<18 February 2015>

Submission of comments on ' Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" ' (EMA/ 641479/2014)

Comments from:

Name of organisation or individual
European Society for Paediatric Oncology – SIOPE

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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

SIOPE strongly supported the inclusion of the articles in the Regulation (EU) No. 536/2014 'The Clinical Trial Regulation' that aim to promote transparency in reporting of clinical trials including the registration of all clinical trials within a public registry.

We have responded to the specific questions raised in the 'Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014' below. In general we are supportive of the proposals as outline and strongly support the principle that the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine.

There are 2 specific points with which we do not agree and that we propose should be amended:

1. **Differentiation of processes for assessing commercially sensitive information (CSI) for phase IV and low-intervention trials:** the proposal to apply a different process of assess the time points for release of data pertaining to a trial for phase IV and low-intervention trials adds unnecessary complexity to the process. A decision of whether the trial has commercially sensitive information should be part of the assessment process and the outcome should follow a simple algorithm with decision points; ie no CSI or CSI and if CSI; the options for time points for release of information defined for each scenario.

   The division of the trials into simple categories of phase I, II, III, IV will lead to confusion. The innovations in methodology being applied to modern trials; ie randomised phase II, multi-arm, multi-stage (MAMS), Adaptive designs, and Bayesian methodology are blurring the margins between phases of trials. The categories of trials need to be considered more in terms of intended outcome of the trial and whether the trial contributes to the decision to develop a drug towards a marketing application (MA).

2. **Publication of inspection reports and serious breaches**: We have significant reservations regarding the publication of serious breach information and consider that the proposal for the addendum DOES NOT meet the requirements and objectives of the Regulation; as stated in Article 77 but is an excessive public release of trial conduct information which could be inappropriately detrimental.

   To meet the requirement and objectives of the Regulation, it is suggested that a summary of a serious breach and the measure should be published ONLY IF the actions described in Article 77 1a-c occur: i.e. the member state revokes the authorisation of a trial, suspends a trial or requires the sponsor to modify any aspect of the trial. All these points would be clear and in the public interest.

Responses to the specific questions

Question 1: The proposal meets the objectives of the Regulation (EU) No 536/2014

Question 2: It is agreed that the names of Member State Experts do not need to be included in the data base and therefore the proposal meet the objectives of the Regulation (EU) No 536/2014

Question 3: It is agreed that personal information identifying sponsor staff do not need to be included in the data base and therefore the proposal meet the objectives of the Regulation (EU) No 536/2014

Question 4: It is agreed that information relating to individuals named in the CSR, ie investigators can be made public and therefore the proposal meet the objectives of the Regulation (EU) No 536/2014

Question 5: Contact for a Functional role of the sponsor and /or MAH is a sensible approach rather than a natural person who may move on from that role in the future. Contact details for an investigator may become obsolete as clinicians move posts or retire and therefore contact details of a more fixed role; ie the sponsor is more reliable

Question 6: we support the proposal not to differentiate between non-commercial and commercial sponsors in the definition of trials with commercially sensitive data. This is of particular relevance in trials which are collaborations between academia and industry partners and avoid discrimination against these important collaborative efforts.

The definition of the time period for which data remains commercially sensitive must be precisely defined. The concept of overriding public interest is open to interpretation and the body who make this decision will need very clear guidelines to follow and would need to be very exceptional cases.

In terms of the preferred proposal for inclusion in the final rules; we would prefer option 1.1:' once a marketing authorisation has been issued, by at least one Member State, for the active substance contained in that medicinal product'. Both options 1.2 and 1.3 carry of risk of minor alterations in use of substance being used as a reason to revert back to being highly commercially sensitive. This would not be in the public interest and could result in unnecessary duplicate

trials being undertaken. Once an active product has MA, subsequent studies looking at different application of that active substance should NOT carry the same level of commercial sensitivity.

Question 7: it is entirely appropriate to consider information relating to the IMPD-Q section to be commercially sensitive

Question 8: the question states: **Please comment and give a brief rationale for your support or disagreement with this proposal regarding clinical trials on products without a marketing authorisation;** however the section of text referred to pertains to low intervention trials and trials using products **WITH** marketing authorisation.

Question 9 states: **Please comment on proposals one, two, three or four regarding clinical trials on products with a marketing authorisation indicating which proposal best meets the requirements and objectives of the Regulation. Please provide a brief rationale for your choice of proposal and explain briefly disagreement with the other proposals.** however the section of text referred to pertains to trials using products **WITHOUT** marketing authorisation.

Answering both questions 8 and 9 REFERRING TO THE APPROPRIATE TEXT

We believe there should be no differentiation between the processing of trials in terms of decision making on commercially sensitive information, regardless of the phase or category of the trial and the definition of the timing of release of information should be the same; ie the definition of when it is no longer commercially sensitive. Under the definition of low intervention trial, it is hard to for see a circumstance where the data can be justifiably referred to as commercially sensitive. The products will have MA and be used as such or outside the MA according to published guidelines.

