The Clinical Trial Regulation Implementation in Germany

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The Clinical Trial Regulation (CTR)

- **Objectives**
  - To harmonise the rules for clinical trials (CTs) with medicinal products by replacing the current Directive 2001/20/EC
  - To implement a coordinated joint review process for clinical trial applications (CTAs), substantial modifications and safety reports to foster multinational CTs in the EU
  - To facilitate multinational CTs by ensuring a single decision and single contact point per Member State (“One shop stop”)
  - To demand the solely use of an electronic communication platform (EU portal)
  - To enhance transparency by establishing a public accessible EU database on CTs

The Clinical Trial Regulation (cont'd)

- **<u>Not</u> within the scope**
  - To harmonise the rules for independent committees (ECs)
  - …

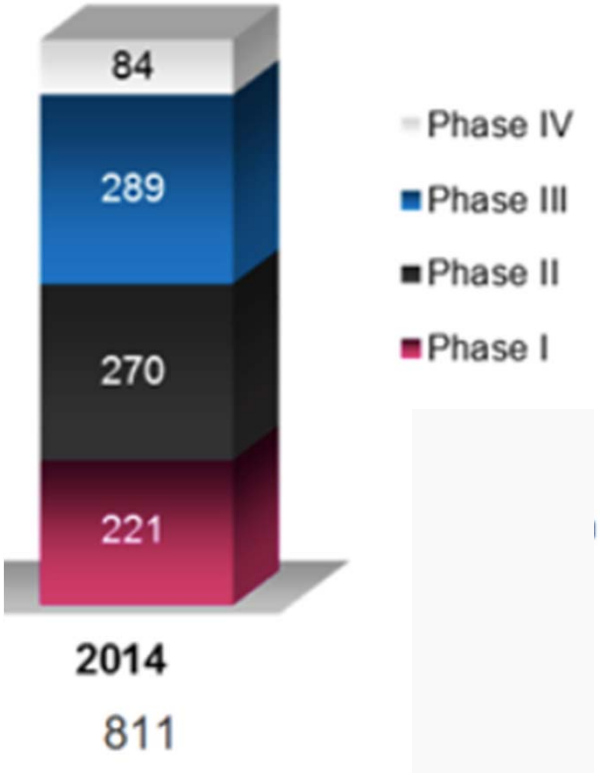
Current Situation in Germany

- **2 NCAs: BfArM and PEI (Paul-Ehrlich-Institute)**
  - Competence based on investigational product

- **53 Independents Committees (ECs), located at**
  - Medical faculties at universities
    - For physicians located at university hospitals
  - Physician chambers of the medical associations of the German states (“Länder”)
    - For all other investigators

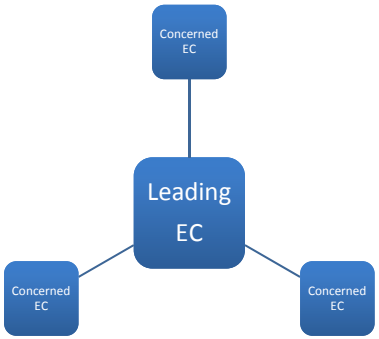
- **NCA and EC issue their own decision/opinion independently of each other**

BfArM Statistics



Phases may overlap

Current Situation: Leading and concerned ECs



Leading EC

- The EC where the coordinating investigator is located is the leading EC
- Tasks: Assessment of the complete trial except appropriateness of centres and investigators and IMPD (only NCA)
  - Trial Protocol
  - Investigators' Brochure
  - Informed consent forms and written patient information
  - Recruitment measures
  - Insurance
- May request additional information from the sponsor (only once, clock-stop)
- Makes the final decision including appropriateness of centres/investigators

Concerned EC

- The ECs of all other participating investigators are concerned ECs
- Task: Assessment of the appropriateness of the local centres and local investigators for each trial
  - Trial dependent assessment
- Must not request additional information on the trial protocol from the sponsor
- May send comments on the trial protocol to the reporting EC
  - Reporting EC may neglect comments

