The new EU clinical trial regulation 536/2014 : Low interventional trials

KCE

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Agenda:

1: Legal framework

- EU regulation 536/2014
- Q&A document : algorithm

2: Risk adaptation

- Risk assessment
- Risk categories
- Risk adaptation possible for:
  - → Reduced role for approval
  - → Content of application
  - → Labelling
  - → Safety surveillance
  - → IMP management
  - → Documentation
  - → GCP inspections

3: Ethical considerations → ICF

4: Next steps

- At national level
- At EU level

1: Legal framework - Definitions in the EU CTR

- Clinical Studies
- Clinical trials
- Non interventional trials
- Low interventional trials

1: Legal framework - Definitions in the EU CTR

The risk to subject safety in a clinical trial mainly stems from two sources:

- **the investigational medicinal product**
- **the intervention**

1: Legal framework - Definitions in the EU CTR

(11) Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice.

Those **low-intervention clinical trials** are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. **Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products.** In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.

1: Legal framework - Definitions in the EU CTR

(57) Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the Union. **The rules for labelling should be adapted to the risks to subject safety and the reliability and robustness of data generated in clinical trials.**

Where the investigational or auxiliary medicinal product have already been placed on the market as an authorised medicinal product in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council (2), as a general rule **no additional labelling should be required for clinical trials that do not involve the blinding of the label.** Moreover, there are specific products, such as radiopharmaceuticals used as diagnostic investigational medicinal product, where the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.

1: Legal framework - Definitions in the EU CTR

Clinical study

means any investigation in relation to humans intended:

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

b) to identify any adverse reactions to one or more medicinal products;

c) or to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;

1: Legal framework - Definitions in the EU CTR

Clinical trial

means a clinical study which fulfils any of the following conditions:

a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;

c) or diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects

1: Legal framework - Definitions in the EU CTR

Low-intervention clinical trial

means a clinical trial which fulfils all of the following conditions:

(a) the **investigational medicinal products**, excluding placebos, are **authorised**;

(b) according to the protocol of the clinical trial,

- (i) the investigational medicinal products are **used in accordance with the terms of the marketing authorisation**;
- **or** (ii) the use of the investigational medicinal products is **evidence-based and supported by published scientific evidence** on the safety and efficacy of those investigational medicinal products in any of the Member States concerned;

(c) the **additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden** to the safety of the subjects compared to normal clinical practice in any Member State concerned;

Non-interventional study means a clinical study other than a clinical trial

1: Legal framework - Algorithm

Questions and answers document will be published in the near future by EC

Annex II: Decision tree to establish a whether a trial is a "clinical trial"

1: Legal framework - Algorithm

	A	B	C	D	E	F
A CLINICAL STUDY OF A MEDICINAL PRODUCT?					**A NON-INTERVENTIONAL CLINICAL TRIAL?**	**A LOW-INTERVENTION CLINICAL TRIAL?**
Is a medicinal product administered before or during the start of the 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?	Is the product authorised in any EU Member State?
If a medicinal product is administered before the start of the clinical trial, and it falls under current practice, please go to column E. If a medicinal product is administered before the start of the clinical trial and it falls not under current practice, column E is excluded.	If you answer no to all the questions in column A, the activity is not a clinical trial on a MP.	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 all the questions in column C the activity is not a clinical trial under the scope of Regulation EU No 536/2014.	If you answer no to all the questions in column D the activity is not a clinical trial under the scope of Regulation EU No 536/2014.	If you answer NO to all these questions the activity is a non-interventional trial which is outside the scope of Regulation EU No 536/2014.	If your answer in column E is YES, and you answer NO to any of the questions below, the activity is a clinical trial within the scope of Regulation EU No 536/2014 but is NOT a low-intervention clinical trial as defined in the Regulation.

1: Legal framework - Algorithm

If a medicinal product is administered after the start of the clinical trial, please go to column A.	If you answer yes to <u>any</u> of the questions below go to column B.	If you answer no to this question below go to column C.	If you answer yes to <u>any</u> of the questions below go to column D.	If you answer yes to <u>any</u> of the questions below go to column E.	If your answers in columns A,B,C & D brought you to column E and you answer YES to <u>any</u> of these questions the activity is a clinical trial within the scope of the Regulation.	If your answer in column E is YES, and if you answer YES to ALL of the questions below, the activity is a low-intervention clinical trial as defined by the Regulation.

