efpia
European Federation of Pharmaceutical Industries and Associations

Position Paper

EFPIA Principles for the Development of the EU Clinical Trials Portal and Database - Final, 29th June 2014

Executive summary

EFPIA sees the implementation of the Clinical Trials Regulation[1] as an opportunity to demonstrate Europe's commitment to clinical innovation, scientific collaboration and transparency of clinical trials information.

EFPIA has conducted a systematic analysis of the CT Regulation, especially of the introduction of a single EU Clinical Trial Portal and Database, and subsequently formed this position paper. The analysis has revealed that the CT Regulation will push the current EudraCT and EU CT Registry far beyond the current use; it has further highlighted that 48% of all actions in the CT Portal are the responsibility of sponsors, and that less than 40% of those are reflected in EudraCT or the EU CT Registry today. Thus, establishing a technically advanced and user-friendly CT Portal requires collaborative efforts, including with sponsors, to overcome inherent complexities and avoid technical duplications, while operating under a strict timeline.

In order to meet the essential elements[2] for success, EFPIA has identified three key and distinct needs as follows:

1. Deliver flexible, efficient and **streamlined execution** of the authorisation procedure to avoid administrative delays;
2. Enable the required **collaboration** between concerned Member States, as well as sponsors;
3. Appropriately manage the **transparency** of data over the life of the clinical trial;

The EFPIA analysis has further identified the need to adhere to the following key principles:

1. Compulsory use of the Database for Parts I&II review and approval to ensure streamlined and efficient execution whilst avoiding duplicate systems at national level;
2. Workflows and timelines to be embedded in the CT Portal to operate the application process without any delays e.g. tacit approval/withdrawals triggered from non response;
3. Delineation of public and non-public data at different stages of the clinical trial to make the CT portal trusted; this will reinforce the need for collaboration amongst the different parties during the application process, while guaranteeing appropriate level of transparency;
4. Continuous harmonisation and opportunities to standardise on the format and exchange of clinical trial registration and results data, reflecting the growing number of CT registries;

Additional considerations are also provided in this paper.

Finally, EFPIA appreciates the challenges EMA is facing for the development of a user-friendly system. Thus, we invite EMA to rapidly initiate the dialogue with all stakeholders, including sponsors. Collaboration is indeed paramount to ensuring the timely delivery of a workable portal and database, and we trust that this paper will contribute further to this exercise.

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on

[2] Essential elements' are those aspects that are needed to meet the system requirements stated in the Regulation, in order for the system to be verified by the EMA Management Board

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I. Introduction

EFPIA has welcomed the recent adoption and publication of the Clinical Trials (CT) Regulation[3], which aims to introduce a single submission process for CT applications, together with an overall streamlined assessment.

EFPIA is further calling for collaboration[4] to ensure consistent and harmonised implementation of the Regulation across Europe. More specifically, EFPIA is seeking assurance that the EU Portal (Article 80) and Database (Article 81) will be developed in a way that fully supports the aims of the Regulation, i.e. to develop a technically advanced and user-friendly portal, and to avoid unnecessary duplication between the new database and the existing EudraCT and EudraVigilance.

Timely development of the portal and database are key elements of the Regulation, whose exact implementation date is contingent upon a well-functioning IT system to first be audited and subject to the satisfaction of the European Commission.

EFPIA acknowledges that EMA, in collaboration with the Member States and the European Commission, is the body responsible (and accountable) for developing the functional specifications for the EU Portal and Database (Article 81). Thus, industry wishes to contribute our experience and collaborate with EMA and the system's developers throughout the process. It is important to stress that whilst a swift release is desirable, this must not compromise the significance of delivering a successful EU Portal in eyes of the Regulation.

To that end, EFPIA has conducted an initial review of the Regulation to extract requirements for the EU Portal and Database; this document is providing the key findings of this analysis.

