Clinical trial disclosure and transparency:

Regulation EU No. 536/2014
Public disclosure at the clinical trial level

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Abstract
The initial requirements of clinical trial disclosure were to register a clinical trial to make it publicly accessible to patients and thereby making the enrolment into a clinical trial easier. In the meantime, the disclosure of clinical trials in public databases has progressed to a new level, encompassing not only registration of new trials but also the disclosure of summary results for completed clinical trials for *all* drugs investigated in clinical trials, irrespective of their marketing approval status. Further development currently being implemented is the sharing of de-identified/anonymised trial participant data sets, thereby enabling re-analysis.

The Regulation EU No. 536/2014 is an EU law that instructs trial sponsors on the organisational, reporting, and disclosure aspects of clinical trials. The content of Regulation EU No. 536/2014 is intertwined with other obligations relevant to clinical trial disclosure and transparency efforts. Overlaps of the Regulation EU No. 536/2014 to other pertinent laws, policies, or required practices are summarised in this article, and some practical examples are provided for stakeholders who are involved in the planning, evaluation, and preparation of documents relevant to clinical trials.

Introduction
Clinical trial disclosure is an evolving topic, with almost daily published contributions worldwide. The initial goal some 20 years ago of requirements that clinical trials be registered in a publicly accessible database was to inform patients, relatives, and treating physicians that a clinical trial exists, thereby making the enrolment into a clinical trial easier. In the meantime, the registration of clinical trials in large public databases has progressed to a new stage, involving disclosure of summary results for completed clinical trials for *all* drugs investigated in clinical trials, *irrespective* of the drug's marketing approval status. Further development currently being implemented is the sharing of de-identified/anonymised trial participant data sets, which would enable re-analysis by a wider community of researchers. Such additional analyses could potentially expand the insights into the safety or efficacy of the investigated product. Also, data from several trials could be pooled into a meta-analysis, thereby enriching the level of information available to inform medical and prescribing decisions that would otherwise be based on individual studies.[1,2]

Countries of the EU and of the European Economic Area (EEA: Iceland, Liechtenstein, and Norway) as well as the US are particularly active in advocating and enforcing clinical trial disclosure. Additionally, some 40 countries worldwide have further national disclosure

obligations; indeed, in some countries there is even more than one relevant registry or database that needs attention.

The aim of this article is to summarise the Regulation EU No. 536/2014, which is the updated EU law that instructs trial sponsors on the organisational, reporting, and disclosure aspects of clinical trials. Key requirements of the new regulation and practical examples are described, with emphasis placed on topics of frequent discussions and relevance to medical writing, as well as other stakeholders closely involved in planning, supervising, evaluating, and reporting on clinical trials performed in the EU or relevant to an EU marketing authorisation application (MAA).

The content of Regulation EU No. 536/2014 should not be seen in isolation from other obligations relevant to clinical trial disclosure and transparency.[3,4] For this reason, in some sections of this article, similarities or overlaps to other pertinent laws, policies, or required practices are mentioned.

Current disclosure obligations and requirements in the EU/EEA

Regulation vs Directive

In legal hierarchy, any EU *regulation* is directly applicable under European Commission (EC) law and automatically becomes part of national law of the 28 EU member states (and also the EEA states). Therefore, a regulation is likely to achieve the intended purpose of the law in a fast and harmonised way among all the EU/EEA member states. In contrast, a *directive* is not directly applicable under the EC law; EU member states are required to implement directives, but they choose the form and methods of how to do that at a national level. This can result in a protracted process that often leads to imbalanced interpretation and realization of the law among the EU/EEA member states.

Regulation EU No. 536/2014

Regulation EU No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use was adopted on April16, 2014[5-7] (the "Clinical Trials Regulation"), repealing the Directive 2001/20/ EC from 2004.[8] Furthermore, Regulation EU No. 536/2014 fulfils most of the requirements previously set by the Paediatric Regulation (EC) No. 1901/2006 from 2006[9] regarding clinical trials in paediatric subjects, conducted in the EU.

