EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30th September 2010

Submission of comments on Draft Implementing Technical Guidance – List of fields for result-related information to be submitted to the EudraCT clinical trials database, and to be made public.

Comments from:

Name of organisation or individual
AstraZeneca

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone ☐44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-m☐il info@em☐.☐uropa.eu **Web☐ite** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We share and support the comments put forward by EFPIA in relation to (i) whether this guidance is the correct interpretation of primary legislation; and (ii) the timing of disclosure of results from unapproved medicinal products and potential impact to sponsors to protect our legitimate business interests, seek patent protection for our inventions and conduct clinical research in the EEA. We also support the comments put forward by EFPIA to ensure harmonisation with the data requirements for clinicaltrials.gov. A stated objective of this guidance is to provide coherence with other public databases to ensure that sponsors do not have to provide different versions of results for any given trial. Many of the following comments address this - format, content, process, terminology and timelines – to highlight where further coherence is needed if the objective is to be realised.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Implementing Technical Guidance			
Section 2: Modalities of submission and processing of results related data fields. Submission		**Comment:** In line with the EC detailed guidance covering declaration of the end of the trial, clarification should be provided to indicate that results-related data need only be submitted to the EMA via the web interface and that it is no longer necessary for Sponsors to submit a Clinical Trial Summary report as part of the end-of-trial declaration made to all national competent authorities and Ethics committees. In addition the implementing technical guidance should clearly state to whom results-related data for Phase I clinical trials conducted in adults should be provided.	
Section 2: Modalities of submission and processing of results related data fields. Submission		**Comment:** Need clarification on user access so that there is an ability to create a company account consisting of multiple users, all of whom can view all the records/trials on the user interface side. It is not clear whether the "Annex 1" referenced is the same as the Annex 1 currently used for the Initial Application CTA created in the EudraCT web interface form (XML), or, if there are actually 2 different forms/Annex 1's. If there are 2 different forms, propose that the CT results Annex/form be given a different number than the one used for the IA e.g., "Annex 4" (as Annex 1 is for IA, Annex 2 is for SA and Annex 3 is for the GEOT). If the form is one and the same, then this makes the process	

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		over complicated as it will require the Sponsor to go back into the EudraCT system to upload the original/latest version of the Annex 1 .xml file, + update same to record the results.	
Section 2: Modalities of submission and processing of results related data fields. Processing		**Comment:** There should be a means whereby amending the results related data amends previously entered protocol-related data. For example, where the 'Variable title, 'Variable time frame' for the primary and/or secondary endpoints are listed differently in the results section. This could imply that a sponsor does not actively manage the data, or worse, that a sponsor is trying to 'manipulate' the results.	
Section 2: Modalities of submission and processing of results related data fields. Processing		**Comment:** There is no formal content review analogous to the clinicaltrials.gov review. There needs to be more detail on the validation process and definition of a 'valid data set'. It is proposed that the validation is similar to the ClinicalTrials.gov process, i.e., a member of a Quality Assurance team, with clear description of how the EMA will provide comment, seek clarification to the submitted data and define the fixed timeframe in which EMA respond to submitted results.	
Section 2: Modalities of submission and processing of		**Comment:** So that sponsors can appreciate the end-to-end process, what activities take place during the 5 working days after sponsor submission? Please clarify if this 5 working days from sponsor submission or from final EMA	

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results related data fields. Timing		acceptance/approval?	
Section 2: Modalities of submission and processing of results related data fields. Language		**Comment:** There needs to be more guidance on the practicality of a sponsor having to potentially provide free-texts fields in multiple native EU languages. In addition to English: For trials conducted in a single country or countries with shared language: It is proposed that the sponsor submits language in native language. For trials conducted in multiple EEA countries: It is proposed that the EMA results database includes in-line translation to official languages of the EEA, whereby a sponsor can select pre-select languages to be translated to/from. This removes the need for sponsor to have to submit results many times over in different languages.	
Section 2: Modalities of submission and processing of results related data fields. Follow-up		**Comment:** Locking of result-related information should be linked to a set period after declaration of end-of-trial, and not to a period after the first submission of results. The rationale for this is that a number of clinical trial designs incorporate more than one pre-specified data cut-off e.g. • Phase I / II integrated clinical trials where data from Phase I is used to define details (e.g. dose or dose	

