Federal agency for medicines and health products

Submission of a clinical trial dossier to the famhp, substantial amendments and safety follow up

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famhp

.be

Overview of the presentation

- Submission of initial trial dossiers

- Submission of modifications to the original documentation

- Safety reporting during the trial

- End of trial notification and final study report

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Submission of initial trial dossiers (1)

Current legal context …

- Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

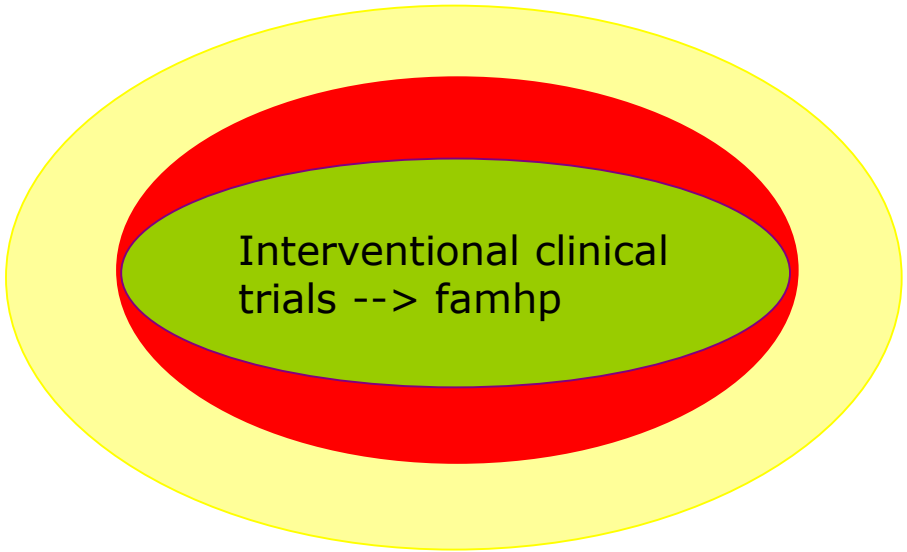
- Law of 7 May 2004 related to experiments on human people

… keeping in mind that the purpose of all requirements is to insure the protection of all participants to the studies.

Submission of initial trial dossiers (2)

- Law 7 May 2004 : larger scope than EU directive

All experiments in humans where subjects are selected in function of future observations



Submission of initial trial dossiers (3)

Definition of a Clinical Trial

'Clinical trial': any **investigation in a human subject intended to discover or verify the clinical,** pharmacological and/or other pharmacodynamic **effects of one or more investigational medicinal product(s)**, and/or to **identify any adverse reactions** to one or more investigational medicinal product(s) and/or to **study absorption, distribution, metabolism and excretion** of one or more investigational medicinal product(s) with **the object of ascertaining its (their) safety and/or efficacy**;

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				**A NON-INTERVENTIONAL CLINICAL TRIAL?**
Is it a medicinal product (MP)?[i]	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to <u>any</u> of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC. If you answer yes to <u>any</u> of the questions below go to column D.	If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC. If you answer yes to <u>any</u> of the questions below go to column E.	If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C & D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.
A.1. Is it a substance[ii] or combination of substances presented as having properties for treating or preventing disease in human beings ? A.2. Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3.Is it an active substance in a pharmaceutical form?	B.1. Are you <u>only</u> administering any of the following substances? • Human whole blood[iii]; • Human blood cells; • Human plasma; • A food product[iv] (including dietary supplements) not presented as a medicine; • A cosmetic product[v] • A medical device	C.1. To discover or verify/compare its clinical effects? C.2. To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3. To identify or verify/compare its adverse reactions? C.4. To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1. To ascertain or verify/compare the efficacy[vi] of the medicine? D.2. To ascertain or verify/compare the safety of the medicine?	E.1. Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned? E.2. Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3. Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol[vii]? E.4. Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5. Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6. Will epidemiological methods be used for the analysis of the data arising from the study?

Eudralex volume 10, chapter V, Q&A document http://ec.europa.eu/health/documents/eudralex/vol-10/

Submission of initial trial dossiers (4)

General principles

• Compliance to the international recognised ethical and scientific quality requirements (GCP) is mandatory

• Before an interventional clinical trial can start in a EU Member State :

- a (single) positive opinion of an Ethics Committee is needed
- a valid submission to the Competent Authority without major objections within the predefined timelines

Submission of initial trial dossiers (5)

Content of the dossier: guidance documents

- **CT1 guidance**

Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial

- **Circular letter 575**

Practical considerations for submissions of initial trials and amendments following new version of the CT1 guidance in 2010

Submission of initial trial dossiers (6)

Content of the dossier

- Cover letter
  - Info on RSI (Reference Safety Information)
  - Any scientific advice related to the trial?
- EU application form
- Protocol
- IMPD (Investigational Medicinal Product Dossier)
- Investigator's Brochure
- GMP requirements (non registered products)
- Labels