II. Essential elements for a successful EU Portal and Database

EFPIA believes it is important to focus on the essential elements[5] for the initial rollout of the system. On reviewing the Regulation, we consider that the majority of requirements can be aligned to three key and distinct elements; these are that the EU Portal and EU Database must:

1. Deliver flexible, efficient and **streamlined execution** of the authorisation procedure to avoid administrative delays;
2. Enable the required **collaboration** between concerned Member States as well as sponsors;
3. Appropriately manage the **transparency** of data over the life of the clinical trial to balance public health needs, innovation and legitimate economic interests of sponsors; it must further protect commercially confidential information and personal data in accordance with Article 81.4.

[3] 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

[4] EFPIA press release of 3rd April 2014 http://www.efpia.eu/mediaroom/157/43/EFPIA-Calls-for-Collaboration-in-the-Implementation-of-Clinical-Trials-Regulation-Following-Vote-in-the-European-Parliament

[5] 'Essential elements' are those aspects that are needed to meet the system requirements stated in the Regulation, in order for the system to be verified by the EMA Management Board

Throughout the Regulation, there are many activities that are explicitly or implicitly described as actions to be carried out via the EU Portal/EU Database. We have noted that 48% of these activities are to be carried out by the sponsors, with less than 40% of these currently reflected in EudraCT. Distribution of other activities has been identified as follows: concerned member states: 34%, reporting member state: 16% and Commission: 2%. This strongly highlights the importance of engaging with sponsors in the development of the systems.

Underpinning these key elements, EFPIA fully supports a "user-friendly and technically advanced" system as required by Article 80 that should largely re-use data from existing systems. Easy and clear transition rules from the existing EudraCT to the new EU Database must be assured without the need to re-enter or backfill legacy data sets. Data that sponsors have already entered into existing systems should be used as much as technically and feasibly possible. Experience with other database projects has demonstrated that additional data entry by stakeholders is likely to generate delays due to expected data quality and validation issues, and must be avoided.

This new IT development provides a unique opportunity to drive a harmonised European strategy encompassing the whole lifecycle of medicinal products. It would start from one active substance code, for a compound entering clinical development for the first time in Europe, to be linked to a unique CT number for the life of a clinical trial, the EudraVigilance database, and marketing authorisation information (EVMPD/IDMP[6]). The same rules should apply irrespective of the product registration route, i.e. Centralised, Decentralised or National. During the design phase, these important elements for future development stages should be considered to maximize the usefulness of the system to all stakeholders in future rollout phases.

III. The Regulation key principles and associated recommendations

Throughout the Regulation, we have identified a number of areas where interpretation given to the text can substantially impact the resulting IT systems that will be built. Therefore, specific discussions shall take place to align the views of the stakeholders and we propose the following four points along with our recommendations to be identified as key principles around which to build the required solutions.

1) Compulsory use of the Database for Parts I&II review and approval

One fundamental aspect of the Regulation is that Member States will be responsible for determining the appropriate bodies to be involved in the assessment and to ensure involvement of ethics committees within the timeframe set out in the Regulation.

A 2-years time period is provided to allow for the organisation and adaptation of the local legislation. The Regulation therefore specifies the processes to be setup, and results to be achieved. Although the principles behind that aspect of the text are fully understandable, EFPIA sees a risk that national requirements may be issued during these 2 years in such a manner to weaken the advantages in terms of administrative efficiency that the Portal and Database should bring.

[6] EVMPD: EudraVigilance Medicinal Product Dictionary; IDMP: Identification of Medicinal Products

⇒ We would therefore propose that the system is designed so that:

- Each and every required Part I & II assessment document can only be submitted through the EU Portal and gathered from the Database;
- All Parts I & II communication with the sponsors (back and forth) are recorded in the system;
- All Parts I & II approvals are issued exclusively in the system;
- Ethics Review Boards are considered as end users of the EU Portal and Database;
- The EU portal supersedes all existing national clinical trials registration portals, even for single country trials (cf. recital (4) and Article 5).