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submission		interval) for the Phase II part of the trial; or • Oncology clinical trials that may have a primary data cut-off for progression free-survival, and then continue to follow-up patients in order to analyse overall survival. The time lag between the data analyses differs between trials but may be greater that 1 year. Locking of the results record based on the time of first submission of trial results may discourage Sponsors from disclosing trial data as it becomes available. **Proposed change (if any):** The results-related data of a given trial may be locked so that no new submission for that trial is accepted by the system, after a period, to be established, but usually within 2 years of the end of the clinical trial.	
Section 2: Modalities of submission and processing of results related data fields. Provisions for results of clinical trials which have ended in the past		**Comment:** For trials that completed prior to the coming into operation of the systems set out in the implementing technical guidance, disclosure of results related data should not be required. The reasons for this are provided below: • The format of results will not be consistent and this may lead to confusion; • Searching for trials may be problematic as full protocol related information will not available; • Data from these trials will have to be publicly disclosed via other public databases e.g	

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		clinicaltrial.gov, PhRMA or company websites.	
Section 2: Modalities of submission and processing of results related data fields. Provisions for results of clinical trials which have ended in the past		**Comment:** Trial synopses, in the format of ICH E3, are intended for scientists and not the general. Some synopses may have been written with 'promotional' wording (e.g. drug A was clearly more effective than drug B). Any expectation on sponsors to revise and release ICH E3 synopses (many of which may already be public on sponsor websites and/or via the IFPMA portal), will create confusion. For trials whose results have been submitted to ClinicalTrials.gov, may not appear to be consistent with the ICH E3 synopses submitted to EudraCT due to the different requirements of each format. For example, the Objectives, Number of Patients, Treatment Duration, etc. which is taken from the Clinical Trial Application may be different from what in listed in ClinicalTrials.gov for the same trial. It may appear that there are different efficacy and safety conclusions for the same trial. Rather than submit an authorised copy of a medical journal article, sponsors should be able to submit a hyperlink to the article where access is publicly available. Please provide information on the process for sponsors to provide PDF copies of ICH E3 synopsis to EudraCT.	

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Section 2: Modalities of submission and processing of results related data fields. Provisions for results of clinical trials which have ended in the past		**Comment:** The starting date for those trials which "have ended more than 6 or 12 months…..prior to the coming into operation of the systems set out in the present guidance." Please clarify what will be used as the basis of the 'starting date'. Will this be when Version 9 of EudraCT becomes available? Please clarify which fields in EudraCT will be 'required' in the reduced set of fields?	
Section 2: Modalities of submission and processing of results related data fields. Non-compliance, factual inaccuracy		**Comment:** Please clarify how the process for sponsors to make corrections to published information. To facilitate an inspection, the process implemented, whereby a sponsor amends data, should address (i) the need for consistency between changes made to the results-related data compared to what is entered in EudraCT, (ii) the need for consistency the protocol-related information or the results-related information, without the need for dual entry by the sponsor and/or NCA. Where the EMA has the possibility to add a notice to the public record, the EMA should provide a sponsor with a defined timeframe in which to correct data, and provide explanation, after which a public notice is served when a sponsor fails to act. "*Member States should verify that for clinical trials authorized by them the result-related data are submitted to the Agency*". Please clarify if this means that member	

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		states have the responsibility to submit the same information entered on the EudraCT database to the individual member states.	
Section 3: Structure and Format of results-related data to be submitted		See comments below – Annex 1	
Section 4: Presentation of the result-related data fields to the public		**Comment:** Only the trial Sponsor should be able to retrieve an XML file of the submitted data. Please confirm whether this means the public can download the XML. If yes, what is the reasoning for providing this format in addition to the "printable format"?	
Annex 1			
General comment protocol fields		**Comment:** Some of the protocol elements described here are optional in clinicaltrials.gov. We request that distinction be made between which elements are considered mandatory and/or if any elements presented here are optional.	
General comment protocol fields		**Comment:** There are a number of EudraCT fields identified that are common to the fields of the other Annexes used throughout the life-cycle of the trial and not all of which, "default from the protocol data" for example: "P2 Reasons for premature termination" is similar to Section D.3.3.1 of the	

