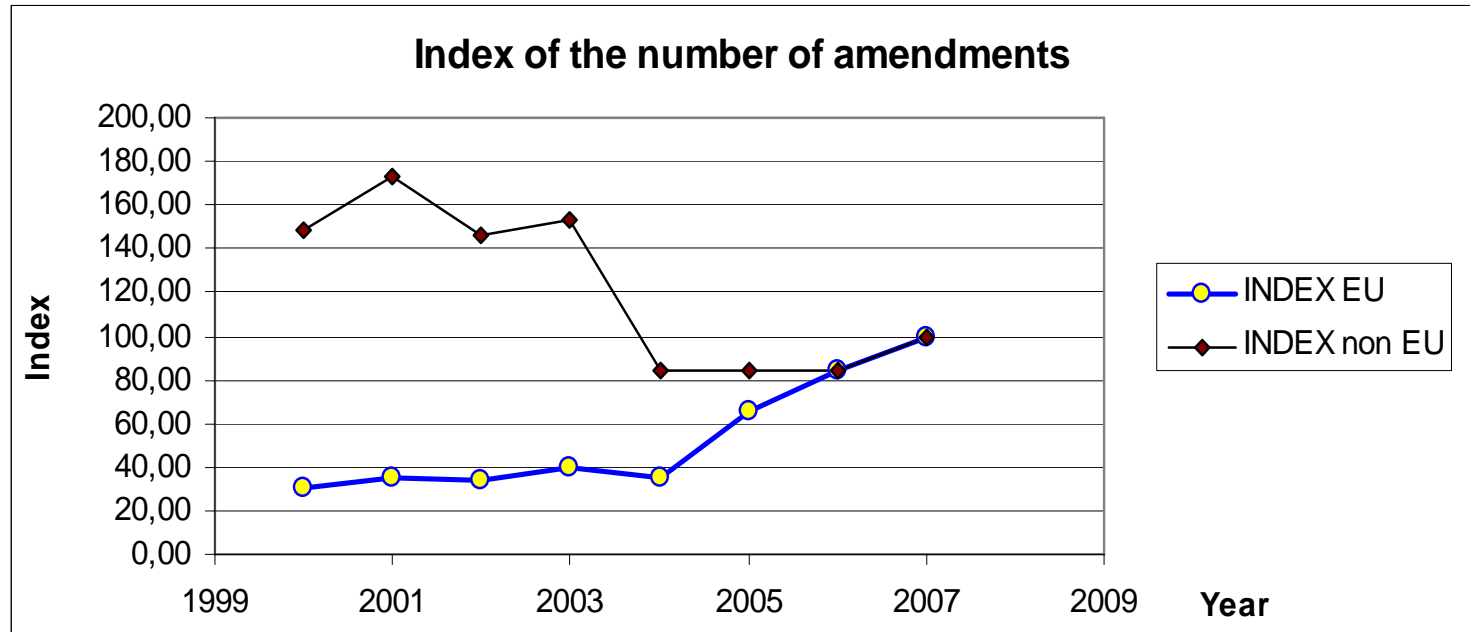
# Index of Total Number of CTAs



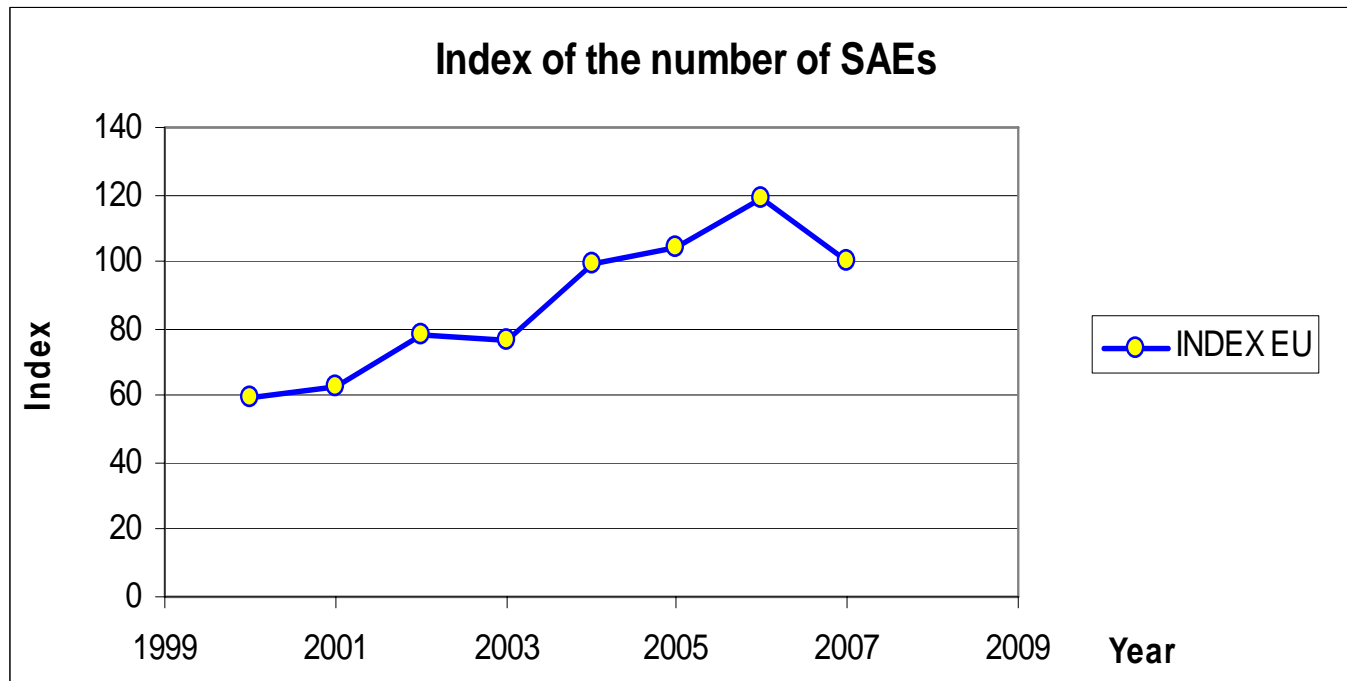
# Number of CTAs Submitted