Clinical Trials Regulation (EU) No 536/2014
Perspective of the CROs

17th DGRA Annual Congress
Bonn - 7 May 2015

Dr. Dagmar Chase
Vice-President EUCROF
Chair BVMA e.V.

Outline

- Sponsor
  - Co-Sponsorship
  - Legal Representative
- Timelines
- Transparency Rules
  - Phase I Trials
  - Inspection Reports

Sponsor

Sponsor

EU CT Reg Recital 58

In order to ensure clear responsibilities, the concept of a 'sponsor' of a clinical trial, in line with international guidelines, was introduced by Directive 2001/20/EC. This concept should be upheld.

Sponsor

EU CT Dir:
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial

EU CT Reg:
An individual, company, institution or organisation which takes responsibility for the initiation, management and setting up the financing of the clinical trial

EU CT Reg - Article 72

Co-sponsorship

1. **… where a clinical trial has more than one sponsor, all sponsors shall have the responsibilities of a sponsor under this Regulation, unless the sponsors decide otherwise in a written contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.**

EU CT Reg - Article 72

Co-sponsorship (cont.)

2. By way of derogation from paragraph 1, the sponsors shall be jointly responsible for establishing:

   a) a sponsor responsible for compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;

   b) a sponsor responsible for being a contact point for receiving all questions from subjects, investigators or any Member State concerned regarding the clinical trial and providing answers to them;

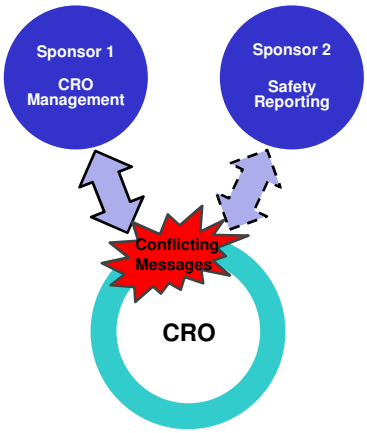
   c) a sponsor responsible for implementing the measures taken in accordance with Article 77
   (Revocation of authorisation, suspension, requested modification)

Co-Sponsorship

Scenarios of Co-Sponsorship

- (multinational) IITs
- Pharma: Co-Development
- Pharma plus Study Group

Example



Sponsor

EU CT Reg Recital 60

In order to ensure that enforcement action may be taken by Member States and that legal proceedings may be brought in appropriate cases, it is appropriate to provide that sponsors that are not established in the Union should be represented by a legal representative in the Union. However in view of the divergent approaches of the Member States as regards civil and criminal liability, it is appropriate to leave to each Member State concerned, as regards its territory, the choice as to whether or not to require such a legal representative, provided that at least a contact person is established in the Union.

EU CT Reg - Article 74

Legal representative of the sponsor in the Union

1. ….. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that legal representative shall be deemed to be a communication to the sponsor.

2. MS may choose not to apply paragraph 1 if the clinical trial to be conducted solely on their territory, or on their territory and the territory of a third country

