2 October 2014
EMA/344107/2014
Chief Policy Adviser

Overview of comments received on 'Publication and access to clinical-trial data' (EMA/240810/2013)

From stakeholder 89 to stakeholder 108

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
89	General comment 1	EORTC strongly disagrees with the fact that the policy does not foresee any independent scientific review to assess the robustness of the science and methodology of the project to be performed with the requested data. Full scientific review of the proposed project is an absolute prerequisite for data sharing. Incorrect analysis and interpretation of results could result in considerable damage to public health. This damage could be irreversible. For instance, should any positive results be released (though not supported by the appropriate methodology and	

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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		therefore possibly wrong), this may change clinical practice and preclude further collection of objective and solid data. Therefore, it is essential to ensure that data will be analysed using appropriate methods. This can be done by a panel of independent experts and would ensure full transparency of the process with the possibility of appeal in case of a negative decision.	
89	General comment 2	EORTC is surprised by the lack of clarity regarding responsibilities. Indeed, the liability of the EMA for the numerous assessments and judgements outlined in this policy is unclear. For instance, it is unclear who would be held responsible or liable if a patient's identity was divulged due to inappropriate handling of data (EMA, trial sponsor or data receiver)? More comments on responsibilities could be found within line comments.	
89	General comment 3	EORTC suggests that EMA considers some degree of retrospective application of this policy (at least within the limits of data available in the usable formats). Indeed, most drugs currently used or which will be used in the near future, at least in Oncology, would not be affected by this policy since their development often takes 10 years or more.	
89	47-48	EORTC agrees that the data sharing covered by the policy may only operate within the boundaries of the existing patient's consent, unless these data are made fully anonymous. It should be kept in mind that the current trend is to make patient consent very narrow (in terms of the possible future use of data, but also in terms of organisations and individuals authorized to access the data). Therefore, it is possible that in practice instances of data use through sharing would be quite limited.	

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		EMA should give guidance on the recommended wording for patient information for future trials (subject to approval by competent ethics committee). EORTC highly recommends allowing the use of broader consent with regard to data storage, access and use (with the usual safeguard of a decision of the ethics committee).	
89	57-61	EORTC strongly disagrees with the assertion that it is not possible to access the robustness of the methodology. See general comment 1	
89	122-123	EORTC does not believe that every project will require access to SAS (statistical analysis software) programs and logs. We maintain that the knowledge used to program an analysis may be considered as intellectual property of the organisation having produced it. However, in case the aim of the project is to reproduce the results of the previous analysis, there might be instances (i.e., heavily divergent results) where consultation of these data should be permitted. Therefore, we recommend that these data should not be released by default, but rather on a project by project basis.	
89	143 & 165	Please clarify whose responsibility it is to verify/confirm that data has been adequately de-identified prior to the transfer? In a situation where insufficient de-identification leads to a claim and/or damage to an individual, who is liable (the trial sponsor, EMA or the data receiver)?	
89	150	Open access to category 2 data is very encouraging and will be very valuable to support scientists in their work.	
89	172	EORTC welcomes the recommendation of a minimum standard for de-	

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		identifying data.	
89	183	Please clarify, within the scope of controlled access, who will determine, and how that an analysis is in the interest of public health? Are there objective criteria?	
89	183bis	Please clarify, within the scope of controlled access, who will determine and how that analysis is in line with the informed consent (trial sponsor, EMA or independent body)?	
89	191	EORTC believes that the secondary use of data, though outside the initial scope of consent, should be allowed provided this use is approved by the Ethics committee (which is currently possible according to the laws of many member states). This possibility (and its modalities) should be specified.	
89	198	Please clarify, whose responsibility it is to define what is appropriate in terms of Ethics committee submission (trial sponsor, EMA or data receiver)?	
89	203-204	Please clarify, who would judge and how that results can be made public later than one year after accessing the data? EORTC would like to emphasize that some projects (i.e. follow-up of late toxicities) may require additional collection of data and therefore could not be completed within one year after the accessing the data.	
89	205	Please clarify, who will check that the data is destroyed after the analysis is finished (e.g. collection of certificates of destruction)?	
89	205bis	EORTC suggests that the EMA ensures that data requestors make appropriate acknowledgements (recognition of the effort made to collect all these data), disclaimers (no responsibility of trial sponsor vis-à-vis the results of the project or the way data are used) and conflict of interest	

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		declarations on any public release of results.	
89	210	EORTC believes that the project description and statistical analysis plan should always be uploaded and publically available.	
89	216-218	EORTC strongly recommends that the methodological robustness of the analysis is assessed by an appropriate panel of independent experts. Further to the comments on lines 57-61, EORTC emphasises that controlled access should not be given for any purpose which has not been adequately evaluated for scientific and methodological robustness. See general comment 1.	
89	278-281	Please clarify whose responsibility it is to verify/confirm that data have been adequately de-identified prior to the transfer? In cases where insufficient de-identification leads to a claim and/or damage to an individual, who will be liable (trial sponsor, EMA or data receiver)?	
90	General	LIF – Sweden would like to express the same views as Efpia. Please refer to the input from Efpia (see Stakeholder no. 05 for EFPIA comments)	
91	General	EFSPI supports responsible data access. EFSPI believes access to clinical trial data should be implemented in a way which supports good research, avoids misuse of such data, lies within the scope of the original informed consent and fully protects patient confidentiality.	
91	General	The majority of EFSPI's comments relate to the provision of 'C' type data. EFPSI recognises the EMA's commitment to put in place appropriate standards, rules and procedures for de-identification of these data and to work with concerned parties towards this goal. EFSPI is committed to contributing to this work. EFSPI objective in providing these comments is to help ensure that the ultimate provision of 'C' type data leads to the best	

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		possible science within the constraints posed by the need to protect confidential information.	
91	General	EFSPI believes that there is a need for the policy to have a clear process mapped out with governance from submission of a research proposal up to and including publication of the additional post hoc analyses, including the consequences for not complying.	Include a process map from start to end, and describe all the steps in the process clearly.
91	General	A controlled system where the requestor can analyse the raw data but download only summary results is preferable with respect to patient confidentiality and the enforcement of any requirements for pre-specification of analysis plans. The controlled access system should allow the ability to combine data from multiple companies, e.g. to conduct patient level meta-analyses.	Include references to setting up a controlled system to manage access requests.
91	033-035	Allowing researchers to re-analyse and replicate primary analyses seems misaligned with the EMA current practice of not receiving the CT data themselves to re-analyse it before they make their decision to grant regulatory approval. Will the EMA analyse the CT data themselves?	Clarify if the EMA will begin to analyse CT data themselves as part of assessing a regulatory submission.
91	038-39	There is a reference to 'established ways and means to anonymise data and protect patients from retroactive identification.' References or details should be provided for these processes.	Add references of protecting patients from retroactive identification
91	047-48	The patient consent process for analyses outside the initial scope of the trial needs to be clarified. An Informed Consent template or, at a minimum, a list of minimum or essential elements that should be included in an informed consent should be specified in the policy.	Clarify the minimum elements, or provide an example of, an informed consent template that would be sufficient to prevent informed consent issues to grant access to data in line with the policy.
91	057	The use of the term "secondary" analyses is unfortunate and in relation to respected ICH guidelines, such as ICH E9, not appropriate. In E9 there is	It is better to reference these analyses as "post hoc additional" or "replicate" analyses depending on their

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		mentioning of secondary variables and secondary parameters, but this is then still in the context of pre-specified variables and parameters. This is, however, clearly not the setting of the analyses at stake in this draft policy, which are all post hoc, after the trial results have already been presented and in statistical language the “alpha” has been spent.	objectives.
91	059-61	EFSPI endorses EMA’s plan to put measures in place to protect against claims resulting from inappropriate analyses. In our view, these measures should include: • Scientific rationale • Pre-specified statistical analysis plan • Qualified personnel • Independent review of the research proposal • Communication between the researcher and owner of the data • A governance process, including arbitration, in case of replicating analyses show results relevantly different form the original analyses	The measures to protect against claims resulting from inappropriate analyses should be stated. These measures should be mandatory and not optional as in the current draft policy.
91	070-72	It is stated that those conducting secondary analyses should be given a reasonable time to conduct their analyses without anyone being informed. We would feel it to be fair that the market authorization holder is informed about the identity of the requestor and the aims of the analysis, at the time when access to “C” data is granted. This would give the opportunity for researchers to communicate with the data owners on the proposed analyses. It also enables other researchers yet to request access to the data visibility to the proposed analyses, thus avoiding unnecessary duplication by other	Requests for data to be published when access to “C” data is granted. Clarify whether there is a limit to the number of requesters proposing to conduct a re-analysis of the primary analyses.

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		researchers to conduct similar proposed analyses. Is there a limit to the number of requesters who wish to re-analyse and replicate the primary analyses? Is one sufficient? If not how does more than one request support knowledge in the interest of public health?	
91	083	There are major drawbacks with the policy only covering submission data, which is only a subset of trials that are available.	Note the limitation of the policy not covering all trials that could be available.
91	092	It is not true that “raw data” is customarily submitted to the EMA.	Delete this statement.
91	096-097	There will be situations where the sponsor will not have access to observational research data supporting a regulatory filing as they did not have direct access to the data but instead through a third party.	Clarify what is in scope for observational research methodologies.
91	120-121	CDISC differentiates between so-called SDTM and ADAM data sets, the first basically referring to “raw data”, the latter to the “derived analysis data” underlying the statistical analysis and data presentation.	It would be helpful in case the policy more clearly indicates what is meant here in terms of required data and associated formats.
91	120-121	Annotated CRFs, variable definition, data specifications etc would better fall under another heading (and potential another process in terms of disclosure) than raw CT data – these are meta-data and don’t have the confidentiality issues of the actual data.	Separate descriptions of meta-data from descriptions of actual data.
91	121	It is not clear what is meant by “test outputs”. We would think of test output as being output that is created by a program prior to the program being peer-reviewed, validated and put in ‘production’ (its final read-only location). We see no purpose in storing test outputs or providing them to anyone. Perhaps “test output” means something different to the guidance authors?	We suggest removing this or define what is meant by test output, as it is not clear how it relates to raw data.

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91	121-123	Statistical analysis software logs, test output of programs and SAS programs are mentioned as “raw CT data” here in the definition, but not later in the draft policy. These documents are not generally part of the CTD and CSR in Annex I and II. In addition, many data owners consider their SAS macros intellectual property. Requesting one-off SAS programs instead would be expensive.	We propose that logs, test outputs and programs are not made public unless they are contained in the CTD and CSR.
91	143	The term “adequately de-identified” should be defined. These definitions must be endorsed by European Data Protection authorities before the policy can be implemented.	Define and reference “adequately de-identified”.
91	149	It is not clear whether the personal names of people involved in the conduct of the study need to stay in the report to be made available for “open access”, or whether they can be deleted should the sponsor choose to do so (as part of the redaction of the study report that anyhow needs to take place).	Allow the sponsor to remove personal names of people involved in the conduct of the study as part of the redaction process.
91	165-175	Guaranteeing confidentiality appears incompatible with making data available for replication of primary analyses or for secondary analyses or meta-analyses. There are certain data elements that are considered personal identifying information (PII), but would be necessary for performing the research/analyses. For example, Race is considered PII but can be very important to determine if there is a specific safety concern for a certain race of the population. How the level of de-identification in Category 3 differs from Category 2 is unclear. The way category 2 and category 3 are currently defined suggests overlap between the 2 categories depending upon what constitutes adequate de-identification.	Clarify and describe what constitutes “adequate de-identification”. Clarify what is the difference between „de-identification" and “anonymization”? Clarify the definitions of category 2 and category 3 data and ensure there is no overlap between these 2 categories.

