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Compliance and Inspections

Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

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Start of public consultation	21 January 2015
End of consultation (deadline for comments)	18 February 2015

Comments should be provided using this template. The completed comments form should be sent to: ctreg@ema.europa.eu

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Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

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1. Executive summary

The new European Clinical Trial Regulation (EU) No 536/2014 aims to foster innovation through simplification of the clinical trial application process, and to increase transparency and availability of information on clinical trials and their results.

The key instrument to ensure transparency of clinical trials is the new clinical trial portal and database that will be used for submission and maintenance of clinical trial applications and authorisations within the European Union. The database will serve as the source of public information on clinical trial applications assessed, and clinical trials conducted in the EU, from the time of decision to authorise a trial up to the finalisation of those trials and inclusion of their results in the database. The Regulation gives EMA responsibility for its development and maintenance.

The Regulation states that the EU database "shall be publicly available unless one or more exceptions apply". These are:

- to protect personal data;
- to protect commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest;
- to protect confidential communication between Member States in preparing their assessment;
- to protect the supervision of clinical trials by Member States.

This consultation document sets out proposals and options on the application of these exceptions in relation to the transparency provisions of the European Clinical Trial Regulation. Once finalised, this addendum will complement the Functional specifications for the EU portal and EU database to be audited (europa.eu), which were drawn up by the Agency and endorsed by its Management Board in December 2014.

The aim of this consultation is to seek stakeholders' views on the application of these exceptions, so that they strike the right balance between respecting patients' and doctors' needs and the publics' entitlement to extensive and timely information about clinical trials and developers' and researchers' need to protect their investments. A balanced approach is needed to protect public health and also foster the innovation capacity of European medical research, thus supporting the EU as a location for innovative, cutting edge research that results in development of novel products and research into new and better uses of existing products.

The information that will be made public for all clinical trials registered in the system will include:

- the main characteristics of the trial comprising design, scientific and, where applicable, therapeutic intent, title, identification of the investigational medicinal products (IMPs), treatment arms, treatment population and number of subjects, inclusion and exclusion criteria and main objectives and endpoints;
- conclusion of the assessment and decision on the trial;
- information updated during the trial to indicate the start and end dates of recruitment;
- substantial modifications to the trial;
- the end date of the trial and 12 months later the summary of results and a summary in lay language;

- clinical study reports for medicines for which a marketing authorisation has been granted, the procedure completed or the marketing authorisation application withdrawn.

Commercially confidential information

Sponsors have a legitimate economic interest in the trial they conduct, either because they seek a marketing authorisation for the investigational medicinal product or because they need to obtain research funding for this and future trials. The legislation does not distinguish between different types of sponsor. The consideration of what might be commercially confidential is therefore based on the nature of the trial and the status of the medicinal product being studied.

Certain documents which are entered into the database are considered to contain significant confidential information, particularly for trials on medicines without a marketing authorisation. These documents include the clinical trial protocol and the related subject information sheet, the investigational medicinal product dossier, and the investigator brochure. A number of proposals are presented for the timing of when these documents should be made public. The time of publication is linked to key time points of the clinical trials and the status of the marketing authorisation as well as to the development stage of the product (Phase I[1], II[2], III[3] and IV[4] trials and low-intervention trials).

Stakeholders are asked to comment on these proposals and to indicate which, according to their view, best meets the requirements and objectives of the Regulation. Phase I trials are commercially particular sensitive and it is proposed to allow for these trials a deferral of publication of information until 12 months after the end of the trial, when the summary of results is published. Phase IV and low-intervention trials carry fewer concerns in relation to the economic interest of the sponsor and a specific proposal is made with respect to those trials.

Additional proposals concern the publication of inspection reports, union control reports, reports of serious breaches, corrective measures and also urgent safety measures.

Protection of personal data

The rules on personal data protection are addressed in relation to trial subjects, investigators, and personnel responsible for the authorisation and supervision of clinical trials in Member States, as well as sponsors and marketing-authorisation holders. The European Clinical Trial Regulation states that no personal data of trial subjects shall be made public nor should such data be included in the database. Consequently the database will not contain any individual patient data listings from clinical trials.

How to use this document

Chapter 2 to 4 describe the purpose, legal background and interpretation of the transparency requirements of the Regulation. They propose how the exceptions to the transparency requirements listed by the European Clinical Trial Regulation should be applied. Stakeholders are invited to comment on the proposed application of the transparency rules.

[1] Phase I: Phase I is the first stage of a clinical trial. It is to test whether a treatment is safe for people to take, rather than to try to treat a condition, and to study pharmacokinetics and pharmacodynamics (where possible). These trials are very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients. Ref: *http://www.mssociety.org.uk*

[2] Phase II: The second phase in clinical trials aims to investigate the safety and effectiveness of a potential therapy, and to investigate potential dose regimes. Usually between 100 and 300 people will be enlisted to take part with the aim of determining whether the treatment will be safe and effective to treat a condition.

[3] Phase III: If previous trials have indicated a treatment is safe and that it also shows promise in being able to treat a condition, Phase III clinical trials begin. These involve large numbers of participants usually from several hundred to several thousand subjects, and are often spread between different hospitals and countries. If these trials show that a drug is safe and effective, the sponsor can apply for a marketing authorisation.

[4] Phase IV: Post marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. They are carried out in accordance with the terms of the marketing authorisation (indication, route of administration and formulation).

Section 4 is structured through a set of direct questions for stakeholders, which support the present consultation. The actual addendum to be added to the functional specifications is set out in Section 5 including the table in that section. Appendices to this document illustrate how the data and documents in the EU clinical trial database may be made public. These, however, are included for illustration purposes only, since the exact data fields of the database are subject to this consultation and have therefore not yet been finalised. The appendices will not be part of the functional specifications.

Stakeholders are invited to send comments using the attached **template.** to ctreg@ema.europa.eu by end of day on 18th February 2015.

2. Background and introduction

1. Clinical trials are performed in many different contexts. They are conducted to generate data to support applications for marketing authorisation and to expand scientific knowledge on medicines through publications in medical journals. Therefore, clinical trials are an indispensable part of clinical research which, in turn, is essential to develop medicinal products and improve medical treatment. Without clinical trials, there would be no new medicines, no further development of existing medicines, and no evidence-based improvement of treatments with medicines.

2. The EU Clinical Trial Regulation (EU) No 536/2014 has a number of objectives and aims amongst others:

    - To protect the rights, safety, dignity and well-being of subjects and the reliability and robustness of the data generated. The interests of the subjects should always take priority over all other interests. To this end clinical trials are subject to prior authorisation.
    - Foster innovation and simplify the clinical trial application process, in particular for multistate trials.
    - To provide publicly available information from the EU database, increasing transparency of clinical trials and their results - this should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.

