



2 October 2015  
EMA/228383/2015 Endorsed

## Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014”

This document was valid until 17 June 2024.  
It is now superseded by a [new version](#).

Draft reviewed with the clinical trials information system expert group	8 December 2014
Consultation with the MS for release for public consultation	9 December 2014 - 13 January 2015
Consultation with the European Commission for release for public consultation	9 December 2014 - 13 January 2015
Public consultation	21 January - 18 February 2015
Consultation of the final document by the European Commission	7 September 2015
Consultation of the final document by the Member States	7 September 2015
Endorsement by European Medicines Agency Management Board	2 October 2015
Sign off by the Deputy Executive Director	5 October 2015



# Appendix, on disclosure rules, 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 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 EU 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 serves 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 the development and maintenance of the portal and database.

The Regulation states that the EU database "shall be publicly available unless one or more exceptions apply". These exceptions 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 in disclosure;
- to protect confidential communication between Member States in preparing their assessment;
- to protect the supervision of clinical trials by Member States.

This Appendix sets out rules and criteria for the application of these exceptions in relation to the disclosure provisions of the European Clinical Trial Regulation. This appendix complements the [functional specifications for the EU portal and database to be audited](#), which were drawn up by the Agency and endorsed by its Management Board in December 2014 and its addendum on functional requirements to support transparency endorsed by the Agency Management Board in March 2015 .

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 the 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 includes:

- 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, with reasons for which trials are ended prematurely where applicable, and, 12 months later, the summary of results and a summary in lay language;
- clinical study reports for clinical trials on medicines for which a marketing authorisation has been granted, the procedure completed or the marketing authorisation application withdrawn.

The list of abbreviations of the functional specifications of the EU portal and EU database to be audited will be updated to include the abbreviations contained in this document.

## 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<sup>1</sup> from the point of their authorisation to the publication of the results of those clinical trials. Information published at the time of decision on the trial should be updated, if it is changed (e.g. by substantial modification or other notification) during the course of the trial. The application of the disclosure rules and criteria 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 in future all clinical trials used in support of a clinical trial application are publicly registered in a register providing data to the WHO ICTRP (WHO International Clinical Trials Registry Platform). Older clinical trials conducted before the Regulation comes into application, may alternatively have been published in an independent peer reviewed scientific journal.
  - 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.
  - Provide patients, trial subjects, their legally designated representative, and healthcare professionals:

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<sup>1</sup> References in this document to the EU should also be read as references to the EEA (European Economic Area).

- 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 EU database 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 appendix sets out rules and criteria for the application of the disclosure 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 disclosure 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 disclosure 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. Only applications on which a decision has been made by a Member State will be made public.

Information on clinical trials which are authorised will be made public in accordance with the rules set out in section 4 of this document. Information on clinical trials which are refused will be made public according to the same rules, in which case the date of the refusal decision will be taken as equivalent to the date of the end of the trial (see Table one for further details).

Information on applications which are only for assessment of Part I of the dossier (Article 11 applications) will not be made public. Information on applications which are not validated or those withdrawn by the applicant before a decision is made will not be made public. In exceptional circumstances the above mentioned information may be made public if there is an overriding public interest in disclosure.

The EU database will need to be primary or partner registry of, or a data provider to, the WHO ICTRP and must therefore meet the data requirements of the WHO ICTRP. Article 25(6) of the Regulation requires 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), and implementation of requirements for information to be submitted set out in article 37 and in the annexes to the Regulation.

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 disclosure 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 most of the requirements previously set by the Paediatric Regulation regarding clinical trials conducted in the EU, this aspect loses its practical relevance, except for the timing of submission of the results of clinical studies which should be without delay and for those referred to by article 46 of the paediatric Regulation, within 6 months of the end of the trial, unless one or more of the exceptions in the Commission Communication 2009/C28/01 apply. 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. These 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 disclosure 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 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 rules on data to be included in EudraCT and made public via the EU Clinical Trials Register. Once Directive 2001/20/EC 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 disclosure rules of Regulation (EU) No 536/2014 will apply only to new trials authorised under that Regulation, or trials authorised under Directive 2001/20/EC 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 disclosure requirements - Data and documents to be made public and timing of publication**

### **4.1. Background**

In order to enable public access to the database, rules for the application of the exceptions, set out in Article 81(4), are required. These rules are 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 when a particular data element or document should 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 are designed in order that the system produces a consistent and predictable outcome so that those submitting data and documents and those viewing them know what will be made public and when.

In addition a manual override will be made available to enable publication in exceptional circumstances where an overriding public interest applies, as provided in the Regulation, or to remediate a publication error.

### **4.2. 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. Article 81(6) of the Regulation states that personal data (other than trial subject data which are not included in the database) should only be included in the database to the extent required for the application of Article 81(2).. 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 and where the medicinal product has or obtains a marketing authorisation in the EU, for as long as that product remains on the market and for 10 years thereafter. Clinical investigators' names and site information are 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.

Contact details of clinical investigators, sponsor or MAH personnel:

- No direct contact details such as direct telephone number or email address is provided for any natural person. Two exceptions to this, required for public registration of the trial, are the sponsor contact point for information on the trial and the sponsor contact point for information on the scientific aspects 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 providers or carers, to enable them to seek further information about trial participation. 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.

