Treasury Building, Lower Grand Canal Street
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30th September 2010

Dear Sir/Madame,

Please find enclosed comments from Elan in respect of the public consultation document:

"IMPLEMENTING TECHNICAL GUIDANCE - LIST OF FIELDS FOR RESULT-RELATED INFORMATION TO BE SUBMITTED TO THE 'EUDRACT' CLINICAL TRIALS DATABASE, AND TO BE MADE PUBLIC, IN ACCORDANCE WITH ARTICLE 57(2) OF REGULATION (EC) NO 726/2004 AND ARTICLE 41 OF REGULATION (EC) NO 1901/2006 AND THEIR IMPLEMENTING GUIDELINES 2008/C168/02 AND 2009/C28/01".

Sincerely,

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Public Consultation Paper
Deadline for Consultation 30th September 2010

Table of Comments

Draft Guidance Document

Draft Guidance Document Headings	Comments
1. Background and Purpose	Background and Purpose The company would like to encourage collaboration between the Food and Drug Administration (with ClinicalTrials.gov) and the European Medicines Agency on what exact data should be submitted and made publicly accessible in the US compared to the EU region in order to minimise duplication of data entry to meet the needs of the two regions. Under such collaboration there may be scope for one region to 'recognise' the data entry made in the other region as fulfilling sponsor obligations under the current guidance. The company suggests that a timeframe be added to the draft guidance and annex, to clarify when the new guidance document will be issued and sponsor compliance will be expected. The commission are asked to consider whether simple text be made acceptable instead of in accordance with XML schema and XML standard.

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	If posted results could be updated on request at any time, the implementation of a final lock (i.e.1-2 years for Phase 1 or 2;2 years for Phase 3 or 4) seems redundant. The guidance may benefit from further clarity on updating the results therefore. Can the commission provide further details on providing results for studies ended more than 6 or 12 months prior. How far will the guidance date back to? The Purpose of the Guidance specifies "details" on the submission of result related information. The details was more on the data to be collected as provided for in Annex 1 Sections A and B; but the details on the "how to"-how clinical trial result information is uploaded in EudraCT (ie gateway technology, specifics on validation testing for the upload) is lacking in the draft guidance.
2. Modalities of submission and processing of result related data fields	<u>Submission</u> The submission of the data is made through the European Medicines Agency and the processing and making public of these data will be controlled by the agency as stated in draft guidance. The guidance should therefore clarify whether a review of the data entry between the MAH/study sponsor and agency is envisaged before the data is locked down and made public. <u>Processing</u> The result-related data to be made public will be accessible in the EU Clinical Trials Register within 5 working days from the submission of a valid data set. Is this possible? The submission of information for studies which have ended more than 6 to 12 months prior to the operation of the systems can be done in a portable document file (PDF) file.

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	It's not clear how far back is this applicable. Again a date certain with the criteria for inclusion (such as database lock or publication) would be the most helpful. Language It is acknowledged that the guidance will accept data entry in more than one language. However the guidance should clarify that data entry by the MAH/sponsor in more than one language will not be required unless so preferred by the MAH/sponsor. Follow-up submission The guidance indicates that the data will be locked at a time point following the first submission of data. This appears contradictory to Annex 1 Section B (R13 Title Arms/Group) which indicates information may be changed in the results section at any time. Provisions for results of clinical trials which have ended in the past Not enough clarity is stated in the draft guidance document. More clarity is needed on the exact information that the MAH/study sponsor would have to provide and in what timeframe. Studies in scope and out of scope should be described. If this is intended to be addressed in a separate guidance then that guidance should be developed and circulated for comment in a similar timeframe to the current procedure. Information on clinical studies that have occurred in the past is already publicly available on ClinicalTrials.gov. Therefore from the draft guidance this would cause retrospective duplication of data entry.
3. Structure and format of the result related data to be submitted	Coherence between EudraCT and other public registers was mentioned in the draft guidance as an objective.

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	However the language on how this will be done is very general "EudraCT will take into account internationally agreed standards" and the effort is mostly focused on interoperability with that of ClinicalTrials.gov.
4. Presentation of the result related data fields to the public	The extent of presentation of the result related data fields as mentioned in the draft guidance does not facilitate the interpretation of the information. There is no mention of Providing a Notice to the Public about how guidance may be needed for a meaningful interpretation on the information provided; There is also no mention regarding a glossary w/c is essential to familiarise the intended audience with common terms; no information on whether a "Help Section" or online training is available for users to enable them to make the most effective use of this register. As the results are technical and scientific in nature, the degree of detail requested does not support standardisation of language to reach an assumed expected level of education within the public to provide the data in a meaningfully context. What are the repercussions for the public and how can we be sure that they are truly informed and gain value from this data access?

Annex I Section A-Protocol related fields

Annex I Section A	Field Name	Comments	Proposal
P3	Date of the global end of the trial (completed or prematurely terminated)	The sponsor should be permitted to define the global end of the trial in the same way as that included in the initial EudraCT application	"Final date on which data was collected *or as defined in the initial application"*
P4	Blinding/Masking specific to period	Recommend if provided that this is kept at a very high level. Too much detail will be confusing for patients and may not be	

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		relevant/meaningful to them	
P5	Blinding implementation details	This level of details appears to be unnecessary. Details on Blinding Implementation is not necessary; although Consolidated Standards of Reporting Trials Statement also know as CONSORT 2010 Statement requires both – *"the who was blinded"* (P4) and *"the how blinding was done"* (P5), CONSORT's audience are editors, authors, investigators. For the general public – Just P4, *"the who was blinded"* will be sufficient since P5, *"the how blinding was done"* may be too technical. Details are appropriate for manuscript publication but complex nature of this may be difficult for the public to understand without appropriately qualified personnel informing them.	
P6	Allocation specific to arm within period	The company believes the level of detail required per period is excessive and will not be helpful to the interpretation of the results. A more simplified approach such as that used in ClinicalTrials.gov should be acceptable.	"Allocation ~~specific to arm within period~~"