by Non-commercial Sponsors



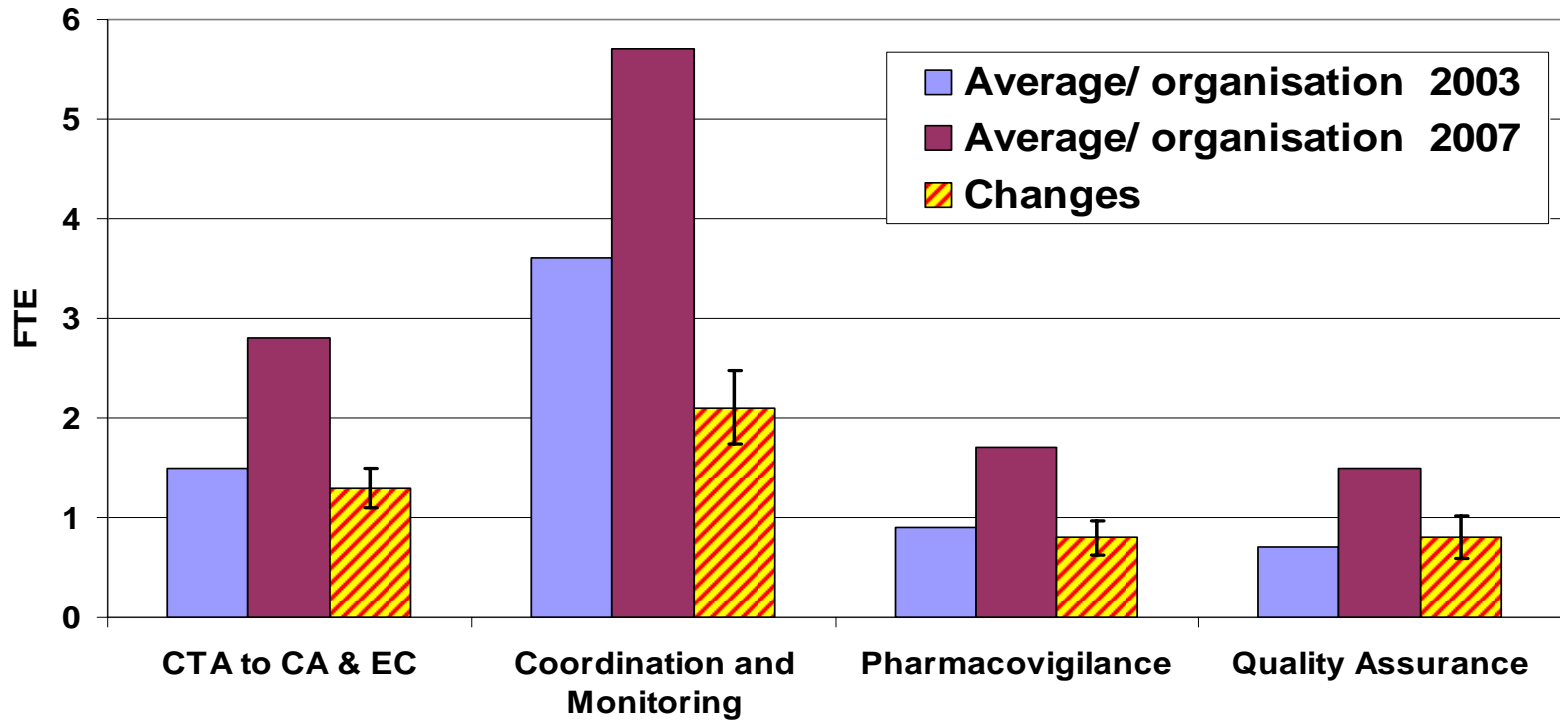
# Number Of Protocol Amendments Submitted to NCAs For Approval