Concepts for the CTR Implementation in Germany (Work in progress)

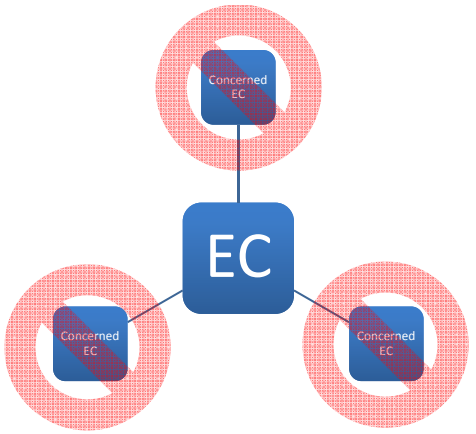
NCAs

- **BfArM and PEI remain NCA**

- **Competence according the character of the test IMP**
  - PEI: sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products(ATMPs), xenogenic medicinal products and blood components manufactured using genetic engineering
  - BfArM: all other IMPs

- **National Contact Point: BfArM**
  - If PEI is NCA all request are directed to the PEI

EC Concept



- **No single central EC but multiple ECs**
- **Primarily only one EC per CTA**
- **No competence according location (in multicentre trials)**
  - Concept: CTA assignment according a predefined randomised list
- **EC is involved in the assessment of part I, part II, substantial modifications and safety assessment**
  - Also SUSARs and DSURs
- **ECs registration**
  - Registration requires defined skill and capacity profile

EC-to-CTA Assignment

- **Yearly(?) list with >100% capacity of the anticipated number of CTAs**
- **ECs will be proportionately listed according their size/capacity**
  - Larger ECs will be listed more frequently
- **EC list will be randomised**
- **EC on top of the list is next to be chosen**

CTA Assessment by NCA and EC

Topic	Part	NCA	EC
Benefit/risk assessment	I	●	●
Low-intervention CT requirements (if claimed)	I	●	●
Investigators' brochure	I	●	●
IMP & AMP manufacturing/import/labelling	I	●	
Informed Consent	II		●
Protection of personal data	II		●
Suitability of investigators/staff/trial sites	II	●[1]	●
Damage compensation	II	●[2]	●
Handling of biological samples (bio-banking)	II		●
Recruitment	II		●
Rewarding / financial compensation	II		●

[1]for trial centres with negative GCP inspection's outcome; [2] for CTAs with GMOs

Cooperation between NCA and EC

- **EU portal will not provide tools for the cooperation within Member State?**

- **BfArM and PEI develop cooperation & tracking tool for the collaboration between ECs and NCAs**
  - Interface to EU portal urgently awaited (import of milestone dates)

What happens in case of divergent opinions?

- **Final decision is a “single opinion of the member state”**

- **It is assumed that the EC may veto a positive NCA decision for Germany**
  - Impact of EC veto if the German NCA is also RMS?
    - Has a negative EC opinion global impact on the NCA decision as RMS or only impact on the national decision?
  - Negative NCA decisions may not be revoked by positive EC opinion

Fees

- **Currently fees in Germany are different for each EC**
  - Wide range of fees between the ECs
- **CTR requires a single fee and single bill per activity**
- **Fees must be transparent and on the basis of cost recovery principles**
- **This CTR requirement will seriously impact the fee calculation in Germany**

Phase I Trials

- **Sponsors wish short review times for phase I trial**
- **BfArM observes increased complexity of phase I protocols over the last years**
  - Integrated protocols with several sub-studies
  - Up to the “All-in-one” phase I trial
- **It is anticipated that BfArM and PEI will provide shorter review times for phase I trials, but this may depend on the complexity of the trial protocol**
  - No legal base, but self-commitment of the NCAs?
  - “The simpler the protocol the shorter the review time”?
  - Shorter review times for follow-up trials?