The document includes the statement *'There are many clinical trials carried out on non-authorised medicines, in the early phases of development prior to marketing authorisation, which are never later used in a marketing authorisation as the development of the medicines is discontinued (approximately 80% of medicines which enter trials in human subjects are discontinued) or indeed the trials may not have been conducted in preparation for a future marketing authorisation, but rather as basic research'. (line 630-634).* ..It is not clear whether it is the intention for the data from these trials to be made public. We believe that there should be a defined time-period after which such trial data should be made available. This would be consistent with the principle of ensuring that even negative results are made freely available to avoid the conduct of duplicate and futile clinical research

With respect to the selection of the most suitable proposed text for inclusion in the amendment; **we would support proposal 3** as being the most appropriate. We agree with the principle that the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine. It is noted that it will be the responsibility of the sponsor to provide information on the status of the marketing authorisation of the product on submission of the application for clinical trial authorisation and that the final decision will be by the member states as part of

the trial authorisation process. This should be applied to all trials, rather than a differentiated system for low intervention and phase IV trials. This would provide a clear decision point on the defining the time-points for the release of data at the onset of the trial.

We feel that there are no circumstances where a trial deemed to be in the low intervention category should be deemed as having commercially sensitive information.

Question 10: We are in agreement with the proposed time-points for triggering publications

Question 11: There is no clear justification given in the consultation document for the proposal made for phase I trials in healthy volunteers and the commercial sensitivity of data and therefore timing of release of data should be evaluated by the same criteria as other studies

Question 12: this proposal is appropriate

Question 13: we believe this proposal to be appropriate

Question 14: We **do not** support this proposal. We consider the publication of inspection reports to be unnecessary and are not required to fulfil the requirements and objectives of the Regulation. They may contain commercially sensitive data and findings identified in an initial inspection report are often subject to an interactive discussion and clarifications. They would not be very informative to the public and could be subject to considerable misunderstanding which could be a reputational risk to sponsors. This will most likely also slow down clinical research due to very burdensome additional reporting and communication regarding inspection results.

Question 15: Unable to respond as terminology unclear in this context

Question 16: We have significant reservations regarding the publication of serious breach information and consider that the proposal DOES NOT meet the requirements and objectives of the Regulation as stated in Article 77 but is excessive public release of trial conduct information which could be inappropriately detrimental.

Whilst it is understood that the proposal has the intention of supporting transparency in the conduct of the trial, Article 77 refers to circumstances where the trial is no longer meeting the requirement of the Regulation and major action is initiated by the Member State, for example; suspension of a trial or revocation of the clinical trial authorisation (Article 77 1a-b). Whilst this type of intervention may arise as an action following the reporting a serious breach, in many cases, simple measures are put in place to avoid recurrence of the breach and there is no substantial change imposed on the trial status by the member state.

The investigation and reporting of a potential serious breach is an important part of the role of the sponsor and is intrinsic to the sponsor's quality management and audit processes. Whilst it is proposed that the published report would be a summary with personal data and commercially sensitive data redacted, the nature of a serious breach is often complex and needs to be seen in a more detailed context of the report.

Point 1.1.1. in particular is excessive and exceeds the Regulation's requirement. Currently sponsors will err on the side of caution and report a potential serious breach, while a more detailed investigation is on-going. In the subsequent investigation it can become apparent that the event does not meet the criteria of a serious breach or in the opinion of the competent authority, no serious breach has occurred. There is no value in publishing this exchange of information and does have the potential to lead to mis-understanding or mis-interpretation when released in the public domain.

To meet the requirement and objectives of the Regulation, it is suggested that a summary of a serious breach and the measure should be published ONLY IF the actions described in Article 77 1a-c occur: i.e. the member state revokes the authorisation of a trial, suspends a trial or requires the sponsor to modify any aspect of the trial. All these points would be clear and in the public interest.

Question 17: Whilst we agree that publishing of reported unexpected events and safety measures as defined in article 53 and 54 is of public interest, there is potential for mis-interpretation of such data when in the public domain. It is crucial that this also includes the measures taken and there needs to be sufficient time for the full investigation unexpected events by the sponsor and the measures to be implemented before such information is made public. This full investigation by sponsor is likely to extend beyond the required initial reporting time-frame via the EU portal (15 days). Ensuring a time-interval between the initial reporting of unexpected events and safety measures and making publically available will also enable time for information to be provided to participants before there is a public release of information.

Question 18: no comment as it relates to the processes around applying for MA

Question 19: see answers to qu 8-10

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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.