2) Workflows and timelines to be embedded in a new system

Another fundamental characteristic of the CT Regulation is that it outlines a succession of events to happen with specific stakeholders' responsibilities and associated timelines. In other words, the concept of workflows is clearly predominant and is a very notable difference with the actual process behind the use of EudraCT.

Appendix A on page 8 provides a summary of the high level workflow for the CT application process and highlights that almost every step is combining business processes with specific timelines, a clearly defined stakeholder and automated actions. The consequence to be drawn is that to meet the goals of the CT Regulation requires a totally new paradigm in terms of how the IT system needs to facilitate the business process. It is indeed important that the system automates the sequence of actions that are in the Regulation and that it enforces the associated rules and timelines to some processes (e.g. tacit approval/withdrawal triggered in case of non response from Health Authority/Sponsor).

The important question that is then connected is to know whether or not EudraCT can be considered to be the basis of the new system.

⇒ Given the presence of workflows and the relatively low number of required features that are already present in EudraCT, we recommend considering the building of a new system with embedded workflows from the design phase. EFPIA would favour that approach rather than modifying the existing EudraCT to support requirements it was not designed for, and which, based on experience, often looks falsely like a quick win.

3) Delineation of public and non-public data in the EU Portal over the life of the clinical trial

One of the objectives of the Regulation, and that EFPIA fully supports, is the use of the IT system as a vehicle for citizens to access various information related to upcoming, ongoing and completed EU clinical trials. In addition, the system will be used to host exchanges of information in between the sponsors and the Health Authorities as well as collaboration between Member States and at least the outcome of the Part II related communications. In addition, it will be used as a repository as sponsors are invited to refer to applications previously submitted (Article 81.1) and also for EU Member States and third country inspection reports.

⇒ In order to be supported by the system, these various needs will demand a clear delineation between public and non-public information, keeping in mind that this status will in some cases change over time (for instance the content of the application cannot be accessible until a decision on the clinical trial has been made (Article 81.5). It is important that patients' privacy is also protected in accordance with EU data protection legislation. In addition, further clarity on the definition of commercially confidential information expected later this year should be factored in.

4) Continuous harmonisation and opportunities to standardise

The global nature of clinical research warrants standardising all (approved and disclosed) data for the dual benefit of efficiency in the running of clinical trials and in the reuse of data. It is clear from the Regulation that many of the new actions in scope of the EU Portal and Database are already in scope of the FDA ClinicalTrials.gov system, but not all of them.

The alignment of the public data fields with ClinicalTrials.gov for clinical trial registration and reporting of results would ensure harmonised information across regions. This will in turn support clear and consistent communication of information to patients, doctors and the research community. This would also facilitate easier identification of global trials from multiple registries. Experience gathered from the registry and results publication can subsequently be used to facilitate further development of the EU database.

⇒ The design of the EU system is an opportunity to enhance standardization with already existing databases, which should not be missed. To this effect, industry has also proposed to the EU Commission that EU and US collaborate to establish a harmonised list of CT results data fields under the Transatlantic Trade Investment Partnership negotiations.

IV. Additional important considerations for developing the EU Portal and Database

This section is a collation of additional elements that have been identified as specific points for consideration/discussion with EMA. Although less fundamental than the 4 principles of § III, they are being flagged for consideration in the initial development steps.

1) Security and access

It is implicit that the new system will encompass the required levels of security however, given the sensitivity around clinical trials, the new categories of stakeholders to be brought in, and the complexity of the workflows to be implemented, EFPIA would like to flag the topic of security as an area requiring closer collaboration.

A number of questions will need to be explored in detail. It is not always clear throughout the Regulation if and when specific content is meant to be public or secured (for instance the additional information submitted through the portal during the evaluation, or the many notifications that the system will need to accommodate) and which measures will be implemented to ensure confidentiality, restrict access and ensure security. The system shall also be able to define different security levels for Parts I and II documents.

