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Interventional or Non-Interventional? Analyzing the Differences Between Clinical Studies Using Medicines in the European Union

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Clinical Trial Regulation (EU) No. 536/2014 (REG 536/2014),{1} signed off on April 16, 2014, aims to simplify current rules, streamline trial application procedures, improve transparency, and harmonize clinical trial practice throughout all the Member States of the European Union (EU), in alignment with the tenets of the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guideline.{2} This regulation has an extensive scope within clinical trials, covering authorization procedures, ethical considerations, implementation, operations, and disclosure, among other topics.

However, REG 536/2014 is not yet in force; currently, researchers rely on the Clinical Trial Directive (DIR 2001/20/EC),{3} which merely provides the definitions and requirements Member States must adopt into their own local legislation. It is important to note that non-interventional studies are out of the scope of both the current DIR

2001/20/EC and the upcoming REG 536/2014. As a result, there is significant variability in the classification of non-interventional studies across EU Member States with consequent impacts on their planning and execution on a multinational scale.

This paper aims to overview each type of clinical study referred to within the upcoming REG 536/2014 and analyze their impact upon the implementation of this Regulation, as well as the expected framework for non-interventional studies. For improved navigation, please refer to Table 1 for a list of abbreviations and acronyms used in this paper or otherwise tied to this topic.

Table 1: Useful Abbreviations and Acronyms

DIR 2001/20/EC	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
PASS	Post-authorization safety study
PRO	Patient-reported outcome
REG 536/2014	Clinical Trial Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Clinical Studies

Article 2 of REG 536/2014 defines a "clinical study" as 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, or c) 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.

This section further defines clinical studies as either "clinical trials," "low-intervention clinical trials," or "non-interventional studies." Table 2 compares each clinical study type in terms of study objectives, methods, population, and regulatory/ethical requirements, in alignment with REG 536/2014.

Table 2: Comparison of Study Types

	Clinical trial	**Low-intervention trial**	**Non-interventional study[a]**
Objectives	**Pre-marketing**: pharmacology, safety, and efficacy information for MAA. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.	**Pre-marketing**: pharmacology, safety and efficacy information for MAA, but IMP use is evidence-based and supported by published evidence. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.	**Pre-marketing**: not applicable. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions, in accordance with the MAA and following normal clinical practice.{9}
Methods	Usually prospective, although there may be exceptions (case study 2 in Table 4).	Usually prospective, although there may be exceptions (case study 2 in Table 4). Treatments and procedures	Can be retrospective, cross-sectional, or prospective. Treatment and procedures follow clinical practice and

	Treatments and procedures defined in the protocol. Monitoring and operations according to the ICH GCP guideline.	defined in the protocol. Less stringent operations compared to other clinical trials.	cannot be imposed by the protocol.{3} Treatment prescription independent from study inclusion.{3} No harmonized European guidance or regulation for operational activities.
Population	Sample size depends on the study objectives. Usually stricter eligibility criteria.	Sample size depends on the study objectives. Sample sizes may be higher and eligibility criteria may be less strict than early-phase clinical trials.	Large sample sizes and heterogenous populations to reflect real-world conditions. Exclusion criteria usually compliant with the MAA.
Ethical requirements	EC favorable opinion. ICF mandatory.	Same as other clinical trials.	EC favorable opinion. ICF typically mandatory (may be waived under specific conditions).
Regulatory requirements	Competent authority(ies) authorization. Registration and disclosure in EudraCT. Country-specific regulations may require additional steps.	Same as other clinical trials.	Imposed PASSs: approval from PRAC (or local authority, if conducted in only one Member State).{9} PASSs: registration in the EU PAS.{9} Country-specific regulations may require additional steps. Local authority consulting may be advisable to confirm non-interventional status.

[a] Non-interventional studies are not scoped in the REG 536/2014. This table presents guidance and requirements from other regulatory sources applicable to the European Union.

References: Directive 2001/20/EC,{3} Guideline on good pharmacovigilance practices Module VIII.{9}

Abbreviations: EC Ethics committee; EU PAS European Union Electronic Register of Post-Authorization Studies; EudraCT European Clinical Trials Database; GCP Good Clinical Practice, ICF Informed consent form; ICH International Council for Harmonization; IMP Investigational medicinal product; MAA Marketing authorization application; PASS Post-authorization safety study; PRAC Pharmacovigilance Risk Assessment Committee.