3. Clinical trials to be conducted in more than one MS, all those MS may choose not to apply paragraph 1

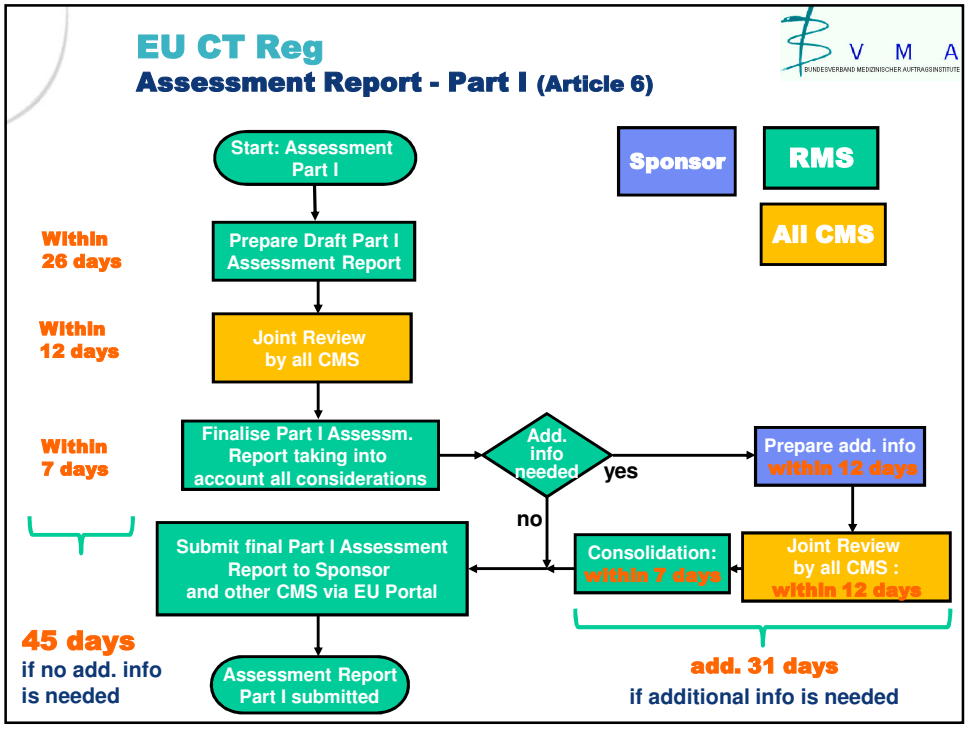
If at least a contact person in the Union is established

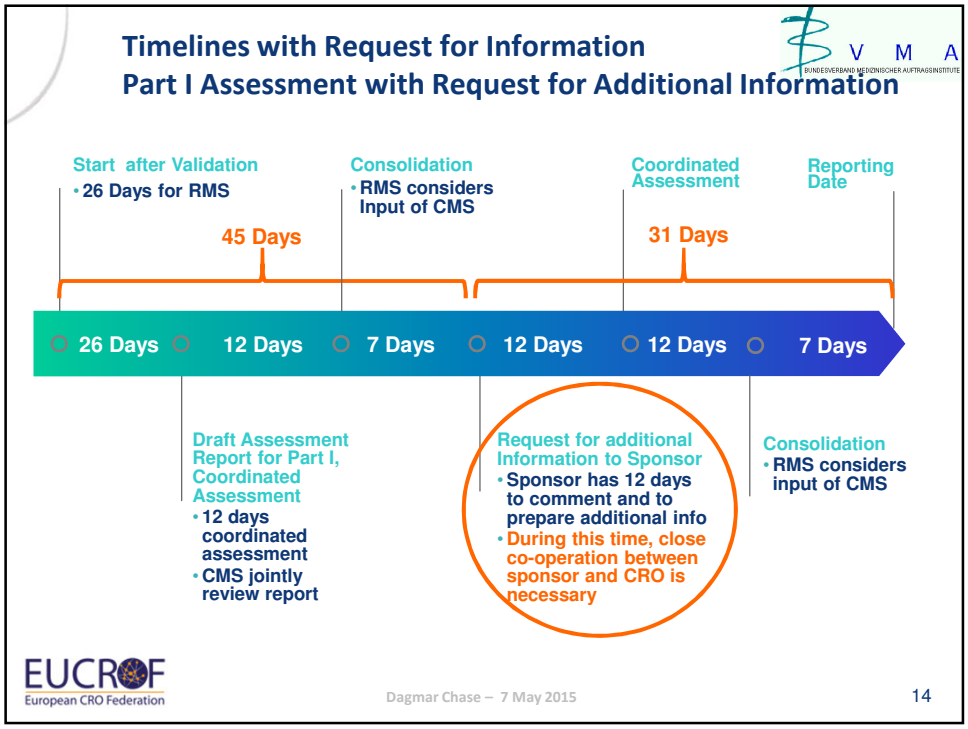
EU CT Reg - Article 74

Q: What if a CT starts without LR and a MS is added later on which requires a LR?

A: LR will have to be established during the run-time of the CT (establishing access rights for the EU Portal, etc.)