Although Regulation EU No. 536/2014 came into force in 2014, its provisions will not take effect before mid 2020. This delay is due to challenges concerning the single EU portal and database system and are caused by complex technical demands regarding clinical trials data entry, as well as storage and information flow between the EMA and EU/EEA member states. During the interim (while the portal and database are being developed, tested and validated), the applicable laws remain in force, i.e. the Clinical Trials Directive 2001/20/EC[8] and the Paediatric Regulation (EC) No. 1901/2006[9] (the relevant items of the Paediatric Regulation are Articles 41, 45, and 46, which specifically deal with situations that may occur for clinical trials involving children). The clinical trial portal and database represent the key instrument that will be used as a single entry point for the submission of data and information and maintenance of clinical trial applications and authorisations within the EU/EEA (allowing interaction and collaboration of the member states and the EC). Only data and information defined in the Regulation EU No. 536/2014 as being submitted via the portal and/or stored in the database shall be held in that database (Articles 80 and 81 of the Regulation).

Public disclosure of clinical trial information is just one of the many aspects that are addressed in Regulation EU No. 536/2014 (sometimes referred to as "the new EU Regulation"). Overall, the law consists of 19 chapters with 99 articles, describing a precise and detailed procedure for the submission, assessment, and evaluation of requests for authorisation of clinical trials by the Concerned Member States (Part I and Part II), safety reporting procedures during the trial, the protection of subjects, and informed consent.[10] Once the new EU Regulation is fully adopted and operational, most of the activities between the member states and the EMA (on behalf of the European Commission) will flow through the new EU portal and all documents will be housed in the new database (that is currently being developed and tested). The functional specifications for the newly established EU portal and EU database were summarised by EMA in an informative document.[7]

Regulation EU No. 536/2014 applies to all interventional clinical trials performed in the EU;

it does not apply to non-interventional studies or studies of medical devices (unless the devices are part of a clinical trial involving a medicinal product).

For pragmatic purposes, the terms *clinical trial* and *clinical study* are used interchangeably in this article. However, it is noteworthy that in Regulation EU No. 536/2014, the EU regulators have emphasised a distinction between the terms *clinical trials* (which are "interventional clinical studies") and *clinical studies*.[5,6] In this context, the term clinical study represents a broader concept; a clinical trial is defined as a specific type of a clinical study. In practice, a clinical trial is

characterised by specific elements including the presence of:

- An investigational medicinal product
- An active human intervention in defining the treatment
- A subject treatment assignment that does not fall within the normal practice of health care
- Monitoring of subjects throughout the course of the trial

European Medicines Agency

Implementation of Regulation EU No. 536/2014 falls under the responsibility of the EMA, which also manages the EU portal and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database – known as the EU Clinical Trials Register (www.clinicaltrialsregister.eu), which is currently used to store information on clinical trials performed in the EU/EEA.

The current database (and also the future database) is available *only* to clinical trials performed in the EU/EEA (i.e., those that have a EudraCT number) or to trials associated with regulatory applications in the EU/EEA and need to be disclosed because they are part of the Paediatric Investigation Plan (PIP) – such as those trials performed outside of the EU/EEA, in the so-called "third countries". Currently, the EudraCT database contains registration details on about 32,600 clinical trials (status May 2018) and is the largest source of information in the world on paediatric clinical trials.

Registration, disclosure of summary results, and disclosure of other data and documents for clinical trials in the EU/EEA

As shown in Figure 1, there are currently three main aspects of clinical trial disclosure in the EU, represented by Regulation EU No. 536/2014 and being at a level of a clinical trial:

1. Registration of a new clinical trial
2. Disclosure of summary results for a completed clinical trial
3. Upload of data and documents relevant to a clinical trial

In this context, it is essential to understand that Regulation EU No. 536/2014 addresses the public disclosure of clinical information, including the registration of *all* interventional clinical trials and release of result summaries from clinical trials for *approved* as well as *not yet approved* medicinal products.[5,6] Furthermore, when a clinical trial authorisation is denied, the date of decision on the trial is also taken as the date of the end of the trial, for the purposes of application of the disclosure rules and the posting of relevant documents (such as study protocol, Investigator's brochure, etc) that are explained below and summarised in Table 1.

Similar rules also apply in the US, where legally binding requirements have been adopted for disclosure of clinical trials that are applicable under the US law, FDAAA 801 of 2007, which was expanded by the final rule making in 2016, known as the Final Rule.[11,12]

Registration of a clinical trial in the EU/EEA

Registration of a clinical trial in a public database (currently the EudraCT database) is required by law in the EU/EEA. The submitted information consists of details that are based on the clinical study protocol and includes the studied indication, primary and secondary outcomes, inclusion and exclusion criteria, estimated number of trial participants, and estimated time of outcomes completion. As the study proceeds, relevant study and timeline updates must be made (Table 1); the dates and the details of the updated information are part of a version control trail and available to the public view.

