EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Publication and access to clinical-trial data

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1. Introduction and purpose

The aim of the European Medicines Agency ('the Agency') is to protect and foster public health. Transparency is a key consideration for the Agency in delivering its service to patients and society.

There is growing demand from external stakeholders for full transparency, not only about the Agency's deliberations and actions, but also about the data and results from clinical trials (CTs) on which regulatory decisions are based. Following consultations with a broad range of external stakeholders and European bodies, including the European Ombudsman and the European Data Protection Supervisor, the Agency has drafted this policy, which complements the existing 'Policy on access to documents (related to medicinal products for human and veterinary use)' (POLICY/0043) (EMA/110196/2006), which came into effect in December 2010. To ensure consistency, the existing policy on access to documents and this policy on publication and access to clinical-trial data, once finalised, will be aligned.

Allowing external parties access to CT data held by the Agency will directly or indirectly affect different stakeholders' rights, interests and values. In addressing many competing objectives, the Agency takes the following views and positions, which inform the policy:

Enabling public scrutiny and secondary analysis of CTs: Access to CT data in an analysable format will benefit public health in future. It will make drug development more efficient by establishing a level playing field that allows all drug developers to learn from past successes and failures, and it will enable the wider scientific community to make use of detailed and high-quality CT data to develop new knowledge in the interest of public health. The Agency also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines. Independent replication of CT data analysis is a legitimate

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scientific and societal goal. Access to CT data will enable third parties to verify the regulatory authority's positions and challenge them where appropriate.

Protection of personal data (PPD): PPD is enshrined in EU legislation; it is a fundamental right of EU citizens. The policy has to ensure adequate PPD; it must be fully compliant with applicable regulations in the EU, in particular Regulation (EC) No 45/2001 and Directive 95/46/EC. There are established ways and means to anonymise data and protect patients from retroactive identification. Yet, the Agency is concerned that emerging technologies for data mining and database linkage will increase the potential for unlawful retroactive patient identification. The Agency therefore takes a guarded approach to the sharing of patient-level data. This is done to enable the legitimate learnings from the sharing of patient-level data while preventing rare but potentially damaging instances of patient identification.

Respect for the boundaries of patients' informed consent: Patients participate in clinical drug trials in the hope that their data will support the development and assessment of a particular medicine that is useful for the treatment of their disease, and will benefit the advancement of science and public health. The Agency takes the view that any other use of patient data oversteps the boundaries of patients' informed consent, and shall not be enabled by the policy.

Protection of commercially confidential information (CCI): The Agency respects and will not divulge commercially confidential data or information. In general, however, CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI.

Ensuring future investment in bio-pharmaceutical research and development (R&D): A sustained and high level of bio-pharmaceutical research activity is a precondition for future improvements in public health. The policy has no intentions to negatively impact on the incentives to invest in future bio-pharmaceutical R&D; it is designed to guard against unintended consequences, e.g. breaches of intellectual property rights that might disincentivise future investment in R&D.

Addressing the consequences of inappropriate secondary data analysis: The Agency cannot guarantee that all secondary data analyses that are enabled by the policy will be conducted and reported to the highest possible scientific standard; this is not possible with a truly open approach. However, the Agency will put in place measures to ensure the best-possible protection of public health (and regulatory decisions) against claims resulting from inappropriate analyses.

Protecting the Agency's and the European Commission's deliberations and decision-making process: Regulators have a legal mandate to evaluate medicines. In doing so, they should only focus on the science and the best interests of patients. The decision-making process should be protected against external pressures in whatever direction. Once a decision has been reached, this consideration no longer applies.

Ensuring that transparency is a two-way street: The Agency takes the view that those who make secondary use of patient-level CT data shall be held to the same standard of transparency as those who generate CT data in the first place; hence, all secondary analyses shall also be in the public domain and accessible for further scrutiny by the scientific community. However, those who conduct secondary analysis should also be allowed a reasonable period of time during which their analyses and deliberations are protected against external interventions.

These competing objectives needed to be balanced against each other when developing the policy. The Agency is aware that not all stakeholders can be fully satisfied; it has aimed at striking a compromise that it deems will best ensure the overarching, long-term goal of protecting and fostering public health.

