SUBMISSION OF COMMENTS ON the Draft list of data fields of the clinical trials database (EudraCT) and the information on trial results for paediatric clinical trials to be made publicly available.

COMMENTS FROM: EFPIA /Christine-Lise Julou

GENERAL COMMENTS

We agree with the aims of the Regulation "*to increase the availability of information on the use of medicinal products in the paediatric population and to avoid unnecessary repetition of studies in the paediatric population which do not add to the collective knowledge.*" However, the draft list of fields to be made public from EudraCT should be amended to ensure this aim is achieved in a pragmatic, consistent and practically implementable manner.

The comments submitted by EFPIA in relation to the public consultation concerning the draft guideline that this list is aimed at supplementing are still valid.

The present public consultation paper raises a number of additional comments as follows:

1. Many Pharmaceutical companies already make information on ongoing clinical studies publicly available via clinicaltrials.gov[1] or other such databases[2]. By implementing a bespoke and duplicative European system for doing the same thing but from a different route of information

[1] Experience with the information disclosed on other clinical trials sites e.g. *clinicaltrials.gov* in the USA, would indicate that the level of information disclosed in those databases has been found sufficient both by patients who may want to participate in clinical trials and also for physicians who are interested in the trials either on their own behalf or on behalf of their patients. Therefore we would strongly recommend that a similar level of disclosure of information should be made on the EudraPharm website.

[2] A comparison of the WHO-20 data set with the EUDRACT fields identified these discrepancies as examples of the above need for harmonisation:

- EUDRACT uses "Trial Identification" while WHO-20 uses both "Trial Identifying Number" and "Secondary Identifying Numbers" to capture the unique ID numbers assigned to a particular trial.
- EUDRACT uses "Sponsor" while WHO-20 uses both "Primary Sponsor" and "Secondary Sponsor" to name the individuals, organizations, or groups which take responsibility for managing and/or financing a particular trial. EUDRACT does not recognize a "Secondary Sponsor".

(distilled from that provided to the national competent authorities for clinical trial applications), there is a significant risk that discrepancies will exist between the different public databases. These discrepancies will only serve to confuse rather than inform patients.

2. As the aim of making information about paediatric trials public is "to increase awareness on the use of medicinal products in the pediatric population and avoid repetition of studies in the pediatric population which do not add to the collective knowledge", publication of the level of detail from EudraCT proposed seems unwarranted. Furthermore the high level of detail on a protocol included in the draft list means that there will be a greater number of occasions when changes to a clinical trial will result in a need to update the public database. This could result in greater resource being required to maintain the public database and keeping it up to date unless an efficient and elegant IT solution is provided.

3. While the Member States remain unable to agree on whether comparator, standard of care, co-administered or reference products are investigational medicinal products or non-investigational medicinal products, important inconsistencies will occur in the information provided on medicines being used in a trial that is made public from EudraCT.

4. To address these issues, it is proposed that the public European database displays the necessary administrative fields from EudraCT, but that all protocol-related information for the trial is provided by cross-linking to an existing public database, such as clinicaltrials.gov. This could be readily achieved by including a field in EudraCT for the link to the clinicaltrial.gov or similar database summary to be entered.

5. There is no description on how information on individual studies conducted in multiple Member States will be made available to the public. It is not clear which Annex 1 forms (will be used to transfer information to the EudraPharm website. In every EU member state participating in a multi-country study 2 different Annex 1 forms are generated - one for the Ethics Committee and one for the Competent Authority. In some