In the EU, after submitting an application for authorisation to perform a clinical trial to the EMA, selected information fields about the trial are released *automatically* to the public view by EMA representatives in the designated member state; currently the information can be found in the EudraCT database (www.clinicaltrialsregister.eu). In contrast to the EU/EEA , for clinical trials covered by the law FDAAA 801/Final Rule, it is the responsibility of the study sponsor (or a third party, assigned by the sponsor) to register the trial on www.clinicaltrials.gov.

It is noteworthy that regulators in the US involved in the Final Rule of the FDAAA 801 law have declined to require lay summaries of the clinical trial results for the time being *until* further research is conducted to determine whether summaries can be reliably and consistently produced without being promotional or misleading.

Disclosure of clinical trial summary results in the EU/EEA

Under the EU law, disclosing summary results (or *posting of summary results*, as it is also known) in the EudraCT public database has been mandatory since July 21, 2014, for all clinical trials that are shown in the EU database. This applies to trials that include at least one site in the EU/EEA and to clinical trials conducted in "third countries" that are linked to the EU PIP (Table 3).

For an interventional clinical trial in *adults* completed *before* July 21, 2014, disclosure of results can be made using the synopsis of an ICH E3-conforming clinical study report, or a pre-specified data set of summary results ("full data set"), or both. For clinical trials in *adults* that were completed on or *after* July 21, 2014, the full data set must be posted in the EudraCT database. The usual timeline for posting results of trials in adults is within 12 months from the *last patient last visit (LPLV)* completion date. Notably, for *all* paediatric trials, summary results posting must be performed as full data set within 6 months from the LPLV completion date. Sponsors should be aware that trials involving children are those that include at least one participant that is younger than 18 years of age. Even the unintended inclusion of a trial participant younger than 18 *may* turn the clinical trial into one covered by paediatric rules. The timelines and modalities for posting results in the EudraCT database are explained in a document provided by EMA[13] (Table 1).

An item that is often discussed by those involved in the interpretation of the new regulation and preparing disclosure documents, concerns the scope of the results disclosed with respect to the primary and secondary endpoints. The Regulation EU No. 536/2014 (Appendix IV) contains the following statement: *"Information shall be provided for as many end points as defined in the protocol."*[5] Therefore, it is expected that the clinical trial summary should include results of *all* primary and secondary endpoints defined in the study protocol and in the statistical analysis plan – *not* just the main or key endpoints as is sometimes assumed. Endpoints that are evaluated post-hoc, as exploratory analyses, or "other" are not expected to be disclosed; however, such endpoints may be disclosed and the appropriate entry fields are available in the database.

Another subtle item of the EU law involves the reporting of results from the *intermediate analysis* of a trial. According to Regulation EU No. 536/2014, when the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial and the respective results of the clinical trial are available, a summary of those intermediate results should be submitted to the EU database within 1 year of the intermediate data analysis date.[5]

Finally, unlike the general understanding that details of Phase 1 trials will not be in the public view, the Regulation EU No. 536/2014 does have a provision for publicly disclosing these documents. Indeed, this is expected to start when the new database becomes fully operational.

These considerations are examples that have implications on study planning, defining of endpoints in the clinical study protocol, evaluation frequency of the data during the course of the study, and preparation of the clinical study report(s).

Such requirements are similar to those adopted for clinical trial results disclosure through the Final Rule of the FDAAA 801 law in the US. It is noteworthy that under the US law, results reporting is based on the primary endpoint completion date and is expected within 12 months (adult and children studies), followed by the disclosure of the secondary endpoints as they are completed. Under the US law, all endpoints included in the statistical analysis plan are mandatory for disclosure, whereas those designated as "other" endpoints are not expected to be disclosed.[11,12,14] Nevertheless, voluntary disclosure of "other" endpoints or analyses (meta-analyses) is encouraged, and the entry

Table 1. Clinical Trial Disclosure: Summary of the main requirements in EU/EEA Regulation EU No. 536/2014

EU/EEA (Regulation EU No. 536/2014)[5,6]

Register and disclose all *interventional* clinical trials with EudraCT number. Trial registration is performed by the EMA (Member State), upon receiving the official request for authorisation of a clinical trial on a medicinal product for human use

Applies to trials ongoing or started:

- After May 2004 for trials in adults
- After May 2006 for trials in children

Applies to trials in:

- Children: Trial category 1, 2, 3[4][7]
- Adults: Trial category (1), 2, 3[4][5]

Disclose summary results for:

- Any tested medicinal product, regardless of the regulatory approval status

Timelines for disclosure of summary results:

- Trials in children within 6 months of LPLV[1]
- Trials in adults within 12 mosnths of LPLV[1]

Additional documents to disclose:

- Lay person language summary[1][3]
- Study Protocol (*each* version and modification)[1]
- IMPD (Section S and E)[3][6]
- Investigator's brochure[3]
- Subject information sheet[3]
- Clinical study report (redacted)[3]

EU=European Union; EEA=European Economic Area; IMPD=Investigational Medicinal Product Dossier; LPLV=Last patient last visit:

[1] Completion date of clinical trial is defined as the date when the final subject was examined or received an intervention for the purposes of final collection of data, whether or not the clinical trial was completed according to the study protocol or was stopped prematurely.

[2] Deferred disclosure of results and documents is possible. A conditional deferral of posting is possible for trials with adults but not with children.

[3] Timing of publication of these documents varies, depending on the trial category.[6]

[4] For definitions, see Table 2.

[5] Currently, data on Phase 1 trials in adults (that are not part of a PIP) are not made public; this situation may change when the single portal and database become functional.

[6] Structure the IMPD sections as modules that can be easily separated and sent for public posting at different timelines (IMPD section S=Safety, section E=Efficacy; section Q=Quality is *not* disclosed).

[7] A paediatric trial is a trial that includes at least one participant < 18 years of age.

Figure 1 Overview of Disclosure EU/EEA Regulations EU No. 536/2014[5-7]

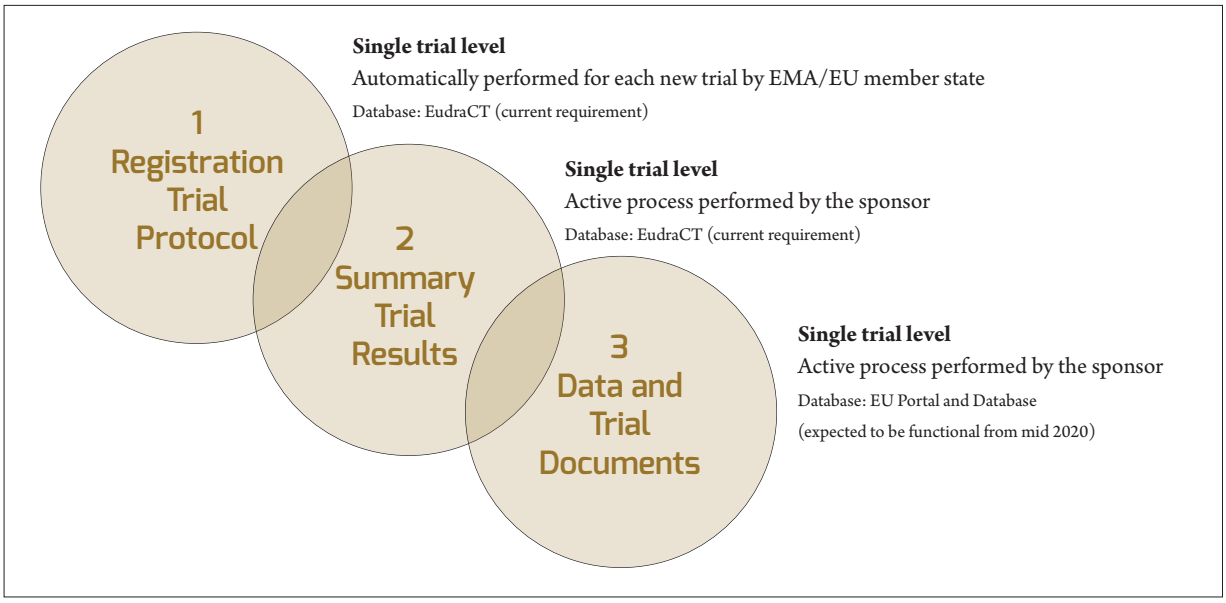

Table 2. Clinical trial disclosure EU/EEA: Supporting documents and definitions based on Regulation EU No. 536/2014