2. Scope

The policy is prospective in that it concerns only those CT data that will be submitted to the Agency after the policy comes into effect as outlined below. All other CT data currently held by the Agency (e.g. those on products already on the market) or pre-existing CT data of marketed products that will be submitted to the Agency, e.g. in the context of a referral procedure ('legacy data'), continue to be made available to external requesters on a 'reactive' basis as outlined in the Agency's current policy on access to documents.

Data from CTs that are not held by the Agency are outside the scope of this policy, even if they concern a medicinal product that has been authorised by the Agency (e.g. CTs on an authorised product conducted by independent investigators and not submitted to the Agency).

Pharmacovigilance data based on Individual Case Safety Reports (ICSRs) are also outside the scope of the policy. Access by third parties to ICSR data is addressed in the Agency's 'EudraVigilance access policy for medicines for human use' (EMA/759287/2009 corr.).

3. Definitions

Clinical-trial (CT) data: In the context of the policy, 'CT data' refers to the entirety of data and information listed in Annex I (according to ICH M4E (R1)) and Annex II (according to ICH E3). These data and information elements are customarily submitted by sponsors in an 'ICH-compatible' format in the Common Technical Document (CTD)[1], and included in CTD Modules 2.5 (Clinical Overview), 2.7 (Clinical Summaries) and 5 (Clinical Study Reports). In the context of the policy, the term 'CT data' is not limited to conventional randomised controlled trials (RCTs), but is meant to include other types of interventional or observational clinical research methodologies, such as large simple trials, cohort studies, case control studies, or registry data. Reports form such studies may sometimes differ from the CTD format. In such cases, the Agency shall ensure that *proactive publication of clinical-trial data* shall follow the same general principles as described for RCT data (see below, and Annexes I and II). Aside from overviews, summaries and study reports, CT data include the 'raw data' containing patient-level data.

Personal data (PD): shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity (Article 2(a) of Regulation (EC) No 45/2001). Personal data in the context of the policy mainly fall into the following categories:

A. Personal data related to patients/subjects enrolled in a CT.

B. Other personal data, including those from e.g. experts or designated personnel involved in CTs.

Commercially confidential information (CCI): For the purpose of the policy, CCI shall mean any information that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the owner of the information. CCI falls broadly into two categories: trade secrets (including formulas, programs, process or information contained or embodied in a product, etc.) and commercial confidences. It is emphasised that categorisation of information as CCI in the policy does not limit access to documents or information under other Agency policies, e.g. access to documents or other transparency initiatives (e.g. paediatric information).

[1] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4__R1__Efficacy/M4E__R1_.pdf

Clinical Study Report (CSR): designates the entirety of elements submitted as study reports in CTD Module 5, following the format of the ICH E3 document (see Annex II).

Raw CT data: For the purpose of the policy, raw CT data shall mean individual patient data sets, individual patient line-listings, individual Case Report Forms (CRFs), and documentation explaining the structure and content of data sets (e.g. annotated CRF, variable definitions, data-derivation specifications, data-set definition file). It also includes supporting documents, such as test outputs (if not contained in the statistical analysis plan (SAP)), Statistical Analysis Software logs and SAS statistical programs (if code not included in the SAP).

4. Policy statement

4.1. Categories of CT data

The following categories of CT data are defined; the categories determine the level of proactive publication.

4.1.1. Category 1

CT data/documents containing CCI: a small number of CT data/documents can contain CCI. This applies to information such as details of the investigational medicinal product itself, some in vitro studies, or bioanalytical data characterising the product (points 2.7.1, 5.3.1 and 5.3.2 of Annex I). However, this information will only be deemed CCI in duly justified cases.

If a document is deemed to contain CCI, it will not be made available under the policy (designated 'CCI' in Annexes I and II). Such documents could still be requested under the Agency's policy on access to documents, which encompasses Regulation (EC) No 1049/2001, but different procedures and guarantees will apply.

CT data/documents that are not categorised as 'CCI' in Annex I are considered to contain no CCI.