3. The Regulation foresees transparency on the conduct of trials in the European Union[5] from the point of their authorisation to the publication of the results of those clinical trials. Published information should be updated, where applicable, if it changes during the trial. The application of the proposed transparency rules should ensure that all of the following requirements are met. Public access to clinical trial information is provided to:

    - Ensure that a public record exists of all clinical trials conducted in the EU and their outcome, thus, providing the EU contribution to the global objective of ensuring that all clinical trials in human subjects are publicly registered. The Regulation requires that all clinical trials used in support of a clinical trial application are publicly registered in a providing data to the WHO ICTRP (WHO International Clinical Trials Registry Platform).
    - Support public confidence in the clinical trial process and in the EU medicines regulatory system. This confidence is important to ensure that EU citizens are willing to participate or support participation in clinical trials as an essential part of medical progress. Public information on clinical trials also reinforces public trust in clinical trial outcomes and the decisions taken by regulators based on those outcomes.

[5] References in this document to the EU should also be read as references to the EEA (European Economic Area).

- Provide patients, trial subjects, their legally designated representative, and healthcare professionals:
  - with access to information on clinical trials, as of their beginning, to facilitate their participation in suitable trials where possible,
  - who have participated in clinical trials with a summary of the results of those trials once they have been completed,
  - with a summary of the results of all completed EU clinical trials, for their reference, regardless of the marketing authorisation status of the medicinal products involved.
- Provide the public, in particular patients and their carers as well as healthcare professionals and academia, with information on clinical trials conducted in the EU that relate to medicines available on the market and on the data used to support decisions on marketing authorisation, or use in practice.
- Act as a knowledge management resource to foster innovation and stimulate and accelerate further research by building on accumulated knowledge and technical ability. This aims to avoid unnecessary duplication of clinical trials, and repetition of trials that have been terminated due to major safety or efficacy failures, or have demonstrated such failures even if the trial was completed.
- The information made available to the public under the Regulation should be freely viewable, searchable and downloadable from the portal without entering into any further agreement, or intervening restrictions being required.
- Innovation and development also need investment in research. To ensure that such investment is attracted to the EU and is sustained investors and researchers have to be able to benefit from their engagement. It is therefore important to recognise the legitimate economic interests of sponsors.
- The transparency aimed for needs to balance the public interests set out above with the need to stimulate and attract investment in innovation thus contributing to the growth and development of commercial and academic research centres, medical facilities and expertise.

4. This document sets out proposals for the application of the transparency rules of the Regulation in order to achieve a correct balance that respects both, the patients' and public's entitlement to extensive and timely information on clinical trials, and developers' and researchers' need to benefit from investments thus enhancing the EU as a destination for innovative, cutting edge research and development of novel products and research into new and better uses of existing products.

3. Legal basis

3.1. The transparency requirements of the Clinical Trial Regulation

The Regulation sets out requirements for increased transparency of EU clinical trials. These requirements apply specifically to information contained in the EU database but not to information held outside of the EU database. The Regulation specifies what information should be held in the EU database.

Any data and documents submitted via the EU Clinical Trial Portal (hereinafter "the portal") defined in Article 80 of Regulation (EU) No 536/2014 (hereinafter "the Regulation") are held in the EU Clinical Trial Database (hereinafter "the database"). Only data and information defined in the Regulation as

being submitted via the portal and/or stored in the database shall be held in that database and subject to the transparency rules set out in the Regulation. Article 81(4) of the Regulation states that the EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

a) protecting personal data in accordance with Regulation (EC) No 45/2001;

b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;

c) protecting confidential communication between Member States in relation to the preparation of the assessment report;

d) ensuring effective supervision of the conduct of a clinical trial by Member States.

No data from the clinical trial application dossier can be made public before the decision on the clinical trial has been taken (Article 81(5) of the Regulation), unless there is an overriding public interest to do so earlier for a particular clinical trial. Although not explicitly stated in the legislation, in principle only information on validated applications should be made public, since invalid applications may contain incomplete or erroneous information.

Every clinical trial should, as a minimum, be registered in a public register prior to its start and its results summary also made public. This standard for public registration at the start of the trial is reinforced by the requirement in Article 25(6) that data from a clinical trial shall only be submitted in an application dossier (in support of a new clinical trial application), if that clinical trial has been registered prior to its start in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP. Therefore if EU clinical trials (which are registered in the EU database) as well as non-EU clinical trials (which are registered in other registers) are to be acceptable in support of an EU clinical trial application, they must also meet the public registration standard set out in Article 25(6) (for trials started before the Regulation comes into application this can also be achieved by publication of the results in an independent peer reviewed scientific journal).

In accordance with Article 93(2) of the Clinical Trial Regulation, Regulation (EC) No 45/2001 applies to the processing of personal data by the Agency. The Agency is the controller of the EU database (Article 81(1) of the Clinical Trial Regulation - "data controller" is defined in Article 2 (d) of Regulation (EC) 45/2001. In accordance with Regulation (EC) No 45/2001 the processing of personal information and its publication on the website will be limited to the information that is justified as a necessary interference into the private sphere of the persons involved.

The EU database shall contain personal data only insofar as this is necessary for the purposes of Article 81(2) of the Regulation (i.e. to enable cooperation between the competent authorities of the Member States for the application of the Regulation and to facilitate communication with sponsors).

Article 81(7) of the Regulation requires that no personal data of subjects (participating in a clinical trial) shall be publicly available and Recital 67 provides further clarification that no personal data of trial subjects should be recorded in the EU database. Article 37(4), final paragraph, of the Regulation further reinforces this point by setting out that for cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.

The Regulation provides further details on how these provisions should be applied in Recital 67 which sets out that publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while

recognising the legitimate economic interests of sponsors. Recital 68 sets out what as a minimum should be public on each trial (on the basis that it is not in general confidential) - the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination. In addition for clinical trials included in a marketing authorisation application in the EU, Article 37(4) requires that the applicant for a marketing authorisation submit the clinical study report to the EU database within 30 days after the day the marketing authorisation has been granted, the procedure for granting marketing authorisation has been completed, or the applicant has withdrawn the application. Recital 68 provides further clarification stating that for the purposes of this Regulation the data included in a clinical study report, in general should not be considered commercially confidential once one of the conditions set out above for submission of the clinical study report to the EU database has been met.

The importance of providing and maintaining public information is further reinforced by Article 94 of the Regulation which requires Member States to make provisions for penalties to be imposed in cases of non-compliance with its provisions on submission of information to be made publicly available to the EU database.

The EU portal and database will be updated in accordance with the experience acquired during the implementation of the Regulation (Article 84) and the functional specifications revised, accordingly, in preparation for each update.

3.2. The transparency requirements of the Paediatric Regulation (EC) No 1901/2006

Article 41 of the Paediatric Regulation (EC) No 1901/2006 stipulates requirements for the publication of results of paediatric clinical trials conducted in the EU and in third countries. As the Clinical Trial Regulation fulfils all of the requirements previously set by the Paediatric Regulation regarding clinical trials conducted in the EU, this aspect loses its practical relevance. However, additional requirements with regard to non-EU trials included in a paediatric investigation plan (PIP), as per Article 41 or reported in accordance with Article 46 of the Paediatric Regulation continue to apply. Those additional requirements are not part of this document. They will be addressed in the detailed requirements for the EU portal and database, but outside of the present functional specifications and outside of the audit foreseen by Article 82 of the Regulation.