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91	166-168	It is important that there is general acknowledgement that full transparency and full protection of data privacy (also for the long term future) is not feasible. Indeed there will be cases whereby data anonymisation will still leave the researchers with a data set that has a high level of utilization. But that is not the point. The point is that there will be cases whereby data anonymisation will simply mean that replication/reproduction of the original primary results will not be possible. And it is important that that limitation is a given and to be fully understood by everyone because it is key in understanding the intrinsic incompatibility of patient privacy and full transparency, whether we like it or not.	Add sentence acknowledging that "However, there will also be cases whereby data anonymisation (because of having to leave out parts of the raw data) will simply mean that full replication/reproduction of the original primary results will not be possible."
91	168	It is unclear to us whether EMA intends a full release of all data or a minimum release of only the data needed for the request's objective. In order to increase patient data confidentiality, a limited release is preferable as many of the data sets will contain tens if not hundreds of variables. Many of these will not be required for the intended purpose of the analysis.	In our view, a limited release requires a pre-specified analysis plan that specifies the variables to be analysed. Who will prepare the dataset with the limited data for each request?
91	168-171	It cannot be guaranteed that appropriately de-identified data sets will always preserve the ability to replicate the main analysis as it depends on the patient identifiers included in the main analysis and how much of the data requires de-identification to protect patient confidentiality.	Add *"if this is possible"* to the last sentence in this paragraph.
91	172	The reference [2] in the document regarding the de-identification requirements, while appropriate for the minimal data that usually appear in publications, would likely lead to problems when applied to the considerably greater amount of data that is collected in clinical trials supporting a regulatory submission.	Provide more details of how data should be de-identified and clarify what is expected to be submitted to describe how data was de-identified, or add a reference that this will be explained in a separate guidance document.
91	174-175	De-identified data will remain vulnerable to a persistent, intelligent match effort with access to databases of additional personal data such as medical	EMA should consider a closed environment for analyses that precludes the download of patient level

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		records, insurance claims, vital statistics, and/or similar as well as social media. This is especially true in rare diseases. Data redacted to withstand a robust, sophisticated match effort would likely also lose much or all of its scientific and transparency value. It may be very difficult to implement the recommendation to de-identify data in such a way that "adherence will preclude subject de-identification, even when applying linkages with other data carriers (e.g. social media)." Even the cited reference (Hrynaszkiewicz and Norton, 2010) suggest some options that are difficult to implement such as "Consent for publication of appropriately anonymised raw data should ideally be sought from participants in clinical research" and that in some cases there should be a review by an ethics committee. As de-identification is very complex, it would be helpful to elaborate more on this topic rather than providing just one reference. We believe that a standard for de-identifying data needs to be developed that all can follow.	data. Provide additional references on de-identification or note further guidance will be developed.
91	176-205	We would recommend adding expectations around appropriate storage of PPD data between downloading and destroying (e.g. Access, security – Physical/logical etc…). Ideally the data would stay in a "closed secure environment" that helps ensure appropriate protection of personal data. Data if accessed outside of a controlled system should only be destroyed after all the analyses have been completed, reported and published. If the data are destroyed after the analysis is completed but before the results are published, the researcher is unable to address any questions that may arise	Clarify expectations on appropriate storage, access and the destruction of data to researchers who are granted access to data. Confirm data should be destroyed once all the data analyses are completed, reported and published and there are no questions on the results. However, the statistical programs that generated the results of the post hoc analyses should be kept to allow for reproduction, if necessary (similar to the practice for primary results).

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		from the publication of the results.	
91	188-190	The policy does not make clear who will take responsibility in case of re-identification. What will the penalties be if patient confidentiality is breached? Who will be held liable?	Clarify who is responsible if data is retroactively identified and who is liable if patient confidentiality is breached.
91	191-192	It is unclear to us what is deemed "outside the boundaries of patient's informed consent".	Please clarify what is meant by "outside the boundaries".
91	198	The requester is required to 'have obtained ethics committee approval, as appropriate'. How would the requester know when this is required and to whom must they apply for approval?	Clarify how the requester obtains the necessary information on ethic committees to approach to see approval.
91	199	EMA's standards for good analysis practice should be made publically available and not just communicated to requestors.	EMA should publish the standards they expect for good analysis practice and this should be referenced in the policy.
91	203-204	All additional analyses conducted by the requester including all their supportive documents e.g. data derivation rules should be posted next to the request to ensure a similar transparency of the secondary analyses to the primary analysis.	Clarify the requestor has to post or publish all of their supporting documents for their additional analyses to promote full transparency. The publication should also mandatory have to indicate that it concerns a post hoc analysis after the trial results have already been published (and the acceptable error rate level (alpha) has already been spent).
91	203-204	Data owners should be notified/informed of the results prior to publication especially if there is discrepancy. If there are any deviations to the pre-specified plan, these should be identified appropriately and referenced in publications.	EMA should expect requesters to collaborate with the data owners if discrepancies arise in the re-analysis of primary results. For example, this might be to confirm the researcher hasn't used an inappropriate variable or misunderstood the data.

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			EMA needs to put a governance process in place for publication of results that relevantly deviate from originator's analyses. Clarify that the requestor should include any deviations from their pre-specified analysis plan when publishing their results.
91	205	Destruction of accessed data: should not happen when the analysis is completed, but after publication. All data and statistical programs used to produce the secondary analysis should be archived for at least 5 years to facilitate further validation if needed. Certification of destruction is mandatory and should be enforced. How does the Agency intend to do so?	Data should not be destroyed for a period of time after additional results have been published. The same rules as for the original analyses should be applied cf. line 67ff.
91	210-215	The statistical analysis plan should be mandatory. The three issues 1. Replication of analysis / re-analysis (using different approaches / robustness of results) 2. Post hoc analysis, new questions 3. Meta analysis should be clearly separated. Regarding 1): use of the original analysis plan is needed as the additional analysis is a new sensitivity analysis. A dialogue between the researcher and the data owner should be encouraged. Regarding 2): there needs to be considerations to multiplicity as any additional analyses will be exploratory and not confirmatory. In addition the principles of ICH E9 should be followed: pre-specify population, endpoints, analysis model, handling missing data etc. Regarding 3): no additional requirements as there are plenty of existing guidance for conducting meta	EMA consider working with industry and academic bodies to provide a template for a SAP for re-analysing data or for conducting secondary analyses. Access to 'C' type data should be contingent on the provision of an analysis plan.

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		analyses. EMA could provide a SAP template that could ensure the above aspects are considered.	
91	214, 222-231	It is stated that the requester can decline to upload any documents, like an analysis plan, *at the time* of requesting access to 'C' data. The reference to the *time* of requesting access makes us wonder if there will be subsequent opportunities for the requestor to upload documents like an analysis plan. If the requestor does not submit it with the request for access, can they still submit it before receiving the data (assuming the request is approved)? Is there any time when the analysis plan is *required* to be submitted, for example at the time of disclosure of results?	Clarify if there will be subsequent opportunities for a requester to upload documents and if there is a time when a SAP is required to be submitted.
91	216	To ensure scientific validity, the EMA should always judge the validity of the request and the competence of the requester.	EMA should review a request for access to data to confirm the scientific and statistical validity of the proposed analyses.
91	217	EFSPI believes that the same professional standards should be applied by EMA for secondary analyses as for the primary analysis of CT data.	Add the requirement of a qualified statistician as required by ICH E9 also for secondary analyses of CT data.
91	222-225	Is the requester of data required to share their computer code when information about the requestor is published by the agency (line 222-225)?	Clarify if the requestor should publish their computer code of their additional analyses.
91	222-231	The access to 'C' data should be fully transparent. The delayed publication of requests to access to 'C' documents/data and their aims may lead to duplicating research.	Requests including scientific rationale and statistical analysis plan should be published immediately, so that anyone (e.g. sponsor) can comment publically. In addition, immediate publication avoids other researchers developing duplicate requests for access

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			to data.
91	242-244	Will somebody at some point during the process have to confirm that data have been appropriately de-identified when the data are provided to EMA? If the sponsor has performed an integrated analysis in the submission, the data set containing the integrated clinical trial data should not need to be resubmitted. There are no details provided on how CT data are to be submitted.	Clarify the process for who will be confirming data have been appropriately de-identified. Clarify that integrated data sets containing multiple clinical trial data will not need to be submitted if the sponsor has conducted integrated analyses. Clarify how CT data is to be submitted and will the EMA put in place similar guidance to the FDA on data standards and how to submit compliant data sets?
91	251-252	The policy states that for a variation of a centralised marketing authorisation, CT data not previously submitted to the Agency would be in scope. For older studies the informed consent used previously may not permit the release of data to third parties. How will this conflict be resolved?	Clarify how CT data for a variation is allowed to be in scope of the policy with respect to informed consent in place when the study(s) were conducted.
91	251-252	The policy seems to only hold for centralised procedure submissions. It would be helpful to clarify that the policy does not hold for any submission as part of a decentralised and/or mutual recognition procedure even though it involves submission to an EU Member State.	Add statement that decentralized procedure and mutual recognition procedures are not within the scope of this policy.
91	260-261	Typically, a submission contains clinical trials that were conducted over a considerable time span. Do data and study reports e.g. from phase II studies need to be retrospectively adapted to the new rules?	Clarify the scope of the policy.
91	260-261	If a guidance document is made available 31Oct2014 then 1Jan2015 (2 months including the end of year holidays) could be a challenging timeline for a data owner to de-identify data as per the final guidance, especially if	Could the final guidance document be available before the 31Oct2014 or the time between the final guidance being available and the effective date is more than 2

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		the regulatory filing includes many trials.	months apart?
91	279	It would be helpful to explain further what is meant by “key codes”.	Clarify what is meant by ‘key codes’
91	291-292	There are concerns about the legality of allowing access to the names and addresses of the personnel working on the trial. It is difficult to understand why this is in the public health interest.	Information concerning personnel involved in clinical trials should not be made public as the data is confidential.
91	Annex 2 page 15, Sections 14.3.1 – 14.3.3. compared with Annex 2, pg. 16, Section 16.2	We are wondering about the rationale for making listings of deaths, other serious and significant adverse events, narratives etc. with access “O, 1”, while the access for patient listings of discontinued patients, adverse events are “C” category. They seem to be very similar in nature. Section 16.2 implies that all of these patient data listings will be available for every CSR. Whereas in reality, very few patient listings are now included in CSRs as the need to generate patient listings is substantially reduced.	All listings of patient data should be classified as ‘C’. Clarify that ‘C’ access will only be granted where documents exist and the policy is not expecting that these listings be created for every CSR.
92	General	This June, the European Medicines Agency released its draft Policy on the publication and access to clinical-trial data, for a three-month public consultation closing on 30 September 2013. ARPIM, the Romanian Association of International Medicines Manufacturers, structure representing 28 R&D based pharmaceutical companies, feels the need to respond to the EMA"s call for comments. Through this position paper, ARPIM is expressing the opinion that the EMA"s proposal may result in greater transparency, but also the concerns that some provisions might compromise certain critical public health interests,	

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		As it stands, the EMA draft Policy would have impact on three essential elements for promoting public health, as follows: 1. The privacy of patients and other individuals identified in marketing authorization application (MA) files ARPIM is supporting EFPIA position that "protection of patient privacy is a paramount concern when sharing raw CT data". However, ARPIM as well as EFPIA is concerned that the draft policy does not do enough to protect against re-identification of patients based on this data. As written in the EMA draft Policy, it appears that the Agency plans to widely release de-identified patient data. Recent studies have shown that there is particular risk of re-identification when such data are made widely available. Additionally, we must consider that re-identification technology is advancing rapidly. ARPIM considers also that the EMA's draft policy neglects to address the protection of personal data of investigators and study personnel in MA submissions; the privacy of all individuals involved in clinical studies needs to be protected. In addition to considerations of personal data privacy, there remains the imperative of respect for the terms of the informed consent given by the patients participating in clinical trials, both in the EU and 3rd countries, with regard to the subsequent or secondary use of their data (whether "anonymised" or not), as a matter of ethics and a central tenet of good clinical practice. In the draft Policy, the EMA appears to infer a broader scope to individual patient informed consent than is usually the case, especially historically in past clinical trials, when the current issues now being debated were not envisaged. The draft Policy ambiguously refers to the "spirit of informed consent", whereas in reality trial sponsors (and by definition, any other party handling the data, including the EMA) must	

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		respect the informed consent in its particular terms and according to the laws of the country where it was given. The release of clinical trial data-whether by the sponsor or EMA-can only ethically and lawfully take place within the scope of the specific informed consent given by the patient to the trial sponsor and is not distorted so as to deprive the concept of "informed" of its meaning, and the party releasing the data must bear this responsibility. 2. Introduce risks of misinterpretation and misuse of clinical data into the process, decreasing the level of trust in the assessment of regulatory authorities ARPIM is concerned that the control set out by the draft for consultation is inadequate to ensure that the research/secondary analysis of clinical trials data is robust and for good scientific purposes. Data can be misunderstood, misrepresented and misused through inappropriate secondary analysis. The misuse of data can lead to public health scares and undermine confidence in regulatory systems. The EMA draft policy fails to secure the legitimacy and scientific rigor of the use of the data: • It does not require the requester to provide or publish statistical analysis plans; • It does not allow for a prior review of the requestor's statistical analysis plan or qualifications. ARPIM is considering that these missing elements are essential to avoiding poor secondary analyses which may threaten public health as well as trust in regulatory systems. 3. Potentially decrease the level of investments in biomedical research by	