4.1.2. Category 2

CT data/documents *without protection of personal data (PPD) concerns*: all documents where PPD is not an issue for concern. The lack of concern for PPD may result from the fact that:

- the document does not contain personal data in the first place (e.g. summary tables presenting only aggregated data), or;
- any personal data in the document have been adequately de-identified, or;
- there are public-health reasons why personal data can be made public, overriding considerations of PPD (Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data; and Regulation (EC) 45/2001on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data). This is the case with personal data of CT personnel.

All CT data/documents without PPD concerns are 'open access' (designated 'O' in Annexes I and II); such data will be available as downloads from the Agency's website, at the time of publication of the European Public Assessment Report (EPAR) for positive decisions, negative decisions or withdrawals (or 30 days following withdrawal, in case no withdrawal EPAR is published).

4.1.3. Category 3

CT data/documents with PPD concerns: all documents, data and information contained in a Clinical Study Report (see Annex II) that do not fall under Category 2. These are essentially 'raw CT data' (see definition above).

Protection of patient privacy is a paramount concern when sharing raw CT data. The goals of transparency and PPD have to be carefully balanced against each other, and proactive publication (as is foreseen for Category 2 documents) is not an option.

Therefore, all CT data with PPD concerns are 'controlled access' (designated 'C' in Annex II).

Two complementing levels of protection are foreseen to provide best-possible assurance against retroactive patient identification.

1. Appropriate de-identification:

Adequately de-identified data can be valuable, and de-identifying the data does not necessarily compromise the analytical utility of the data.

The data to be made available may include all the data sets or a relevant subset (e.g. the main analysis set, containing a limited number of indirect identifiers, so that the risk of compromising subjects' identity in case of wide publication of those data is considered to be absent or sufficiently low, while preserving the ability to replicate the main analysis).

A recommended minimum standard for de-identifying data is described in Hrynaszkiewicz[2]. In some situations, this minimum standard may need to be supplemented by additional de-identification methods (e.g. statistical). The methods of de-identification should be such that adherence will preclude subject de-identification, even when applying linkages with other data carriers (e.g. social media).

2. Controlled access:

'Controlled access' shall mean that access to 'C' data will only be granted after the requester has fulfilled the following requirements:

- requester has identified themselves, and the Agency has verified the identity of the requester;
- requester, whether a natural or legal person, is established in the EU;
- requester has agreed, by way of legally binding data-sharing agreement, to:
  - access controlled data for the sole purpose of addressing a question or conducting analyses that are in the interest of public health, in line with the spirit of informed consent; this may include, inter-alia, meta-analyses, re-analysis, or exploratory analyses for additional hypothesis generation. An exhaustive and detailed list of the aims of accessing the data shall be submitted at the time of the request (though not necessarily a statistical analysis plan; see below),
  - refrain from any attempt to retroactively identify patients in CTs; this includes linkage of CT data accessed with other databases or programs that could result in the identification of patients,
  - refrain from using CT data accessed for any purposes that are deemed outside the boundaries of patients' informed consent,

[2] Hrynaszkiewicz, I., M. L. Norton, et al. (2010). 'Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers.' BMJ 340: c181.

- refrain from using CT data accessed to gain a marketing authorisation in a non-EU jurisdiction,
- not share, in any way or format, CT data accessed from the Agency with anyone else; where research groups wish to collectively access a data set, the names of all members of the group shall be communicated to the Agency, and all members will have to individually commit themselves to the conditions for access,
- have obtained ethics-committee approval, as appropriate,
- be aware of standards for good analysis practice; a document describing the Agency's views on good analysis practice will be made available to the requester; this is for information only,
- agree to the Agency publishing their identity, aim(s) of accessing the data, and (statistical) analysis-plan status (see below),
- make all results of their analyses public within a reasonable period of time; a 'reasonable period' would normally be considered to be one year after accessing the data,
- destroy CT data accessed, once the analysis is completed.