Document/Item	Content/Definition/Comment	Citation
Regulation EU No. 536/2014	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.	5
Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014"	This document sets out rules and criteria for the application of the Regulation EU No. 536/2014.	6
Low-intervention clinical trial[1]	A clinical trial which fulfils *all* of the following conditions:	6
	• The IMPs, excluding placebos, are authorised;	
	• According to the protocol of the clinical trial, (i) the IMPs are used in accordance with the terms of the marketing authorisation; or (ii) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the member states concerned; and	
	• 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.	
Category 1 trial[1]	Pharmaceutical development clinical trials include:	6
	• Phase I clinical trials in healthy volunteers or patients; test whether a treatment is safe for people	
	• Phase 0 trials – trials in healthy volunteers or patients; explore pharmacokinetics or pharmacodynamics	
	• Bioequivalence and bioavailability trials	
	• Similarity trials for biosimilar products	
	• Equivalence trials	
Category 2 trial[1]	Therapeutic exploratory and confirmatory clinical trials include:	6
	• Phase II and III trials	
	• Not only trials by the MAH but also trials by other researchers looking at safety and efficacy in new indications, pharmaceutical forms and routes of administration, or patient populations and not covered by the definition of category 3.	
Category 3 trial[1]	Therapeutic use clinical trials include	6
	• Phase IV clinical trials	
	• Low-intervention clinical trial	

[1] Definition that applies for the purpose of Regulation EU No. 536/2014;
IMP= Investigational medicinal product; MAH = Marketing authorisation holder

fields are available in the clinicaltrials.gov database.

Disclosure of data and trial-relevant documents in the EU/EEA

The third aspect of the Regulation EU No. 536/2014 shown in Figure 1 is related to the public disclosure of data and trial-relevant documents for *each* completed clinical trial; this aspect will become relevant when the new EU portal and database are active. Reports and other documents being placed into the public database should be redacted by the sponsor (or party submitting the document or data to the database). It is the sponsor's responsibility to redact/anonymise the documents before loading them into the system so that personal data (especially of clinical trial subjects) and commercially confidential information is not disclosed. A separate guidance is planned to be developed by the EMA regarding redaction/anonymisation of disclosed documents that fall under the Regulation EU No. 536/2014; it is expected that the scope of these processes will be consistent with that already available for EMA Policy 0070 (described later in this article).[15,16]

Based on the Regulation EU No. 536/2014, the documents that must be disclosed in an EU public database for each clinical trial are summarised in Table 3. The timelines for posting the various documents are not uniform; they depend on the category of the trial (i.e., category 1, 2, 3, as defined in Table 2) and on the age of trial participants.[6] By taking into account the development stage of the drug products, the regulators allowed a later disclosure of information for category 1 trials in comparison with category 3 trials. A general deferral of posting of these documents is possible for trials

with adults, but not for trials that have paediatric participants or for trials included in the PIP.[6]

Analogous requirements apply to clinical trials that are under the auspices of the FDA. The Final Rule of the FDAAA 801 law in the US mandates that the study protocol and statistical analysis plan (and *all* their amendments) be uploaded at the time of the summary results disclosure in the database clinicaltrials.gov (usually 12 months after the completion of the *primary* endpoint of the study).[11,12,14]

Plain language summary

The Clinical Trials Regulation EU No. 536/2014 (Article 37) requires sponsors to provide results summaries of clinical trials in a format understandable to laypersons (plain language summary), irrespective of the outcome of a clinical trial. Annex V of the Regulation EU No. 536/2014 lists 10 elements that must be addressed in summary of the results of the clinical trial for laypersons.[5]

When Regulation EU No. 536/2014 is fully adopted, the plain language summary must be provided by the sponsor as a separate document within 12 months of end of the clinical trial for each trial in category 2 and category 3. Thus, the plain language summary should be provided at the same time as the technical summary of trial results. Limited time deferral is possible, depending on the trial category and the disclosure option chosen by the sponsor.[6] A detailed guidance on how to prepare the plain language summary is available from EMA as well as from other health or clinical trial disclosure-relevant organisations and patient groups interested in this document.[17,18] The effort of preparing the plain language summary should not be underestimated. The challenges and experiences of preparing plain language summaries are described in a separate contribution in this issue of the journal. (See pages 49 – 54)

It is noteworthy that regulators in the US involved in the Final Rule of the FDAAA 801 law have declined to require lay summaries of the clinical trial results for the time being *until* further research is conducted to determine whether such summaries can be reliably and consistently produced without being promotional or misleading.[11,12]

Transition period for Regulation EU No. 536/2014

As is common with new rules and regulations, a transition period will also apply to Regulation EU No. 536/2014.[5] Once the new regulation is fully adopted and the EU portal and database are functional, sponsors of clinical trials will have a 3-year transition period as follows:

Year 1. Trial can be submitted under either the new EU Regulation or the old EU Directive.