A small number of documents that are loaded into the EU database may require a signature. The requirement for copies of signatures to be loaded into the system will be minimised. If on certain documents a signature is required then the system will enable a full copy of the document to be uploaded with the name of the signatory and date of signature entered, but without the actual signature, this document will be made public. The system will enable a copy of the actual signature page with a scan of the signature to be uploaded at the same time; this will not be made public.

#### **4.2.1. Clinical trial subjects participating in a trial**

The clinical trial Regulation makes clear that no personal data of trial subjects should be included in the database and no personal data of trial subjects shall be publicly accessible, from the database. It follows that individual subject 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.

In addition personal data of trial subjects that may be included in clinical study report narratives or tables will need to be anonymised prior to being loaded in the system by the applicant for the Marketing Authorisation. Guidance is being developed in the context of the Agency Policy 70 on this point and will also serve as the basis for anonymisation of the clinical study reports to be loaded into the EU database (see section 4.5, last paragraph).

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.

#### **4.2.2. Clinical trial investigators**

Annex I M of the Regulation requires that a list of the clinical trial sites, the name and position of the principal investigator in charge of the trial at a site are included in Part II of the application dossier, their qualification and Curriculum Vitae (CV) and description of Good Clinical Practice 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 following information from the database will therefore be made public. In this context reference to principal investigator means the one investigator in charge of the clinical trial at each trial site:

1. The list of principal investigators' names and the names and addresses of the clinical trial sites.
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. 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. Where the conduct of a clinical trial by an investigator is not authorised, this information will not be made public.
4. The 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, will include the name of the person issuing that statement.

#### **4.2.3. 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, except where necessary for the application of Article 81(2) of the Regulation (Article 81(6)). There is no specific requirement in the Regulation for the names of Member State experts to be included in the database.

Therefore, in application of Article 81(4)(a), to the extent that personal information identifying Member State experts is collected in the database at all, it will not be made public.

#### **4.2.4. Sponsor staff (or consultants, contractors, agents or staff of those acting on behalf of the sponsor).**

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, except where necessary for the application of Article 81(2) of the Regulation (Article 81(6)).

Therefore, in application of Article 81(4)(a), to the extent that personal information identifying them is included in the database it will not be made public except for those persons with legal roles including the legally designated representative of the sponsor, or where the sponsor is a natural person (e.g. an investigator who is also the sponsor).

#### **4.2.5. MAH/applicant personnel (or consultants, contractors, agents or staff of those acting on behalf of the sponsor or MAH) and investigators or other parties.**

The clinical study report loaded into the database by the MA applicant should not reveal personal information identifying MAH/applicant personnel (or consultants, contractors, agents or staff of those acting on behalf of the sponsor or MAH), the MA applicant should redact such names before loading the clinical study report. If certain personnel remain identified in the clinical study report that is loaded into the database by the MAH/applicant they will be made public. The names (not signatures) of the sponsor and coordinating investigator signatories of the clinical study report and the identities of the investigator(s) who conducted the trial should remain visible in the clinical study report loaded into the database, and will be made public.

#### **4.3. 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 Rules on disclosure are set out below taking into consideration Article 81(4)(b) and Recitals 67 and 68 of the Regulation. These rules have to balance the objectives of promoting the EU as a location for clinical research (encouraging innovation), and providing extensive public information on clinical trials conducted in the EU.

##### **4.3.1. Commercially confidential information.**

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 factors including their intention to seek a marketing authorisation for the investigational medicinal product (IMP) or because the information derived from this trial may contribute to the obtaining of future research funds. 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 IMP being studied, rather than 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.

##### **4.3.2. Overriding public interest in disclosure.**

Overriding public interest in disclosure 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 appendix.

The “overriding public interest in disclosure” may prevail in some particular ad hoc situations over and above the general disclosure rules established for the database. Documents and data not usually made public may be published or made public at an earlier time point than would be usual. The database will 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 be established in order to invoke use of the overriding public interest in such ad hoc cases. This decision should be made by the Member States concerned by the trial or trials in question, supported for technical, regulatory and consistency purposes by the EMA and the EU Commission. Such decisions will only be made in exceptional circumstances (e.g. where there are very serious safety incidents such as occurred in the clinical trial of TGN1412).

Similarly the sponsor may also elect to make information public at an earlier stage than that foreseen.