3.3. Application of Regulation (EC) No 1049/2001

The implementation of the transparency rules of the Clinical Trial Regulation is without prejudice to the application of Regulation (EC) No 1049/2001 and citizens' right to request documents under that Regulation.

3.4. Status of clinical trials made public under the current clinical trial legislation in the EU Clinical Trial Register

Clinical trials conducted under the current legislation – Directive 2001/20/EC – are registered in the EudraCT database and summary information on the protocols of those trials, and summaries of their results are included in EudraCT and made public in the EU Clinical Trials Register. Those clinical trials will continue to be subject to the current rules on data to be included in EudraCT and made public via the EU Clinical Trials Register. Once the existing legislation has been repealed and no further trials or their result summaries remain to be registered, the EudraCT and EU CTR data content will be retained

as a reference for the competent authorities of the Member States, the Agency and the Commission on the one hand and for the public on the other. The transparency rules of new Regulation (EU) No 536/2014 will apply only to new trials authorised under that Regulation, or trials authorised under the old legislation but still ongoing 3 years after the Regulation comes into application. Provisions will have to be made, for these "transition" trials to have relevant information entered into the EU portal and database, in time before those 3 years have elapsed.

4. Application of the transparency requirements - Data and documents to be made public and timing of publication

4.1. Background

All of the data and documents that are explicitly designated by the Regulation to be submitted via the EU portal, and/or stored in the EU database shall be public, by default, unless one or more of the exemptions set out in Article 81(4) apply. This rule includes all of the data and documents listed in Annexes I, II, IV and V of the Regulation which set out the content of the application dossier for the initial application, the application dossier for substantial modification, the content of the summary of results of the clinical trial and the content of the summary of results of the clinical trial for lay persons. The assessment reports of the Member States, their questions to the sponsor (and sponsor responses to these) and the decisions of the Member States are included in the database. In addition the Regulation also stipulates that further information is submitted via the portal and or to the database by the sponsor including notifications from the sponsor on the start and end of recruitment, the end of the trial, unexpected events which affect the risk-benefit of the trial, urgent safety measures, third country inspection reports, serious breaches of the Regulation or the protocol, or by Member States on the planning of inspections, inspection reports, corrective measures required by the Member States, reports on Union controls by the Commission and clinical study reports submitted by the applicant/MAH [provisional lists of data and documents are provided as appendices to this paper to illustrate the practical impact of the proposals set out below, the details of the data fields of this list may change as the database is developed, so the appendices should not be taken as a definitive list].

In order to establish rules for the public access to the database, rules for the application of the exceptions, set out in Article 81(4), need to be established. These rules will need to operate in an automatic way which means that there should be fields in the data or metadata that enable the system software to determine if and for how long a particular data element or document should not be made public. Automatic rules are necessary because there will be 4-5000 clinical trial applications and multiple additional processes per trial taking place in the system every year. The rules need to be applied in a fair and systematic way, in accordance with established rules, and not based on repeated human judgment and intervention, which would be impossible to control and create a very large burden on authorities and on sponsors. The rules must be designed in order that the system produces a consistent and predictable outcome so that those submitting data and documents and those viewing them benefit from legal certainty as to what is made public and when.

The exceptions to publication set out in Article 81(4) are each considered below and where relevant different proposals are considered in section 4.3. below.

Section 4.2. below summarises the information to be made available for every clinical trial.

4.2. What will be made public for every clinical trial

Recital 68 refers to "the main characteristics of a clinical trial" – these can be considered to be its main design characteristics, its scientific and where applicable, therapeutic intent, title, identification of the IMPs (Investigational Medicinal Products), treatment arms, treatment population characteristics and number of subjects, inclusion and exclusion criteria and main objectives and endpoints (see Appendix 1 to this document).

The current EU CTR (EU Clinical Trials Register) is a primary registry of the WHO ICTRP, and the new database should make public a similar level of information and provide it to the WHO ICTRP. Information should also be equivalent in nature (though may be differently arranged, with different fields) to that already made public for Phase II-IV adult and all paediatric clinical trials under the present EU legislation in the EU Clinical Trial Register.

For every clinical trial, regardless of the marketing authorisation status of the medicinal product and regardless of the phase of the trial, the following information will be made public, as soon as it is available, once the decision on the trial has been made:

At the time of decision on the trial:

- the main characteristics of the trial (as set out in the clinical trial application form - being in effect a structured synopsis of the clinical trial protocol),
- the protocol summary,
- the conclusion on the assessment of Part I of the trial,
- the decision on the trial including reasons for refusal if the trial is not authorised (or where applicable the reason for its withdrawal),
- the start of the trial,

During the trial:

- the first visit of the first subject in the trial in each MS concerned,
- substantial modification of the trial (the fact that a substantial modification has been submitted and assessed, the conclusion on Part I (if applicable) and the decision on the substantial modification, as it relates to the major characteristics of the trial, or the sponsor or investigators involved at the time of the decision on the substantial modification, or other modifications to previously published information),
- notification on the temporary halt or early termination of the trial for reasons affecting the risk-benefit,
- notification on the end of recruitment in each MS concerned,
- notification on the end of the trial (per MS concerned, in all MS concerned and global),
- other documents and notifications set out in the Regulation and its annexes (unless other exceptions below apply to them – see details in the appendices to this paper). Refer to the appendices 2, 3 and 4 to this document for listing of potential items that may be made public.

After the end of the trial:

- the summary clinical trial results as set out in Annexes IV and V of the Regulation.

In the case of Phase I clinical trials in healthy volunteers there is particular sensitivity about the commercial confidentiality of information on the trial. Section 4.4.3., part 7, contains a proposal for an option for the sponsor to defer the publication of information from the start of the trial to the point at which the summary of results is included 12 months after the end of the trial.

The clinical trial protocol and related subject information sheet will be made public for all clinical trials but this publication may be deferred (see proposals in section 4.4.3.).

The investigational medicinal product dossier (IMPD) safety and efficacy sections will be made public for all clinical trials but this publication may be deferred (see proposals in section 4.4.3.).

The IMPD quality section will not be made public as it contains detailed information on manufacturing processes and related information which remain commercially confidential even after the marketing authorisation has been given (see section 4.4.3.).

4.3. Protecting personal data in accordance with Regulation (EC) No 45/2001

The data retained in the database and made public are there to provide public information on medicines and support the further development of these and other medicines. Personal data (other than trial subject data which are not included in the database) included in the database are made public only to the extent required for the application of the Regulation (Article 81(6)). Data subjects have the right to have personal information corrected and incorrect personal information deleted in accordance with Regulation (EC) No 45/2001. Data protection rules set out that personal data should not be retained for longer than is necessary. The rules supporting the WHO ICTRP require that information published in a clinical trial registry should not be removed from the public domain, even where a particular piece of information is superseded by new information. The Regulation imposes a minimum 25-year retention rule on trial master files, which should therefore serve as a minimum. Clinical investigators names and site information are however integral to the authorisation of the trial and should be retained for as long as data on the clinical trials is retained in the system.