Year 2 to 3. Trial authorised under the old system remain under that system.

All new trials must be submitted under the new regulation.

Year 4. All ongoing trials running under the EU Directive must switch to Regulation EU No. 536/2014.

Non-compliance

It is evident that throughout the world, information on numerous clinical trials eligible for registration and/or results disclosure is not fully disclosed. Nevertheless, until now no penalties have issued for non-compliance. In the EU and US, this may just represent a grace period to allow education and adjustment to the new legal requirements and to inform the regulated community of its obligations and ways of fulfilling them.[12] It is likely that this grace period is coming to an end.

In the EU, the importance of providing and maintaining public information is reinforced by Article 94 and 95 of the new regulation, which requires member states to develop penalties for failure to submit required information for public disclosure to the EU database.[5,6]

In the US, the Final Rule specifies civil or criminal proceedings and judicial consequences as well as monetary penalties (which could be calculated per day for each day of non-compliance if not corrected within 30 days after notice of non-compliance) and which affect not only the sponsor of a particular study but also the grantee institutions.[11,12]

Regulation EU No. 536/ 2014 vs EMA Policy 0070

As described above, Regulation EU No. 536/2014[5] covers documents at the *single clinical trial* level (trials performed in the EU/EEA). Another disclosure requirement in the EU/EEA is EMA Policy 0070,[15,16] which deals with clinical trial documents and data at the *dossier level* (Figure 2).

EMA Policy 0070 has been in effect since January 1, 2015; it applies to the medicinal products whose marketing authorisation had been *approved* through a *centralised procedure* (… *and* also to those products for which marketing approval was *rejected* or *withdrawn*).[15,16] EMA Policy 0070 applies to "clinical reports" of studies that are beyond the scope of the Regulation EU No. 536/2014 (such as clinical trials that are conducted outside the EU but are submitted to EMA for marketing authorisation in Europe). The key characteristics of Regulation EU No. 536/2014 and EMA Policy 0070 are summarised in Table 3. Please note, that under EMA Policy 0070, the term "clinical reports" means several key regulatory documents of the Common Technical Document (CTD), submitted as part of the centralised marketing authorisation procedure, listed in Table 3.

In practical terms, this means that after submitting the dossier to the EMA for a marketing authorisation through a centralised procedure, clinical reports within the dossier are proactively released by the EMA into a dedicated clinical data database (https://clinicaldata.ema.europa. eu) soon after the decision on the marketing authorisation application has been reached. Documents in this database are available to the public either through an online application process or a contract agreement via "Terms of Use" between the applicant and trial sponsor. To prevent the release of personal data of clinical trial participants and certain commercially confidential information of trial sponsors, the documents anticipated for release into the database must first be redacted, de-identified, or anonymised by the sponsor – in conjunction with the EMA. This is a relatively new intense process that requires careful planning and organisation; this requirement should be taken into account early because it contributes to extra time and costs for sponsors when preparing and submitting documents for drug marketing authorisation through a centralised procedure.

Implications of Regulation EU No. 536/2014

At the operational level, specific requirements of the new Regulation apply to the disclosure of information and documents. Although these requirements often differ only slightly from the usual reporting practices of a clinical trial, they do need to be planned by the trial managers and