Timelines


EU CT Reg
Assessment Report - Part I (Article 6)
Start: Assessment Part I
Sponsor
RMS
All CMS
Within 26 days
Prepare Draft Part I Assessment Report
Within 12 days
Joint Review by all CMS
Within 7 days
Finalise Part I Assessm. Report taking into account all considerations
Add. info needed
yes
Prepare add. info within 12 days
no
Submit final Part I Assessment Report to Sponsor and other CMS via EU Portal
Consolidation: within 7 days
Joint Review by all CMS : within 12 days
45 days
if no add. info is needed
Assessment Report Part I submitted
add. 31 days
if additional info is needed


Timelines with Request for Information
Part I Assessment with Request for Additional Information
Start after Validation
• 26 Days for RMS
Consolidation
• RMS considers Input of CMS
Coordinated Assessment
Reporting Date
45 Days
31 Days
26 Days
12 Days
7 Days
12 Days
12 Days
7 Days
Draft Assessment Report for Part I, Coordinated Assessment
• 12 days coordinated assessment
• CMS jointly review report
Request for additional Information to Sponsor
• Sponsor has 12 days to comment and to prepare additional info
• During this time, close co-operation between sponsor and CRO is necessary
Consolidation
• RMS considers input of CMS
EUCROF
European CRO Federation
Dagmar Chase – 7 May 2015
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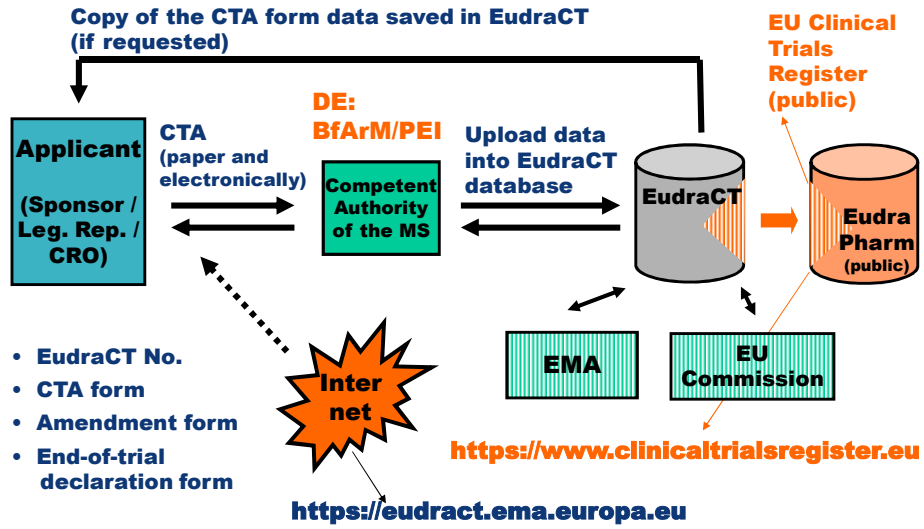
Transparency Rules
Phase I Trials

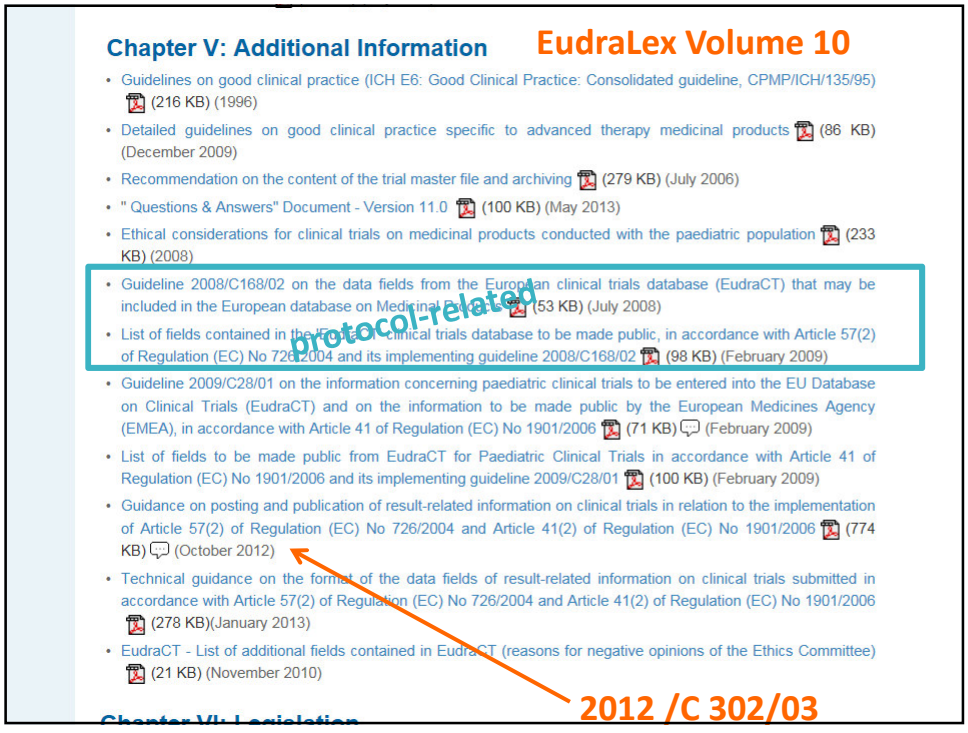
EU CT Dir
Working with EudraCT (before /during /end of CT)