There are several categories of personal data that need to be considered:

4.3.1. Clinical trial subjects being evaluated for or participating in a trial

The Clinical Trial Regulation makes clear that no personal data of trial subjects may be included in the database and no personal data of trial subjects should be publicly available, from the database. It follows that individual patient data listings (sometimes referred to as raw data) which form some of the appendices included in clinical study reports may neither be included in the database nor made public.

It should be noted that the reporting of SUSARs and annual safety reports which contain individual trial subject data in pseudo-anonymized form are not part of the EU database but are submitted to the separate EudraVigilance system, and are therefore out of scope of this document.

The clinical trial result summaries (as per Annex IV and V of the Regulation) are structured in such a way that even where an individual element of data relating to a single subject (most likely a single adverse reaction) is presented it does not include trial subject identifiers.

4.3.2. Clinical trial investigators and their staff

Annex I M of the Regulation requires that a list of the clinical trial sites, the name and position of the investigator or principal investigator in charge of the trial at a site, their qualification and CV and description of GCP training and any conditions such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented, as part of the application dossier. The (principal) investigator is a key actor identified in the Regulation (and internationally in all rules and guidelines on good clinical practice, ethics of clinical trials, national legislation in non EU countries etc.) with a legally assigned responsibility for conduct of the clinical trial at a given site and for the care and treatment of the trial subjects in the context of the trial. The (principal) investigators are responsible for ensuring the protocol is followed at their site, and for the collection and reporting to the sponsor of the data required by the trial protocol which form the basis of the clinical study report, which they or a chosen reporting investigator is required to sign where it is prepared for potential submission in a marketing authorisation application.

1. Therefore it is considered an integral part of the clinical trial authorisation of every trial that the list of principal investigators and their sites is made public as part of that authorisation.

2. The (principal) investigators' CVs, containing only professional information relevant to the conduct of clinical trials, are part of the application dossier and therefore the database. It is considered that these should be public, as they document the qualification of the investigator to conduct the trial. A template or list of information that should be included in the CV will be made available.

3. Any conditions such as economic interests and institutional affiliations that might influence the impartiality of the investigators which are submitted, as part of the application dossier should be made public. A template or list of information that should be included will be made available.

4. A written statement issued by the head of the clinic/institution or some responsible person testifying to the suitability of the facilities and human resources available for the trial is part of the application dossier. It is proposed that when the statements are made public the name of the signatory of the statement is included, on the basis that they are fulfilling a specific role in signing a statement required by the Regulation.

Question 1: Please comment on whether these proposals meet the requirements and objectives of the Regulation (EU) No 536/2014.

4.3.3. Member State experts (mainly scientific assessors, regulatory officials, ethics committee members, inspectors)

In general, the names of Member State experts will not be included in the database. To the extent that personal information identifying them is collected in the database at all, it will not be made public.

Question 2: Please comment on whether this proposal meets the requirements and objectives of the Regulation (EU) No 536/2014.

4.3.4. Personnel of the clinical trial sponsor or other parties acting on their behalf

In general, personal information identifying sponsor staff (or consultants, contractors, agents or staff of those acting on behalf of the sponsor) will not be included in the database. To the extent that information is included it will not be made public except for those persons with certain legal roles such

as the legally designated representative of the sponsor, or where the sponsor is a natural person (e.g. an investigator who is also the sponsor).

Question 3: Please comment on whether this proposal meets the requirements and objectives of the Regulation (EU) No 536/2014.

4.3.5. Personnel or experts of the marketing-authorisation holder/applicant for MA, or of the sponsor or the investigators, laboratory personnel or other actors in the conduct of a trial named in or signing clinical study reports

Personal information identifying MAH/applicant personnel (or consultants, contractors, agents or staff of those acting on behalf of the sponsor or MAH, investigators or other parties) identified in the clinical study report that is loaded into the database by the MAH/applicant will be made public. As a minimum the signatories of the clinical study report and the investigator(s) who conducted the trial should be identified.

Question 4: Please comment on whether this proposal meets the requirements and objectives of the Regulation (EU) No 536/2014.

4.3.6. Contact details of clinical investigators, sponsor or MAH personnel

It is proposed that no direct contact details such as direct telephone number or email address is provided for any natural person. Two exceptions to this are the possibility to include a sponsor contact point for information on the trial and a sponsor contact point for information on the scientific aspects of the trial required for public registration of the trial. These may be provided as functional roles, but if they are provided as contact details of natural persons these will in any event always be made public.

An option will also be provided for investigator sites to provide a contact point for trial subjects or their healthcare provides or carers, to enable them to seek further information about trial participation.

Question 5: Please comment on whether this proposal meets the requirements and objectives of the Regulation (EU) No 536/2014.

4.4. Protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure

The Regulation has two key objectives, to promote the EU as a location for clinical research (encouraging innovation), and to provide extensive public information on clinical trials conducted in the EU. These two objectives, need to carefully balanced, as reflected in Recitals 67 and 68 and in Article 81(4)(b) of the Regulation.

4.4.1. What should be considered to be commercially confidential information?

4.4.1.1 Definitions

Commercially confidential information can be considered as meaning any information contained in the data or documents submitted to the database that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the sponsor.

Sponsors have a legitimate economic interest in the trial they conduct which may derive from their intention to seek a marketing authorisation for the investigational medicinal product or because they need to obtain research funding for that and future trials. The legislation does not distinguish between different types of sponsor organisation (e.g. commercial, non-commercial or academic). The consideration of what might be commercially confidential is therefore based on the nature of the trial and status of the medicinal product being studied, rather that the nature of the sponsor organisation conducting the trial.

By having a legitimate economic interest in their trial the sponsor can claim that certain information relating to the trial should be considered commercially confidential, at least for a certain time period. Information may be commercially confidential because the clinical trial forms part of the development of a medicinal product for commercialisation of that product (i.e. seeking a marketing authorisation or variation). Alternatively it may be commercially confidential because the clinical trial is conducted to further basic or applied research on medicines and as such may be part of a process for which research funds have been obtained or may contribute to the obtaining of future research funds. The sponsor may need to retain some confidentiality of research plans in order to sustain their ability to conduct original research and maintain funding for that research, the ability to publish that research in journals and to pursue their research programme in the future. Since these concepts are necessary to research funding they can also be considered to represent legitimate economic interests and fulfil the definition of commercial confidentiality expressed in the first paragraph of this section, for the purposes of application of this Regulation.

Overriding public interest can be considered, in this context, as meaning that the general public interest in having information made publically available may outweigh considerations that the same information should remain confidential. The public interest per se is multifactorial, but includes access to information that supports the objectives for transparency set out in chapter 2 part 3 of this document.

Specific situations may occur where the "overriding public interest" would prevail in ad hoc situations over and above the general transparency rules established for the database and documents and data not usually made public may be published or made public at an earlier time point than would be usual. The database would have to provide functionality to enable non–public documents or data to be made public on such occasions. Outside of the database a decision making process will need to be established in order to invoke use of the overriding public interest in such ad hoc cases.