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- EUDRACT uses "Contact Point" while WHO-20 differentiates between "Contact for Public Queries" from "Contact for Scientific Queries". EUDRACT requires a FAX #, while WHO-20 does not.
- EUDRACT uses "Full Title" while WHO-20 requires both "Public Title" and "Scientific Title".
- EUDRACT requires "Ethics Committee Information" while this not part of WHO-20 at all.
- EUDRACT uses "Medical Condition" (in very much detail) while WHO-20 uses "Health Condition or Problem Studied" in minimal detail.
- EUDRACT uses "IMP" (in very much detail) while WHO-20 uses "Intervention" with generic, chemical, and serial # information only.
- EUDRACT uses a variety of terms to capture the elements of study design, such as "Design", "Objective", "Scope", "Planned Population", etc. while WHO-20 asks for only specific elements including: Key Inclusion and Exclusion Criteria, Study Type, Primary and Secondary Outcomes.
- EUDRACT asks for "Target Sample Size" vs. "Planned # of Subjects to be Included" in WHO. Labels differ but definitions are the same.

countries these forms are in the local language. The same clinical trial will be subject to separate applications to each competent authority in participating Member States. Applications might be made in a staggered fashion to different agencies during which time information might have been supplemented or otherwise adjusted to meet differing national requirements. This is likely to affect the following fields: A.1, E.8.3-E.8.6, F.4 and N. How is the EMEA going to keep the public information current if different application forms exist for one trial? We assume that this information will be combined and made available to the public as single entry. This should be confirmed, as making multiple sets of information for the same trial publicly available would be confusing.

6. When submitting a patent application on, for example new indications/combinations/formulations, etc, the innovative pharmaceutical companies are required to support the application with clinical data. Increasing the extent of disclosure related to sensitive information that a company has to disclose impacts significantly patentability since the applications must be made earlier and subsequently with little or no supporting clinical data, a 'catch-22' position. In short, the negative impact on intellectual property is significant unless there is a possibility to delay disclosure of sensitive information until the prompt approval of any patent applications.

7. Disclosure of personal contacts details as proposed in G is not advised. The details should be retained for administrative purposes only and not made public. Public contact details should be for a Helpdesk or Information Desk where the staff will have received appropriate training.

8. There is concern that the database which was established to provide information on medicinal products authorised in the Community (EudraPharm) is now being used to provide information on unauthorised products. This is in addition to the concern that the original intent of EudraCT was originally established to include information for the regulatory authority and ethics committee assessment for approval of clinical trials, and access was to be limited to competent authorities and the Commission. Proprietary information may be included in documents shared with the competent authorities, but companies would not be willing to share that information with the public and their competitors. Furthermore, the intended audience for the public information needs to be defined. Different language/terminology would need to be used depending on whether it is for the lay public or scientific members of the community.

9. With regard to the provision and publication of results, the ICH-E3 synopsis template should be used and only the information included in the template should be required. Companies already have to provide this type of information to be compliant with other legislative requirements (e.g. the US State of Maine legislation). Sponsors will also soon be required to provide data tables to be compliant with US Federal legislation. It is becoming an undue burden to provide essentially the same results in different formats, with varying degrees of detail in different websites throughout the world. Efforts should be made to harmonise the clinical trial registration and results requirements. Ideally, the public should be able to locate clinical trial information for all applicable trials in one location (regardless of where the website is located and where the "public" is located).

The above-mentioned comments are considered to be critically important. Additional comments concerning specific fields are listed below.

SPECIFIC COMMENTS		
A Trial identification		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
A.1	There is no information on how information on individual studies conducted in multiple Member States will be made available to the public. The same clinical trial will be subject to separate applications to each competent authority in participating Member States. We assume, however, that this information will be combined and made available to the public as single entry. This should be confirmed, as making multiple sets of information for the same trial publicly available would be confusing.	
A.6	The clinicaltrials.gov and US NCT numbers are essentially the same thing. Clinicaltrials.gov provides the US NCT Number when the trial is registered on their system.	Delete clinicaltrials.gov from the list of additional international study identifiers.
A.6	It would be helpful to indicate that this information should be provided 'if available' since this may not be the case at the time the CT application is made	Additional international study identifiers (e.g. WHO, ISRCTN, US NCT Number1), <u>if available</u>.