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		disclosing companies "commercially confidential information (CCI)", without due consideration of the competing interests that may or may not justify disclosure. ARPIM considers that the CT data in a MA dossier may contain commercially sensitive information. The protectior of this information helps to maintain the incentive for companies to continue innovating and making the enormous investments needed in medical and scientific research. The EMA's plans to release this data are therefore a threat to research and innovative medicine development. Problems with the EMA's proposal include: According to the EMA draft Policy, CCI will not be disclosed; "in general, however, CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI". This is not consistent with the definition of CCI stated in the EMA draft policy, as "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". The EMA draft Policy's claim that "CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI" is inconsistent with EU law, which requires that analysis weighing the relative CCI and public health interests be made on a case-by-case basis . The EMA draft Policy fails to give CCI and public health interests the equitable due consideration required. The draft Policy's assertion that MA data can be disclosed because it cannot be considered CCI, has already been challenged in the recent interim decision on EMA data release as determined by the General Court of the EU in the AbbVie and Intermune cases. The Court ordered the EMA not to release certain clinical trial information from the MA dossiers - considered to contain CCI by the applicants in these cases	

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		- pending the final outcome of this litigation. The Court determined that it is not "entirely unfounded" to conclude that a clinical study report - hundreds of pages long - could contain CCI. These cases are ongoing. ARPIM believes that implementation of the joint EFPIA-PhRMA Commitments to Data Sharing is the best means of advancing responsible transparency - that will promote public health interests by safeguarding patient privacy; preserving the integrity of regulatory systems; and maintaining incentives for investment in biomedical research . EFPIA and PHRMA companies have committed to: 1. Share upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines. 2. Enhance public access to clinical study information, by making publicly available, at a minimum, the synopses of clinical study reports (CSRs) for clinical trials submitted to the FDA and EMA. 3. Share results with patients who participate in clinical trials. 4. Certify on a publicly available web site that they have established policies and procedures to implement these data sharing commitments. 5. Consider all company-sponsored clinical trials for publication in the scientific literature irrespective of whether the results are positive or negative. ARPIM believes that publicly sharing its concerns regarding the EMA draft policy is an important element- and integral to the spirit of the public consultation process - in advancing the debate on data transparency, and	

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		continues to encourage open dialogue on the topic. ARPIM as well as EFPIA will continue to engage with all relevant stakeholders on the topic of clinical trial data sharing, in pursuit of a responsible data sharing solution that will serve innovative research and the patients who benefit from its output.	
93	General	**Introduction** The European biotechnology industry represented by EuropaBio welcomes the opportunity to submit comments on 'Policy 0070 on publication and access to clinical-trial data'. EuropaBio supports responsible transparency. However, we feel that the current proposal diminishes the protection of personal data and of commercially confidential information (CCI), in a way which would be detrimental to the innovation and growth potential of European biotech companies, large and small. We have therefore included our proposed suggestions in the following document but would also like to ask that once the consultation period is closed and the proposal has been amended as a result of the consultation, EMA and DG SANCO: • Conduct an impact assessment of the proposed EMA policy with regard to: - The level of risk for re-identification of patients through access to patient-level data -, particularly in light of recent experience with genetic data privacy; and - The likely effect of sharing clinical-trial data on the industry's confidence in the regulatory framework in light of the disclosure	

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		requirements as outlined in the draft Policy/0070 • Make the above-mentioned impact assessment public; and • Extensively consult with other relevant Directorate Generals - including DG Research and Innovation, DG Entrepreneurship and Industry, DG Internal Market, DG Trade, the EU Data Supervisor and the Secretariat General of the European Commission responsible for the implementation of Regulation (EC) No 1049/2001 regarding access to European Parliament, Council and Commission documents – in order to ensure a certain degree of alignment between all existing and ongoing initiatives in this field.	
93	General	**Fundamental Comments** **Responsible transparency** Access to European Parliament, Council and Commission-held documents by any European Union citizen and any natural or legal person residing, or having its registered office, in a Member State is a legitimate right granted by the Treaty1. This right is implemented through Regulation 1049/20012 of 30 May 2001. While the Regulation intends to enhance the transparency of EU decision-making processes, it also recognises the need to protect other vital interests such as privacy, integrity and commercial interests (including trade secrets and intellectual property). This ensures that a right balance is struck between transparency on one side and the protection of individual privacy and of innovative potential of European industries on the other side.	

[1] Article 255 of the Treaty establishing the European Community
[2] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents

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		Maintaining this balance is what we refer to as responsible transparency. **Data privacy in biotech specific fields** As EMA acknowledged3, appropriate protection of personal data is crucial. EuropaBio member companies and associations fully concur with EMA that protecting patient integrity and privacy should be paramount in any transparency initiative. As sponsors of clinical trials our member companies comply with data privacy rules (Directive 95/46/EC) and patients entrust sponsors with the responsibility to ensure protection of their personal data based on their informed consent. Industry has therefore a material and legal duty to appropriately protect personal data. We are concerned that the current standards proposed in the draft policy are inadequate to ensure that confidentiality of personal data is maintained, particularly if the information is to be released electronically. The re-identification of patients after disclosure of patient level data, even if anonymised, is a critical issue and re-identification technologies (e.g. data mining) are developing rapidly as larger quantities of personal data are being collected (e.g. through social media). Data privacy is even more important in biotech-specific areas such as rare diseases. As an example, clinical trials in the field of rare diseases include by nature only a very limited number of participants with a very specific clinical profile. As the “uniqueness” of this patient population is high, particular attention should be given to the evaluation of risk of re-identification before the data is disclosed. In the field of genomic data privacy, it has long been recognised that the	

[3] Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open Clinical Trial Data for All? A View from Regulators. PLoS Med 9(4): e1001202

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		"current set of privacy protection methods does not guarantee the protection of the identities of the data subjects" therefore suggesting that particular attention should be given to the protection of genetic data4. A recent experience showed that with access to a DNA sequence in an open database, DNA could be traced back to a donor relatively easily5. Considering issues of genetic data privacy is timely and relevant, as more and more personalised medicine solutions are being developed. As risks of de-identification always exist, such risks need to be highlighted to participants during the informed consent process in a prospective manner, before implementing any significant changes to the current controlled-access systems. Therefore, EMA should include appropriate safeguarding clauses in the draft Policy which would effectively address this important issue.	
93	General	**A robust regulatory framework** The process for authorising medicinal products within the EU is based on the scientific evaluation of three key principles: quality, safety and efficacy. This process ensures that medicines available in the marketplace have demonstrated a positive risk-benefit balance in favour of patients. As such, applicants for new marketing authorisations are requested by law to provide all particulars and documents to regulatory authorities to demonstrate that	

[4] B. A. Malin, An Evaluation of the Current State of Genomic Data Privacy, Protection Technology and a Roadmap for the Future, J Am Med Inform Assoc. 2005;12:28–34. DOI 10.1197/jamia.M1603.
[5] A Hacked Database Prompts Debate about Genetic Privacy: Experts urge transparency and new regulations to protect DNA donors, by William Ferguson. As consulted on 01 September 2013 on: http://www.scientificamerican.com/article.cfm?id=a-hacked-database-prompts

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		their products met these principles. The scientific evaluation of medicinal products is carried out by qualified European experts following a rigorous and well-established process6. This provides a high level of integrity of the scientific opinions. This has also led to the EU having a strong reputation among its peers globally for the excellence of its work as well as trust among stakeholders, healthcare professionals and patients. Over the past decades, EuropaBio supported the development of this world-class regulatory system in Europe to provide adequate oversight for quality, safety and efficacy of some of the most innovative medicinal product. This regulatory oversight does not only span the drug development and authorization process, but also the post-authorization development and product safety. Many new tools have recently been implemented by the EU pharmacovigilance legislation and are now used in practice to strengthen the regulatory oversight during clinical trials and post-marketing studies. Regulators and industry invest significant resources in developing and agreeing standards to ensure high quality research. EuropaBio welcomes enhanced transparency, but it is concerned about the potential impact of premature disclosure of clinical information without appropriate guidelines on its use. Furthermore, premature disclosure of clinical information would affect the integrity of the European regulatory framework which builds upon trust and confidence between the various relevant stakeholders and foresees a number of safeguards. The draft Policy/0070 does not set sufficient requirements for secondary	

[6] Central authorisation of medicines, EMA. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		research. On the one hand it states that an analysis plan would be of utmost importance; on the other hand, it does not require that such a plan be submitted prior to the granting of access to the data. The level of disclosure required of the requester regarding analyses and results should be the same as required of the Marketing Authorization Holder.[7] It is noteworthy, that the above mentioned article contains also a few paragraphs explaining why clinical trial data should not be open for all: "(…) independent analysis per se is no guarantee of high quality. The regulatory community has been confronted with meta-analyses that were later contradicted by additional evidence or found to be flawed." Reanalysing underlying clinical data without appropriate methods would be second-guessing regulators and could, if poorly conducted, create unnecessary public health scares over drugs[8]. Misinterpretation of data if it were made public could have significant consequences for patients since it carries morbidity and mortality implications"[9]. The EMA draft policy, if implemented as it stands, would not sufficiently guarantee that secondary research conducted on regulatory submission data is of the same quality and applies the same rigorous scientific standards as the original research, thus potentially impacting public health as illustrated above. To correct misleading results would not only consume resources which would be needed elsewhere but also have a negative impact on health.	
93	General	**Fostering the innovative potential of European Biotech Industries**	

[7] See e.g. Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open Clinical Trial Data for All? A View from Regulators. PLoS Med 9(4): e1001202: "We argue that independent analyses warrant a similar level of scrutiny as sponsor-conducted analyses do."
[8] A. Jack, Drug test rules 'would eliminate biotechnology sector in UK', April 21, 2013, Financial Times
[9] A. Jack, Drug test rules 'would eliminate biotechnology sector in UK', April 21, 2013, Financial Times

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		EuropaBio believes that the draft Policy/0070 in its current form risks negatively impacting incentives for biomedical innovation. The biotechnology industry is particularly concerned about the possible misuse or unfair commercial use of information and documents disclosed under the current draft EMA policy. The biotechnology sector is one of the world's most research-and-development-intensive sectors. During the development of a biotech product, a substantial amount of data is generated and significant know-how is developed. This includes an intimate knowledge about the product, company-specific characterisation of data, technological and manufacturing processes or computer codes. The generation of this know-how also requires substantial financial investments[10] and, sometimes, it cannot be protected by the usual intellectual property tools (e.g. patent, copyrights etc). This is notably why companies seek to protect their proprietary information as CCI. Competition is an important driver for innovation. Premature release of critical development information including applications or pending applications for marketing authorisation, or variations to existing marketing authorisations, without adequately protecting trade secrets or CCI significantly increases business risk for research-and-development-based biotech sectors. Premature disclosure could indeed provide competitors with an unfair commercial advantage to fashion similar or identical products globally, in regions where the originator company does not have a marketing authorisation, or where no stewardship or adequate protection for CCI exists. It is worth noticing that the majority of all requests for information	

[10] J. Mestre-Ferrandiz, J. Sussex, A. Towse, The R&D cost of a new medicine, Office of Health Economics, December 2012

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		held by EMA were made by industry, thus proving the commercial value of this information[11]. Furthermore, to ensure that any company continues to invest in Europe – at a time when competition is global, companies of all sizes must be confident that the fruit of their investments will be adequately protected. This assumption holds particularly true for small and mid-sized biotech companies (SMEs) that may depend on only one single invention to strive and survive. In a recent report, the European Commission (EC) stated that *"trade secrets and confidential business information are probably at the core of competitiveness of any European company, with many companies not realising how valuable these assets are until they lose them*[12]". The EC went on to state in a related consultation paper that "*the protection of trade secrets against misappropriation (…) is particularly important to SMEs*".[13] This is why the European Commission is considering a new legislative proposal to address the misappropriation of CCI and ensure that Europe strengthen and maintain its ability to innovate. SMEs are core contributors to innovation and economic growth in Europe. As any other innovative company, they regularly use and produce CCI on which they rely heavily for the long-term survival of their operations. If and when SMEs prefer to protect their trade secrets instead of patenting their invention (or protecting it through another IP right), then such trade secrets may well be their "only intangible asset". During the April 2013 survey organised by DG Internal Market, aiming at improving the "*protection of*	