# Number of SAEs or SUSARs Reported to NCAs



# Increases in Work Forces for CT-related Tasks in NCS



# Mean Time To Obtain Authorisation

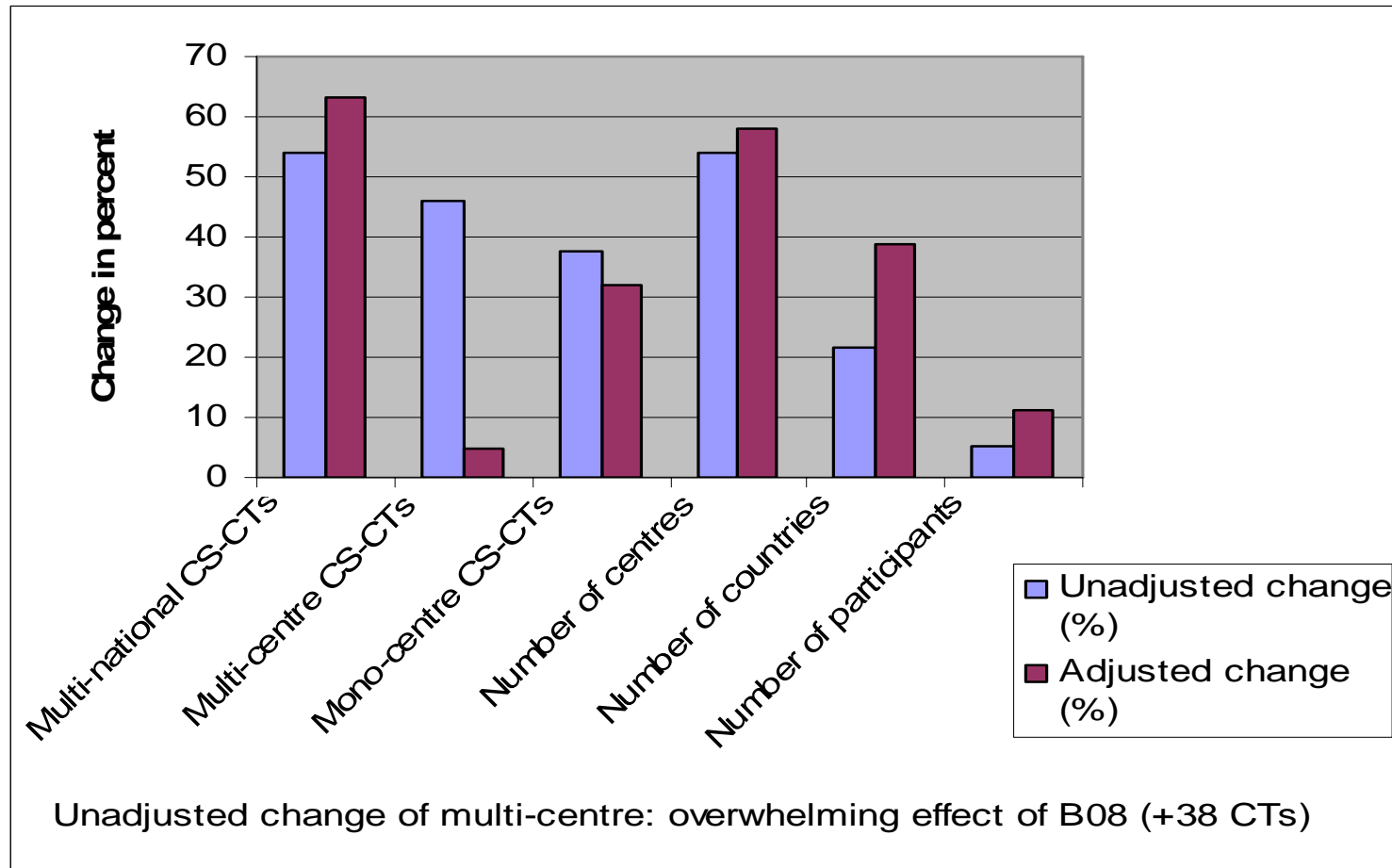
Mean time to obtain authorisation per NCA