B Identification of the sponsor		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
B.3.1/B.3.2	**Status of sponsor - Commercial or non-commercial** The publication of this information does not support the	Delete

	intent of transparency around paediatric trials to increase awareness on the use of medicinal products in the paediatric population or avoid repetition of studies in the paediatric population, which do not add to the collective knowledge. In addition, this field is not proposed to be made public for non-paediatric studies nor is it consistent with the WHO data fields and should not be included in the list of fields which will be made public for paediatric studies.	
B.4	**Source(s) of Monetary or Material Support: Commercial Non-commercial** The publication of this information does not support the intent of transparency around paediatric trials to increase awareness on the use of medicinal products in the paediatric population or avoid repetition of studies in the paediatric population, which do not add to the collective knowledge.	
B.5	If a call-centre is used as a point of contact, it should not be necessary to also include an address, fax, and email. The establishment of a single general point of contact for a sponsor or even for an individual clinical trial is likely to be highly problematic, due to, for example, privacy issues, availability of toll free phone numbers, different national requirements and the ability to support different languages. It should be possible to include different contact points to facilitate the handling of queries from different countries or in different languages.	Allow for the entry of either: Address AND/OR phone number AND/OR Fax AND/OR E-mail, but not all 4 items. Confirm that information on multiple contact points for a single study can be accommodated.

D Information on each Investigational Medicinal Product (IMP)		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
Description of the IMP		
D.3.10 to D.6.6 - Description of the IMP	Detailed information on the IMP is not of value to the public and is confidential to the sponsor The amount and level of detail in Fields D3.10 to D.6.6 is very high. As such public availability of this information may be detrimental to the patentability of inventions associated with e.g. the concerned vaccine. Patentability according to Article 54 and 56 of the European Patent Convention (EPC) is based on information not publicly available prior to the submission of patent applications. Also, the availability of clinical data is necessary to support patentability (Articles 56 and 83 of the EPC) which prevents innovative pharmaceutical companies to apply for patents early in the development. Hence, public availability of this information as early as phase 1 could prevent the pharmaceutical industry or any other innovator to obtain the patents necessary to protect their innovations Further more detail on the type of product, origin of cells, type of cells, genes of interest, etc is not of primary interest to the persons who are seeking information on paediatric trials they may be interested to participate in or the lay public. However competitors may find such information quite useful.	Recommend not including such detailed information (detail on the type of product, origin of cells, type of cells, genes of interest, etc) for public disclosure on EudraPharm.

E General information on the trial		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
E.1 Medical Condition or disease under investigation		
E.1.1 and E.1.1.1	The condition being studied is likely to be included in the study title, so the need for a separate field for this information is unclear. "Medical condition in easily understood language" is subjective. Different sponsors could use different descriptions for the same condition, which would lead to confusion for the public, devaluing the public availability of the study information. Standard language here is exceptionally important for searching.	Suggest use of something like the MeSH dictionary, as used on ClinicalTrials.gov
E.1.2	E.1.2 is technical and very detailed thus possibly confusing for the lay public. Relevant information is provided in E.1.1	Consider deleting E.1.2
E.2 Objective for the trial		
E.2.3, E2.3.1	It is not clear what constitutes a "sub-study". This information is not likely to be of interest to, or understood by, the lay public.	Delete unless a clarification on the meaning of "sub-study likely to be understood by the lay public" can be found.
E.5-E.5.2.1	Endpoints and timing could be proprietary and are not likely to be of interest to the lay public. This benefits competitors, not the public.	Recommend not including detailed information such as time points of evaluation of endpoint for public disclosure on EudraPharm.
E. 6 Scope of the trial		
E.6	We are not sure that this is of public interest/benefit.	
E.7 Trial type and phase		
E.7.1 (inc. E.7.1.1 -	We are not sure that this is of public interest/benefit. In addition, these fields (for Phase I studies) are not included	Recommend not including this information for public disclosure on EudraPharm.