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		Annex 3. In any process implemented, it should address the need for consistency between all Annexes, for example, ability to map or carry-over or data electronically.	
P3		**Comment:** The definition should be changed so it is consistent with section 4.1 of the detailed guidance CT-1 **Proposed change (if any):** End-of-trial as defined in the trial protocol. Currently, the definitions for trial completion differ under EMA and FDA Amendment Act, with the outcome that trial results are subject to different release schedules. Recommend that the EMA consult with NIH in the US to put forward a harmonised definition that is unambiguous.	
P5		**Comment:** In this field, and other similar fields, please clarify the character limitation. Providing an inappropriate character limitation has led to problems for sponsors when submitting data to cliniclatrials.gov. Consequently, the NIH has had to increase this on request from sponsors.	
P6		**Comment:** Please clarify the process timings for this and other similar fields. Namely, some sponsors may interpret that the details regarding the Trial Protocol are to be entered after the trial has been completed, yet the original information	

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		that was sent to EMA at the start of the trial would be kept unchanged.	
P7		**Comment:** Information is generally readily available for controlled clinical trials, but will not be applicable for observational or epidemiological trials. Therefore, there must be an option for valid "NA" in the system.	
P10		**Comment:** Although EMA definition of IMP may exist, the guidance should clarify if IMP is inclusive of Biological/Vaccine, Genetic.	
P11		**Comment:** Annex 1 indicates that IMPs that do not yet have a generic name, a chemical name or company code may be used on a temporary basis. Clarification is sought on when and how this field is to be updated.	
P11		**Comment:** Correction to text suggested as comparators are, in accordance with Directive 2001/20/EC, IMPs. **Proposed change (if any):** For non-IMP intervention types ~~(as comparator)~~ or background therapy, provide an intervention name …	
P14		**Comment:** Describe the mechanism in place to update recruitment status in the system as this is protocol information that is not part of the CTA. Also, it is unclear if	

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		the recruitment status is referring to the overall status, or the status for individual trial sites. In fact, recruitment status is not relevant to the EU as will not be updated by the Sponsor / EMA during the trial. This section should cover trial status – completed or prematurely terminated.	
R10		**Comment:** Is this element required for all trials or only those involving paediatric and other vulnerable populations? How is "vulnerable population" defined? Since information on protection of subjects is not related to the contact information for the trial, this information should be moved to the section on 'Population'.	
R10		**Comment:** *"Paediatric trials and trials in other Vulnerable populations should report on how they ensured that the vulnerable participants were protected against various sources of harm".* This is not a "result" but rather a GCP question and thus would be more appropriate in the protocol section of the CTA or Risk Management Plan.	
R12		**Comment:** Consideration should be given to how to manage information on historical controls, which have been part of a trial previously and therefore not simultaneously in the currently reported trial.	

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R15		**Comment:** If the intention of this optional field is to list concomitant medications, it should state so explicitly. This is not routinely reported to this level of detail but is usually collected, e.g., Case Report Form. However, for observational or epidemiological trials, it is not routinely available. It could potentially be an unwieldy amount of data to manage.	
R23		**Comment:** Please provide more detail on expectation of this field. In some trials there is only 1 period, therefore would the default be Y unless multiple periods in a trial?	
R27		**Comment:** This field is "*only conditionally required". What are conditions?* Some of the required elements are not routinely reported to this level of detail but are usually collected, e.g., Case Report Form. All non-serious AEs are not routinely reported other than for complying with Basic Results for ClinicalTrials.gov. For example, "*Withdrawal by subject"* is not currently reported in Summary Results tables and moreover since harmonisation is a goal in this guidance, will be discrepant with ClinicalTrials.gov Basic Results requirements, leading to confusion rather than desired clarity and consistency. From an implementation perspective, this would result in a very complex algorithm and process of reporting.	