### **4.3.3. Balancing commercial confidentiality and overriding public interest in disclosure.**

#### **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 in disclosure, a graduated approach should be taken to the release of information on clinical trials. Thus, the extent of information made public will be timed differentially according to the use of the IMPs in the clinical trial in relation to the marketing authorisation status of the indications, pharmaceutical forms and routes of administration being investigated.
2. Currently there is no consolidated, structured codification of the indications, pharmaceutical forms and routes of administration that would allow these to be used automatically to control the release of public information. Each clinical trial application submitted will be required to be categorised according to one of the three categories described below. The sponsor will be asked to state whether the indications, pharmaceutical forms and routes of administration being investigated fall within the authorised uses of the IMPs, and to which of the categories described below, the trial belongs, in response to questions in the clinical trial application form. As part of the assessment of the dossier the Member State (RMS (Reporting Member State) in the case of a multistate trial) will assess this status and decide whether or not the statement of the sponsor is correct, or where a sponsor does not indicate a category the Member State will categorise the trial. If the Member State has had to categorise the trial or considers it is in a different category, the sponsor will be informed in the request for additional information issued as part of the assessment of Part I of the clinical trial application dossier. The sponsor may agree with the Member State view or provide additional justification to support their chosen category. The Member States will review and decide on the final classification of the trial in the final conclusion on Part I of the dossier.
3. The timing of publication of data and documents are adjusted according to whether the clinical trial falls into category 1, 2 or 3 (see below) in order to balance the need to protect the legitimate economic interests of sponsors, in particular by taking into account the marketing authorisation status of the IMP, with overriding public interest in disclosure. Where a clinical trial protocol sets out a multiphase or adaptive study design that falls in both category 1 and 2, the trial will be treated according to the higher of the potential designations.

4. 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, or the studied aspect of the IMPs is discontinued (approximately 80% of IMPs 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 by academic research institutions or pharmaceutical industry. Information on these trials also needs to be made public.

In order to recognise the legitimate economic interests of sponsors and take account of the marketing authorisation status of the IMPs under study in a clinical trial, but still have a predictable and automatic system for publication of information from the database, the rules and criteria are established below by grouping clinical trials (based on the use and status of their IMPs) into three categories:

#### **Category 1 clinical trials (pharmaceutical development clinical trials):**

Category 1 clinical trials are:

- Phase I clinical trials in healthy volunteers or patients, that are carried out to test whether a treatment is safe for people to take, rather than to try to treat, prevent or diagnose a condition, and to study pharmacokinetics and pharmacodynamics (where possible). These trials are usually very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients.
- So called Phase 0 trials - trials in healthy volunteers or patients, without therapeutic or prophylactic intent, and often used at low doses (though this may include pharmacologically active doses) to explore pharmacokinetics or pharmacodynamics.
- Bioequivalence and bioavailability trials of innovative products, new generic products and bio-similar products. This includes such trials on new formulations of products with a marketing authorisation (originator, generic or biosimilar).
- Similarity trials for biosimilar products including those conducted in patients where efficacy endpoints are used to determine biosimilarity, where pharmacokinetic and or pharmacodynamic studies are not possible.
- Equivalence trials for combination products or topical products where a pharmacodynamic or efficacy endpoint is used to determine equivalence, and where pharmacokinetic and or pharmacodynamic studies are not possible.

#### **Category 2 clinical trials (therapeutic exploratory and confirmatory clinical trials):**

Category 2 trials are safety and efficacy trials in patients, or target populations for prophylaxis. They are therefore being carried out for treatment, diagnosis or prevention in the subjects included in the clinical trial. They include the phase II and III trials carried out during clinical development of a new product or during exploration of new indications, pharmaceutical forms, strengths and routes of administration for an existing product that already has a marketing authorisation. This category includes not only trials by the MAH but also trials by other researchers looking at safety and efficacy in new indications, pharmaceutical forms and routes of administration, or patient populations and not covered by the definition of category 3.

- Phase II: clinical trials to investigate the safety and efficacy of a potential therapy, and to investigate potential dose regimes.

- 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 are conducted to confirm safety and efficacy.

### **Category 3 clinical trials (therapeutic use clinical trials):**

Category 3 clinical trials are clinical trials carried out for treatment, diagnosis or prevention in the subjects included in the clinical trial, using an authorised IMP, used in accordance with the terms of the marketing authorisation, or the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States concerned.

Category 3 therefore includes both phase IV clinical trials and low-intervention clinical trials.

- Phase IV trials are post marketing studies to delineate additional information including the IMP'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 pharmaceutical form and strength).
- A low-intervention clinical trial is defined by the Regulation as a clinical trial which fulfils all of the following conditions: (a) the IMPs, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the IMPs are used in accordance with the terms of the marketing authorisation; or (ii) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

#### **4.3.4. Timing of publication of data and documents**

Table 1 of this appendix gives an overview of the timing of publication of data and documents in relation to the conduct of the clinical trial according to the classification of the clinical trial as category 1, 2 or 3. The timing is based on key milestones of the clinical trial identified in the clinical trial regulation – decision on the trial, end of the trial, 12 months after the end of the trial and one additional milestone defined here to simplify and standardise release of data and documents, which is set up to 7 years after the end of the trial for category 1 trials and up to 5 years after the end of the trial for category 2 trials. This period of 5 (or 7) years is considered appropriate as it ensures that adequate up to date investigator brochures and IMPDs can be submitted with confidence to the EU portal, that sponsors have sufficient time before their publication to protect their economic interest, but information is nonetheless made public, including where IMPs never reach marketing authorisation. Five years has been taken as a mid-point in the average development time of a new medicine which is generally considered to be about 10 years, and 7 years is used for category 1 trials as they often start earlier in development and are generally shorter in duration. It therefore balances the economic interests of the sponsor with the overall objective that information contained in the database is made public.