Documents and data included in the EU database can be grouped in two broad categories for this purpose – study specific and (active substance/medicinal product) specific documents.

These documents are complex and mixtures of commercially confidential and non-confidential information are present together in different sections. In many multicentre trials they will be in use in the EU and outside of the EU. To require that they be structured in confidential and non-confidential parts would impose a significant burden on sponsors who would have to prepare them for input into the portal in a very different way for the EU compared to elsewhere. It would also impose on sponsors of EU trials a more detailed structure, as different information would need to be entered in different fields, whereas at present it is included in a single document. Such an approach would increase the administrative burden of the clinical trial application process.

4.4.1.2 Categories of documents

a) Study specific documents:

Protocol: The protocol is defined in Article (2)(22) of the Regulation as: *"'Protocol' means a document that describes the objectives, design, methodology, statistical considerations, and organisation of a trial. The term 'protocol' encompasses successive versions of the protocol and protocol modifications."* The protocol contains extensive detailed information on the IMP, its mode of action and plans for its testing at least in the authorised trial. Such details can involve the scientific hypotheses being tested, and the test methods and endpoints being used. The details in the protocol which can be commercially confidential are not confined to any particular part of the document but may be entered in many different sections, so it should be treated as one entity for the purpose of transparency rules. Summarised elements of the protocol are to be found in the clinical trial application form ("the major characteristics of the trial") and result summaries, which are made public.

The protocol can therefore contain extensive detail of a commercially confidential nature, especially for clinical trials conducted before a marketing authorisation has been granted, or for new indications or formulations of a product already on the market.

Subject information sheet: The subject information sheet is a detailed description of the trial subject's rights and of the details of the potential risks and benefits of participation in the trial, details of the trial purpose and methodology and of any tests, sample collection or other impositions on the trial subject due to their participation in the trial. As such it will contain details, albeit possibly in lay terms, of the medicinal product, the purpose of the trial and its objectives and the tests that will be undertaken. It will also contain up to date information on the safety of the product based on preclinical testing and on any earlier clinical trial data that is available.

The subject information sheet can therefore contain extensive detail of a commercially confidential nature, for clinical trials conducted before a marketing authorisation has been granted, or for new indications or formulations of a product already on the market.

Related list of questions, responses and assessment reports: Assessment reports contain a detailed analysis and critique of the protocol, subject information and the purpose, design and supporting data of the trial. These will contain information from the documents submitted by the sponsor both in the initial application and additional information provided in response to questions from the Member States.

The list of questions, responses and assessment reports related to the protocol and subject information sheet can therefore contain extensive detail of a commercially confidential nature, particularly for clinical trials conducted before a marketing authorisation has been granted, or for new indications or formulations of a product already on the market.

b) Product specific documents:

Investigator brochure: The investigator brochure is defined in Article 2((23) of the Regulation as: *"'Investigator's brochure' means a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in humans"*. The investigator brochure contains extensive detail on the pre-clinical and clinical testing and development of the IMP as well as further lines of investigation for future development. These details are often not trial specific but cover all trials, as generally there is one investigator brochure for each active substance in development. The details include extensive scientific background on the toxicology, safety and efficacy of the IMP, detailed information on pharmaceutical development, pharmacokinetic and pharmacodynamic testing and methods, results of absorption, distribution and

metabolism and excretion tests, the mode of action of the product, discussion of endpoints and clinical development methods. The investigator brochure includes the reference safety information (RSI). Investigator brochure are frequently provided in confidence to investigators to thoroughly acquaint them with the IMP being tested, and are regularly (at least annually) updated, so provide a detailed update on the development of an IMP.

The investigator brochure therefore contains extensive detail of a commercially confidential nature, particularly for clinical trials conducted before a marketing authorisation has been granted, or for new indications or formulations of a product already on the market.

Investigational Medicinal Product Dossier (IMPD): The IMPD is a detailed technical and scientific description of the investigational medicinal product. According to Annex I(G)(36) of the Regulation *"The IMPD shall give information on the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use."* It is regularly updated, and these updates will be submitted to the EU database in accordance with the Regulation, so long as there are related trials ongoing in the EU.

For the purposes of the present document the IMPD is considered to have three sections one each on quality (IMPD-Q), safety (IMPD-S) and efficacy (IMPD-E).

The IMPD-Q section provides extensive detail on the manufacturing methods and controls, the chemical or biological characterisation of the product, its stability, stage of pharmaceutical development and further plans in that respect.

The IMPD-S and E sections provide extensive non-clinical and clinical trial data, plans for future trials and details of the current risk benefit assessment. They include extensive details relevant not only to the trial applied for but for any anticipated trials, including those in other indications or formulations that may be developed further in the future.

The IMPD is regularly updated to support all ongoing trials so individual updates may be more relevant for some trials than others, it provides and detailed updated review of the current state of knowledge and plans for the active substance/product.

The IMPD therefore contains extensive detail of a commercially confidential nature, particularly for clinical trials conducted before a marketing authorisation has been granted , or for new indications or formulations of a product already on the market., and the IMPD-Q section can always have extensive commercially confidential information.

Related list of questions, responses and Assessment Reports: Assessment reports contain a detailed analysis and critique of the information in the investigator brochure and IMPD Q, S and E sections. These will contain information from the documents submitted by the sponsor both in the initial application and additional information provided in response to questions from the Member States.

The list of questions, responses and assessment reports related to investigator brochure and IMPD therefore contain extensive detail of a commercially confidential nature, particularly for clinical trials conducted before a marketing authorisation has been granted, or for new indications or formulations of a product already on the market.

4.4.2. How should the status of marketing authorisation of the medicinal product be applied in the context of Article 81(4)(b) of the Regulation?

The status of the marketing authorisation for the medicinal product shall be taken into account in deciding which information/documents in the EU database shall be publicly accessible, and at what time point, unless there is an overriding public interest in disclosure (Article 81 (4)(b)).

1. Article 81(4)(b) of the Regulation states the commercially confidential information should be considered taking account, in particular, of the marketing authorisation status of the medicinal product. In order to apply this exclusion it is necessary to determine how the concept of marketing authorisation will be applied. Three proposals are made below (1.1, 1.2 and 1.3 but only one will be selected for inclusion in the final rules):

    1.1. once a marketing authorisation has been issued, by at least one Member State, for the active substance contained in that medicinal product,

    or:

    1.2. once a marketing authorisation has been issued, by at least one Member State, for a medicinal product using that active substance and for the indication under study,

    or:

    1.3. once a marketing authorisation has been issued, by at least one Member State, for a medicinal product using that active substance and for the indication and formulation/route of administration under study.

2. For the purposes of the proposals 1.2 and 1.3 medicinal products containing active substances which are bio-similars should be considered separately from the originator products (i.e. as not having a marketing authorisation until that is granted for the biosimilar product in question).

Question 6: Please comment on which of proposals 1.1. or 1.2. or 1.3. above best meets the requirements and objectives of the Regulation.