Furthermore, the addition of new categories of users from what we see with EudraCT today will trigger a significantly more complex user access management that should be

thoroughly evaluated through robust use case testing with all foreseen stakeholders. Even within a given category, different roles will have to be created. For instance, within Industry, regulatory personnel would handle the application, clinical or drug safety personnel may need to do specific updates when the trial is running and disclosure teams would need to be involved when the results are ready to be uploaded. Third party contractors, e.g. appropriately trained CRO staff, who are duly authorized by the sponsor to perform the tasks delegated to them by the sponsor, may also perform some of the tasks.

⇒ Business rules will have to be agreed regarding the categories of users/roles, the timing and type of access to be granted.

2) Protecting data posted on the database from unfair commercial use

In view of the shortly upcoming EMA policy on 'clinical trials data sharing', EFPIA recommends the incorporation of some additional technical requirements to the database for access to redacted Clinical Study Reports (CSRs).

Specifically, the holder of the database, i.e. EMA, should implement a robust control system. EMA should also require persons to register and agree to legally binding terms of use that restrict the use of the documents to non-commercial purposes. These agreements should be enforceable by sponsors.

It would be necessary to develop robust policies to ensure monitoring, compliance and enforcement of the above restrictions and protection measures.

It will also be essential to determine how compliance with the following requirements will be implemented in practice:
(1) To protect the confidentiality of data, including those included in the EU Portal and Database such as Clinical Trial Applications (CTAs) and the Investigational Medicinal Product Dossier (IMPD),
(2) To take the status of the marketing authorisation for the medicinal product into account, and
(3) To balance various interests.

3) Protecting private life and personal data

It is important that the system is developed in a way that will guarantee the protection of private life and personal data.

4) Ambiguous scope and recommendations

Items identified as 'in scope':
- Serious Breach reporting to MS (recital 47) should remain in scope, and be carried out through the system in a mandatory manner;
- The appeal process to be created (Article 8.4) shall be included in the scope (for the record aspect of it) although the modalities of its organisation are likely to be a national matter;

Items identified as 'out of scope':
- The fee to be levied (recital 71) should be out of scope;
- Safety and annual reporting shall continue to be done via EudraVigilance rather than via the creation of "a module" for EudraVigilance (Article 40);

- The voluntary submission of raw data by the sponsors shall be left out of scope as specific systems are being put in place for that aim.

Other recommendations:
- Both terms “EU portal” and “submission portal” are being used throughout the Regulation, and it shall be made clear that there is no difference in the meaning of both terms;
- Inspection reports submitted to the portal by MS conducting the inspection (Article 78.6) should remain confidential;
- The declaration of conflict of interest of the decision makers is not clearly in-scope. This should be disambiguated although EFPIA does not have a specific preference as to keeping such records in the system or not.

5) Ensuring flexibility for adding other functionalities

Currently, focus is put on the essential elements required for the initial roll-out of the system. Nevertheless, it is important to also consider allowing addition of other functions. For instance, an interesting extension to the system could include an automatic notification mechanism on newly authorised clinical trials for patients and healthcare professionals, and following registration with EMA. The collection of stakeholders feedback after a certain period of use of the system should be envisaged.

=> The architecture of the system shall be sufficiently flexible to allow for such subsequent addition, or any others, also taking into consideration experience gained with the system.

V. Conclusion and next steps

This initial systematic review of the CT Regulation conducted by EFPIA continues to emphasise the central role that the EU Portal and associated Database must perform to achieve the aims of the CT Regulation. The system to be developed is complex when taking into consideration the number and variety of actions in the system, the breadth of users, the sensitivity of the data, the time critical nature of the process, and the lack of an equivalent system in the EU or US.

All of these reasons have motivated EFPIA to conduct this analysis and make it available to the EMA in order to address these risks proactively through partnership.

The EU Portal and Database provide the opportunity to demonstrate Europe’s commitment to clinical innovation, to encourage collaboration that advances science and provide transparency to patients.

EFPIA looks forward to on-going dialogue with EMA as plans for development and implementation of the EU Portal unfolds, and is available to respond to any questions in relation to the systematic analysis.