Current Transparency Rules EU

- Since 2011, protocol-related information of all Phase II to IV clinical trials and of all paediatric trials is published on the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu)

- Since 2014, submission of result related information (summary of clinical trial results) is mandatory for all clinical trials on the basis of Article 57(2) of Regulation (EC) no 726/2004 and Article 41(2) of Regulation (EC) no 1901/200, however, result-related information on non-paediatric Phase I trials is not made public.



Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004

(2008/C 168/02)

3. SCOPE

Taking into consideration that the EudraCT database is only accessible to the competent authorities of the Member States and the European Medicines Agency in order to ensure that the confidentiality of the data is strictly observed and to protect the legitimate interests of sponsors, the information to be made publicly available keeps the balance between this principle and the need to inform the public in the interests of public health and transparency.

With these objectives in mind the information to be made available needs to be meaningful for the public, also by following agreed standards at international level. Moreover, phase I trials, certain details of the characterisation of the investigational medicinal products, certain details of the clinical trial design, information on batch release aspects, legal status of the sponsor, clinical trial sites and any personal related information are excluded from publication.

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Chapter V: Additional Information

EudraLex Volume 10

- Guidelines on good clinical practice (ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95) (216 KB) (1996)
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (86 KB) (December 2009)
- Recommendation on the content of the trial master file and archiving (279 KB) (July 2006)
- " Questions & Answers" Document - Version 11.0 (100 KB) (May 2013)
- Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (233 KB) (2008)
- Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (53 KB) (July 2008)
- List of fields contained in the EudraCT clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02 (98 KB) (February 2009)

protocol-related

- Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (71 KB) (February 2009)
- List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01 (100 KB) (February 2009)
- Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (774 KB) (October 2012)
- Technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (278 KB)(January 2013)

result-related

- EudraCT - List of additional fields contained in EudraCT (reasons for negative opinions of the Ethics Committee) (21 KB) (November 2010)

2012 /C 302/03

Current Transparancy Rules EU
EudraLex Volume 10
Guidance 2012/C 302/03

3. CONTENT OF POSTED RESULT-RELATED INFORMATION

The result-related information should be posted in accordance with this Guideline for all clinical trials referred to in Section 2.

The content of the results-related information is set out in the Guideline 2009/C28/01. The information set out there applies for paediatric as well as non-paediatric clinical trials.

The implementing technical guidance on the format of the data fields (hereinafter 'full data set') is published in a separate

Current Transparancy Rules EU
EudraLex Volume 10
Guidance 2012/C 302/03

5. PRESENTATION OF THE RESULT-RELATED INFORMATION TO THE PUBLIC

The posted result-related information is made public through the EU Clinical Trials Register of EudraPharm in accordance with the Commission guidance documents set out under Section 1, i.e. only result-related information on non-paediatric Phase-I clinical trials is not made public.

Current Transparancy Rules EU

EuraCT FAQs:

Q:

Are results required in EudraCT for phase 1 studies in adults. Will they be publicly posted in the EU CTR?

A:

All the results for phase I-IV clinical trials are required to be posted to EudraCT. However, Phase 1 trials, which are conducted solely in adults and which are not part of an agreed PIP are not made public.