Please provide a brief rationale for your choice of proposal and explain briefly disagreement with the other proposals.

4.4.3. When should information that may be considered commercially confidential, be made public taking into account the marketing authorisation status of the medicinal product and unless there is an overriding public interest?

General considerations

1. In applying the concepts of protecting commercially confidential information, in particular taking account of the marketing authorisation status of a product, and of overriding public interest, a graduated approach could be taken to the release of information on clinical trials. Thus, the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine from first in human Phase I trials to post-authorisation Phase IV and low-intervention trials.

2. Currently there is no structured codification of the indications and formulations that would allow these to be determined automatically. The sponsor would have to indicate the marketing authorisation status of the medicinal product, in response to questions in the clinical trial

application form. As part of the assessment of the dossier the Member States would have to assess this status and decide whether or not the clinical trial is using the IMP within or outside the labelled indications/formulations/routes of administration or established therapeutic guidance (for low-intervention trials). The decision of the Member States should be final. This also relates to the determination of the low-intervention trial status of some trials so both aspects could be considered together.

3. There are many clinical trials carried out on non-authorised medicines, in the early phases of development prior to marketing authorisation, which are never later used in a marketing authorisation as the development of the medicines is discontinued (approximately 80% of medicines which enter trials in human subjects are discontinued) or indeed the trials may not have been conducted in preparation for a future marketing authorisation, but rather as basic research.

Publication of study specific and product specific documents (see 4.4.1.2)

4. Regardless of marketing authorisation status the IMPD-Q section on IMP quality and the related lists of questions, responses and assessment report sections should be considered to be commercially confidential and not be made public for any trial at any time, as this deals with the manufacturing and related pharmaceutical development information which continues to be CCI, indefinitely, post marketing authorisation.

Question 7: Please comment and give a brief rationale for your support or disagreement with this proposal regarding the IMPD-Q section.

5. Clinical trials on products with a marketing authorisation:

Taking into account the general considerations under 1, 2 and 3 the following should apply to trials of products with a marketing authorisation (the so called Phase IV trials and low-intervention trials[6]) with respect to the publication of study specific and product specific documents. The study and product specific documentation should be made public at the time of the decision on the trial. However, the sponsor will be given the option to defer this publication until the time that the summary of trial results is loaded into the database and made public (i.e. 12 months after the end of the trial), in cases where protection of commercially confidential information would be required. The sponsor should indicate in the clinical trial application form if they are opting for this deferral.

Question 8: Please comment and give a brief rationale for your support or disagreement with this proposal regarding clinical trials on products without a marketing authorisation.

6. Clinical trials on products without a marketing authorisation:

Taking into account the general considerations under 1, 2 and 3 above, the following should apply to trials of products without a marketing authorisation (the so called Phase I, II and III trials) with respect to the publication of study specific and product specific documents. Four proposals are made but only one will be selected for inclusion in the final rules:

[6] Low-intervention trial – defined in Article 2(2)(3) of the Regulation. Low-intervention clinical trials are carried out with IMPs which have a marketing authorisation (placebos excepted), and are used in accordance with the terms of the marketing authorisation or where the use is evidence-based and supported by published scientific evidence on their safety and efficacy. The additional diagnostic or monitoring procedures do not pose more than a minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

6.1. **Proposal One:** The study specific and product specific documents are made public at the time of the decision on the trial, and the exception set out in Article 81(4)b would only apply to the IMPD-Q section, which would not be made public at any stage.

6.2. **Proposal Two:** The study specific and product specific documents (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public after the earlier of the conditions set out in paragraph 6.5 below are met.

6.3. **Proposal Three:** A differential approach is taken equivalent to different stages of development – i.e. conservatively for Phase I and II trials, but then less conservatively for Phase III trials. This can be justified by interpreting that the degree of commercial confidentiality diminishes during development as information on the product and active substance and related clinical trials are more and more available in the public domain. Conversely the concept of overriding public interest increases due to the wider availability of the IMP/active substance and its use in larger subject populations for therapeutic/prophylactic purposes.

The study specific and product specific information (with the exception of the IMPD-Q section, which would not be made public at any stage) for Phase I and II trials should only be made public when the earlier of the conditions set out under paragraph 6.5 below are met.

For Phase III trials the study specific information should be made public at the time the summary of trial results is loaded into the database and made public (i.e. 12 months after the end of the trial) and the product specific information (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public when the earlier of the conditions set out in paragraph 6.5. below are met.

6.4. **Proposal Four:** A differential approach is taken during different stages of development – i.e. conservatively for trials without therapeutic (or prophylactic) intent, but then less conservatively for trials with therapeutic (or prophylactic) intent (a question in the clinical trial application form would ask if the trial has a therapeutic (or prophylactic) intent for the participating subjects. This can be justified by interpreting that the degree of commercial confidentiality diminishes during development as information on the product and active substance and related clinical trials are more and more available in the public domain. Conversely the concept of overriding public interest increases due to the wider availability of the IMP/active substance and its use in larger subject populations. Article 81(4)(b) requires that both the marketing authorisation status, and overriding public interest be considered when establishing the exception on the basis of commercial confidentiality.

For trials without therapeutic[7] or prophylactic[8] intent the study specific and product specific information (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public when the earlier of the conditions set out under paragraph 6.5. below are met.

[7] Clinical trial without "therapeutic intent" - a clinical trial carried out in healthy volunteers, or in patients who do not suffer from the disease to be treated or where the dose regime does not have the potential to have a therapeutic effect (e.g. a single dose trial).
[8] Clinical trial without "prophylactic intent" - a clinical trial carried out in healthy volunteers, or in patients who would not normally be considered for such prophylaxis, or would not usually benefit from it or where the dose regime does not have the potential to have a prophylactic effect (e.g. a single dose trial).

For trials with therapeutic[9] or prophylactic[10] intent the study specific information should be made public at the time that the summary of trial results is loaded into the database and made public (i.e. 12 months after the end of the trial) and the product specific information (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public when the earlier of the conditions set out in paragraph 6.5. below are met.

Table 1. Description of proposals 1 - 4 and optional deferral for Phase IV trials

	Clinical trials on medicinal products without marketing authorisation				Clinical trials on medicinal products with marketing authorisation
	Proposal One	Proposal Two	Proposal Three	Proposal Four	Phase IV and low-intervention trials
Study specific documents – protocol and subject information sheet	Time of decision on trial	Time of MA or 9 years after first summary results posted	Phase I and II time of MA or 9 years after first summary results posted Phase III – time when first summary results are posted	Non therapeutic trials – time of MA or 9 years after first summary results posted Therapeutic trials – time when first summary results are posted	Time of decision on trial, but sponsor may opt to defer to time when first summary results are posted
Product specific documents – IMPD S and E sections and investigator brochure	Time of decision on trial	Time of MA or 9 years after first summary results posted	Time of MA or 9 years after first summary results posted	Time of MA or 9 years after first summary results posted	Time of decision on trial, but sponsor may opt to defer to time when first summary results are posted on trial

[9] Clinical trial with "therapeutic intent" - a clinical trial carried out in subjects suffering from the condition which the investigational medicinal product is intended to treat and where at least one of the treatment arms is carried out with a dose regime that has the potential to have a therapeutic effect. The trial may still involve placebo, or standard of care arms.