E.7.1.3.1)	in the list of fields to be made public for non-paediatric studies (Commission Public Consultation Paper, 15 July 2008).	
E.8 Design of the trial		
E.8.3 – E.8.6.2	The information requested in these fields may change during the trial, but the information in EudraCT may not be updated, either because a change would not constitute a substantial amendment, or because the change concerns sites located outside of the EEA. For this reason, and as the information is of limited interest or benefit to the public, it should not be made public.	Recommend not including this information for public disclosure on EudraPharm.

F Planned population of trial subjects		
Field number (e.g. D. 2.1.1.1)	**Comment and Rationale**	**Proposed change (if applicable)**
F.1 Age span		
F.1 - Age span	It is not always possible to plan in advance or anticipate the distribution of the trial subjects in the various age span categories (e.g. in the case of vaccine trials). It would not be appropriate to require that this information be systematically provided.	For section F.1, provide sufficient information to inform the public the age span of the population that may be included in the trial.
F.2 Gender		
F.3 Group of Trial Subjects		

F. 4 Planned number of subjects to be included		
F.4	The information concerns “planned” trial details, which may change over the duration of the trial. We question whether it is really relevant for the public to know how many patients are planned in an individual country or in the trial. This information is more likely to be of benefit to competitors than to the public.	Recommend not including detailed information for public disclosure on EudraPharm. The WHO target sample size requirement would be more appropriate.

G Clinical trial sites/investigators in the Member State or country concerned		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
G	There are security concerns with listing names, addresses and telephone numbers on a public website. A contact point for enquiries regarding the trial is already provided In addition, these fields are not included in the list of fields to be made public for non-paediatric studies (Commission Public Consultation Paper, 15 July 2008). There should be no difference in the fields to be made public for paediatric and non-paediatric trials, and there is no obvious reason for making these fields public.	Recommend not including personal information for public disclosure on EudraPharm.

N Review by the Competent authority or Ethics Committee in the country(ies) concerned)		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
First three lines	There is no obvious reason for making these fields public. The publication of detailed information on such matters does not support the intent of transparency around paediatric trials to increase awareness on the use of medicinal products in the paediatric population or avoid repetition of studies	Recommend that only information serving the stated objective of the legislation in relation to transparency and communication is posted and that it is presented in such a way it can be easily

	in the paediatric population, which do not add to the collective knowledge. One of the comments made on the draft guideline released for public consultation is particularly relevant in this context and therefore re-stated: "*The presentation of information released to the general public will need to be clear, in order for the general public to understand its context and meaning and to avoid the creation of incorrect expectations/speculations in relation to research if issues are not fully and appropriately presented"* Rather than publishing detailed information on Competent Authority(ies) or Ethics Committee(s) approvals/opinions it might be more relevant and useful to publish the anticipated or actual date of enrolment of the first trial subject.	understood by any member of the lay public.
Fourth line (Recruitment status of the trial)	It should be clarified if this refers to the status of the study globally, or to the status in the European Community. The forms submitted by applicants do not supply information regarding the start of the study. How would the information be collected?	
	Promptly making information on trial results available to the Regulatory Authorities is supported. However, there is no identifiable benefit to the public of making results information available for new products not commercially available prior to marketing authorisation, or for already authorised products before the trial information has been assessed. Publication of summary trial results, following assessment and approval of new products, indications and dosing information, would provide the public with information placed within the context of the Regulators assessment and at a time when the product was likely to be labelled and commercially available for that use. This would still meet the obligations of the Regulation, which does not indicate a specific timeframe for public disclosure. Studies for authorised products, not submitted and assessed by Regulatory Authorities within one year of study completion, should however be	**Anticipated date of the availability of results for authorised medicinal products (study synopsis to be provided no more than end of trial date plus six months unless it cannot be reasonably expected that such a deadline can be met because of the duration of some tests or analysis required to appropriately assess the efficacy and/or the safety of the IMP. In that case the currently globally accepted timeframe will be applicable (i.e. within 12-months of trial completion).**