<b>Table 1:</b>	<b>Overview of the timing of publication of data and documents from the clinical trial database in relation to the category of the trial as detailed in section 4.3.3 <sup>a,b,c</sup></b>		
	<b>Category One Phase I, Bioequivalence and Bioavailability trials and bio-similarity trials</b>	<b>Category Two Phase II and III trials, essentially those that are neither category one nor category three</b>	<b>Category Three Phase IV and low-intervention trials</b>
<b>Date of decision on a trial, start of the trial, the first visit of the first subject, end date of subject recruitment, dates of temporary halts and end dates of the trial, (including early termination) (per member state, in the EU and globally as required).</b>	Time when each date is posted in the database.		
<b>Main characteristics of trial including WHO ICTRP data fields, cover letter and details of clinical investigators and their sites (including the summary CVs, statements of the head of the institution regarding the site and the statement regarding conditions such as economic interests and institutional affiliations that might influence the impartiality of the investigators)</b>	Time of decision on trial. <sup>d,c,r</sup>		
	Sponsor may opt to have a restricted number of fields <sup>e</sup> made public at the time of decision on the trial and updated if applicable during the trial and defer the publication of the remainder to the time when the first summary results are made public. <sup>c,f,g</sup> The sponsor will be required to include a justification for the requested deferral. <sup>h</sup>		
<b>Notifications occurring during the trial: unexpected events, urgent safety measures, including those relating to quality defects or GMP</b>	At the designated time for publication – see section 4.6 below for details. Sponsor or Member State(s) may decide to make such information public at an earlier stage (see 4.3.2).		
	Sponsor may opt to defer to time when summary results are posted. <sup>f,h</sup> except for early terminations for		

<b>non-compliance in relation to an IMP and reasons for temporary halts and early terminations.</b>	reasons involving subject safety.		
<b>Subject information sheet, including each version and modification that has occurred.</b>	Time of decision on the trial. <sup>c,d</sup>	Time of decision on the trial. <sup>c,d</sup>	Time of decision on the trial. <sup>c,d</sup>
<b>Protocol, including each version and modification that has occurred.</b>	Sponsor may opt to defer this up to the time of MA <sup>i</sup> using this trial or up to 7 years <sup>k,m</sup> after the end of the trial whichever is earlier.	Sponsor may opt to defer this up to the time of MA <sup>i</sup> using this trial or up to 5 years <sup>k,m</sup> after the end of the trial whichever is earlier.	Time of decision on the trial. Sponsor may opt to up to the time when the summary of results is made public usually 12 months <sup>k,m</sup> after the end of the trial in the EU. <sup>h</sup>
<b>Product specific documents – IMPD S and E sections and investigator brochure,</b>	Time of decision on the trial, or substantial amendment updating these documents, or notification of an updated document. <sup>d,j,l,m</sup>		
	Sponsor may opt to defer this up to the time of MA <sup>i</sup> using this trial or up to 7 years <sup>k</sup> after the end of the trial whichever is earlier. <sup>m</sup>	Sponsor may opt to defer this up to the time of MA <sup>i</sup> using this trial or up to 5 years <sup>k</sup> after the end of the trial whichever is earlier. <sup>m</sup>	Sponsor may opt to defer this up to the time when the summary of results is made public usually 12 months <sup>k</sup> after the end of the trial in the EU. <sup>m</sup>
<b>Substantial modifications</b>	At the time of decision <sup>d</sup> on a substantial modification the fact that a substantial modification has occurred and the decision relating to it will be made public. In addition and at the same time changes to previously public information, or changes adding information to data types or documents that are designated for publication at that stage of the trial or earlier, will be made public. Changes or additions to data types or documents not yet made public will be made public when those data or documents (e.g. the protocol) are scheduled for publication. Each version of documents or data changed by the substantial modification will remain visible. Old versions therefore remain public but indicated as superseded and when. If the substantial modification alters information not yet made public then only the fact that a substantial modification has occurred and the decision relating to it will be made public.		
	If the sponsor has opted to defer information until the time of publication of the summary results,		