[10] Clinical trial with "prophylactic intent" - a clinical trial carried out in subjects where at least one of the treatment arms is carried out with a dose regime that has the potential to have a beneficial prophylactic effect in the trial subjects receiving it. The trial may still involve placebo, or standard of care arms.

Question 9: Please comment on proposals one, two, three or four regarding clinical trials on products with a marketing authorisation indicating which proposal best meets the requirements and objectives of the Regulation. Please provide a brief rationale for your choice of proposal and explain briefly disagreement with the other proposals.

6.5. **Triggers for timing of publication** (in relation to proposals two, three or four above regarding clinical trials on products without a marketing authorisation):

6.5.1. The granting, refusal, or the withdrawal of the marketing authorisation application has triggered the loading into the EU database (and therefore publication) by the marketing authorisation applicant of the clinical study report for the same trial.

6.5.2. Nine years have elapsed from the date on which the first summary of results of the trial should have been published and therefore at least 10 years after the end of the trial, taking into account that for some trials an extension of the time limit for publication of the summary of results can be justified (for scientific reasons) in accordance with Article 37(4) of the Regulation). The period of 10 years have been chosen to give a reasonable period after the trial has been completed, before publication, 10 years corresponding, by analogy, though not actually linked to, the data protection period provided for in the EU.

Question 10: Please comment on the proposed time points in paragraphs 6.5.1 and 6.5.2 and indicate whether they meet the requirements and objectives of the Regulation. Please provide a brief rationale for your support or disagreement.

Information to be made public at the time of decision on the trial – possible deferral for Phase I trials in healthy volunteers (see 4.2.).

7. Section 4.2. above describes the information to be made public, as soon as it is available, once the decision on the trial has been made. That information will be made public for all trials regardless of their marketing authorisation status or of the phase of the trial.

For Phase I trials (in healthy volunteers), the default information made public at the start of the trial, and during the course of the trial, will remain that described in section 4.2. "What is made public for every trial".

However, the sponsor will be given the possibility to opt (by indicating this in the clinical trial application form) to have only a very minimal public information at the time of decision on the trial. In this case the minimum information made public at the time of decision on the trial would be a subset of the fields of the WHO ICTRP, in particular the EU number of the trial, the sponsor, the investigator site, the phase of the trial (i.e. Phase I), the number of trial subjects and the population under study (i.e. healthy volunteers). The decision on the trial would also be made public, but identifying the trial only by this minimum set of information. The information that would usually have been made public at the start of the trial and during the trial will, in case of a deferral, be made public at the point when the summary of trial results is published 12 months after the end of the trial. This option for deferral will not apply to Phase I trials conducted in paediatric populations.

Question 11: Please comment and give a brief rationale for your support or disagreement with this proposal regarding Phase I trials.

The arrangements for payment of investigators and sites as set out in Annex I (P) (69-71) of the Regulation, should not be published as they relate in all cases to the commercial financial arrangements between the parties and the exception set out under Article 81(4)(b) should apply in all cases, because this information can be considered to be commercially confidential.

Question 12: Please comment on whether this proposal meets the requirements and objectives of the Regulation.

4.5. Protecting confidential communication between Member States in relation to the preparation of the assessment report

The confidentiality of communication between Member States in relation to the preparation of the assessment report is required to enable the preparation and drafting of assessment reports to be conducted in confidence to ensure that the assessment and hence where applicable the decision making process is not subject to interference.

The Regulation does not require the draft assessment reports to be submitted through the portal to the database and therefore they will not be made public.

Question 13: Please comment on whether this proposal meets the requirements and objectives of the Regulation.

4.6. Ensuring effective supervision of the conduct of a clinical trial by Member States

Supervision of a clinical trial by the Member States encompasses the planning, conduct, reporting and follow-up of inspections conducted in accordance with Article 78 of the Regulation. Article 78 also includes certain inspection coordination activities of the Agency, and the taking of corrective measures by the Member States in accordance with Article 77 of the Regulation. Supervision also includes the Union controls foreseen by Article 79 of the Regulation. The receipt, evaluation and follow-up of reports of serious breaches reported in accordance with Article 52 of the Regulation, are also part of the supervision of clinical trials.

In the context of supervision of clinical trials it will be necessary for certain documents to contain personal data or commercially confidential information in order to fulfil their scientific and regulatory purpose.

In this context the exception under Article 81(4)(a),(b) and (d) should be taken into account in the publication of inspection reports, Union Control reports, serious breach reports and their follow-up and corrective measures.

4.6.1. Inspection reports

1. Information on the planning of an inspection, its conduct, reporting and follow-up should remain confidential until the final inspection report has been issued.

2. Inspection reports should be made public once the inspection process is completed and the final inspection report signed off and issued by the Member State(s) inspectorate. This may be deferred where its publication would be prohibited by ongoing legal proceedings in the Member State.

3. Where an inspection has been requested as part of the assessment of a marketing authorisation application, the final inspection report should be released at the time point set out for inclusion of clinical study reports in the database, or later if the inspection process is not yet completed for that inspection, in which case paragraph 2 above applies.

4. The inspection report made public should be redacted, by the responsible inspectorate, in line with the principles set out in accordance with exceptions under Article 81(4) (a) and (b). The report should nonetheless identify the relevant clinical trials by their EU number and or protocol number (for third country trials) and the site of the inspection, including where applicable the name of the investigator, and the name of the institution, or for other facilities the name of the facility (e.g. laboratories). Redacted and un-redacted versions should be submitted to the database but only the redacted version made public. No personal data of trial subjects should appear.

Question 14: Please comment on whether these proposals meet the requirements and objectives of the Regulation.

4.6.2. Union Control reports

The final report of a Union Control submitted by the European Commission through the portal should be made public at the time it is submitted via the portal. Redaction of personal data or commercially confidential information, if applicable, will be carried out by the Commission.

Question 15: Please comment on whether this proposal meets the requirements and objectives of the Regulation.

4.6.3. Serious breaches and corrective measures

1. Serious breaches reported in accordance with Article 52 should not be made public until they have been investigated and a conclusion reached by the Member State to whom the breach has been reported or in whose territory the breach occurred if different. Where the same serious breach is reported to several Member States, they may decide to agree on one Member State taking the lead in evaluating the case, and preparing text to support the following notices in the database.

    1.1. If the Member State concludes that there is no case to answer a notice should be included in the database and published, to the effect that a serious breach reports was received but that the Member State concluded that no serious breach had been substantiated, thus closing the process. No details of the reported breach would be published as none had been substantiated.

    1.2. If the Member State concludes that there is a serious breach without requiring further action by the Member State, then a final notice should be included in the database and published, describing the serious breach and the conclusion of the Member State.

    1.3. If an inspection is initiated then the serious breach notice should be included in the database and published, at the same time as the associated inspection report (or after corrective measures have been taken in accordance with Article 77(see below) whichever is later).