Clinical Trials

Article 2 of the REG 536/2014 defines a “clinical trial” as a clinical study whose treatment strategies, diagnostic assessments, and clinical monitoring procedures are determined and scheduled in advance by a clinical trial protocol, and do not fall within normal clinical practice.

Clinical trials are required before an investigational medicinal product (IMP) is authorized to be commercialized for the intended therapeutic indication(s). These trials collect pharmacological, safety, and efficacy information from human participants needed for marketing authorization.{4} Clinical trials are also performed after marketing authorization is granted, to refine understanding of the benefit/risk relationship under real-world therapeutic use conditions.{4}

All clinical trials performed in the EU should receive authorization from the competent authority(ies) and be registered in the European Clinical Trials Database (EudraCT) prior to starting.{1,5} Country-specific regulations may require additional regulatory steps (e.g., approval of local data protection authorities or registration in local clinical trial databases). A favorable opinion from all applicable ethics committees (ECs) and an approved informed consent form are required.{1,6}

Low-Intervention Clinical Trials

The concept of “low-intervention clinical trial” is first introduced in the upcoming REG 536/2014 and is not part of the DIR 2001/20/EC. These trials use authorized drugs (excluding placebos) in accordance with the marketing authorization, or non-authorized drugs, if their use is evidence-based and supported by the published scientific evidence. These trials should not pose more than a minimal additional safety risk or burden to participants compared to normal clinical practice.{7}

As in all clinical trials, the assessment and treatment procedures of low-intervention clinical trials are to be determined by the protocol. However, less stringent requirements may be applicable. Specific conduct requirements should be based on a risk evaluation assessment to be performed for each trial.{7} Sponsors must be familiar with REG 536/2014, the European Commission guidance document describing Risk Proportionate Approaches in Clinical Trials, and applicable legislation of the target EU Member States to perform an appropriate risk evaluation and propose adequate conduct approaches. On the other hand, regulatory and ethical submission and authorization requirements for low-intervention clinical trials are the same as for other clinical trials.{1}

One potential concern regarding the introduction of the low-intervention trial concept is the lack of EU-consistent regulatory definition for “minimal additional safety risk or burden” in the upcoming REG 536/2014. As such, upon implementation of the new Regulation, there may be difficulties in defining a study that falls upon the borderline between a non-interventional and low-intervention definition. This can result in a single study being considered as non-interventional in some Member States and as a clinical trial in others. Due to this situation, it can be difficult for sponsors to meet the study application requirements and compliance expectations.

To avoid such inconsistencies, the REG 536/2014 aims to provide a clear and harmonized definition for low-intervention clinical trials. To further reduce ambiguity, in June 2019, the European Commission issued the REG 536/2014 Draft Questions & Answers document, which has been frequently updated since that time (currently Version 2.3, dated November 2019, at time of writing).{8} Annex II of this document includes a decision tree aiming to establish whether a study is a clinical trial, a non-interventional study, or a low-intervention clinical trial, following some key aspects

(i.e., whether the drug is an IMP, what effects is the study looking for and their purpose) (see Table 3).

Table 3: Decision Tree for Determining Study Type (Transcribed from Regulation [EU] No 536/2014 Draft Questions & Answers Version 2.3)

	A	**B**	**C**	**D**	**E**	**F**
A clinical trial of a medicinal product?					**A non-interventional study?**	**A low-intervention clinical trial?**
Is a medicinal product administered before or during the start of the clinical trial?	Is it a medicinal product?[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 these effects?	Is the product authorized 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 <u>all</u> the questions in column A, the activity is not a clinical trial on a medicinal product. If you answer yes to any 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 medicinal product. 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 Regulation EU No 536/2014. 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 Regulation EU No 536/2014. If you answer yes to <u>any</u> of the questions below, go to column E.		

If a medicinal product is administered after the start of the clinical trial, please go to column A.						
	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 with a	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?		

	view to making a medical diagnosis; or is it otherwise administered for a medicinal purpose?) A.3. Is it an active substance in a pharmaceutical form?					

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

[ii] Substance is any matter irrespective of origin e.g. human, animal, vegetable, or chemical that is being administered to a human being.

[iii] This does not include derivatives of human whole blood, human blood cells, and human plasma that involve a manufacturing process.

[iv] 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.

[v] The Cosmetic Directive 76/768/EC, as amended harmonizes 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 odors.

[vi] 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.