1: Legal framework - Algorithm

	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 only 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 pharmacokinetics, e.g., 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. Does the assignment of any patient involved in the study to a particular therapeutic strategy decided in advance by a clinical trial protocol[vii] and does not fall within current practice? E.2. Is the decision to prescribe a particular medicinal product clearly taken together with the decision to include the patient in the study? E.3. Will 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?	F.1. Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned? F.2. Does the protocol of the clinical trial specify that (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; F.3.Do the additional diagnostic or monitoring procedures not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned?

1: Legal framework - Algorithm

Cf. Article 1(2) of Directive 2001/83/EC, as amended

Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.
This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.
Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.
The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product "means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.
Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.

2: Risk adapted approaches

Risks to participant safety in relation to the IMP

Non-interventional, Type A , B , C

Risk adaptation can be possible for low interventional trials for the defined categories ?

Diversification needed for:

- Within SmPc
- Off label use

2: Risk adapted approaches

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type A: no higher than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: - they relate to the licensed range of indications, dosage and form or - they involve off-label use (such as in paediatrics and oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines
Type B: somewhat higher than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: - Such products are used for a new indication (different patient population/disease group) or - Substantial dosage modifications are made for the licensed indication or - If they are used in combinations for which interactions are suspected Trials involving medicinal products not licensed in any EU Member State if: - The active substance is part of a medicinal product licensed in the EU (A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)*
Type C: markedly higher than that of standard medical care	Trials involving a medicinal product not licensed in any EU Member State (A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)*

2: Risk adapted approaches

Increasing potential risk of IMP

Are Risk adaptions possible?	Non-Interventional	Type A	Type B	Type C
1. Reduced role for NCA approval	*	**Yes**	No	No
2. Content of application	*	**Yes**	(Yes)	No
3. Labelling	*	**Yes**	(Yes)	(Yes)
4. Safety Surveillance	*	**Yes**	(Yes)	No
5. IMP management	*	**Yes**	(Yes)	(Yes)
6. Documentation	*	**Yes**	(Yes)	No
7. GCP Inspections	*	**Yes**	(Yes)	(Yes)

Table 2

Key: Yes – possible; (Yes) – may be possible on case by case basis;
*No – little, if any flexibility in requirements; * no specific clinical trial regulatory requirements*

2: Risk adapted approaches

Risk Adaptions	Areas impacted
1. Reduced NCA role in approvals	Notification v Approval
2. Contents	a. IMP dossier b. Investigator's Brochure c. Good Manufacturing Practice (GMP)
3. Labelling of trial drugs	a. Need for trial labelling b. Content of labelling
4. Safety Surveillance	a. Adverse Drug event recording/reporting b. Safety Monitoring
5. IMP management	a. Tracking and Accountability b. Storage
6. Documentation	a. Trial Master File (TMF) Content b. Essential Documents retention times
7. GCP Inspections	a. Organisation and selection processes for routine GCP systems inspection b. Inclusion in routine GCP inspection reviews at the study level c. Frequency and duration of inspections

Table 3

2: Risk adapted approaches

•**ADMINISTRATIVE INFORMATION**

EudraCT number	
Title of the study	
Name of sponsor(s) Note: if there is more than one sponsor the primary contact should be identified	
Trial category (as per EMA Appendix on disclosure rules: EMA/228383/2015 Endorsed)	Category 1 ☐ Category 2 ☐ Category 3 ☐
Trial category- low intervention trial	Yes ☐ No ☐
First in human ☐ Phase I ☐ II ☐ III ☐ IV ☐	

2: Risk adapted approaches

Reduced role of NCP:

- Notification only is no longer an option
- Critical validation step for RMS (harmonised approach @ EU needed: certainly in view of justification of "off label evidence")

Contents: for IMPD and IB referring to SmPC

Labelling: trial specific labelling may not be required

Safety: referring to Pharmacovigilance system in place for licensed medicinal products

GCP issues:

- GCP inspections : triggered vs system inspections
- Simplified procedures for traceability , follow-up etc

3: Ethical considerations

- Competence of the Ethics Committees
- ICF waiver not an option, simplification however?
- Requirements for part 2: simplification possible?

3: Next steps

- Pragmatic trials recognised as very important part of clinical research

- Additional guidance needed in general but more specific for academic sponsors
    - 38 % academic trials at EU level versus 20 % in Be
    - Phase IV versus Phase II trials to be analysed
    - EUPD

- Working group at national level: famhp multidisciplinar team, college, ethics committees and external partners

  Applications to be sent to greet.musch@fagg.be

- Discussion at CTFG , GCP inspectors WP and expert meeting clinical trials at EU Commission

5 : Acknowledgments



- Famhp R&D team
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Thank you for listening

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