Before access to 'C' data is granted, the requester will be:

- made aware of a document on CT data-analysis standards; in the document, the Agency will communicate its own expectations relating to good analysis and transparency; requesters are advised to read the document, but there are no legal obligations resulting from this document;
- given the opportunity to upload a (statistical) analysis plan (and/or other relevant documents); the Agency considers preparation and uploading of a detailed protocol/statistical analysis plan before data access of utmost importance, to ensure the credibility of subsequent results; availability of an analysis plan will influence the Agency's interpretation of any subsequent reported results; however, the requester may decline to upload any documents at that time; the granting of access to 'C' documents is not influenced by the requester's choice to upload or not.

The Agency will NOT, at the time of allowing access to 'C' data:

- judge the requester's professional competence to conduct analyses;
- judge the requester's (statistical) analysis plan (if uploaded; see above).

'C' documents will be made available at the time of publication of the EPAR for positive decisions, negative decisions or withdrawals (or 30 days following withdrawal in case no withdrawal EPAR is published).

The Agency will not immediately disclose any information about the requester, but will publish the identity (name, affiliation and contact details provided), the list of the aims of accessing the data provided, and any uploaded documents (statistical analysis plan and/or others), or the requester's decision to decline to upload documents (as applicable):

- one year after the date of accessing the data, or;
- upon publication, in whatever format or medium, of results, conclusions, or other communications that resulted from the requester accessing 'C' data, or;
- in case of an urgent public-health need, or;
- upon court order,

whichever comes first.

For a detailed list of the elements of ICH Module 2 or Module 5 or individual CSRs that are considered 'O', 'C', or 'CCI', please refer to Annexes I and II.

4.2. Data standards

All documents listed in Annexes 1 and 2 — whether categorised 'O' or 'C' — shall be provided in portable document format (PDF), and should be fully searchable.

Section 5.2 of Module 5: for each product shall be published a full cumulative list of clinical trials, including a unique study identifier and basic information about each study (e.g. study title, interventions and indications). In addition to the study number provided by the applicant, relevant unique study identifiers shall be included in the list, e.g. EudraCT number, US NIH clinicaltrials.gov registry number and ISRCTN registry number.

Wherever technically possible, analysable, de-identified raw CT data shall be made available for downloading in the format in which they have been analysed by the applicant, submitted and evaluated. For the time being, this can be according to CDISC (Clinical Data Interchange Standards Consortium) or other appropriate standard. In future, CDISC shall be the required standard, in line with future guidance from the Agency. No conversion of formats is recommended, either by the marketing-authorisation holder or the Agency.

4.3. Date of coming into effect

The policy comes into effect on 1 January 2014.

Marketing-authorisation holders or sponsors applying for centralised marketing authorisation or for variation of a centralised marketing authorisation are advised that any CT data (or, for variations, CT data not previously submitted to the Agency) submitted to the Agency on or after 1 March 2014, and designated 'O' in Annexes I and II, shall be subject to the policy. Marketing-authorisation holders/applicants shall provide the Agency with an additional set of 'O' documents that are appropriately de-identified to ensure protection of personal data, as per Annexes I and II.

The Agency is committed to making 'C' data available as early as is practical. However, in light of the paramount importance of ensuring patient confidentiality, preparatory steps are required to put in place appropriate standards, rules and procedures for de-identification. The Agency will work with sponsors and other concerned parties towards this goal, and expects to publish a guidance document no later than 31 October 2014, with a view to making available all 'C' data submitted by sponsors on or after 1 January 2015.

5. Related documents

European Medicines Agency policy on access to documents POLICY/0043 (EMA/110196/2006).

6. Changes since last revision

Not applicable, new policy.

The impact of the policy shall be assessed and the policy revised as appropriate not later than 18 months after coming into effect.

London, <DD Month YYYY>

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Annexes

Abbreviations used in Annexes I and II

O: Open access.

C: Controlled access.

CCI: May contain commercially confidential information.