[11] Doshi P, Jefferson T (2012) The First 2 Years of the European Medicines Agency's Policy on Access to Documents: Secret No Longer. JAMA, December 19, 2012. doi:10.1001/jamainternmed.2013.3838
[12] Report, European Commission Conference of 29 June 2012, "Trade Secrets: Supporting Innovation, Protecting Know-How"
[13] Refer to http://ec.europa.eu/governance/impact/planned_ia/docs/2013_markt_002_trade_secrets_en.pdf

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		trade secrets/confidential business information from misappropriation and misuse by third parties"[14] 75% of the respondents ranked trade secrets as "*strategically important to their company's growth, competitiveness and innovative performance*" and "*91% of participating companies see trade secrets as an important tool*".[15] Premature disclosure of CCI, misappropriation of research know-how and the lack of a predictable EU intellectual property/trade secret protection framework are factors that can undermine the ability of EuropaBio members to operate and innovate, and ultimately "their value proposition" for potential investors. Again the European Commission recently acknowledged that fact by recognising that "*it appears that trade secrets/confidential business information are often regarded as key protecting tools by small and mid-sized companies (SMEs) and researchers in (non-profit) research institutes, who use trade secrets both to replace as well as to complement IPRs*[16]".	
93	Lines 31 to 35	EuropaBio does not share the current EMA vision that enabling untracked and unsupervised secondary analysis of CT data that founded the basis of MAAs will provide substantial benefits for the public health. There is no evidence that having a large number of additional experts reanalysing submitted datasets would offer any positive benefit over a high quality review by the health authorities. Actually the potential benefit will be meaningfully outweighed by the risks of weakening the trust in institutions that should themselves determine the scientific basis and reliability of	**Suggest removing this premise** **Revise to read:** "Access to CT data **submitted in a MAA to EMA** will enable third parties to verify..." **Clarify if the EMA will also begin to re-analyse the raw data**

[14] Refer to http://ec.europa.eu/governance/impact/planned_ia/docs/2013_markt_002_trade_secrets_en.pdf
[15] Refer to http://ec.europa.eu/internal_market/iprenforcement/docs/20130711/final-study_en.pdf
[16] European Commission, Public Consultation on the Protection of Business and Research Know-How. As consulted on 01 September 2013 on: http://ec.europa.eu/internal_market/consultations/docs/2012/trade-secrets/121211_trade-secrets-consultation_en.pdf

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		medicines evaluation. The proposal to allow third parties to be able to use the raw data to verify the authority's decisions seems misaligned with the current practice where the EMA themselves do not receive the raw data to re-analyse it before they make their decisions.	
93	Lines 49 to 51	EuropaBio cannot agree with EMA's statement that *"In general, however, CT data cannot be considered commercially confidential information"*. One of the issues which the EU courts will need to examine is the question whether CT data benefit from a general presumption of confidentiality, in which case such data shall be considered as CCI in their entirely, unless an exemption applies. In addition, the issue of confidentiality of CT data may be impacted in the context of the ongoing legislative process related to the EU clinical trial regulation. Thus, we believe it is premature for EMA to express such a view. In addition, the statement is inconsistent with the CCI definition adopted by EMA and set out in line number 109-111. EuropaBio considers that some information in certain MA dossiers, depending on the sponsor, product at issue, competitive landscape, therapeutic area, and value of the information to competitors (and other factors) may, indeed, be CCI. Considerations of an overriding public health interest are relevant for the distinct purpose of determining whether in certain circumstances, public health interests in disclosure of CCI outweigh considerations supporting non-disclosure of protected information. It is only if information in a MA dossier meets the definition of CCI adopted by the EMA in this draft policy at lines 109-111, and if the EMA seeks to release such information over the owner's objections, that a separate inquiry then needs to be made prior to public disclosure to determine whether an overriding public health interest justifies release of the information. CT data shared precariously, during development of a molecule or resubmission, can seriously harm the competitive position	**Delete the statement** "CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI" **and replace with the following**: "CT data and other information present in MA dossiers submitted by sponsors may qualify as CCI, as defined below in this policy. If EMA seeks to release such information over the owner's objections, then a separate inquiry will be made prior to public disclosure to determine whether an overriding public health interest justifies release of the information."

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		of the sponsor. This is particularly the case for SMEs, including many EuropaBio members. It could even impact on the "value" of the company itself and its attractiveness for investors, for instance during so-called "due diligence". This is particularly relevant in the biotech sector, where mergers and acquisitions often take place.	
93	Lines 52 to 56	EuropaBio considers that allowing external parties access to CT data held by the Agency may negatively impact on the value, competitiveness, ownership and intellectual property rights of undertakings, especially SMEs, including many of its members, as well as researchers and their ability to share information and innovate. As the European Commission recently pointed out: **"the protection of confidential business information as a trade secret** is, for many businesses, **often the only or the most effective way to protect their intellectual property**. Such protection would allow innovators to reap the benefits from their innovations, at least for some time, and hence to earn sufficient return on their investment in innovation. In particular, it appears that **trade secrets/confidential business information are often regarded as key protecting tools by small and mid-sized companies (SMEs) and researchers in (non-profit) research institutes**, who use trade secrets both to replace as well as to complement IPRs. Concerns regarding the effectiveness of the protection of trade secrets in the Internal Market are already being voiced. (…) The (current) protection would not represent a sufficiently strong deterrent against theft of such confidential business information. Therefore, this could dissuade the sharing of confidential business information across borders with business partners who could offer valuable possibilities to develop new market possibilities for	**Add the following**: "The Agency will take into consideration risks of a negative impact on the value, competitiveness, ownership and intellectual property rights of undertakings, especially SMEs, on researchers and their ability to share information and innovate in the Union and on regulatory data exclusivity."

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		innovative products (our emphasis)" [17] EuropaBio believes that information protected by regulatory data exclusivity should be considered as being included among the sort of information as CCI.	
93	Lines 59 to 61	Unless these measures are appropriate, comprehensive, and effective, then the public health benefit intended to be realized by release of otherwise protected CT data and MA dossier information, will not materialize. These measures will need to be detailed, explained and validated before legitimate determinations can be made about whether the public disclosure of otherwise protected information is in the public health interest.	**Clarify what are the measures to ensure the best-possible protection of public health against claims resulting from inappropriate analyses**
93	Lines 67 to 72	There are no details about how to implement/enforce the policy regarding secondary use of patient-level CT data. By what legal authority is EMA intending to ensure compliance with standards of transparency? Does the Agency have the authority to compel submission of such information? As noted later in the document at line 83, data not held by the Agency is outside the scope of this policy. What is a reasonable period of time during which those conducting secondary analyses should be protected from external interventions? What interventions are meant here?	**Provide details on how to ensure that the requesters are going to be held at the same standard as the sponsors and will be granted protection from external interventions**
93	Lines 77 to 82	The scope is not clear. It is stated that the policy only concerns data that will be submitted to the Agency after the policy comes into force. In other words, the trigger is submission post coming into force. However, the paragraph goes on to state that pre-existing data submitted to the Agency (presumably post coming into force) e.g. in the context of a referral procedure is out of scope. In addition, informed consent issues may occur	**Change sentence to read:** *"The policy is prospective in that it concerns CT data submitted to the Agency after the policy comes into effect as outlined below (and for any product or purpose). All other CT data currently held by the Agency (e.g. those on products already on the market) or pre-existing CT data of*

[17] http://ec.europa.eu/internal_market/consultations/docs/2012/trade-secrets/121211_trade-secrets-consultation_en.pdf

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		during the early phase of implementation given that submissions will contain studies that ran before the draft policy was in place. Therefore very few sponsors would have updated their informed consent templates to accommodate the proposed data sharing measures.	*marketed products that will be submitted to the Agency, e.g. in the context of a referral procedure (''''legacy data''''), whether such data currently exist or will be generated after such entry into effect, continue to be made available to external requesters on a ''''reactive'''' basis as outlined in the Agency's current policy on access to documents."*
93	Lines 102 to 106	It is not clear from the definition of personal data whether data related to deceased persons is within or without scope. The Article 29 Working Party takes the view that the current EU law on data protection does not apply to information relating to deceased persons. The position will likely be the same under the new Regulation.	**Clarify whether data from deceased individuals is in the definition of personal data**
93	Lines 109 to 112	In view of the ongoing dispute in front of the EU courts and legislative process related to the EU clinical trial regulation, it is not possible to establish with a necessary degree of legal certainty what is to be understood as CCI. As per Regulation (EC) No 1049/2001, one of the exceptions to the principle of access to the documents held by the EU institutions include the possibility that such disclosure would "*undermine the protection of commercial interests of a natural or legal person, including intellectual property, court proceedings and legal advice, the purpose of inspections, investigations and audits".* EuropaBio considers that the definition of CCI needs to be expended notably to include internal knowledge (e.g. development strategy for the compound) and data obtained from 'third parties' where access/publication of such data is restricted or prohibited by contract.	**Add the following sentence:** *"However, in view of an ongoing court dispute and the review by the EU institutions of a proposal for an EU clinical trials regulation, it is not possible to unambiguously establish what is to be defined as CCI."*
93	Lines 113	The statement "It is emphasized that categorisation of information as CCI in	**Delete the sentence beginning** "*It is emphasised*

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	to 115	the policy does not limit access to documents or information under other agency policies" is inappropriate, and misleading because it suggests that standards used to designate certain information as CCI, and the consequences with respect to disclosure flowing from such designation, vary across regulatory processes administered by the EMA. The definition of CCI set forth and adopted by the EMA at lines 109-111 should in principle reflect general EU legal principles, natural and fundamental rights, and apply across all EMA purposes and policies. Access to such information is subject to the analysis set forth at Article (4) (2) of Regulation 1049/2001. This is true regardless of the EMA access to documents policy or transparency initiative at issue in any particular situation involving disclosure of CT data or MA dossier CCI information over the objections of a sponsor.	*that categorisation of information as CCI …*"
93	Line 129 to 132	EuropaBio considers that EMA must apply the definition it adopts at line 109-111 to determine what information is CCI. Categorization of information as CCI is not limited to "details of the investigational product itself, in vitro studies, or bioanayltical data characterizing the product." Nor is it appropriate to declare that only "a small number" of CT data/documents can contain CCI. Such a restricted application of the definition, one that pre-defines down the scope of information present in MA dossiers that can constitute CCI, is inconsistent with rights afforded to residents of the EU, and the findings of the general court in the 25 April, 2013 Interim Measures ruling in case T44-13. As noted in paragraphs 59-61 & 68 of that ruling, "it is not unreasonable to infer that clinical study reports, commonly comprising hundreds of pages of information, contain a substantial amount of commercially confidential information and manufacturer know-how." EuropaBio would like to ask EMA to confirm that all data will remain subject to regulatory data exclusivity protection and cannot be used in or referred	**Delete lines 129-132. Consider replacing by the following language**: "Any information contemplated for release by the agency will be shown to the sponsor and owner of the information, prior to release, in order to ensure that no information contemplated for disclosure constitutes CCI. A reasonable time will be afforded the sponsor to confirm that information to be released by the EMA is already in the public domain, or is otherwise not information the sponsor considers confidential, or not the sort of information that, if released, could harm relevant interests. Justification in support of CCI claims should be provided by the sponsor to EMA. Such justification will be respected by the agency, but may be rebutted on legitimate grounds (e.g. by indicating that information to be

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		any (art. 10 or Art 8) subsequent applications until the end of the exclusivity period. In many cases, an innovator will not necessarily know whether there is patentable subject matter hidden in the clinical data until a retrospective review has been undertaken. Because it would be difficult to identify with specificity, EuropaBio believes the data is confidential before a formal review of the data has been undertaken. EuropaBio does not support the statement that "information will only be deemed CCI in duly justified cases". Moreover, clarification is needed for the process by which companies can justify that information is CCI, and disputes resolved. This process would have to involve a case-by-case analysis of the relevant factors defining CCI, and a precise and careful weighing of any public interest at stake sufficient to justify release of otherwise protected information. Finally, as stated by the President of the General Court in paragraph 69 of the interim measures case, judicial review of disclosure disputes is needed because "the weighing up of the various interests present will call for delicate assessments which must be a matter for the Court adjudicating on the substance of the case."	released has in fact already been made available, or is the sort of information is not normally protected from disclosure, or is information that may not cause harm if released). Likewise, because even CCI may be released if justified by reference to an overriding public interest, the EMA will have the opportunity to justify release of CCI by articulating such a public health interest, as warranted and appropriate under the circumstances of any particular case. Ultimately, disputes over release of purportedly CCI information that cannot be resolved by consultation between agency and applicant will be subject to judicial resolution, through well-established, fair and orderly processes regarding judicial review of regulatory agency decision-making.
93	Line 137	EuropaBio does not agree with this statement.	**Revise the sentence to state that** "*CT data/documents not pre-categorised as 'CCI' in Annex I may still contain certain CCI that may necessitate removal*. "
93	Line 149 See also	Under Regulation 1049/2001, EMA must refuse access if disclosure would undermine the privacy and the integrity of the individual. In other words,	**Please delete:** "*This is the case with personal data of CT personnel*."