	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU (d)	64	63.83	70.14	60.38	50.43	49.63	47.34	48.66
Sample size EU	6	6	7	8	8	9	11	15

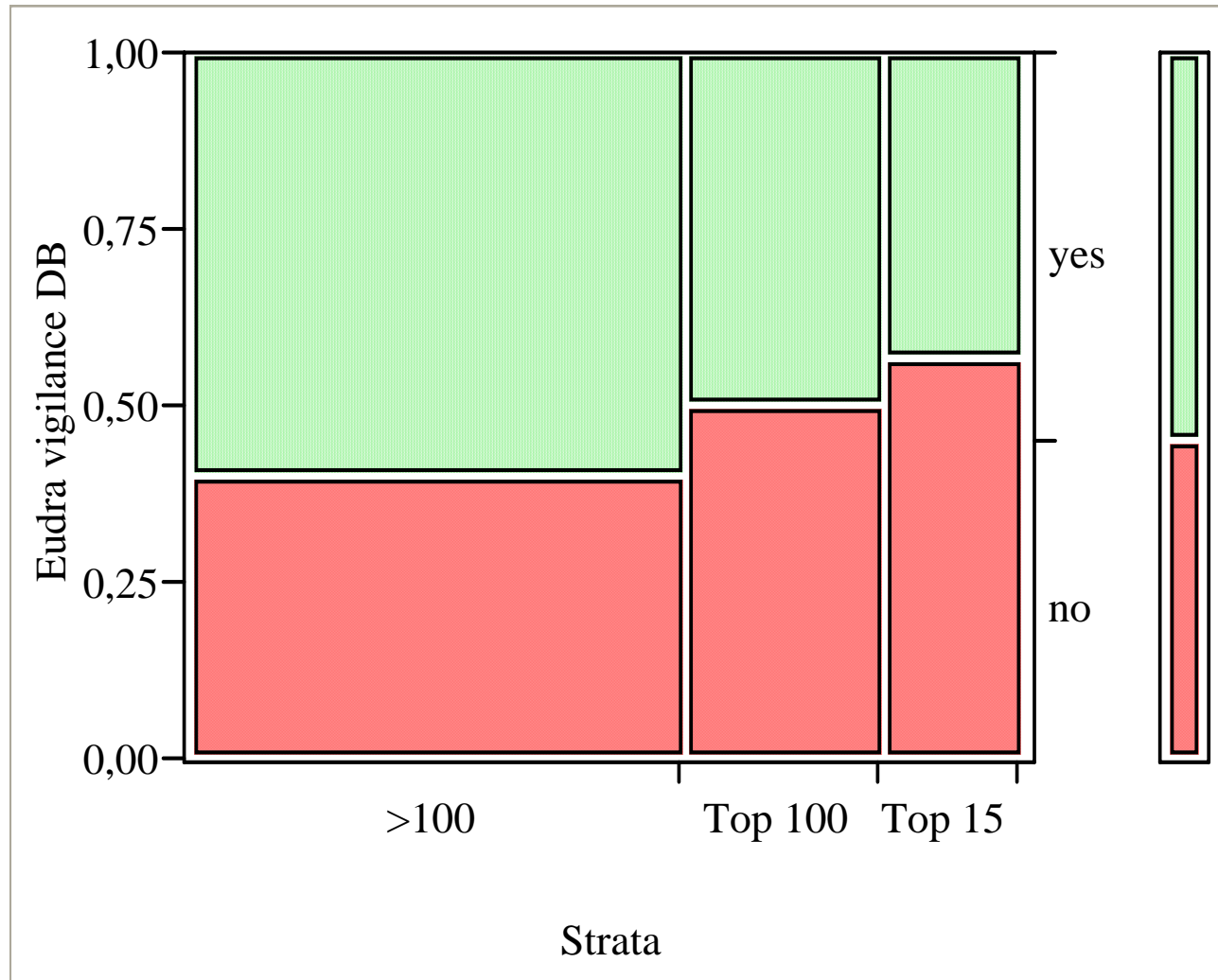
Time lines from CS protocol finalisation to inclusion of first patient and from (substantial) amendment release to first implementation in 2003 and 2007