Footnotes used in Annexes I and II

1. Particular care should be taken by the sponsor to ensure that no personal data are included in this section. Key codes, dates of birth and any other indirect identifiers shall not be included unless adequately de-identified (e.g. date of birth transformed to age group), particularly if many indirect identifiers appear jointly for the same individual.
2. Please refer to Annex II for categorisation of individual elements of CSRs.
3. Controlled, because some material may be copyright protected; publication on the Agency's website may infringe copyright. Note that the reference list is openly available.
4. This section contains personal data, such as the list of investigators; individual investigators' names, addresses, appointments, qualifications and clinical duties; similar information of other persons carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist or house staff physician; the author(s) of the report, including the responsible biostatistician(s). The Agency takes the view that these persons have a role and responsibility for public health in ensuring the integrity of trial data and protecting patients' welfare. In light of the overriding public interest, these personal data are considered exempt from PPD considerations.

294 # Annex I

Detailed list of the elements relating to clinical trials and contained in 'The common technical document for the registration of pharmaceuticals for human use' (from ICH harmonised tripartite guideline, Modules 2 and 5)	Access
2.5 CLINICAL OVERVIEW	O
Preamble	O
Table of Contents	O
Detailed Discussion of Content of the Clinical Overview Sections	O
2.5.1 Product Development Rationale	O
2.5.2 Overview of Biopharmaceutics	O
2.5.3 Overview of Clinical Pharmacology	O
2.5.4 Overview of Efficacy	O
2.5.5 Overview of Safety	O
2.5.6 Benefits and Risks Conclusions	O
2.5.7 Literature References	O
2.7 CLINICAL SUMMARY	O
Preamble	O
Table of Contents	O
Detailed Guidance on Sections of the Clinical Summary	O
2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods	CCI
2.7.1.1 Background and Overview	CCI
2.7.1.2 Summary of Results of Individual Studies	CCI
2.7.1.3 Comparison and Analyses of Results Across Studies	CCI
2.7.1.4 Appendix	CCI
2.7.2 Summary of Clinical Pharmacology Studies	O
2.7.2.1 Background and Overview	O
2.7.2.2 Summary of Results of Individual Studies	O
2.7.2.3 Comparison and Analyses of Results Across Studies	O
2.7.2.4 Special Studies	O
2.7.2.5 Appendix	O
2.7.3 Summary of Clinical Efficacy	O
2.7.3.1 Background and Overview of Clinical Efficacy	O
2.7.3.2 Summary of Results of Individual Studies	O
2.7.3.3 Comparison and Analyses of Results Across Studies	O
2.7.3.3.1 Study Populations	O
2.7.3.3.2 Comparison of Efficacy Results of all Studies	O
2.7.3.3.3 Comparison of Results in Sub-populations	O
2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations	O
2.7.3.5 Persistence of Efficacy and/or Tolerance Effects	O
2.7.3.6 Appendix	O
2.7.4 Summary of Clinical Safety	O

Detailed list of the elements relating to clinical trials and contained in 'The common technical document for the registration of pharmaceuticals for human use' (from ICH harmonised tripartite guideline, Modules 2 and 5)	**Access**
2.7.4.1 Exposure to the Drug	O
2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies	O
2.7.4.1.2 Overall Extent of Exposure	O
2.7.4.1.3 Demographic and Other Characteristics of Study Population	O
2.7.4.2 Adverse Events	O
2.7.4.2.1 Analysis of Adverse Events	O, 1
2.7.4.2.2 Narratives	O, 1
2.7.4.3 Clinical Laboratory Evaluations	O, 1
2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety	O
2.7.4.5 Safety in Special Groups and Situations	O
2.7.4.5.1 Intrinsic Factors	O
2.7.4.5.2 Extrinsic Factors	O
2.7.4.5.3 Drug Interactions	O
2.7.4.5.4 Use in Pregnancy and Lactation	O
2.7.4.5.5 Overdose	O
2.7.4.5.6 Drug Abuse	O
2.7.4.5.7 Withdrawal and Rebound	O
2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability	O
2.7.4.6 Post-marketing Data	O, 1
2.7.4.7 Appendix	O, 1
2.7.5 Literature References	O
2.7.6 Synopses of Individual Studies	O
MODULE 5 CLINICAL STUDY REPORTS	2
Preamble	O
Detailed Organisation of Clinical Study Reports and Related Information in Module 5	O
5.1 Table of Contents of Module 5	O
5.2 Tabular Listing of All Clinical Studies	O
5.3 Clinical Study Reports	2
5.3.1 Reports of Biopharmaceutic Studies	CCI
5.3.1.1 Bioavailability (BA) Study Reports	CCI
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	CCI
5.3.1.3 In Vitro – In Vivo Correlation Study Reports	CCI
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	CCI
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials	CCI
5.3.2.1 Plasma Protein Binding Study Reports	CCI
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	CCI
5.3.2.3 Reports of Studies Using Other Human Biomaterials	CCI