Submission of initial trial dossiers (7)

Content of the dossier (simplified)

For registered products available on the Belgian market

- Cover letter
- EU application form
- Protocol
- ~~IMPD (Investigational Medicinal Product Dossier)~~
- ~~IB (Investigator's Brochure)~~
- ~~GMP requirements (non registered products)~~

=> All replaced by SmPC

- ~~Labels~~

=> No specific label for NIMPs (see circular letter 575) and simplified label for IMPs to comply with point 32 of annex 13 of GMP (may be added at the hospital pharmacy without GMP autorisation needed – see circular letter 596)

Submission of initial dossiers (8)

Use of a product which is not registered as a medicinal product in EU or an ICH country

- The product has to be manufactured following the Good Manufacturing Practice (GMP)
- A full IMPD and an IB have to be provided

Submission of initial dossiers (9)

Frequent issues identified during validation of the dossiers

- EU application form not entirely completed

(advices or help from the helpesk: https://servicedesk.ema.europa.eu)

- Protocol sometimes very brief
- IMPD, IB and GMP information not provided for non registered products
- Use of a registered product in a non registered indication: at least clinical rationale should be provided (sometimes also non clinical)
- Simplified labels not provided for registered IMPs

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Submission of substantial amendments (1)

Definition of a substantial amendment

Amendments to a clinical trial are regarded as 'substantial' where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the clinical trial participants, or
- the scientific value of the trial

Submission of substantial amendments (2)

General principles

- The sponsor should assess whether an amendment is to be regarded as 'substantial'
  - Examples can be found in the Detailed guidance CT-1

- 'Non-substantial' amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment.

- Before a substantial amendment can be implemented :
  - a valid submission to the Competent Authority without major objections within the predefined timelines
  - a positive opinion of the Ethics Committee is needed

  => in case of substantial amendments « for EC only » (eg. change in PI), *only EC approval is needed*, but notification + payment to the FAMHP is requested (Ref Circular letter 575)

Submission of substantial amendments (3)

Content of the dossier: guidance documents

- **CT1 guidance**

Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial

- **Circular letter 575**

Practical considerations for submissions of initial trials and amendments following new version of the CT1 guidance in 2010

Submission of substantial amendments (4)

Content of the dossier

-Cover letter

- Description of the modifications
- In case of changes to the safety information in the IB, clarify what risk mitigation measures are already in place in the protocol to manage the new safety issues if the new IB with significant new safety info is not accompanied by a protocol amendment

- Substantial amendment notification form (Annex II)

- xml EU application form (also if no changes)

- Modified documents (protocol, IMPD, IB,…)
  - clean version and track changes version (Ref. CT-1 art 133 (c))

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Safety reporting during the trial (1)

General principles and guidance documents

- Detailed guidance on the collection, verification and presentation of adverse event/ reaction reports arising from clinical trials on medicinal products for human use (CT-3)

- Circular letter 586

-Definition

-Adverse event: 'any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does **not necessarily have a causal relationship** with this treatment'.

-Adverse reaction: 'all untoward and unintended responses to an investigational medicinal product **related** to any dose administered'.

-Safety reporting

- The investigator should report adverse events (serious/non-serious) to the Sponsor

- Generally **serious adverse events** must be reported **within 24h** to the Sponsor

Safety reporting during the trial (2)

General principles and guidance documents

-Safety reporting

-The Sponsor should:

- Record the adverse events
- Report the suspected unexpected serious adverse reactions ('SUSARs')

-to the EC and to the FAMHP (through the Eudravigilance Clinical Trials Module - for additional questions (eg. waivers for non-commercial Sponsors: adversedrugreactions@fagg-afmps.be)

Fatal or life- threatening SUSAR's must be reported **within 7 days**, other SUSARs must be reported within 15 days

- Inform the investigators
- Provide an annual safety report (DSUR) to the FAMHP and the EC according to the ICH E2F Guideline (low-interventional/phase IV trials: eg. waivers possible for IMPs that are SoC)

- Reference Safety Information (RSI): 'expected' adverse reactions (including a degree of frequency and severity), based on the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product => contained in SmPC or IB

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End of trial notification and final study report

End of trial notification

- Within 90 days by means of the end of trial notification form
- Early termination: within 15 days + clearly explain the reasons
- End of trial should be defined in the protocol

Final study report

- For BE it is sufficient to post the Clinical Study Report/synopsis on EudraCT-EU Clinical Trials Register. No separate submission to the FAMHP is required.

Guidance on posting and publication of result-related information on clinical trials (2012/C 302/03)

Overview of most relevant guidance documents

- **CT1 guidance**: Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial
- **CT3 guidance**: Detailed guidance on the collection, verification and presentation of adverse event/ reaction reports arising from clinical trials on medicinal products for human use

- **Circular letter 575**
- **Circular letter 586**
- **ICH Guideline E2F on DSUR**

Additional information and templates on EudraLex

Volume 10 – Clinical Trials Guideline

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