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		For these reasons consideration should be to given to the merit of including *Physician Decision, Pregnancy, Withdrawal by Subject, . . . Lost to Follow-up, Other: specify*.	
R28		**Proposed change (if any):** This field can be deleted as covered in Section R27.	
R37		**Comment:** Please refer to points raised for R27. Typically the reasons subjects are not included in a population is not always categorised. In addition, subjects could have multiple reasons why they are not included in a population.	
R41		**Comment:** Age, race and ethnicity categorisation are not consistent with the NIH classification on ClinicalTrials.gov, e.g. the EudraCT draft list categorizes the younger patients as 'less than 18 years' whereas ClinicalTrials.gov categorizes as '<=18 years', so the 18 year old patients are included. EudraCT also foresees additional categories such as 'Children (2-11 years)' and 'Adolescents (12 – 17 years)'. Since harmonisation is a goal in this guidance, this must be addressed.	
R44		**Comment:** Please ensure there is functionality for entry of non whole numbers, e.g., as in the case of results expressed as median difference of two time points for some quality of life variables, which are measured on a scale of 0 to 100.	

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R54		**Comment:** As an example, this field highlights inconsistency in terminology with ClinicalTrials.gov: EudraCT uses 'Variable Type' instead of 'Outcome Measure' as used by ClinicalTrials.gov. This field, and other similar fields, should use same terminology and definition to meet stated objective of coherence and consistency.	
R62, R63		**Comment:** The descriptions are for one specific type of evaluation. For example, the lab values appear to be for the number of subjects with values meeting a certain criteria. However, there are other types of lab analyses that do not fit this approach. Further clarity is needed for sponsors to complete this information correctly.	
R63		**Comment:** How does this differ from a requirement to enter all baseline measures used in endpoints? "Title Baseline Variable: Name and description of a characteristic measured at the beginning of the trial. Note that baseline measure data for "Age" (at least one of the three types) and "Gender" are required. There is no limit to the number of additional "Study-Specific Measures" that may be provided. All variables measured at baseline used for an endpoint should be included."	

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		Request clarity on expectation of this requirement.	
R67		**Comment:** Please clarify "*Should be presentable*". If this is at sponsors' choosing, there will be much variation.	
R68		**Comment:** The ability to provide results in graphical format is welcomed. It can allow for better depiction of results that involve continuous measurement, especially where no other analysis has been performed. However, clarity is required whether graphs can be added/imported from clinical trial reports generated by a sponsors or whether the EudraCT results database can generate an equivalent graph.	
R75		**Comment:** Please clarify if this is specific to each statistical analysis that may be reported. Will it be a required field if statistical analyses are reported? It could lead to discrepancies in reporting unless clearly documented in clinical trial documents.	
R98		**Comment:** This is not available in ClinicalTrials.gov, therefore it will be a different presentation of AEs between the two public databases, which is contrary to the goal of coherence and consistency.	
R103		**Comment:** This will only be reasonable if more than one AE	

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		table is allowed. Otherwise it would need to have the option to select a per-event assessment type (e.g., Vaccine trials – solicited vs spontaneous events). It would seem that EudraCT can include other AE tables. It is recommended that sponsors use the standard AE table included in the full report and summary reports.	
R112		**Comment:** This is not routinely reported to this level of detail but is usually collected, e.g., Case Report Form. This data is currently available in a clinical trial report listings, and is usually quite lengthy. For larger trials, it is not reasonable to include in the report, and would make for a very large AE section if required for each results posting. It is recommended that this field is not required since it is also not required by clinicaltrials.gov.	
R114		**Comment:** This is not routinely reported to this level of detail but is usually collected, e.g., Case Report Form. This information is not always presented a clinical trial report, especially for trials with large number of expected deaths.	
R115		**Comment:** In the absence of a Sponsor discussion field, this section should be deleted.	

Please add more rows if needed.