Current Transparancy Rules US

In the US, Phase I trials are exempt from registration and results submission to a publicly accessible database (except interventional trials of FDA-approved drugs, biologics or devices)

EU CT Reg Transparency Rules

Administrative Notification Requirements (Articles 36, 37)

- Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all CMS, the sponsor shall submit to the EU database a summary plus a summary for laypersons of the results of the clinical trial (see Annex IV and V).
- However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.
- In addition to the summary of the results, where the clinical trial was intended to be used for obtaining a marketing authorisation (MA) for the IMP, the applicant for MA shall submit to the EU database the clinical study report within 30 days after the day the MA has been granted, …

EU CT Reg

Article 81 – EU Database

4. The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

(a) protecting personal data in accordance with Reg. (EC) No 45/2001;

(b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;

(c) protecting confidential communication between Member States in relation to the preparation of the assessment report;

(d) ensuring effective supervision of the conduct of a clinical trial by Member States.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2015
EMA/42176/2014 Rev. 1
Compliance and Inspections

Functional specifications for the EU portal and EU database to be audited

Sign off by the Deputy Exec. Director 10 April 2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2015
EMA/129363/2015 Final
Compliance and Inspections

Revision of section 6 of the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" setting out features to support making information public

EUCROF European CRO Federation

Questions in the CTA Form which will Influence Transparency Rules for an Individual Clinical Trial

1. Does the trial have a therapeutic (or prophylactic) intent?
2. Does the active substance appear in any marketing authorisation already granted in the EU?
3. Does the indication(s) under study in this trial appear in any marketing authorisation already granted in the EU for that active substance?
4. Does the formulation(s) appear in any marketing authorisation already granted in the EU for that active substance?
5. Does the route(s) of administration appear in any marketing authorisation already granted in the EU for that active substance?
6. What is the phase of the trial?
7. Is this a low interventional trial?
8. Does the sponsor request a deferral of the publication of the registration data until the publication of the summary results (for phase I trial only).

EUCROF European CRO Federation

EU CT Reg
Transparency Rules

- The Appendix to the Functional Specifications of the EU Portal and EU Database is expected in October 2015
- Clarification as to which information/data/documents fall under the term Commercially Confidential Information

Excerpt from the EUCROF Comments: Revision of Section 6 of the Functional Specifications …
Publication of result-related Information: Phase I Trials

….

We therefore suggest the following in relation to the publication of summary reports:

- If summary reports are to be published 12 months after the end of a trial, then the information provided should be limited to non-CCI. In case of Phase 1 clinical trials, this would further limit the benefits of publication, whilst at the same time increasing the administrative burden of providing redacted/abbreviated reports.
- An alternative would be to set an automatic trigger to publish Phase 1 summary reports when the first therapeutic study's summary report for that same IMP (indication, formulation, route of administration) is published.

Transparency Rules
Inspection Reports

EU CT Reg
Publication of Inspection Reports

Draft proposal for an addendum, on transparency, to the Functional specifications …

4.6.1. Inspection reports

1. **Information on the planning of an inspection, its conduct, reporting and follow-up should remain confidential until the final inspection report has been issued.**

2. **Inspection reports should be made public once the inspection process is completed and the final inspection report signed off and issued by the Member State(s) inspectorate. This may be deferred where its publication would be prohibited by ongoing legal proceedings in the Member State.**

EU CT Reg
Publication of Inspection Reports

Other reporting obligations relevant for subject safety
(Article 53)

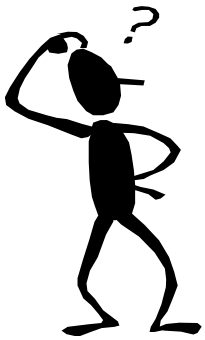
1. …
2. **The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the clinical trial. When requested by a Member State concerned, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request.**

Will these report be published as well?

Excerpt from the EUCROF Comments: Revision of Section 6 of the Functional Specifications …
Publication of Inspection Reports

- **EUCROF does not agree with the unrestricted publication of inspection reports. The publication of inspection reports should have a defined purpose. Only findings that are of relevance to the public should be made publicly available.**
- **Publication of inspection reports within the current inspection systems will inevitably lead to unfair commercial advantages afforded to individual CROs and unintended commercial damages to others. This could have legal implications. Until a standardised and harmonised inspection system and process is available in the EU which includes all CROs, the approach of publishing inspection reports for CROs is considered unfair by EUCROF.**

Any Questions?



Thank you very much for your attention!

www.bvma.de
www.eucrof.eu