Table 3. Summary of Regulation EU No. 536/2014 versus EMA Policy 0070

Item	Regulation EU No. 536/2014[5-7,13]	EMA Policy 0070[15, 16]
Medicinal products covered	Investigational medicinal products, irrespective of marketing authorisation status	Centrally authorised products only (approved products)
Clinical trials covered	Clinical trials conducted in the EU/EEA, non-paediatric trials included in a PIP, paediatric trials performed outside the EU/EEA that are included in a PIP, and paediatric trials involving an IMP covered by an EU marketing authorisation and sponsored by the MAH whether or not included in a PIP and whether performed in- or outside the EU/EEA (IMP=Investigational medicinal product; MAH=Marketing authorisation holder; PIP=Paediatric Investigation Plan)	Clinical trials submitted to the Agency in the context of a Marketing Authorisation Application, Article 58 procedure, line extension or new indication, regardless of where the study was conducted
Documents disclosed	Clinical trial-related information generated during the life cycle of a clinical trial, including the documents*: Clinical study protocol, Assessment and decision on trial conduct, Summary of trial results including a Plain Language Summary/Lay Summary, Clinical Study Reports (main part), Inspections reports, Investigator's Brochure, Investigational Medicinal Product Dossier sections S and section E, Subject information sheet. (IMPD section S=Safety and section E=Efficacy)	Clinical data (modules of Common Technical Document (CTD), including the following clinical reports and individual patient data* CTD 2.5 Clinical overview, CTD 2.7 Clinical summaries, CTD 5 Clinical study reports main body of the report, Appendix 16.1.1 Protocol and Protocol amendments; Appendix 16.1.2 Sample case report form; Appendix 16.1.9 Statistical analysis plan), and the Anonymisation report that specifies and justifies the redactions and anonymisations indicated in the supplied documents.
Disclosure channel	EU Portal and EU Database Currently these are being developed, tested, and validated During the interim time, the EudraCT database is used www.clinicaltrialsregister.eu	EMA clinical data publication website https://clinicaldata.ema.europa.eu/web/cdp/home
Date when it applies	Expected mid 2020	January 1, 2015 (new Marketing Authorisation Applications) or July 1, 2015 (Line extension or New indication)
Disclosure	Transition period of 3 years from the time of functional EU Portal, EU Database	Since October 2016

*The disclosed documents need to be redacted/anonymised to protect trial participant personal data and sponsor-relevant commercially confidential information (CCI)[16]

Table is modified from a presentation by Ioana Ratescu, Legal aspects on transparency of clinical data – EMA perspective, 16Dec2016. Available at https://ius.unibas.ch/fileadmin/user_upload/ius/11_Upload_Personenprofile/02_Assistenzprofessuren_oIT/Seitz_Claudia/Vergangene_Veranstaltungen/2016.12.16/Ratescu_Ioana_EU_Clinical_Trail_Regulation_Legal_aspects_on_transparency_of_clinicalvdata_-_EMA_Perspective_05.pdf

Figure 2. Regulations EU No. 536/2014 versus EMA Policy 0070 [5-7,15,16]

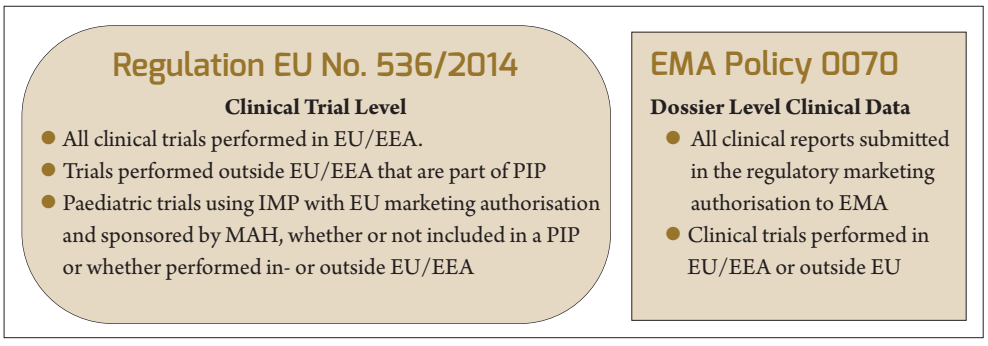

Diagram is based on a presentation by Ioana Ratescu, Legal aspects on transparency of clinical data – EMA perspective.
16Dec2016. Available at:
https://ius.unibas.ch/fileadmin/user_upload/ius/11_Upload_Personenprofile/02_Assistenzprofessuren_oIT/Seitz_Claudia/Vergangene_Veranstaltungen/2016.12.16/Ratescu_Ioana_EU_Clinical_Trail_Regulation_Legal_aspects_on_transparency_of_clinical_data_-_EMA_Perspective_05.pdf

other stakeholders (medical writers, statisticians, and data managers) to ensure efficient information entry into the public database. Some requirements for the EudraCT database are summarised below:

Demography:

- Prepare a randomised trial participants list **by country** and **by pre-specified age categories** (for overall number of participants and for each treatment group)

Endpoints:

- Provide result information on ***all* primary endpoints** and ***all* secondary endpoints** that are pre-specified in the study protocol and in the statistical analysis plan. Statistical analysis of results is expected at least for the primary endpoints. If no statistical analysis is made for the primary endpoint, a "justification" is required by the database validation system. For such cases, have a brief justification statement ready.