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
	line 289	there is no public interest test to be applied. By advocating disclosure of details regarding CT personnel, EMA would be applying a different standard in its policy compared to the requirement under the Regulation.	
93	Line 165 to 170	In the area of research and developments work for rare diseases, which is the case for several EuropaBio members, due to a small number of participating patients in respective trials, a broad release of patient-level data would increase risks to patient privacy, including re-identification of patients from anonymized data.	**Consider adding the following statement:** De-identification faces further challenges in small study populations, especially in the rare diseases area. All data sharing should be on a case by case basis and data should be shared only with the consent of the marketing authorization holder.
93	Line 172 to 175	It may be very difficult to implement the recommendation to de-identify data in such a way that "adherence will preclude subject de-identification, even when applying linkages with other data carriers (e.g. social media)." Even the cited references (Hrynaszkiewicz and Norton, 2010) suggest some options that (1) do not provide details for how data should be de-identified and/or (2) are difficult to implement. Also, in some cases there should be a review by an ethics committee.	**Provide more details of how data should be de-identified and clarify what is expected to be submitted to describe how data was de-identified, or add a reference that this will be explained in a separate guidance document**
93	Line 181 to 183	EMA proposes to condition access to Category 3 documents on execution of a "legally binding data sharing agreement," but it is not explained the legal basis for EMA entering into such an agreement, who the parties to such an agreement will be, how EMA will ensure the enforcement of such agreements, or the penalties or remedies available to a company or an individual harmed by use of data released inconsistent with such agreements. Implementation of a controlled access regime is impossible until these critical questions are answered. If parties qualifying for controlled access must comply with certain contractual conditions, then EMA must spell out the enforcement mechanisms and penalties to be enforced in cases of	**Clarify that the following will be included in the agreement: the legal basis, the parties, the monitoring and enforcement mechanisms, the right to audit, possible sanctions, remedies etc.**

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		breach or noncompliance.	
93	Line 191 to 192	The risks with this approach could soon materialise into reduced patient compliance.	**Indicate what kind of mechanism will be put in place to ensure that use of patient data is compatible with the informed consent.**
93	Lines 207 to 209	It is not sufficient to make requesters aware of expectations relating to good analysis and transparency. EuropaBio believes that it would be equitable to require third-parties to adhere to good analysis and transparency practices to avoid inappropriate use and/or misuse of clinical trial data.	**Good analysis practices should be included in the data-sharing agreement as a requirement**
93	Line 219 to 231	If an application is withdrawn, there may still be an ongoing development program requiring more data or exploring a different indication. This is often the case in the biotech sector, where different indications are often developed by the same or different sponsors. Proactive dissemination of the data on this compound could impact commercial competitiveness and IP rights. It is unclear why the information on the requestor and the analysis plan are withheld for a year. Transparency and collaboration should be encouraged and this seems to go against the principles already espoused in this policy.	**Consider adopting another timing for publication of ‘‘‘C’’’ documents when there may still be on an ongoing development program**
93	Lines 222-231	It is not clear what the rationale is for delaying release of the requestors' details, especially in case the requestor is a legal person (and not a natural person). The criteria for disclosure appear arbitrary.	**Requestor's details shall be shared at the time access to data is granted and it shall be possible to object to disclosure on reasonable grounds.**
93	Lines 253-255	A duplicate set of documents from which identifying data has been removed will be made available through 'open access' or 'controlled access' but apparently without a possibility to also remove CCI. This is not an acceptable process for sponsors. The legal basis for such unilateral request is unclear. It is also unclear how the Agency can legally implement this request.	**The policy should specify that the duplicate set of documents should be de-identified and CCI removed by the Applicant / Marketing Authorisation Holder** **Alternatively, the Applicant / Marketing**

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		Additionally, what happens if there is disagreement between the Agency and the MAH as to the extent of the redactions of CCI or PPD? Furthermore, from a data protection perspective it is the EMA that will make the actual disclosures and which is therefore responsible for the publication of released information which includes assumption that personal data has been appropriately de-indentified.	**Authorisation Holder must be granted sufficient time after the Marketing Authorisation to redact CCI from the concerned documents**
93	Lines 256-261	Section 16 and Annexes I-VIII can be extremely voluminous documents. A total de-identification of each new MAA would be a resource-intensive and expensive task. What is missing from the draft policy is a justification why access to all these documents is considered of public health interest. EuropaBio considers that access to Case Report Forms is not necessary to conduct a re-analysis and is disproportionate. It is important to avoid adding more administrative burdens for EuropaBio members, especially SMEs. There is also a question mark as to when it would be "practical" to submit 'C' data. If the guidance document is finalised by the end of October 2014 as suggested, there will only be 2 months available to create the 'C' data sets for the regulatory submissions that fall in scope of the policy. This time is insufficient to get all the supporting documentation in place.	**Include new category, e.g., 'PD' (personal data) for Case Report Forms meaning that these documents fall outside the scope of the policy** **Change the current timeline from the final policy becoming available and the implementation date to enable sponsors to put in place all necessary steps to meet the new requirements in the policy.** **State that submission of 'C' data will be expected 6 or 9 months after finalisation of the relevant guidance documents.**
93	Lines 266 to 267	We fully agree that the impact of EMA's final policy should be thoroughly evaluated and assessed. In order to facilitate this assessment, EMA should provide a formal consultation process so stakeholders could provide input into the EMA's methodologies for assessing the impact (i.e., impact not only on the Agency, but also on MAH's, clinical trial participation, overall investment in medicine R&D in Europe, etc.)	
94	General	The Irish **Pharmaceutical Healthcare** Association (IPHA) represents the	

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		international research based pharmaceutical industry in Ireland. Our members include both manufacturers of prescription medicines and non-prescription or consumer healthcare medicines. The mission of IPHA is to create a favourable economic, regulatory and political environment, which will enable the research-based pharmaceutical industry in Ireland to meet the growing healthcare needs and expectations of patients. It aims also to develop an appreciation of the value of medicines, in particular innovative medicines, to healthcare and society as a whole thereby ensuring patients' continued, timely access to the full range of available medicines, regardless of their ability to pay. Numbered amongst the companies with a manufacturing presence here are 13 of the top 15 global players, producing 5 of the top 12 medicines in the world. In order for our industry to optimise its leading role in driving the development of new medicines and treatments, it is essential that conditions prevail that will continue to allow innovation and excellence to thrive. Additionally, the development of medicines, including clinical trials, is a global process and it is important that any proposals in this area are managed at an international level to ensure a consistent approach which benefits both patients and industry. Thus we welcome the commitment to Patients and Researchers outlined in European Federation of Pharmaceutical Industries and Associations (EFPIA) and Pharmaceutical Research and Manufacturers of America (PhRMA)'s joint Principles for Responsible Clinical Trial Data Sharing[18] which will dramatically increase the amount of information available to researchers, patients and the general public. Published in July, ***Principles for Responsible Clinical Trial Data***	

[18] http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf

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		Sharing: Our Commitment to Patients and Researchers will put in place a system where the issues of patient and commercial confidentiality can be considered on a case-by-case basis, rather than a free for all and broad-brush approach being advocated in draft policy 0070. As the representative body for the research-based pharmaceutical industry in Ireland, IPHA recognises the importance of showing leadership in advancing responsible transparency. The industry supports measures that will enhance relationships between industry, healthcare professionals, patients and citizens at large. However, we are deeply concerned that the EMA sponsored transparency proposals will jeopardise patient privacy, the integrity of regulatory systems, and incentives for investment in biomedical research. Thus, while we support enhanced sharing of clinical trial information as a tool to broaden knowledge about medicines in the best interests of patients and public health, there is a need to protect patient confidentiality and commercially sensitive information.	
94	General	IPHA fully supports and endorses the EFPIA response to the European Medicines Agency draft 'Policy 0070 on publication and access to clinical-trial data. (see Stakeholder no. 05 for EFPIA comments)	
95	General	Medico international strongly supports the full public access to available scientific evidence about the effects of medicines on human health and specifically all data of clinical trials of medicines. This is a necessary precondition to prevent unwanted harm to patients (and the wider public) and improve existing therapeutic options for diseases. We see this as an important part of the Right to Health as enshrined in international (e.g. the International Covenant on Economic, Social and Cultural Rights (ICESCR), WHO constitution) and European (European Social Charter) Treaties	

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		We welcome the opportunity to contribute to the public consultation on the European Medicines Agency (EMA) draft policy on the publication and access to clinical trial date aiming to improve the current situation. We see “The proactive publication of data from clinical trials submitted in support of a marketing authorisation application” proposed by the EMA as a very welcomed step towards greater clinical data transparency. Furthermore, the EMA mentions in its policy proposal that “In general, however, CT data cannot be considered CCI (commercially confidential information); the interests of public health outweigh considerations of CCI.” We welcome this statement and call on the EMA to commit to it. Nevertheless, several points are important to keep in mind in this process: 1. it is necessary not only to provide access to data from new trials, but also retrospectively to clinical-trial data to all drugs approved in the European Union, either centrally (at EMA) or via decentralised procedure or through mutual recognition (CMDh) 2. Increased access to clinical trial data and other medicines related information, particularly on Adverse Drug Reactions should be included in other EMA processes as well, particularly into pharmacovigilance and safety issues. European public assessment reports (EPARs) should be updated quickly if variation is prompted by safety issues. 3. Restricting transparency and access to clinical data on the grounds of commercial confidentiality is not acceptable, Public access to clinical data contributes to increased public knowledge on the real effects of medicines and the protection of citizen’s health. Public Health concerns need to be	

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		paramount to claims of economic interests. 4. In the same way, the use of “patient data protection” as a pretext to prevent clinical data disclosure needs stringent scrutiny and cannot be used as a loophole to avoid transparency and a barrier to complete public data access. Following EU regulations, patient level data from clinical trials submitted to medicines regulatory authorities has to be anonymised. Granting public access to clinical trial data does not jeopardise patient’s confidentiality. In very exceptional situations (e.g. rare diseases), when - after taking into consideration all available means- re-identification is possible, additional measures can be implemented to avoid it. Anonymisation standards need to be implemented in ways maintain the detail of the data, in order to allow for re-analysis. Medico international is a health and human rights organisation with a history of 45 years striving for health and justice worldwide. Access to essential medicines and Rational Use of medicines as important elements of the Right to Health for everyone has been a mainstay in our work in these years. The efforts of medico as a co-founder of the International campaign to Ban Landmines were awarded with the Nobel Peace Price in 1997	
96	General	The International Alliance of Patients’ Organizations (IAPO) is the only global alliance representing patients of all nationalities across all disease areas and promoting patient-centred healthcare worldwide. Our members are patients’ organizations working at the local, national, regional and international levels to represent and support patients, their families and carers. IAPO has over 200 members which span over 60 countries and 60 disease areas and	

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		through its membership represents an estimated 365 million patients worldwide. IAPO welcomes the opportunity to comment on this European Medicine Agency (EMA) consultation on: *Publication and access to clinical-trial data*. IAPO is fully supportive of EMA's efforts to balance the need for transparency in the reporting of clinical trial results whilst protecting patient data. IAPO is engaged with this issue and has endorsed the AllTrials campaign which calls for all clinical trial data to be reported. The publication of clinical trial results is vital in improving the quality of healthcare to patients. Without full access to the results of clinical trials, healthcare professionals and regulators cannot make informed recommendations on treatment options and patients are unable to make informed decisions on their healthcare. The publication of clinical trial results is critical to ensuring that patients have accurate information on treatments, their efficacy and their relative benefits versus risk. Patient information is a core principle of patient-centred healthcare. To IAPO, accurate, relevant and comprehensive information is essential to enable patients and carers to make informed decisions about their healthcare. A key component of good quality patient information is that it is presented in an appropriate format. Therefore, it is essential that clinical trial results are published in a way that can be understood by patients and the general public. IAPO strongly supports measures to increase transparency on clinical trials results, but this should not come at the expense of patient privacy. Where there are trials that are undertaken on small sample sizes, particularly in the development of orphan drugs, it is critical that patient privacy is protected	