	information on substantial modifications will also be deferred unless it changes the restricted number of fields made public.		
<b>Requests to sponsor on any aspect of the trial (initial authorisation, substantial modifications or any other notification).</b>	<p>Time of decision on trial or decision on substantial modification<sup>d</sup>, or conclusion on other assessments. The Member State (or RMS (Reporting Member State) in a multistate trial) will decide whether to defer this publication of the assessment report, taking into account the conditions provided in Article 81(4) of Regulation (EU) No.536/2014 and the time point entered by the sponsor for the publication of the protocol or investigator brochure. In order to streamline the process the database will inform the Member State (or RMS for part I, in a multistate trial) of the time(s) for which the sponsor opted for release of the investigator brochure and protocol. If the Member State(s) consider that the assessment report does not fulfil any of the criteria listed in Article 81.4, they will be able to override the deferred publication.</p>		
<b>Assessment reports in relation to any aspect of the trial (initial authorisation, substantial modifications or any other notification).</b>			
<b>Conditions for the conclusion on part I or II or decision on the trial</b>			
<b>Responses from sponsor in relation to any aspect of the trial (initial authorisation, substantial modifications or any other notification).</b>	<p>Time of decision on trial or decision on substantial modification.<sup>d</sup> Sponsor may opt to defer this up to the time of MA<sup>i</sup> using this trial or up to 7 years<sup>k</sup> after the end of the trial whichever is earlier.</p>	<p>Time of decision on trial or decision on substantial modification.<sup>d</sup> Sponsor may opt to defer this up to the time of MA<sup>i</sup> using this trial or up to 5 years<sup>k</sup> after the end of the trial whichever is earlier.</p>	<p>Time of decision on trial or decision on substantial modification.<sup>d</sup> Sponsor may opt to defer up to the time when the summary of results is made public usually 12 months<sup>k</sup> after the end of the trial in the EU.</p>
<b>Conclusion on Part I (acceptable, or acceptable subject to conditions, or not acceptable) including disagreement on the conclusion of the assessment of Part I by a Member State concerned.</b>	Time of decision on trial. <sup>d</sup>		
<b>Conclusion on Part II (acceptable, or acceptable</b>			

<b>subject to conditions, or not acceptable)</b>			
<b>Decision on the trial, or a substantial modification. (authorised, authorised subject to conditions or refused),</b>			
<b>Product specific documents – IMPD Q and all related assessment reports, requests for additional information, and conditions relating to these.</b>	IMPD-Q section will not be made public. If a SmPC is referred to, instead of a IMPD Q section being submitted that reference will be made public.		
<b>Clinical trial results summary for an intermediate data analysis - that should be made public in accordance with article 37(8).</b>	12 months after the intermediate data analysis date where its publication is required in accordance with article 37(8). <sup>n</sup>  Sponsor may opt to defer the publication of the summary of results of an intermediate data analysis (if foreseen) in all or in part up to a maximum of 18 <sup>q</sup> months after the due date (usually 12 months after the end of the trial unless article 37(4) applies) of the final summary of results and layperson summary (in total, a potential maximum of 30 months after the end of the trial) or until the time of MA if the time is earlier. <sup>f,g,h,o</sup>		
<b>Clinical trial results summary and lay person summary</b>	12months after the end of the trial in the EU, unless this is later for scientifically justified reasons in accordance with article 37(4). <sup>p</sup>  Sponsor may opt to defer the publication of the summary of results and layperson summary in all or in part up to a maximum of 18 <sup>q</sup>		

	months after the due date (usually 12 months after the end of the trial unless article 37(4) applies) of the summary of results and layperson summary (in total, a potential maximum of 30 months after the end of the trial) or until the time of MA if the time is earlier. <sup>f,g,h,o</sup>		
<b>Clinical study report</b>	30 days after the marketing authorisation decision (authorisation or refusal of MA application) or 30 days after withdrawal of the application by the applicant. <sup>i</sup>		
<b>Supervisory measures: Serious breaches, inspections (EU and third country), Union Controls, Corrective Measures.</b>	See section 4.5 below for details of timing of publication of these items. The timing of publication is, in essence, the time of conclusion by the Member State(s) (or in the case of Union Controls by the Commission) on the procedure. For inspection reports from third country authorities relating to EU sites and trials, they will be made public at the time they are loaded in the EU database by the sponsor.		
	If the sponsor has requested a deferral of publication of information until the time of publication of the summary of results of the trial the same will apply to the above information with the exception of corrective measures which revoke the authorisation of a clinical trial, suspend a clinical trial or require the sponsor to modify any aspect of the clinical trial.		
<b>Notes on table:</b>			
a. The Member State(s) concerned may decide to make data or documents public at an earlier stage in line with the process referred to in section 4.3.2 if an "overriding public interest in disclosure" prevails in a particular <u>ad hoc</u> situations over and above the general disclosure rules established above for the database.			
b. The main table represents the situation for trials that are authorised. For trials that are refused see c below.			