	made public. The draft CMD(h) Procedural Guidance concerning submission of information on paediatric data according to Article 46 of the Paediatric Regulation, requires that only the cover letter and line-listing be submitted within 6 months of completion of paediatric studies, and that no study report is requested within the 6 month timeframe. The study synopses should be submitted within 12 months of study completion, in accordance with existing practice under the Clinical Trials Directive Requiring results to be available within 6 months of trial completion is not consistent with other requirements (e.g. within 12 months of trial completion, in accordance with guidance applicable to Directive 2001/20/EC). Whilst Regulation 1901/2006 does require that marketing authorisation holder-sponsored paediatric studies be submitted within 6 months of completion, it is not clear that the results must be submitted at that time. Recent draft procedural guidance from the CMD(h) on the application of Article 46 of that Regulation appears to recognise that trial results need not be submitted within 6 months (http://www.hma.eu/uploads/media/Procedural_guidance_Article_46_Rev0.pdf). This approach is supported by EFPIA. Six months may not give the sponsor adequate time to ensure the data are valid and accurate. Furthermore as indicated in the comments submitted in April 2008 such a requirement is in most cases unrealistic (The case of vaccines tests where serological analysis which may take several months have to be performed after the end of trial was mentioned).	

	Therefore the 6-month deadline s appears to be an arbitrary deadline that forces sponsors to rush through data lock, data analysis, and writing the summary of results. The paediatric population is the last population that should have data rushed to be analysed. Sponsors cannot afford to make mistakes to meet an arbitrary deadline.	

TOPICS - Draft list of fields on information concerning Paediatric Clinical Trial results to be made public		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
	As indicated in the comments submitted by EFPIA in relation to the public consultation concerning the draft guideline that this list is aimed at supplementing, we believe that the obligation to submit paediatric results to regulatory authorities apply to all interventional paediatric trials but that the obligation to make such data public applies only to medicinal products commercially available (i.e. which have been authorised) and therefore that publication of the study results should be delayed until such time; However notwithstanding the scope of the legal requirement provided for in Article 46 industry would support the posting of paediatric clinical results for an investigational products that has failed in development especially when they have significant medical importance	
Administrative information	Is this information going to be located separately from the registration information? If not, this is redundant information.	Unless the protocol-related information and results will be in different locations, we recommend not including this information, as it is redundant.

	In addition, it is not clear what is meant by “trial report number”.	
Background for conducting the trial	Scientific background is not included in the ICH E3 synopsis format, and is not likely to be of interest or benefit to the lay public. This information is more suited for a journal article.	
Participants of the trial	The paper requests information on the **“*settings and locations where data were collected…*** *to assess external validity of the trial”...* Is this saying that the public will be invited to make decisions on the external validity of the trial based on where the trial was conducted?? Locations are provided with the protocol-related information.	Delete the text concerning settings and locations
Interventions	Please note that ‘precise’ doses of the IMP cannot always be provided e.g. for diabetes trials where insulin dosage is titrated against blood glucose levels.	
Blinding	This information is probably already included in previous sections (Trial design, randomisation implementation), so its inclusion here seems redundant.	Recommend deleting this section.
Recruitment	This is not going to be of interest or benefit to the lay public.	Recommend deleting this section.
Ancillary analysis	It is not clear what information is expected here. Is this requesting results of all the post-hoc analyses?	
Adverse events	The term "important adverse events" is not defined. To avoid confusion, guidance should be provided on what information is to be included and this definition should be reflected in a glossary to be made available to the public.	Please revise to ensure consistent interpretation of the requirement

Discussion and interpretation of study results.	It is not appropriate to include the sponsor's interpretation of the results or their conclusions. FDA DDMAC in the US has already warned sponsors that interpreting the data or including conclusions in sponsors' results summaries could be considered promotional and subject to fines.	Recommend deleting the section on providing interpretation by sponsor.

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