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		and that all potentially identifiable information is removed prior to publication. The publication of clinical trial results is a sensitive issue and needs the involvement of all stakeholders to facilitate openness and transparency. In particular, the patient perspective must be solicited to make sure that patient needs are met in relation to the protection of personal information and the presentation of clinical trials results. IAPO looks forward to working with the EMA on this issue and supporting their work towards greater transparency.	
97	219-221	A public audit process should be established. C documents should be open to external independent scientists at the time of a new drug application (NDA) request. This public scrutiny can compliment EMEA's internal investigations. Collaboration would be possible. The added external expert capacity can speed up the NDA decisions. Also, this audit would run fully transparent using a public NDA investigation website.	'C' documents will be made available at the time of acceptance of a new drug application request.
98	General	GSK welcomes the opportunity to comment on the EMA's proposed policy on publication and access to clinical-trial data. GSK recognises the benefits of: 1. Publicly disclosing clinical study reports (CSRs), while protecting the privacy and confidentiality of research participants and others involved in the research; 2. Providing access to patient level data for further research, while protecting the privacy and confidentiality of research participants and ensuring the data are used for valid scientific enquiry. To realise these	

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		benefits we have: a) Committed to publicly disclose CSRs for studies of approved medicines, going back to the formation of GSK in 2000, with personally identifiable information removed and/or anonymised; b) Established a system to provide access to anonymised patient level data to other scientists so they can conduct further research (see https://clinicalstudydata.gsk.com/). This system includes a requirement for review and approval of a research proposal by an independent panel, and provides for access to data with controls to prevent data being downloaded. GSK supports increased transparency of clinical trial (CT) data, and agrees with a number of the views and positions included in the policy's introduction. In particular, we welcome the EMA's position on open access to clinical study reports, provided there is detailed guidance on the anonymisation of CSRs which is endorsed by European data protection authorities and consultation with sponsors to ensure commercially confidential information (CCI) is not inadvertently disclosed. However, we do not believe that the EMA is best placed to provide access to patient level data under a controlled access model, particularly because there is no apparent legal basis for EMA to review research proposals and ensure the data are used for only valid scientific enquiry. We also have concerns about some other key aspects of the proposed policy. **Controlled access model for patient-level data:** A robust and effective controlled access scheme must include a review of research proposals to ensure scientific rigour, and must protect patient privacy. EMA's proposed controlled access model does not address the former in any way and there	

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		are significant shortcomings with regard to the protection of privacy. A review of the scientific rigour of research proposals is needed in order to reduce the risk of erroneous concerns about safety or false hopes of a potential benefit for patients. EMA should not provide access to patient-level data unless an assessment of the scientific rigour of the research proposal is a pre-requisite for such access. The current legislation that addresses access to documents held by the EMA (Regulation (EC) No 1049/2001) clearly requires privacy and CCI to be protected, but there is no clear legal basis for the EMA to refuse requests for access on the grounds of poor science where CCI or privacy concerns do not exist. EMA should not request MAH to provide patient-level data for the purpose of granting access to researchers, when EMA cannot lawfully impose conditions on access based on the need for good science. EMA's proposal to make raw data, including patient data sets, available for downloading by researchers does not provide adequate protection of privacy, as the downloaded data may be combined with other information, increasing the risk of re-identification. To reduce this risk, in addition to appropriately approved guidance on de-identification (see below), access to patient-level data should be in a secure environment that does not allow downloading of the data. Such a system is feasible as we have developed a system with SAS where researchers can access data, conduct and download statistical analyses but are not able to download the patient level data provided. Consistent with the above comments, we note that several bodies that are campaigning for or are supportive of increased transparency of clinical trial results, including the Cochrane Collaboration and AllTrials campaign, have	

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		stated that individual patient data should be available with appropriate safeguards to ensure ethical and scientific integrity (e.g. submission and review of a protocol), and to protect patient privacy. **Protection of personal information:** The EMA draft policy contains provisions intended to protect privacy in documents/data provided under both "open" and "controlled" access, but they are not sufficient or described in sufficient detail to be implemented. In addition, we do not believe that the names of company or clinical trial staff should be disclosed without their consent. Detailed descriptions of how CSRs and CT information should be de-identified are required, and must be endorsed by European data protection authorities (in particular the European Data Protection Supervisor and the Article 29 Data Protection Working Party) before the policy can be implemented. Whatever processes or rules the EMA puts in place, it alone will assume legal responsibility for any breach of data protection or other laws under this policy. Further, EMA should indemnify MAH for any liability arising from their compliance with this policy. **Inclusion of negative and withdrawn applications in scope:** The EMA draft policy relates to negative decisions and withdrawn applications, in addition to approved applications. To minimise the risks of erroneous safety or efficacy concerns from secondary analyses, or of disclosure of CCI, information additional to that already made public by the EMA from applications with negative decisions or that have been withdrawn should only be disclosed either following approval of a re-submitted application, or following confirmation from the sponsor that they have no plans to re-submit (i.e. development programme is terminated). Where there are	

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		negative decisions or withdrawn applications, the EMA should consult with the sponsor to agree a period of time after which the policy would apply to information previously submitted in the application whether or not an application has been re-submitted and approved. **Protection of commercially confidential information:** While we believe that there will rarely be commercially confidential information in CSRs for authorised medicines, the possibility that there may be CCI in these and other clinical documents should not summarily be dismissed, particularly in respect of documents prepared before the finalisation of EMA's policy. Whether or not CCI is present, and the nature of what is CCI, will depend on several factors, including the proposed timing of disclosure. The EMA should, therefore, include a process for consultation with the MAH prior to making these documents publicly available, unless the MAH has already confirmed the absence of CCI. Moving forward, efforts should be made to ensure that future CSRs do not include CCI. These general comments are reflected, in more detail, in the line-by-line comments below.	
98	36-43	We agree with the need to protect personal data. The policy elsewhere states the Agency will work with sponsors and other concerned parties to publish a guidance document on appropriate standards for de-identification in October 2014 that will apply to "controlled access" ("C") data. Given that personal data (e.g. patient narratives) will be contained in "open access" sections, it is essential that this guidance be available **well before** preparation of reports of studies that will be disclosed under "open access" (currently all applications from 1 March 2014), to ensure a consistent and appropriate approach to the de-identification of documents and data.	

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		Furthermore, this guidance must be reviewed and authorised by appropriate expert bodies, such as the Article 29 Data Protection Working Party. The policy document refers to concerns that emerging technologies for data mining and database linkage will increase the potential for unlawful retroactive patient identification. We agree. However, by allowing the download of "controlled access" data, the proposed policy fails to adequately protect against these concerns. Once downloaded, data can be combined with other information, increasing the risk of inappropriate use and re-identification. By adopting an approach that attempts to address privacy concerns by primarily relying on adequate de-identification of data, the proposed policy fails to incorporate safeguards that are present in other systems that provide access to individual level clinical and/or health data. It is widely accepted that even where personal health data are de-identified, access systems should incorporate mechanisms of oversight and review (e.g. including review of the scientific merits of the proposed re-use of data) and security (e.g. restricted access via controlled environments or safe havens), that are absent from the EMA's proposal. An appropriate mechanism also needs to include the ability to decline data requests; this does not exist in the EMA proposal. Examples of existing systems that include oversight and review mechanisms include Innovative Medicines Initiative (IMI) projects, and access to health records, such as through the UK CPRD. We support the view expressed by co-convenors of the "Cochrane Collaboration Individual Participant Data Meta-analysis Methods Group" and others, in recent evidence to a UK Parliament Science and Technology Committee enquiry on clinical trials, that while open public access to trial	

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		results and aggregate data is in the public interest, open public access to individual patient level data is not[19]. Similar statements in support of a review process and steps to protect privacy were also included in submissions by other academic and grant-giving bodies, including the UK Medical Research Council (MRC), the Wellcome Trust, and the UKCRC Registered Clinical Trials Units Network. In addition, the AllTrials campaign, which is calling for all clinical trials results to be reported, has confirmed that it "is not calling for individual patient data to be made publicly available"[20].	
98	50-51	We agree with the statement in the draft policy that "in general" clinical trial data is not commercially confidential information. However, the use of the phrase "in general", and the later statement that a claim to CCI can be "duly justified" (line 132), acknowledge, as they must, that there may be cases in which some CT data can be considered CCI. As the absence of commercially confidential information from **all** documents and sections identified as "O" (open access) in the policy annexes cannot be assumed, the EMA should include a process for consultation with the MAH prior to making these documents publicly available, unless the MAH has already confirmed the absence of CCI.	"In general, ~~however,~~ CT data cannot be considered CCI; further, even if aspects of CT data are CCI, the interests of public health may outweigh considerations of CCI. As the absence of commercially confidential information cannot be assumed, the EMA will consult with the MAH prior to making documents publicly available, unless the MAH has already confirmed the absence of CCI."
98	57-61	The EMA states that they cannot guarantee that "all" secondary analyses will be conducted to the "highest possible" standards in a "truly open" approach. This may be true, but the public (health) interest in trying to avoid "inappropriate analyses" to the extent possible may well be greater than that in adopting a "truly open" approach. Inappropriate secondary analyses could give rise to false safety concerns or raise false hopes in patients, both of which could have undesirable public health consequences (e.g. patients	

[19] http://www.parliament.uk/documents/commons-committees/science-technology/Clinical%20trials%20combined.pdf
[20] http://www.alltrials.net/wp-content/uploads/2013/08/What-does-all-trials-registered-and-reported-mean.pdf

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		not taking medicines, or patients using medicines inappropriately). Although these lines state the Agency will put in place measures to protect against claims resulting from inappropriate analyses, it is not clear how they plan to do so, given they propose not requiring a statistical analysis plan or qualified researchers as conditions of "controlled access", nor to review research requests for scientific rigour. We would like to see clear measures outlined before the date this policy is implemented.	
98	65-66	The policy acknowledges the need to protect EMA deliberations and the Commission decision-making process from external pressures, but states that this consideration no longer applies once a decision has been reached. We disagree with this statement in the cases of negative decisions and withdrawal of applications. In many such cases, MAAs will be re-submitted. Making CSRs and datasets available in these cases increases the risk of secondary analyses prejudicing future EMA deliberations or Commission decision-making processes. The considerations as to what may be commercially confidential information will also be different from those for studies concerning authorised medicines. Information additional to that already made public by the EMA from applications with negative decisions or that have been withdrawn should only be disclosed either following approval of a re-submitted application, or following confirmation from the sponsor that they have no plans to re-submit (i.e. development programme is terminated). Where there are negative decisions or withdrawn applications, the EMA should consult with the sponsor to agree a period of time after which the policy would apply to information previously submitted in the application whether or not the application has been re-submitted and approved.	"Once a decision has been reached <u>to grant a marketing authorisation</u>, this consideration no longer applies."

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98	83-85	Data from CTs **not** held by the EMA are outside the scope of this policy, which means that data on at least 20% of CTs in the EU (those with non-commercial sponsors, based on EudraCT data[21]) will not be available. The scientific and public health benefits of greater access to patient level data can only be effectively realised where data from **all** clinical trials sponsored by industry **and** academia is made available. It can be anticipated that the GSK[22] and industry commitments[23] will evolve to include other (non-industry) sponsors in a broader system, where patient level data is available via a single independent data custodian, and subject to appropriate controls. It may be more beneficial for the EMA to engage in discussions with other stakeholders, with a view to achieving such a broader system, rather than implementing a "controlled access" system that gives rise to a number of concerns (see other comments).	
98	95-101	The scope of the Policy is not limited to RCTs, but may include other types of clinical research methodologies. The Policy should make it clear that it does not extend to observational or other studies that have used data from third party databases for which the MAH may not be able to provide "de-identified" versions, and/or for which the 3rd party has imposed restrictions on further distribution.	"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 (with the exception of studies that have used data from third party databases for which the MAH may not be able to provide "de-identified" versions, and/or for which the 3rd party has imposed restrictions on further distribution).