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P7	Randomised allocation implementation details in case of randomisation	This information is already clearly stated in the protocol. It is unclear how this information may be beneficial to patients visiting EudraCT. Confusing for patients if not versed in the area of statistical scientific methodology. Recommend that if this is added it is kept very basic and high level. The randomisation type (central, blocked, stratified) may be too technical/unnecessary for the public. However, the process of sequence generation (eg random-number table or computerised random number); how allocation was concealed (eg study drug and placebo were identical in appearance); the implementation (Who generated the allocation, who enrolled participants, and who assigned participants to interventions) are more important.	
P9	Arm/Group type	It is unclear what Group refers to in this context; alignment to the ClinicalTrials.gov content is requested.	"Arm~~/Group~~ type"
P12	Intervention details	Units should include examples to ensure there is no misinterpretation.	

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P14	Recruitment/Termination status (to be updated by the sponsor during the active phase of the study)	Greater clarity should be provided in the guidance document on how this section is intended to be updated (e.g. with what frequency; under what circumstances etc). Title of Recruitment Status is sufficient; The word "Termination status" is confusing. Recommend that details do not drill down to site level but are rolled up to study level.	
P15	PubMed ID (PMID) or equivalent	Suggest to use "References" instead as -it is more apt as a title and is easily understood by the Public; PubMed ID or Medline identifier are details that are already included in the description anyways.	

Annex I Section B-Results related fields

Annex I Section B	Field Name	Comments
R8	PI Disclosure Restriction Type	FDA requirement – should this be balanced and required by EudraCT also?
R10	Protection of Participants	From the annex it specifies paediatric trials and other vulnerable populations. A specific definition is needed to determine what population is categorised as an

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		'other vulnerable population' and whether this includes elderly patients. If so in what age ranges. The actual measures as described in the annex may not be detailed in a protocol that was for a 'vulnerable population', for example a study in the elderly. Actual measures will be hard to quantify more than what is already included in the protocol and informed consent form. Each physician will execute the protocol and informed consent requirements. Any additional measures would be physician specific. Actual measures to protect subjects are more meaningful in study documents and informed consent more than the study report at the end of a trial. However if the study had some "safety" issues identified during its course (ie, unusual amounts of adverse events from lumbar punctures, or venipunctures or transfusion reactions), these need to be included as part of public health info/ awareness. It can be an optional field as it may not be needed in all studies especially if the informed consent form and study documents already outline the preventive measures prior to study.
R15	Background therapy details	Is this an optional field? Should be more definitive in what is required to ensure standardisation

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R30-R37	Population	The company believes that the extent of detail requested in these sections is excessive. This detail would be in the Clinical Study Report.
R38-R48	Baseline Characteristics	Unclear when this data should be posted. It would not necessarily be peer reviewed and if not published what are the expectations for timelines. Also, multiple fields have redundancy issues. Don't follow ClinicalTrials.gov descriptions; provide new descriptions eliminating redundancy (eg. Baseline variable title and description - R42/R43 could be rolled in together).
Title (page 31 of Annex 1 Section B)	Events table	EudraCT provides for additional separate adverse event table (other significant adverse events), this could be meaningful/valuable as it informs the public on the adverse events of interest specific for that trial. Emphasise/clarify that providing additional tables should be optional based on the discretion of the data provider.
R54	Variable Type	Does not cover co-primary and co-secondary endpoints. In this format, each co-primary would need to be entered separately.
R62 and R63	If safety variable and clinical laboratory evaluation: Criterion If safety variable and vital sign: Baseline value and value type	This will only be applicable if safety was assessed in terms of numerical score or categorical ratings. As safety assessment is a combination of other factors (eg elevated lipase),

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		without clinical information on symptoms and if not correlated with other labs like liver function tests or bilirubin, this information by itself may mislead rather than inform; same goes for vital signs.
R68	Graph/Chart	Descriptive summaries of topline results should be sufficient. Importation of graphs/charts may be challenging (PDF only?) and are often misunderstood and misinterpreted.
R75	Analysis scope	Frequently post-hoc analysis and sensitivity analysis are not relevant for the public but informative for future clinical development plans. This information may be confusing and misleading to the public.
R98	Definition of this table	Clarify/differentiate between TEAE and TESS. Delete "other" – too open ended.
R99	Event term	Mandating dictionary terms will help standardise data but acknowledge that you may loose specific verbatim details as events get reclassified into NOS (not otherwise specified) groupings.
R112	Event severity	As the severity grading scale that is used varies between trials, this may be misleading and therefore may not be significant for the public.
R114	Number of deaths (all causes)	In the interest of Transparency, deaths in a clinical trial are important to be disclosed however it should be in a manner that makes more sense for the general public. We suggest that Section R114 should not focus on the number of deaths but rather on the

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		causes of deaths i.e. a table of fatal serious adverse events, as that would be more relevant. An option to provide a comment text field should also be included.
R124	Was the trial ever interrupted, in any other country	From the proposed annex it just contains a Yes/No description. Therefore more clarity is needed on what exact information the MAH would have to submit.
R128	Was there any protocol amendment after recruitment started with any relevance to the results	More clarity is needed on the proposed annex on protocol amendments. From the proposed annex it just contains a Yes/No description. Therefore more specific detail is needed if all protocol amendments need to be submitted? This would require a large amount of maintenance activities by the MAH and agency and is currently not required by ClinicalTrials.gov. Explaining all relevant historical protocol changes could be very labour-intensive and a bit outdated and irrelevant at the time of final study results posting.