Time Periods	2003	2007	Unadjusted change (%)	Adjusted change (%)
Days from protocol release to FPI	115	152	32.4	89.33
Days from (substantial) amendment release to first implementation	40	53	31.7	37.13

# Number of Involved Countries, Centres and Participants in Commercial Trials



# Impact of Implementation of the EudraVigilance Database on the Safety of Participants per Stratum



**So, what went wrong  
and  
what can be done to improve the  
future of clinical trials?**

# How Can We Resolve the Current Problems with the EU Directive?

---


## History

- **The Directive 2001/20/EC was released on April 04, 2001, and supposed to be implemented in all Member States by May 1, 2004**
- **De facto, the last country implemented the CTD in December 2006**
- **The related guidelines, required for consistent implementation in the MSs, were released at the same time or later**
- **As a result the MSs had much room for adapting the CTD principles into their national legislations**
- **Different MSs have applied the CTD principles to a different range of types of trials**
- **The infrastructure for clinical trials was not much adapted on national levels, e.g. funding level for studies, insurance conditions, hospital infrastructure for clinical trials, etc. Different MSs applied different approaches**

# How Can We Resolve the Current Problems with the EU Directive?

---

## History

- Different stakeholder groups in the process (commercial sponsors, ethics committees, competent authorities) discussed the CTD drafts within their communities, mostly on national level. Academic sponsors did not intensively discuss the legislation / did not express/defend their interests 

The EU Commission had to find the compromise between all the different interests

- A „Regulation“ was not acceptable for the MSs and commercial sponsors
- DG Enterprise can only deal with „products“, not with „science“ or „patient interests“. Ethical review is purely nationally governed

# How Can We Resolve the Current Problems with the EU Directive?

---

## Areas for Improvement

- Reducing the complexity of the study approval process:
- ✓ ONE CTA application dossier, centrally placed, accessible to all CAs and ECs involved
- ✓ Single CTA for multi-national trials
- ✓ Single ethical approval with national input in multi-national trials
- ✓ Clear definition of terms like „Investigational Medicinal Product“, „Non-interventional trial“, „Substantial Amendment“, etc.
- ✓ Clear assignment of responsibilities in the process to NCAs and ECs
- ✓ No additional review hurdles on national levels

# How Can We Resolve the Current Problems with the EU Directive?

---

## Areas for Improvement

- Facilitating sponsor definition and obligations:
- ✓ Possibility of co-sponsorship based on a detailed contractual agreement between the parties
- ✓ Identical application range of the legislation in all countries (e.g. Surgery trials? Medical devices? Radiotherapy?...)
- ✓ Simplification of the administrative requirements according to a „risk-based approach to clinical trial regulation “

# How Can We Resolve the Current Problems with the EU Directive?

---

## Areas for Improvement

- Facilitating sponsor definition and obligations:
- ✓ Coverage of the clinical trial liability insurance by government or healthcare system
- ✓ Facilitating SUSAR-reporting through single entry into EudraVigilance and only periodic safety information to ethics committees and investigators
- ✓ Harmonisation of safety reporting requirements between EMEA and FDA
- ✓ Harmonisation of inspection requirements between EMEA and FDA