[21] https://eudract.ema.europa.eu/document.html#statistics
[22] https://clinicalstudydata.gsk.com/
[23] http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf

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98	92, 116-117	Not all of the CSR appendices and annexes listed in Annex II of the draft policy are "customarily submitted" to regulatory authorities (line 92). The definition of CSR (lines 116-117) refers to "elements submitted as study reports in CTD Module 5". There is, therefore, a lack of clarity over whether the EMA expects all items listed in the annexes to be submitted once the policy comes into effect. It is questionable whether EMA has the legal power to require sponsors to submit datasets, together with statistical programs and other information, for the purpose of providing access to researchers, and not for direct use in the assessment of medicines.	
98	119	The definition of "raw CT data" includes "individual patient line-listings" and "individual Case Report Forms", with the implication that these items would be disclosed to researchers under "controlled access". Such items should not be included in the scope of the policy, as this information will be difficult and too resource intensive to de-identify or redact. In a typical Phase 3 study, there will usually be thousands of pages of listings, and manual redaction is not a reasonable proposition. Even if, instead of redaction, anonymised listings were re-created from anonymised datasets, we estimate that this would take one person at least 1-2 weeks per study, which is a significant amount of resource. As the information in patient listings is derived from the datasets, it would be more appropriate and useful to provide the datasets under a responsible controlled access scheme where the proposed science is reviewed.	"…"~~individual patient line-listings, individual Case Report Forms (CRFs)~~…"
98	121-123	The definition of "raw CT data" includes a number of supporting documents/files which provide helpful navigation of the data (e.g. annotated CRF, variable definitions, data derivation specifications, dataset definition	"~~It also includes supporting documents, such as test outputs (if not contained in the statistical analysis plan (SAP)), Statistical Analysis Software logs and SAS~~

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		files). However, the definition also includes a number of other supporting documents/files which are more than what is needed to navigate the raw CT data (e.g. individual patient line listings, individual CRFs, test outputs, SAS software logs, SAS programs), and the inclusion of these items is neither necessary nor appropriate. The issues surrounding the provision of line listings and CRFs are commented on elsewhere. Specific comments regarding the provision of other files are provided below. The policy earlier acknowledges that "programs" could be trade secrets (line 112), and are therefore CCI. As programs that are written by or for the MAH are proprietary, SAS programs should be excluded from the definition of "raw data". In addition, companies often have CROs analyse studies, for which the CROs write the SAS programs and so own the copyright therein. Hence, the MAH may not be able to provide the programs for some studies and the EMA may not be able to permit 3rd parties to use them. Further, with the provision of the Statistical Analysis Plan, and other supporting documentation regarding the raw data, it should be possible for an independent researcher to recreate any analysis already performed without access to the program itself. We do not see any significant value in providing "test outputs" (the meaning of which is not clear) or software logs, especially when the resource required to create a package of these items, which may be significant, is taken into account.	~~statistical programs (if code not included in the SAP).~~"
98	129-137	It is not clear whether sections listed as CCI in Annex I and II will never be made available under the policy, or whether the applicant/MAH needs to justify in each and every submission that the sections described as "may contain CCI" in Annex I and II are indeed CCI. We suggest, in the interest	"*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

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		of simplicity and predictability, that these sections are always regarded as CCI without further justification. The absence of commercially confidential information from all documents and sections **not** categorised as "CCI" in the policy annexes cannot be assumed. The EMA should, therefore, include a process for consultation with the MAH prior to making these documents publicly available, unless the MAH has already confirmed the absence of CCI. Lines 134-136 highlight a serious shortcoming in EMA's proposed policy, particularly with regard to "controlled" access. The EMA acknowledges that documents can be requested under Regulation (EC) No 1049/2001. While this regulation clearly requires privacy and CCI to be protected, there is no clear legal basis for the EMA to refuse requests for access on the grounds of poor science where there are no CCI or privacy concerns. A review of the scientific rigour of research proposals is essential in order to reduce the risk of erroneous concerns about safety or false hopes of a potential benefit for patients. EMA should not request MAH to provide patient-level data for the purpose of granting access to researchers, when EMA cannot lawfully impose conditions on access based on the need for good science. (See also General Comments and lines 176-231).	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. The absence of commercially confidential information from CT data/documents that are not categorised as 'CCI' in Annex I ~~are considered to contain no CCI~~ cannot be assumed. The EMA will, therefore, consult with the MAH prior to making these documents publicly available, unless the MAH has already confirmed the absence of CCI. Where the Agency considers that an overriding public interest justifies the disclosure of CCI, it will identify the interest in question and give a detailed explanation of how that interest will be served by disclosure of the data. It will also indicate whether it believes that that interest can be served by providing controlled rather than open access to that data and if not, why not. If no agreement is reached as to whether (and if appropriate on what terms) disclosure shall be made,

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			the MAH shall be given the opportunity to challenge the EMA decision to disclose before a court or other relevant body."
98	141-143	There are risks to individuals' privacy through the disclosure of narratives, even where information is removed in an attempt to prevent the identification of the patients concerned. Narratives should, therefore, only be made available through a controlled access mechanism where there are additional controls in place to protect privacy, including a review of the research proposals and access via a controlled environment that does not allow downloading of data. We note that the AllTrials campaign has indicated that narratives may need to be redacted, and "should be available on request to researchers who provide a protocol of their study plan"[24]. In addition to the issues related to the de-identification of narratives, there should be guidance on: Whether new patient code numbers need to be assigned and the link between the original code number and the new code number (key code) destroyed. We understand that, to meet the requirements of anonymisation of certain European data protection authorities, this is required. However we would support a policy that did not require re-coding of patient numbers on the basis that the there is little risk to individuals' privacy, as the key code is held by the investigator and is not accessible by the third party. The removal of indirect identifiers. The policy states (278-281) that key codes, dates of birth and any other indirect identifiers shall not be included, but no list of direct and indirect identifiers is provided.	

[24] http://www.alltrials.net/wp-content/uploads/2013/08/What-does-all-trials-registered-and-reported-mean.pdf

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
98	144-149	It is unclear how or why the EMA has made the determination that "public health" reasons override PPD considerations for personal data of CT personnel. There is no clear provision for a public health override in the personal data legislation cited by EMA. Even if there is such a provision under the legislation, we disagree with the statement that there is an overriding public interest in the disclosure of these names: the names of investigators, site staff and company personnel should not be included in disclosed CSRs without the individuals' consent. The inclusion of company personnel names poses significant risks for individuals. A number of GSK employees have been targeted by animal rights extremists, even though they have not been directly involved in animal research. The EMA's position on information on company staff is also inconsistent with their position on disclosure of information on EMA staff ("Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use", EMA/127362/2006). In response to requests for access to documents held by EMA, names of EMA staff involved in pre- and post-authorisation activities will be redacted, on the grounds that disclosure would undermine the protection of privacy and the integrity of the individual, in particular in accordance with EU legislation regarding the protection of personal data. The same principles should apply to company and CT personnel.	"~~This is the case with personal data of CT personnel.~~"
98	153-154	We do not agree that the EMA should make data available following a negative decision or withdrawal of the application, unless the sponsor has confirmed that they have no plans to resubmit (see also General comments and lines 65-66).	"**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, <u>or</u>**

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			following the sponsor's confirmation that they have no plans to resubmit for negative decisions or withdrawals ~~(or 30 days following withdrawal, in case no withdrawal EPAR is published)~~."
98	165-175	This section discusses "de-identification" of documents/data classified as "C" in Annex II. Further detailed guidance is needed on what constitutes appropriate de-identification of data/documents, for both "open" and "controlled" access, and the various legal responsibilities (and liability) associated with the processing and disclosure of data. Steps to protect privacy need to include not only the de-identification of the dataset, but also technical and organisational measures to prevent undue impact on the data subjects (i.e. controls on who might obtain access and how data can be accessed – see General Comments on controlled access model). We recognise that opinions related to measures to reduce risks to individuals' privacy can differ, and that this is further complicated by different privacy laws and their interpretation. It is critically important, therefore, that the EMA policy and guidance provide more specific requirements on the de-identification of CSRs and datasets, and that these requirements have official endorsement from data protection authorities in Europe and support from the Article 29 Data Protection Working Party. (see also comments on 141-143) In any event, as the EMA will be disclosing data, it will have liability for any breach of data privacy rules. Further, it should indemnify MAH for any liability arising from their compliance with this policy.	

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98	173-174	The meaning of "additional de-identification methods (e.g. statistical)" needs to be clarified.	
98	174-175	It is unrealistic to expect that de-identification will "preclude" re-identification. EMA should be clear that re-identification may only be "reasonably" precluded. There is a typographical error on line 175: "de-identification" should be "re-identification".	"The methods of ~~de~~re-identification should be such that adherence will reasonably preclude subject de-identification..."
98	176-231	As commented above (General Comments and lines 129-137), we question whether the EMA has the legal power to implement an **effective** mechanism for controlled access to data that is submitted in MAAs where there is no privacy or CCI concern. Alternative, effective controlled access mechanisms should be considered (such as those to which PhRMA and EFPIA members have committed), so as to avoid the need for allocation of EMA resources that are better and more appropriately assigned to evaluating the benefits and risks of medicines. If the EMA is to progress with a proposal for "controlled access", a number of improvements are necessary, which are described in the comments that follow below.	
98	180	There seems to be no policy basis for restricting access only to requestors in the EU. Regulation 1049/2001 allows EU institutions to grant access to documents to non-EU requestors. If the policy is truly in the interests of public health and good science, non-EU requestors with legitimate research proposals should also be granted access on exactly the same basis as those in the EU.	"~~requester, whether a natural or legal person, is established in the EU;~~"

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
98	181	It is not clear whether the EMA has any powers to enforce compliance with the data sharing agreement or to impose or seek penalties for non-compliance. Clarification should be provided of how the data-sharing agreement obligations will be enforced and of the financial and other penalties that may be imposed. In addition, given the interest of the MAH in the disclosure of data, the MAH should be a party to the agreement so as to give it the possibility of enforcement of compliance with the agreement.	"requester has agreed, by way of legally binding data-sharing agreement in terms acceptable to the MAH and to which the concerned MAH(s) is (are) party, to:"
98	183	The EMA should clarify how the requester can confirm, and the EMA ensure, that the proposed analysis will be "in line with the spirit of informed consent". This will likely require EMA review of consent forms in relation to the data request, as the informed consent will differ from study to study. This implies that the requestor must provide a protocol or statistical analysis plan so that alignment with the consent can be confirmed.	
98	185-186	Requesters should be required to submit a statistical analysis plan, and a qualified statistician must be part of the research team. It is imperative for good science that requestors submit a plan on how they propose to analyse the data, and that the researchers can use the data appropriately.	"...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)~~, - include a qualified statistician in the research team,"
98	191-192	It is unclear how use of the data outside the boundaries of the informed consent will be determined and avoided. This should not be left only to the judgement of the requester. (See also comment on line 183).	
98	193	The data-sharing agreement should also include a commitment not to use the data to gain a MA **in the EU** (at least, not until after any appropriate period of regulatory data protection has expired).	"refrain from using CT data accessed to gain a marketing authorisation in any ~~a non-EU~~ jurisdiction,"
98	199-200	The requirement to "be aware" of standards for good analysis practice does	"~~be aware of~~ comply with standards for good analysis

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		not seem to align with EMA's stated commitment to serve the public interest. If the document outlining the Agency's views on good analysis practice is for information only, and will not be enforced, it is likely to be of little or no consequence in ensuring good practice. There should be a requirement to comply with good analysis practices.	practice as set out in a document describing the Agency's views on good analysis practice which will be made available to the requester; ~~this is for information only,~~"
98	205	Access to datasets should be provided in a system where there are controls in place to prevent the data being downloaded. This helps to protect privacy and to ensure that the data are used only for the agreed purpose. The EMA draft policy of requiring the third party to destroy data after use is not sufficient, as this cannot be verified and copying the dataset cannot be prevented.	
98	207-209	The same comment as made above on lines 199-200 on good analysis practices applies to these lines.	"~~made aware of~~ provided with a document on CT data-analysis standards; in the document, the Agency will communicate its requirements ~~own expectations~~ relating to good analysis and transparency; requesters are required to comply with ~~advised to read~~ the document~~, but there are no legal obligations resulting from this document~~;"
98	211-215	The EMA considers the preparation and uploading of a detailed protocol/statistical analysis plan to be of "utmost importance", yet provision of such protocol/plan is not a requirement and the lack of such documents will not influence a decision on granting access. Provision of a protocol and analysis plan should be a condition of obtaining controlled access to data under this policy.	"~~given the opportunity~~ required 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~~