    1.4. If the Member State decides to take corrective measure in accordance with Article 77, then the notice detailing the serious breach should be included in the database, and published, at the same time as the notice of corrective measures is issued.

1.5. For corrective measures issued for other reasons (unrelated to a serious breach) the Member State should include in the database, for publication a notice of corrective measures in accordance with Article 77(3). That notice should be published in line with the same conditions set out in 1.6.

1.6. The information provided by the sponsor should include a summary, for publication, of the serious breach with personal data or commercially confidential information redacted. The detailed data supporting the notice serious breach should not be published in order to allow the sponsor to provide all relevant details which may include information on individuals other than the investigator, or commercially confidential information. The notice of serious breaches and/or corrective measures made public by the Member State should use the summary provided by the sponsor. The Member State should redact that part of the notice the Member State generated prior to its publication, in line with the principles set out in accordance with exceptions under Article 81(4)(a) and (b). The notice should nonetheless identify the relevant clinical trials by their EU number and or protocol number (for third country trials) and the sites involved, including where applicable the name of the investigator, and the name of the institution, or for other facilities the name of the facility (e.g. sponsor site, CRO, laboratories). Redacted and unredacted versions should be submitted to the database but only the redacted version made public. No personal data of trial subjects should appear.

Question 16: Please comment on whether these proposals meet the requirements and objectives of the Regulation.

4.7. Reporting of unexpected events in accordance with Article 53 and urgent safety measures in accordance with Article 54

1. A report of an unexpected event made in compliance with Article 53 should be made public at the time it is reported, unless one of the supervision measures itemised in section 4.6.3 is taken, in which case it should be made public in line with the measure concerned.

2. A report of urgent safety measures made in accordance with Article 54 should be made public at the time it is reported.

3. The report made public in accordance with Articles 53 and 54 should be redacted, by the sponsor, in line with the principles set out in accordance with exceptions under Article 81(4)(a) and (b). The report should nonetheless identify the relevant clinical trials by their EU number and or protocol number (for third country trials). Redacted and unredacted versions should be submitted to the database but only the redacted version made public. No personal data of trial subjects should appear.

Question 17: Please comment on whether these proposals meet the requirements and objectives of the Regulation.

4.8. Clinical study reports submitted by the marketing-authorisation applicant/holder

1. Clinical study reports including all appendices except those listing individual patient data, will be submitted to the database by the marketing-authorisation applicant/holder and made public within 30 days after the day the marketing authorization has been granted, the procedure for granting the marketing authorisation has been completed or the applicant has withdrawn the application.

2. The preparation of the content of the reports prior to being loaded into the system should be part of separate guidance to be developed by the appropriate EU expert group, taking account of considerations on what may constitute commercially confidential information, and their redaction, published by the EMA in its Policy 70 on access to clinical study data, and need not be set out here as it is not necessary to the structure of the EU database and therefore need not be specified in the functional specifications.

Question 18: Please comment on whether these proposals meet the requirements and objectives of the Regulation.

5. Proposed addendum to the "Functional specifications for the EU portal and EU database to be audited - EMA/641479/2014"

The following text including the part of Table 2 Section 4.3 will be revised following the consultation and added to the "Functional specifications for the EU portal and EU database" as an addendum.

Below is the text to be added to Section 6 as published in the functional specification document, as an addendum:

"**6. Functional Specifications to be audited (addendum)**

The functional specifications of the EU portal and the EU database and associated workspace are outlined below and are considered necessary to enable the EU portal and the EU database to be fully functional.

In accordance with the Regulation, the EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the grounds outlined in Article 81(4).

Additional principles and details to apply based on the outcome of this consultation should be inserted here describing application of the exceptions, to the rule that the database content is public, set out in Article 81(4).

Any type of document/data that fall under the grounds for exception described in Article 81(4) of the Regulation will not be made publicly available, or only after a particular event/timeframe has occurred/elapsed."

Below is the text to be added to Table 2 Section 4.3 as previously published in the functional specification document, as an addendum:

4.3	Publication of CT data and information	The clinical trial data and information is to be made publicly available through a publication module of the database according to detailed rules to be defined taking into consideration the workflow of the trial. The rules are to be automated and implemented through the publication module of the database. The publication of clinical trial related documents and/or information will be an automatic process operated in accordance with predefined rules and criteria, set out in the present document, with no manual intervention and taking into consideration the workflow of the trial and its status. A manual override will be made available to enable publication in exceptional circumstances where an overriding public interest applies, as provided in the Regulation. The override may also be used to remediate errors where information has been published contrary to the established rules, or where data processing errors have occurred. The system should identify all data and documents in the EU database regarding their public or non-public status and any timeframe/event to trigger that publication, and include the necessary rules to ensure their availability at the required time. For each data field (or set of related fields) or document the system will have metadata and rules to support their publication status and timing publication. For each of these sets of information the database will have a structure to contain a document (or data such as names and addresses in the case of the investigator/trial sites list, sponsors etc.), but the content of the related documents should be defined outside of the design of the database and taking into account whether or not the information should be made public. The appropriate expert group of the EU should develop guidance and/or templates for the content of documents to be included in the database. The IMPD should be structured to enable each section (Q, S, E) to be separate and have different publication rules applied to each. The protocol synopsis and protocol should be separate and have different publication rules applied to each. The application form will contain questions that will provide data points on which to base certain of the publication rules, which are not driven by other actions or data in the database. These questions (to be adjusted based on the final outcome of the consultation on publication rules) will include items such as: 1. Does the trial have a therapeutic (or prophylactic) intent? 2. Does the active substance appear in any marketing authorisation already granted in the EU?

		3. Does the indication(s) under study in this trial appear in any marketing authorisation already granted in the EU for that active substance? 4. Do the formulation(s)/route(s) of administration appear in any marketing authorisation already granted in the EU for that active substance? 5. Is this trial being carried out for commercial purposes? 6. If this trial is not being carried out for commercial purposes can the study specific (protocol etc.) and product/active substance specific (IMPD (S&E sections), IB etc.) be released at the time of the decision on the trial? 7. What is the phase of the trial? 8. Additional questions as required.

Question 19: Please comment on whether the proposed addendum to the functional specifications meets the requirements and objectives of the Regulation.

Appendices:

The appendices are to be added describing the data and documents that may be made public and when. They can be accessed at the following Draft Appendices to Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited" EMA/641479/2014 (europa.eu).

NB These appendices are provided for indicative purposes only to illustrate how the implementation of these proposals might work and will be further refined as the data model for the database is refined.

Appendix 1: The clinical trial application form, and those elements considered to be the "major characteristics of the trial", as referred to in Recital 68 including WHO ICTRP data elements.

Appendix 2: The contents of the clinical trial initial application dossier.

Appendix 3: The contents of the clinical trial substantial modification application dossier.

Appendix 4: Other data and documents submitted to the database.

Appendix 5: The summary of results of the trial.

Appendix 6: The laypersons summary of the trial.

Appendix 7: The clinical study report including its appendices.