References: REG 536/2014 Q&A Version 2.3 (transcribed from Annex II).{8}

Abbreviations: Q&A Questions & answers; REG Regulation.

However, these efforts toward harmonization may have an impact on the current standard practice. As an example, most Member States will currently allow post-authorization safety studies (PASSs; see next section for definition) utilizing patient-reported outcome (PRO) questionnaires to be run as non-interventional studies.{9} Meanwhile, Article 2 of the REG 536/2014 provides that low-intervention clinical trials may include “additional diagnostic or monitoring procedures [that] 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.” Under this definition, it is possible

that, upon implementation of the new Regulation, non-interventional studies using PROs not normally used in routine practice may be classified as low-intervention clinical trials, with regulatory requirements equivalent to a clinical trial. The impact of this attempt at harmonization remains to be seen.

Being only part of the upcoming REG 536/2014, the designation of low-intervention clinical trial is not yet in force in any EU Member State, with the exception of Spain, which adopted REG 536/2014 into local law in December 2015 (Real Decreto 1090/2015).{10} In fact, some national authorities in some Member States have moved ahead with revisions to local regulations that deviate from the low-intervention clinical trial definition provided in the REG 536/2014. An example is the legislation released in France in 2016 (Code de la santé publique – Article L1121-1),{11} following publication of the final EU Regulation text. The French law reorganized study classification into category 1, 2, and 3 research. While category 3 research remained harmonized with the definition of a non-interventional study provided in the current DIR 2001/20/EC, category 2 research is interventional research where the drug product is not the object of the research and where the intervention (i.e., a blood sample) poses minimal risk to patients. Any low-intervention clinical trial involving a drug product would continue to fall under category 1 research, and is subject to full clinical trial requirements according to French regulations. Further modification of the law therefore appears necessary upon REG 536/2014 coming into force.

Non-Interventional Studies

Article 2 of DIR 2001/20/EC defines a “non-interventional study” as a study where the medical product(s) is (are) prescribed independent to inclusion of the participant in the study and as part of a therapeutic strategy, including diagnostic and monitoring

procedures, which is not decided in advance by a study protocol but is applied according to the current clinical practice. As such, these studies seek to understand the use of a marketed product in real-world conditions, including risk/benefit, healthcare resource utilization, and patient/caregiver satisfaction, as examples.

Another example is the non-interventional PASS, a study carried out to obtain further information on a drug's safety, or to measure the effectiveness of risk-management measures{9} (note: PASSs may also be designed as interventional studies, which require following the applicable clinical trials regulations).

In non-interventional studies, clinical procedures and assessments must follow normal clinical practice, as opposed to clinical trials, which follow the protocol. However, the definition of "normal clinical practice" may be subjective and prone to disagreement. For clarity and harmonization, the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP) Module VIII states that in non-interventional studies, "interviews, questionnaires, blood samples and participant follow-up may be performed as part of normal clinical practice." However, the application of such assessments should not be conducted in a way that is considered significantly different from clinical practice.{9}

Although defined in DIR 2001/20/EC, non-interventional studies are outside its scope. Due to the lack of harmonized regulation, some studies designed to be non-interventional may be considered clinical trials by EU authorities. The two blinded studies described in Table 4 were considered clinical trials in the EU for planning on collection of data to support the marketing authorization application of experimental IMPs, despite no IMP being given and normal clinical practice being kept during the study period. Sponsors are thus advised to consult with authorities when planning

studies under these conditions and/or whenever the objectives or design may raise questions.

Table 4: Examples of Decisions and Rationale for Classifying Two Studies*

#	Study description	Authority decision and rationale
1	• Long-term safety follow-up of participants with Disease A, under normal clinical practice. • Participants previously exposed to experimental Drug A in a clinical trial for the management of Disease A. • Drug A had been stopped prior to study initiation.	**Clinical trial** • Drug A was not authorized for Disease A at the time the long-term safety follow-up study was initiated. • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Data collected in consequence of previous experimental exposure to Drug A and to support the marketing authorization of Drug A. • Rationale for this decision was subsequently supported by the REG 536/2014 Draft Q&A Version 2 document (question 1.15).{8}
2	• Use of previously collected blood samples in participants with Disease B to determine potential genetic markers. • Participants previously exposed to experimental Drug B in a clinical trial for the management of Disease B. • Blood samples aimed at correlating Disease B biomarkers with potential efficacy of Drug B. • Drug B had been stopped prior to study initiation.	**Clinical trial** • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Drug B did not have marketing authorization. • Despite no direct patient interaction, blood samples would be tested and results analyzed to support the marketing authorization of Drug B.