Detailed list of the elements relating to clinical trials and contained in 'The common technical document for the registration of pharmaceuticals for human use' (from ICH harmonised tripartite guideline, Modules 2 and 5)	Access
5.3.3 Reports of Human Pharmacokinetic (PK) Studies	O
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	O
5.3.3.2 Patient PK and Initial Tolerability Study Reports	O
5.3.3.3 Intrinsic Factor PK Study Reports	O
5.3.3.4 Extrinsic Factor PK Study Reports	O
5.3.3.5 Population PK Study Reports	O
5.3.4 Reports of Human Pharmacodynamic (PD) Studies	O
5.3.4.1 Healthy Subject PD and PK/PD Study Reports	O
5.3.4.2 Patient PD and PK/PD Study Reports	O
5.3.5 Reports of Efficacy and Safety Studies	O
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	O
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	O
5.3.5.3 Reports of Analyses of Data from More than One Study	O
5.3.5.4 Other Study Reports	O
5.3.6 Reports of Post-Marketing Experience	O
5.3.7 Case Report Forms and Individual Patient Listings	2
5.4 Literature References	C, 3

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297 # Annex II

Structure and content of clinical study reports (CSRs) (From ICH harmonised tripartite guideline, E3)	**Access**
1. TITLE PAGE	O
2. SYNOPSIS	O
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT	O
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	O
5. ETHICS	O
5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)	O
5.2 ETHICAL CONDUCT OF THE STUDY	O
5.3 PATIENT INFORMATION AND CONSENT	O
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	O, 4
7. INTRODUCTION	O
8. STUDY OBJECTIVES	O
9. INVESTIGATIONAL PLAN	O
9.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION	O
9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS	O
9.3 SELECTION OF STUDY POPULATION	O
9.3.1 Inclusion Criteria	O
9.3.2 Exclusion Criteria	O
9.3.3 Removal of Patients from Therapy or Assessment	O
9.4 TREATMENTS	O
9.4.1 Treatments Administered	O
9.4.2 Identity of Investigational Product(s)	O
9.4.3 Method of Assigning Patients to Treatment Groups	O
9.4.4 Selection of Doses in the Study	O
9.4.5 Selection and Timing of Dose for each Patient	O
9.4.6 Blinding	O
9.4.7 Prior and Concomitant Therapy	O
9.4.8 Treatment Compliance	O
9.5 EFFICACY AND SAFETY VARIABLES	O
9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart	O
9.5.2 Appropriateness of Measurements	O
9.5.3 Primary Efficacy Variable(s)	O
9.5.4 Drug Concentration Measurements	O
9.6 DATA QUALITY ASSURANCE	O
9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE	O
9.7.1 Statistical and Analytical Plans	O
9.7.2 Determination of Sample Size	O