<p>c. Where a clinical trial authorisation is refused the date of decision on the trial will also be taken for the purposes of application of these rules as the date of the end of the trial. Options for deferral of publication of data or documents appropriate to the trial category, selected by the sponsor, will apply. Where a multistate trial is authorised by at least one Member State and refused in one or more other Member States the information on the trial will still be made public with the exception of the declaration of financial or other interest of the investigator or institution. The justification for refusal by that Member State will also be made public at that time.</p> <p>If the clinical trial is resubmitted the sponsor will be able to reset the deferral of release of this information on the original clinical trial application, to the publication timepoints selected for the resubmitted trial, in order to maintain the protection of commercially confidential information.</p>
<p>d. For trials involving more than one Member State the date of decision, in the first Member State to issue a decision, will be used as the reference date.</p>
<p>e. The fields to be made public, even in the case of a deferral, are:</p> <p>EU Clinical Trial Number, Sponsor name and address, Investigator name and site address, nature of clinical trial (e.g. bioequivalence in 24 healthy volunteers), decision on the trial, date of decision on the trial, date of start of the trial, dates of start and end of recruitment, date of end of the trial in the Member State(s) in the EU, and globally (including early termination of the trial) and the summary CVs, statements of the head of the institution regarding the site and the statement regarding conditions such as economic interests and institutional affiliations that might influence the impartiality of the investigators)</p>
<p>f. This deferral option does not apply to trials including paediatric subjects or trials listed in a Paediatric Investigation Plan.</p>
<p>g. The sponsor will be given three options.</p> <ul style="list-style-type: none"> <li>• Option one the summary of trial results and layperson summary, along with the main characteristics of the trial (if not already public) will be made public as soon as summary of results and layperson summary are submitted to the EU database.</li> <li>• Option two the sponsor enters the full summary of results and layperson summary along with pdf versions of these from which commercially confidential points have been redacted – these redacted documents will be made public once submitted at the due date (usually 12 months after the end of the trial) and the full summary of results, layperson summary and main characteristics of the trial up to a maximum of 18<sup>9</sup> months later as determined by the sponsor (so 30 months in total from the end of the trial). The main characteristics of the trial are reiterated in the summary of results and will therefore be released to the extent they are not redacted at the due date (usually 12 months after the end of the trial), in the pdf documents. The full dataset of the main characteristics will be released at the time the full summary of results is made public.</li> <li>• In the third case the sponsor enters the full summary of results and layperson summary at the due date (usually 12 months after the end of the trial) but the sponsor may opt to defer the publication of the outstanding main characteristics of the trial and the full summary of results and laypersons up to a maximum of 18<sup>9</sup> months later as determined by the sponsor (so 30 months in total from the end of the trial).</li> </ul>
<p>h. The sponsor will be required to provide a justification for their choice of deferral; this will be included in the EU database. The justification submitted will have two parts, one to be made public immediately and the other providing more detail will be made public at the same time as the Investigator brochure for that trial, i.e. up to 7 years after the end of the trial.</p>
<p>i. The term "Time of MA" in this table refers to MAs in the EU via any route of authorisation, and the time means 30 days after the day the marketing</p>

authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant has withdrawn the application, where the specific clinical trial has been used in that specific marketing authorisation dossier (initial MA or variation or line extension). The database will have this information populated by the MA applicant, when they submit the clinical study report for that trial, at the above time, and this event will trigger the database to publish the related clinical trial documents.

j. For trials involving IMPs with a marketing authorisation, when an investigator brochure and IMPD are not required but a simplified IMPD and SPC are used in accordance Annex I, sections E and G of the Regulation. In this case the SPC will be made public at the same time as the IMPs named in the main characteristics at the time until the main characteristics are made public. Other supplementary information is to be made public at the time of publication of the investigator brochure.

k. In all cases where a time period is specified as "up to" 5 or 7 years or the time of publication of results 12 months after the end of the trial the sponsor will be able to insert a shorter time period, but no longer than the period specified in the table above.

l. For category 3 trials an investigator brochure and IMPD are not required but a simplified IMPD and SPC are used in accordance Annex I, sections E and G of the Regulation. These will be made public at the time of decision on the trial along with the supplementary information (e.g. supporting low intervention).

m. The versions of the IMPD S and E sections and/of the investigator brochure present in that clinical trial application dossier at the time of decision on that trial will be made public.

Later versions will be made public at a time after their submission. This time is to correspond to the time interval between the first decision on the trial and publication of the first investigator brochure and IMPD.

n. Where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date.

o. The sponsor must submit the full summary of trial results and layperson summary into the database 12 months after the end of the trial, or later if article 37(4) applies, regardless of any deferral they may opt for.

p. This will be 6 months for trials authorised to include paediatric subjects or trials listed in a PIP (Paediatric Investigation Plan).

q. The 18-month period is derived from the term, set forth in the Patent Cooperation Treaty, within which a patent application submitted to the relevant Receiving Office will not be published for 18 months from the date of filing (or from an earlier priority date, if the submitted patent application claims the priority of an earlier, e.g. national, patent application).

r. In order to enable the correct coding of all IMPs without MA to be recorded in the clinical trial application form as part of the main characteristics of the trial, in SUSARs and elsewhere, the EU substance and EU product number, the product and substance codes assigned by the sponsor, the INN or other name of substance and product name, will be available from the public listings of the Medicinal Product Dictionary of substances and medicinal product.

The Agency will publish detailed data elements and lists of documents that will be included in the EU database, and their public status in the light of the rules described in the present document.

#### **4.4. 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.

#### **4.5. 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. Supervision also includes the Union controls foreseen by Article 79. The receipt, evaluation and follow-up of reports of serious breaches reported in accordance with Article 52, 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 exceptions under Article 81(4)(a),(b) and (d) need to be taken into account in the publication of inspection reports, Union Control reports, serious breach reports and their follow-up and corrective measures.

Reports or documents being loaded into the database and made public should be redacted by the party submitting the document or data to the database. The redaction of the content of the reports prior to being loaded into the system, in order to protect personal data (especially of clinical trial subjects) and commercially confidential information will be part of separate guidance to be developed by the appropriate EU expert group, and will be consistent with that developed for EMA Policy 70 unless the Regulation would permit less redaction on some elements. This guidance is not 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. This guidance will need to address the redaction of the documents referred to in section 4.5.1 to 4.7 below. Some guidance may be document/context specific (e.g. inspection reports or clinical study reports) or more general for all documents.