Safety:

- Prepare *separate* tables for **non-serious adverse event** and **serious adverse events**; Show the number of trial participants affected by **non-serious adverse event** per treatment group (depending on the safety dictionary used, prepare outputs e.g. by System Organ Class, Preferred term).
- Show the number of occurrences for a particular adverse event (for overall and for each treatment group).
  A threshold can be applied (the threshold can be up to maximum 5% of participants affected by a particular adverse event in any treatment group).
- Show *all* **serious adverse events** (depending on the safety dictionary used, prepare an outputs e.g. by System Organ Class, Preferred term).
  Show the number of trial participants affected by a **serious adverse event**.
  Show the number of occurrences for a particular serious adverse event.
  Show relatedness to treatment.
  Show *all* **fatalities** and specify fatalities related to treatment.
  Some sponsors use a **customised file** for uploading the information on adverse events e.g. using a file in extensible markup language format (XML). Instructions for preparing an XML file for this purpose are available on the EMA Internet website (https://eudract.ema.europa.eu/result.html under Results related documentation; EudraXML schemas and documentation).

Publication of clinical trial results in peer-review journals

Disclosure in public databases vs pre-publication considerations by peer-review journals

A frequently raised question by clinical trial sponsors and investigators is whether the disclosure of clinical results summary in a public database is considered to be a prepublication, possibly affecting a full publication of the trial results in a peer-review journal. A brief excerpt of the response by the International Committee of Medical Journal Editors (ICMJE) on this topic is shown below and is available in the section FAQs (Clinical Trials Registration) on the ICMJE website.[19]

> *The ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov (… or in other ICMJE-accepted public databases) to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting.*[19]

Implications of clinical trial results in the public database vs journal publications

The legally binding requirements on clinical trial disclosure in the EU/EEA are based on the Regulation EU No. 536/2014. The law includes public registration of a clinical trial and disclosure of summary results, all of which affects numerous regulatory documents relevant to a clinical trial. As such, the Regulation EU No. 536/2014 also affects other presentation of data in the public domain (professional conferences, publications in scientific and medical journals).

Demands for widened disclosure and transparency came from the recent "**data sharing**" policy released by the ICMJE. As such, trial sponsors are asked to indicate their readiness and willingness to share individual participant data in a "**data sharing statement**" when submitting a manuscript reporting a clinical trial for publication. This request is effective from July 1, 2018, for manuscripts submitted to journals that follow the ICMJE recommendations. Furthermore, the ICMJE policy request that clinical trials that begin enrolling participants on or after January 1, 2019, must include a "**data sharing plan**" in the trial's registration. If the data sharing plan changes after trial registration, the changes should be reflected in the statement submitted and published with the manuscript and also should be updated in the registry record.[20] The database clinicaltrials.gov has the necessary fields already available for the "data sharing plan", whereas in the EudraCT database these fields are not yet available but are in the planning stage.

Final remarks

It is obvious that demands for disclosure and transparency information on clinical trial arise from numerous sources and stakeholder. Disclosure of clinical trial information is taken seriously by patients and physicians, pharmaceutical industry, journal editors, medical and scientific communities, private and public funders, regulators, politicians, and law makers.[2,21-24]

Publications of clinical trial results in professional journals is an important part of the disclosure endeavours and should be fully consistent with respective clinical study protocols, study reports, entries on company websites, and in public registries or databases. In the world of the internet, discrepancies can be easily identified between papers published in professional journals and information available in the other publicly accessible arenas.[2,25-27] Indeed, a trial tracker that shows sponsors' compliance with disclosure of trial results is already available – at this stage only involving clinical trials registered in the clinicaltrials.gov database (http://opentrials.net/);[28] nevertheless, similar efforts are underway to monitor compliance of sponsors for clinical trials located in the EudraCT database.

Clinical trials will continue to be performed in a global setting. The Regulation EU No. 536/2014 is just one of several instruments mandating compliance in transparency of public information. As such, national or regional laws and other efforts on disclosure and transparency will overlap and redundancies will be inevitable for some time to come. To be on the right path to achieve successful innovations in clinical research, clinical trial sponsors must adopt consistent, harmonised, vigilant, accountable, and transparent approach to the activities of clinical trials and information disclosure.[29]

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Conflicts of interest

The author declares no conflicts of interest.

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