Structure and content of clinical study reports (CSRs) (From ICH harmonised tripartite guideline, E3)	**Access**
9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES	O
10. STUDY PATIENTS	O
10.1 DISPOSITION OF PATIENTS	O
10.2 PROTOCOL DEVIATIONS	O
11. EFFICACY EVALUATION	O
11.1 DATA SETS ANALYSED	O
11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS	O
11.3 MEASUREMENTS OF TREATMENT COMPLIANCE	O
11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA	O
11.4.1 Analysis of Efficacy	O
11.4.2 Statistical/Analytical Issues	O
11.4.2.1 Adjustments for Covariates	O
11.4.2.2 Handling of Dropouts or Missing Data	O
11.4.2.3 Interim Analyses and Data Monitoring	O
11.4.2.4 Multicentre Studies	O
11.4.2.5 Multiple Comparison/Multiplicity	O
11.4.2.6 Use of an "Efficacy Subset" of Patients	O, 1
11.4.2.7 Active-Control Studies Intended to Show Equivalence	O
11.4.2.8 Examination of Subgroups	O
11.4.3 Tabulation of Individual Response Data	O
11.4.4 Drug Dose, Drug Concentration, and Relationships to Response	O
11.4.5 Drug-Drug and Drug-Disease Interactions	O
11.4.6 By-Patient Displays	O
11.4.7 Efficacy Conclusions	O
12. SAFETY EVALUATION	O
12.1 EXTENT OF EXPOSURE	O
12.2 ADVERSE EVENTS (AES)	O
12.2.1 Brief Summary of Adverse Events	O
12.2.2 Display of Adverse Events	O
12.2.3 Analysis of Adverse Events	O
12.2.4 Listing of Adverse Events by Patient	O, 1
12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS	O
12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events	O, 1
12.3.1.1 Deaths	O, 1
12.3.1.2 Other Serious Adverse Events	O, 1
12.3.1.3 Other Significant Adverse Events	O, 1
12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events	O, 1
12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events	O, 1

Structure and content of clinical study reports (CSRs) (From ICH harmonised tripartite guideline, E3)	**Access**
12.4 CLINICAL LABORATORY EVALUATION	O
12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)	O, 1
12.4.2 Evaluation of Each Laboratory Parameter	O
12.4.2.1 Laboratory Values Over Time	O
12.4.2.2 Individual Patient Changes	O, 1
12.4.2.3 Individual Clinically Significant Abnormalities	O, 1
12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY	O, 1
12.6 SAFETY CONCLUSIONS	O
13. DISCUSSION AND OVERALL CONCLUSIONS	O
14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT	O
14.1 DEMOGRAPHIC DATA	O
14.2 EFFICACY DATA	O
14.3 SAFETY DATA	O
14.3.1 Displays of Adverse Events	O
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	O, 1
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	O, 1
14.3.4 Abnormal Laboratory Value Listing (Each Patient)	O, 1
15. REFERENCE LIST	O
16. APPENDICES	O
16.1 STUDY INFORMATION	O
16.1.1 Protocol and protocol amendments	O
16.1.2 Sample case report form (unique pages only)	O
16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms	O
16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	O, 4
16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	O
16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used	O
16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)	O
16.1.8 Audit certificates (if available) (see Annex IVa and IVb of the guideline)	O
16.1.9 Documentation of statistical methods	O

Structure and content of clinical study reports (CSRs) (From ICH harmonised tripartite guideline, E3)	**Access**
16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used	O
16.1.11 Publications based on the study	C, 3
16.1.12 Important publications referenced in the report	C, 3
16.2 PATIENT DATA LISTINGS	C
16.2.1 Discontinued patients	C
16.2.2 Protocol deviations	C
16.2.3 Patients excluded from the efficacy analysis	C
16.2.4 Demographic data	C
16.2.5 Compliance and/or drug concentration data (if available)	C
16.2.6 Individual efficacy response data	C
16.2.7 Adverse event listings (each patient)	C
16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities	C
16.3 CASE REPORT FORMS	C
16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE	C
16.3.2 Other CRFs submitted	C
16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)	C
ANNEX I Synopsis (Example)	O
ANNEX II Principal or Coordinating Investigator(s) Signature(s) or Sponsor's Responsible Medical Officer (Example)	O
ANNEX IIIa Study Design and Schedule of Assessments (Example)	O
ANNEX IIIb Study Design and Schedule of Assessments (Example)	O
ANNEX IVa Disposition of Patients (Example)	O
ANNEX IVb Disposition of Patients (Example)	O
ANNEX V Listing of Patients Who Discontinued Therapy (Example)	C
ANNEX VI Listing of Patients and Observations Excluded from Efficacy Analysis	C
ANNEX VII Number of Patients Excluded from Efficacy Analysis (Example)	O
ANNEX VIII Guidance for Section 11.4.2 – Statistical/Analytical Issues and Appendix 16.1.9	O

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