##### **4.5.1. Inspection reports**

1. Information on the planning of an inspection, its conduct, reporting and follow-up will 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, in which case this will be recorded in the database by that Member State.
3. Where an inspection has been requested as part of the assessment of a marketing authorisation application, the final inspection report will 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),(b) and (d). 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 by the Member State but only the redacted version made public. No identifiable personal data of trial subjects should be publically accessible.
5. Article 53(2) of the Regulation requires that sponsors submit all inspection reports of inspections conducted by third country authorities, concerning the trial through the EU portal, this should include a translation into one of the EU official languages of the report or its summary. These reports will be made public once they have been submitted by the sponsor. They should be redacted by the sponsor in accordance with the exceptions set out under Articles 81(4) (a) and (b).

#### **4.5.2. Union Control reports**

The final report of a Union Control submitted by the European Commission through the portal will 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.

#### **4.5.3. Serious breaches and corrective measures**

1. Serious breaches reported in accordance with Article 52 will 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. Where the same serious breach is reported to several Member States, the publication of the notice will take place alongside the publication of the conclusion of the first Member State to conclude.
  - 1.1. If the Member State concludes that there is no case to answer a notice will be included in the database and published, to the effect that a serious breach report 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 will be published as none will have been substantiated.
  - 1.2. If the Member State concludes that there is a serious breach but is also satisfied with the corrective action taken by the sponsor, then a final notice will be included in the database and published, describing the serious breach, the action undertaken by the sponsor 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 and made public.

- 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 will 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 from which personal data or commercially confidential information is omitted. The detailed data supporting the notified 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 will use the summary provided by the sponsor, as well as a summary of assessment and outcome by the Member State. 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 be publically accessible.

#### ***4.6. Reporting of unexpected events in accordance with Article 53 and urgent safety measures in accordance with Article 54, and temporary halts and early terminations of clinical trials.***

1. A report of an unexpected event made in compliance with Article 53 should be made public once it has been assessed by the Member State, unless one of the supervision measures itemised in section 4.5.3 is taken, in which case it should be made public in line with the measure concerned. Where the several Member States are involved, the publication of the notice will take place alongside the publication of the conclusion of the first Member State to conclude.
2. A report of urgent safety measures made in accordance with Article 54 should be made public once it has been assessed by the Member State.
3. The date of a temporary halt will be made public once it is notified. Where the temporary halt is for reasons of subject safety (Article 38) the reasons will be made public, along with the assessment by the Member State(s), once the Member State(s) has concluded that assessment. In addition the restart of the trial will be made public when the decision has been made on the substantial modification that is submitted to restart the trial, as part of the conclusion on that substantial modification.
4. The early termination of a trial for reasons of subject safety submitted in accordance with Article 38, should be made public at the time of notification of the early termination of the trial. Where the main characteristics of the trial were not yet public these will be made public along with the reasons for the early termination, for safety reasons.
5. Reports of temporary halts or early terminations for reasons not affecting the benefit-risk balance, made in accordance with article 37, will be made public at the time of their notification.
6. The report made public in accordance with Articles 37, 38, 53 and 54 should be redacted, by the sponsor for the parts they provide and by the Member State for the parts they provide, 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 be publically accessible.

#### **4.7. Clinical study reports submitted by the marketing-authorisation applicant**

1. Clinical study reports, as submitted in marketing authorisation applications in the EU, or variation or line extension to these, including all appendices except those listing individual patient data, will be submitted to the database by the marketing authorisation applicant 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 clinical study report should be redacted by the marketing-authorisation applicant before it is submitted to the database (see section 4.5 last paragraph).

#### **4.8. Arrangements for payment of investigators and sites**

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.

# ANNEX I: details of documents supporting clinical trial applications and the rationale for the times at which they are made public.

## 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 information on the IMP, its mode of action and its testing 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 may 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 disclosure rules.

Category 1 trials (pharmaceutical development): the commercial confidentiality of the protocol details are particularly acute for these are the first trials conducted with new medicines or new pharmaceutical forms or routes of administration of existing medicines. There is limited public interest in having access to the protocol and the availability of the structured registration data and summary results data are sufficient to provide information for general reference whilst enabling sponsor to retain confidentiality of details of the first development steps, including new pharmaceutical forms or routes of administration of existing medicines, as well as generic or biosimilar medicines. The economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by making the protocol public up to a maximum 7 years after the end of the trial where the sponsor needs to protect commercially confidential information.

Category 2 trials (therapeutic exploratory and confirmatory clinical trials): the economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by making the protocol public up to a maximum 5 years after the end of the trial where the sponsor needs to protect commercially confidential information. The more confidential details of the IMPs and their development can be addressed in the Investigator Brochure and IMPD.