*The examples in this table are of real clinical studies that have been blinded for confidentiality purposes. These were considered clinical trials by EU authorities, despite not involving exposure to an investigational product during the study period.

References: REG 536/2014 Q&A Version 2.{8}

Abbreviations: EU European Union; Q&A Questions & answers; REG Regulation.

Due to the lack of harmonized EU guidance or regulation regarding non-interventional studies' operations and monitoring activities, sponsors and investigators must ensure the safety of study participants and the collection of high-quality data by following an appropriate study plan. Some EU regulations and guidelines should be followed for this purpose, including, but not limited to:

- Regulation 2016/679 on personal data protection.{12}
- Directive 2010/84/EU on pharmacovigilance and safety reporting (Article 107).{13}
- Directive 2001/83/EC on labelling requirements.{14}
- EMA GVP Module VIII, specific to PASS.{9}
- European Centers for Pharmacoepidemiology and Pharmacovigilance considerations on the definition of non-interventional trials.{15}
- Guidelines for good pharmacoepidemiology practice.{16}
- Applicable legislation and guidance issued by EU Member States.

There is no centralized submission procedure for non-interventional studies with the exception of non-interventional PASSs, imposed as an obligation by an EU competent authority.{9} Because non-interventional studies do not have harmonized legislation, some Member States require submissions to regulatory authorities, while others do not. It is therefore important that sponsors are familiar with the regulatory framework of target EU Member States, and that they consult with local competent authorities and ethics committees (ECs) when justified.

Non-interventional studies generally do not require registration in an EU database, with the exception of non-interventional PASSs, which must be registered in the EU Electronic Register of Post-Authorization Studies.{9} Nevertheless, some Member

States may require registration in local databases, so sponsors should look to confirm this possibility.

As for ethical requirements, a favorable opinion of the central or local ECs (depending on local regulations) is required for all non-interventional studies, with the exception of Denmark. Informed consent is typically required.

After implementation of the upcoming REG 536/2014, the aforementioned variability in local requirements across the EU is expected to continue as these studies do not enter the scope of this Regulation, being only defined as a “clinical study other than a clinical trial” (Article 2). This will not be problematic if all EU Member States are willing or able to update their local legislation to define non-interventional studies consistently across the EU. However, it is not clear that this will be the case.

The lack of a single, explicit regulatory definition for these studies can result in different interpretations from Member States when presented with the same study, with regulatory and operational consequences. If one Member State considers a study interventional, it will need to follow all low-intervention clinical trial–specific requirements defined in REG 536/2014, substantially different from what is expected from a non-interventional study. As addressed earlier, this can be of special concern if a study falls upon the borderline between non-interventional and low-intervention definitions.

The European Authorities are conscious of the challenges that lie ahead. Within the currently available guidance on interpretation of the REG 536/2014{8} there are currently seven questions in the first section of the Q&A document related to the definitions of a low-intervention clinical trial and/or a non-interventional study. In addition, the frequency of updates being applied to this guidance document

(four separate version updates between June and November 2019) indicates the importance of clarifying points such as these.

Based on this history, there can be hope that the European Commission will continue to provide clarifying guidance that sponsors and investigators can use to influence individual ECs and competent authorities within EU Member States if they face disharmonized opinions. However, in order to effectively plan a low-intervention clinical trial, it will remain important that all sponsor-related stakeholders are aware of the potential pitfalls that exist in relation to these definitions.

Conclusion

Upon implementation of REG 536/2014 in the EU, three different clinical study definitions are to be considered: clinical trial, low-intervention clinical trial, and non-interventional study.

Non-interventional studies are outside the scope of this Regulation, similar to the current DIR 2001/20/EC. With the lack of a harmonized EU regulatory definition for these studies, after the implementation of the new regulation it is expected that the variability in the classification of non-interventional studies across EU Member States will continue. In addition, the implementation of a low-intervention clinical definition may lead to studies currently considered non-interventional to be considered clinical trials in the future, with operational and regulatory consequences.

Sponsors must be prepared not only for the upcoming EU Regulation, but also for how the Member States will adapt their own legislation after its implementation, as this will have potential impact in the clinical development of their products.

Disclaimer

The opinions expressed in this paper are the authors' own and not necessarily shared by their employer.

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