Legal Representative
Article 74

- **Article 74 (1) requires where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to the CTR**
  - Article 74 (2) permits Member States not to apply paragraph 1
- **It is anticipated that in Germany a legal representative according Article 74 (1) remains a legal requirement for legal reasons (liability)**

Cluster (randomised) Clinical Trials

Treated with Medicinal Product RED

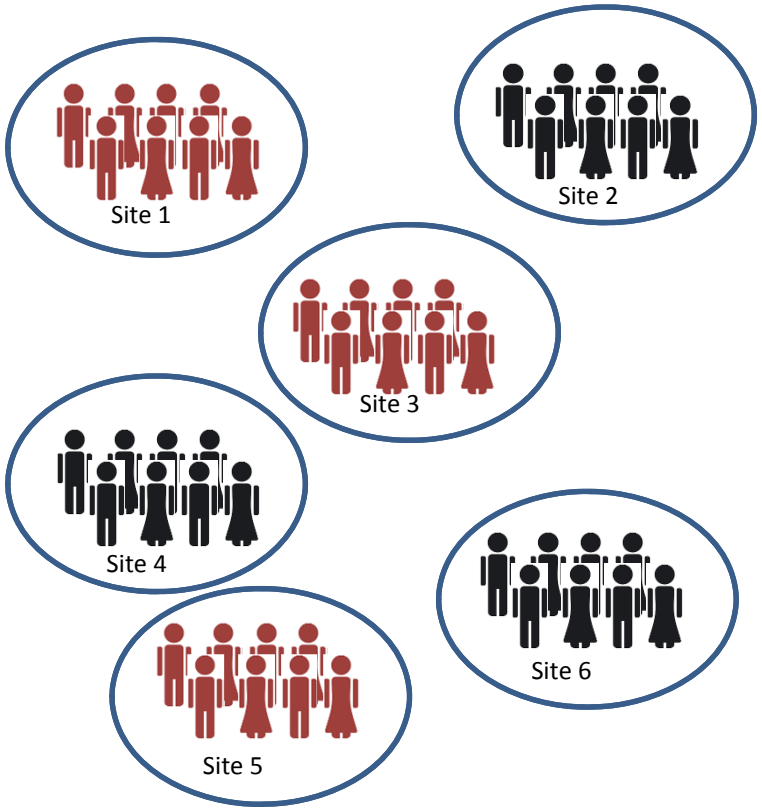
Treated with Medicinal Product BLACK

Standard Clinical Trial

Subjects are randomised

Cluster (randomised) Clinical Trial

Groups of Subjects are selected



Cluster (Randomised) Clinical Trial

- **Member States may establish legal basis for cluster randomised clinical trials**
  - Basically low-intervention clinical trials with no additional study related procedures
  - Reduced requirements for the informed consent process / documentation

- **Current position in Germany**
  - Cluster trials according the CTR are more or less comparable to multi-arm non-interventional studies (NIS)
  - Reduced ICF procedures may reduce the „burden“ only to a very limited extent, but may lead to legal implications
    - Subjects claiming not knowing to be included in a clinical trial

Damage Compensation

- **Current requirement: Insurance covering subject‘s damages caused by the participation in a clinical trial**
  - 500000 € in case of death or permanent serious disability

- **This requirement is expected to be also valid for the CTR**
  - Exemptions for low-intervention clinical trials

Transitional Provision

- **The applicant is permitted to submit CTAs up to 12 months after the CTR became active according the principles of Directive 2001/20/EC**
- **Such trials remain under the principles of Directive 2001/20/EC for 36 month**
- **Therefore, NCAs and ECs must provide both procedures**
  - Additional capacities required

Conclusion

- The CTR will seriously impact the work of the ECs in Germany
- Tight collaboration between NCA and ECs is required which is also fundamental new to BfArM and PEI
- For the functionality of the CTR the EU portal is crucial
- Therefore early publication of the portal data structures and interfaces for IT systems of the Member States are of great importance




Thank you for your attention!