Category 3 trials (therapeutic use clinical trials): for these trials the economic interest of sponsors is confined to the possible novelty of their trial design and hypothesis. The protocol would not normally be considered to be commercially confidential and the public interest is of overriding importance as the IMPs are in routine use in medical practice. If nonetheless the sponsor considers that the publication of the protocol should be deferred until the time of publication of the summary results of the trial, in order to protect commercially confidential information, this should be requested and a rationale provided. The rationale for the request will be published at the time of decision on the trial and the protocol at the time of publication of the summary results, in line with footnote k of table 1.

**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, pharmaceutical forms and routes of administration of a product already on the market.

- Category 1 trials (pharmaceutical development): the commercial confidentiality of the study details in the subject information sheet are particularly acute for these are the first trials conducted with new medicines or new pharmaceutical forms or routes of administration of existing medicines. There is limited public interest in having access to this information available publicly at that time and the availability of the structured registration data and summary results data are sufficient to provide information for general reference whilst enabling sponsor to retain confidentiality of details of their first development steps, including new pharmaceutical forms or routes of administration of existing medicines, as well as generic or bio-similar medicines. The economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by making the protocol public up to a maximum 7 years after the end of the trial where the sponsor needs to protect commercially confidential information.
- Category 2 trials (therapeutic exploratory and confirmatory clinical trials): the economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by providing the subject information up to a maximum 5 years after the end of the trial where the sponsor needs to protect commercially confidential information.
- Category 3 trials (therapeutic use clinical trials): for these trials the economic interest of sponsors is confined to the possible novelty of their trial design and hypothesis. The subject information sheet is not considered to be commercially confidential and the public interest is of overriding importance as the IMPs are in routine use in medical practice. The subject information sheet is therefore made public for category 3 trials at the time of decision on the trial.

**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 brochures 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, pharmaceutical forms and routes of administration of a product already on the market.

Category 1 (pharmaceutical development): the economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by maintaining the confidentiality of the investigator brochure until the time of marketing authorisation in which that clinical trial is first used, or 7 years after the end of the trial, whichever comes earlier.

- Category 2 trials(therapeutic exploratory and confirmatory clinical trials): the economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by maintaining the confidentiality of the Investigator Brochure until the time of marketing authorisation in which that clinical trial is first used, for up to 5 years after the end of the trial, whichever comes earlier. Category 2 trials involving IMPs with a marketing authorisation an investigator brochure may not be required but a simplified IMPD and SPC are used in accordance Annex I, section E of the Regulation. In this case the SPC will be made public at the time of decision on the trial, and other supplementary data at the time of publication of the summary results.
- Category 3 clinical trials (therapeutic use clinical trials): for category 3 trials an investigator brochure is not required but a SPC are used in accordance Annex I, section E of the Regulation. These will be made public at the time of decision on the trial.

**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 the indications, pharmaceutical forms and routes of administration 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 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 the indications, pharmaceutical forms and routes of administration of a product already on the market, and the IMPD-Q section will always have extensive commercially confidential information.

- Category 1 (pharmaceutical development) the economic interests of the sponsor including preparation for publication or furtherance of development plans are given protection by maintaining the confidentiality of IMPD S and E sections until the time of marketing authorisation in which that clinical trial is first used, for up to 7 years after the end of the trial, whichever comes earlier. For category 2 trials involving IMPs with a marketing authorisation an investigator brochure may not be required but a simplified IMPD and SPC are used in accordance Annex I, section E of the Regulation. In this case the SPC will be made public at the time of decision on the trial, and other supplementary data at the time of publication of the summary results.
- Category 2 trials (therapeutic exploratory and confirmatory clinical trials): the economic interests of the sponsor including preparation for publication or furtherance of development plans are given

protection by maintaining the confidentiality of IMPD S and E sections until the time of marketing authorisation in which that clinical trial is first used, for up to 5 years after the end of the trial, whichever comes earlier. For category 2 trials involving IMPs with a marketing authorisation an investigator brochure may not be required but a simplified IMPD and SPC are used in accordance Annex I, section E of the Regulation. In this case the SPC will be made public at the time of decision on the trial, and other supplementary data at the time of publication of the summary results.

- Category 3 clinical trials (therapeutic use clinical trials): for category 3 trials an IMPD is not required but a SPC are used in accordance Annex I, section E of the Regulation. These will be made public at the time of decision on the trial.

Regardless of the category of the trial or marketing authorisation status of the IMP, the IMPD-Q section on IMP quality and the related requests for additional information, responses and assessment report sections should be considered to be commercially confidential and not be made public for any trial at any time, as these deal with the manufacturing and related pharmaceutical development information which continues to be CCI, post marketing authorisation.

**List of questions, responses and Assessment Reports:** Assessment reports contain a detailed analysis and critique of the information in the protocol, subject information sheet, investigator brochure and IMPD 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 the protocol, subject information sheet, investigator brochure and IMPD may 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, pharmaceutical forms and routes of administration of a product already on the market.

The Member State (or RMS (Reporting Member State) in a multistate trial) will decide whether to defer this publication of the assessment report lists of questions and evaluation of responses to these, taking into account the conditions provided in Article 81(4) of Regulation (EU) No.536/2014 and the time point entered by the sponsor for the publication of the protocol or investigator brochure.