# How Can We Resolve the Current Problems with the EU Directive?

---

## **Areas for Improvement**

- **Improving the infrastructure for clinical trials:**
- ✓ **Adaptation of the funding level per study to the increased professionalism of the trial administration**
- ✓ **Public funding of the creation of more dedicated, highly trained and efficiently managed clinical trial centres**

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **DG Enterprise** is hesitating concerning their next steps: they will launch a public consultation phase in Q4/2009 or Q1/2010
- DG Enterprise is afraid that creation of new legislation would take very long and could not solve the problem entirely, however, fast changes are required
- DG Enterprise's preferred approach would be to primarily amend the CTD-related Guidelines and perhaps the CTD as well
- DG Enterprise recently released a revision of the CTA guideline for consultation until 8 September 2009

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **The Heads of Medicines Agencies** created in 2004 the „**Clinical Trials Facilitation Group**“
- ✓ to coordinate the implementation of the CTD in the MSs
- ✓ to act as forum for discussion to agree on common principles and processes to be applied throughout the European medicines regulatory network (EMRN)
- ✓ to promote harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities (NCA).

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **The CTFG has implemented the „Voluntary Harmonisation Procedure“ which is currently running in its pilot phase**
- ✓ **It is meant for FiM studies, trials with „critical“ drugs, multi-national studies with large populations**
- ✓ **Within 30 to maximum 60 days the national assessors come to an agreed approval recommendation. The NCAs provide the approval within 10 days**

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **The „Voluntary Harmonisation Procedure“ weaknesses:**
  - ✓ **It is still a parallel assessment but NCAs agree amongst themselves**
  - ✓ **CTA dossier still needs to fulfill all national requirements**
  - ✓ **Unclear whether all MSs will participate in the system**
  - ✓ **Limited capacity of CTFG**

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **EFPIA** has come up with a suggestion for the approval system: an optional, centralised CTA approval process - enforced by a new Regulation, generating a *Community Clinical Trial Authorisation*
- The new system should run in parallel with the existing system
- Standardised electronic CTA dossier format with electronic repository accessible to all NCAs
- Central coordination
- Community-wide trial authorisation (study start pending upon positive EC opinions)

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **Road Map Initiative for Clinical Research in Europe** is a spontaneous grouping of organisations and consortia that were involved with collecting information on the impact of the CTD:
- ✓ **CLINT**: Facilitating international prospective clinical trials in stem cell transplantation (EU funded project)
- ✓ **EBMT**: European Group for Blood and Marrow Transplantation
- ✓ **ECRIN**: European Clinical Research Infrastructures Network
- ✓ **EFGCP**: European Forum for Good Clinical Practice
- ✓ **EORTC**: European Organisation for Research and Treatment of Cancer
- ✓ **ELN**: European Leukaemia Net (EU funded project)
- ✓ **ICREL**: Impact on Clinical Research of European Legislation (EU funded project)
- ✓ **UCLAN**: University of Central Lancashire, Centre for Professional Ethics

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

- **The Road Map Initiative has identified areas of particular concerns and opportunities for new legislation and will organise workshops between July 2009 and April 2010 on**
- ✓ **Single CTA (took place 07.07. 2009 in Brussels)**
- ✓ **Co-sponsorship (21.09. 2009, London)**
- ✓ **Safety reporting**
- ✓ **Risk –based approach to clinical trial legislation**
- ✓ **Ethical review**
- ✓ **Final workshop summarising the recommendations to DG Enterprise**

# How Can We Resolve the Current Problems with the EU Directive?

---

## Initiatives to Improvement

**Assemble organisations from ALL stakeholder groups**

- **to ensure that all stakeholder-related practical aspects are taken into consideration**
- **to bring in new ideas/creative concepts**
- **to increase the public pressure on the Commission to profoundly change the legislative framework for clinical trials in Europe**
- **to increase the „weight“ of the recommendations**
- **to achieve capacity to create pan-European awareness and „movement“ , also in the political arena**
- **to streamline the preparation and negotiation process of a new legislation**

**We have the rare opportunity of a  
„Second Chance“ –  
Let's do it right this time!!!!**