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			~~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~~."
98	216-218	Research proposals must be assessed for scientific merit before access is provided. This is imperative to help ensure the data are used for appropriate research, and to reduce risks, based on erroneous analyses, that may have a negative impact on public health or on the integrity of and confidence in the regulatory process.	"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)~~."
98	219-221	Access to datasets should be provided in a system where there are controls in place to prevent the data being downloaded. In addition, we do not agree that the EMA should make data available following a negative decision or withdrawal of the application, unless the sponsor has confirmed that they have no plans to resubmit (see also General comments and lines 65-66).	"**'C' documents will be made available, via a system where there are controls in place to prevent the data being downloaded, at the time of publication of the EPAR for positive decisions, or following the sponsor's confirmation that they have no plans to resubmit for negative decisions or withdrawals ~~(or 30 days following withdrawal in case no withdrawal EPAR is published)~~.**"
98	222-231	It is unclear why there is a delay in publishing the identity of someone who obtains patient level data. In line with good scientific practices and with the requirements for the posting of protocol summaries for clinical trials, publication of information about proposed analyses and those who will conduct them should be a condition of access to patient level data. The information should be made publicly available before the analysis is conducted, and not as currently stated in the policy.	"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) within 30 days of~~:~~

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			~~• 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~~.
98	235-236	Clarification should be provided on what is meant by "fully searchable".	
98	245	It is unclear what is considered "other appropriate standard". Proprietary standards should be considered appropriate (i.e. data according to internal company standards, as already accepted by those regulatory authorities that require submission of datasets).	"For the time being, this can be according to CDISC (Clinical Data Interchange Standards Consortium) or other appropriate standard <u>(including data according to internal company standards, as already accepted by those regulatory authorities that require submission of datasets)</u>."
98	253-255	There is a lack of clarity concerning when the 2nd set of "de-identified" documents is to be provided - at the time of submission of the MAA or at a later date. We propose that it should be the latter, to ensure there are no delays to submissions and approvals, and to keep the original and "de-identified" versions clearly separate, to help ensure that personal data are not disclosed. The original MAA is built to a specific format (eCTD), and submitted using well defined processes. Creation and submission of the second set of "de-identified" documents will be resource intensive for industry. The EMA should provide guidance describing the format and expected submission process for any second set of "de-identified"	"Marketing-authorisation holders/applicants shall<u>, following a positive Commission decision,</u> 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 MAH may identify any data in this set which it regards as CCI. Such data will not be disclosed without consultation of the MAH. If no agreement is reached as to whether (and if appropriate on what terms) disclosure shall be made, the MAH shall be given the opportunity to

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		documents. The MAH should be entitled to identify any data in the second set which it regards as CCI.	challenge the EMA decision to disclose before a court or other relevant body."
98	256-258	The EMA indicates that it needs to put in place "appropriate standards, rules and procedures for de-identification" before "C" data can be made available. However, "de-identification" also applies to some "O" documents, which EMA proposes to make available at an earlier date. Consistent standards, rules and procedures should apply to "de-identification" of **all** document and data types. Further detailed guidance is needed, **before** the policy comes into force, on what constitutes appropriate de-identification of data/documents, for **both** "open" and "controlled" access, and on the various legal responsibilities (and liability) associated with the processing and disclosure of data.	
98	274-281, Annex I, Annex II	Although the EMA categorises most documents listed in the annexes as "O", it acknowledges that some will require de-identification before they can be disclosed. Footnote 1 indicates that particular care should be taken to ensure no personal data are included in certain documents or CSR sections. The annexes, however, make reference to this footnote for only a small number of documents and CSR sections. We have identified several additional CSR sections where there is or may be personal data that must be anonymised or redacted. Those sections include: 5.1 "Independent ethics committee" 10 "Study Patients" and subsections	"O: Open access <u>after consultation with MAH</u>. <u>D: Access to de-identified version.</u> C: Controlled access. CCI: ~~May c~~C<u>ontains</u> commercially confidential information" Revise categorisation of documents/sections in accordance with the comment.

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		11 “Efficacy Evaluation” and subsections 12 “Safety Evaluation” and sub subsections 13 “Discussion and Overall Conclusions” 14 “Tables, Figures and Graphs” 16 “Appendices” Some sections designated as “O” (i.e. subject to proactive disclosure) could contain personal data that should only be made available through a controlled access mechanism where there are additional controls in place to protect privacy (e.g. patient narratives, where there are risks to individuals’ privacy through disclosure, even where information is removed in an attempt to prevent the identification of the patients concerned). Other personal data (e.g. investigator’s signatures) should not be disclosed at all. There is, therefore, a lack of clarity and much potential for confusion in the way the policy is written. We suggest that documents/sections that will require anonymisation or PPD redaction should be classified as something other than “O”. This would provide clarity to the applicant regarding the need to anonymise/redact, and would better guarantee that EMA make available the correct versions of documents/sections. In addition, as the absence of commercially confidential information from **all** documents and sections not categorised as “CCI” in the policy annexes cannot be assumed, the EMA should include a process for consultation with the MAH prior to making these documents publicly available, unless the MAH has already confirmed the absence of CCI.	

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		EMA's annexes should be amended accordingly.	
98	283-284	There is no acknowledgment of the possibility that 3rd party rights (e.g. in documents generated by parties other than the MAH) may be impacted, except in the case of literature references (Module 5.4) and publications (Appendices 16.1.11 and 16.1.12). Making 3rd party copyright material available for downloading (lines 151-152) would at least be facilitating infringement of copyright. The EMA should consider the implications in respect of other documents and materials in relation to which parties other than the MAH owns copyright.	
98	285-292	We disagree with the statement that there is an overriding public interest in the disclosure of these names: the names of investigators, site staff and company personnel should not be included in disclosed CSRs without the individuals' consent. (See also comment on lines 144-149)	"~~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.~~ The names of investigators, site staff and company personnel should not be included in disclosed CSRs without the individuals' consent."
98	297 (Annex II)	Annex II indicates that patient listings and CRFs in the CSR and CSR Appendices will be made available, either under "open" or "controlled access". Such items should not be included in the scope of the policy, as they will be difficult and too resource intensive to de-identify or redact. (See also comment on line 119)	
99	General	On behalf of the Hellenic Association of Pharmaceutical Companies (SFEE), I would like to inform you that regarding the clinical trial data-sharing we fully endorse EFPIA's submission and we kindly ask you to take it into	

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		consideration. (see Stakeholder no. 05 for EFPIA comments)	
100	General	In light of the transparency of the clinical trials, JPMA thinks clinical trial data (including Japanese patient data) in MAA dossier will be disclosed to the public. Considering disclosure of the Module 5 requires meticulous attention, such as protection of personal data and protection of commercially confidential information, JPMA disagrees to the widespread release of Module 5. To avoid those issues, JPMA suggests that each company judge by themselves what data to be released and in what way the data to be provided to a requester on an individual basis. JPMA agrees to make the clinical Module 2 available to the public, after approval of MAA by the European Commission, as it is done in Japan.	
101	General	The development of medicines, including clinical trials, is a global process and it is important that any proposals in this area are managed at an international level to ensure a consistent approach which benefits both patients and industry. For this reason, the Association of the British Pharmaceutical Industry (ABPI) supports the European Federation of Pharmaceutical Industries and Associations (EFPIA) response to the European Medicines Agency draft 'Policy 0070 on publication and access to clinical-trial data.' This response is publically available on the EFPIA website. (see Stakeholder no. 05 for EFPIA comments) A review of the scientific rigour of the research proposals behind requests for access to patient level data is needed to reduce the risk of erroneous concerns about safety or false hopes of a potential benefit for patients. There is no clear legal basis for the EMA to refuse requests for access on the grounds of poor scientific rationale or method. The EMA should not request patient level data for the purposes of disclosing it when the EMA cannot	

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		lawfully impose controlled access conditions based on the need for scientific rigour. The clinical trial transparency landscape is evolving, with discussion and developments stretching back over a decade. We therefore welcome the recent agreement between EFPIA and PhRMA on responsible clinical trial data sharing as an important step forward[25] in these discussions. In particular, we emphasise the importance of the commitments to both develop objective and transparent mechanisms to share patient-level and study-level clinical trial data with qualified scientific and medical researchers and share results with clinical trial participants. We encourage the EMA to continue the dialogue with industry to explore how the EFPIA-PhRMA commitments on responsible clinical data sharing can support the implementation of EMA policy in this area. The ABPI is actively engaged in the ongoing UK and international level discussions on clinical trial transparency. In recent months we have run and participated in workshops with key stakeholders involved in clinical research to move forward the debate on clinical trial transparency in the UK. Earlier in the year we also made a commitment to monitor disclosure in relation to the clinical trial transparency provisions contained in the ABPI Code of Practice[26]. In the near future, an independent third party service provider will be appointed to undertake	

[25] http://phrma .org/sites/defau iVfi les/pdf/PhRMAPrincip lesForResponsibleC linicaiTriaiDataSharing .pdf

[26] Specifically, these measures support the current ASP I Code of Practice which requires in Clause 21.3 disclosure of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. The joint positions include requirements that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		this work. All these measures support the current requirements in the ABPI Code of Practice which stipulates that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products. We have also launched a clinical trials transparency toolkit[27] to help our member companies meet these requirements. We would be very happy to follow up on any of the specific points raised in this letter. Many thanks for the opportunity to comment.	
102	General	We, the European Hematology Association (EHA), welcome the proposed draft EMA policy on the publication and access to clinical trial data. In general, we deem this policy to be an improvement of the current situation. The proposed policy will allow for enhanced insight into the studies on the basis of which the Agency bases its positive or negative decisions for market authorization of medicinal products. Moreover, the open and controlled access of clinical trial data should allow for the verification of outcomes, additional analyses (e.g. subgroup analyses, secondary outcomes), and avoidance of duplicate research. There are some issues, however, that we are concerned about and urge the Agency to take into account when formulating the next version of the policy. These issues may be found below.	
102	44-48, 181-187,	The Agency limits patients' informed consent to the usage of their data to implicitly include secondary analysis of their data as long as such is	

[27] http://www.abpi.org.uklour-workllibrary/guidelines/Pages/ABPI-disclosure-toolkit.aspx

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
	191-192	performed towards 'the advancement of science and public health'. This may not be necessarily true as the wording and spirit of the consent forms can differ (and, for instance, include stipulations that explicitly prohibit the use of the data for secondary analysis). Thus, for the policy to be effective, patient consent forms must either include a stipulation that would allow for the secondary use of data under the provisions of this policy, or default approval of secondary use if no mention is made. Either way, this may seriously hamper the ability of trial groups to recruit participants. Moreover, consent for secondary analysis must be granted by all trial participants as the replication of primary analyses is impossible without the availability of the exact same data set. We would urge the Agency to take these considerations seriously in finalizing the policy. As mentioned above, extending informed consent to include secondary analysis may hamper the willingness of patients to participate. To this end, EMA and national competent authorities and regulators, industry, trial groups, all healthcare professionals involved, and academia, will need to gain and ensure public trust. If this could be supported by the creation of one or more independent (from EMA and from industry) ethical boards that would determine whether or not the new research is in the interest of public health, and whether or not the new research is in agreement with the original intention of the consent of the patient, we, the European Hematology Association (EHA), would be willing to participate.	
102	57-61	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'. How does the Agency seek to protect itself from claims deriving from appropriate (namely according to the highest possible scientific standards) analyses with different outcomes (which is entirely	

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		possible)?	
102	205	The Agency will provide controlled access if, among other things, the requester has agreed to 'destroy CT data accessed, once analysis is completed.' We believe that this point needs more thought. One important purpose of the draft policy is to '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.' It is customary for the scientific community to communicate new knowledge in the form of journal articles. Most journals require the author(s) to retain the data their publication is based upon for a period of (at least) five years to enable verification. The policy's obligation to destroy the data upon completion of the analysis would make publication of the results impossible. We therefore recommend the Agency to bring its policy in line with international publication standards.	
102	222-231	The Agency will not immediately disclose any information about the requester of controlled access data. It will do so either upon publication of results or one year after the database access (and in some exceptional cases). This goes against the entire spirit of the draft policy at hand which includes the ambition to prevent duplication of efforts. It won't be too far-fetched to imagine multiple researchers requesting access to the same data to perform identical secondary analyses. We believe that at least some information should be made available about the identity or the intentions of the requestor to at least the 'owner' of the data and the other requestors of the same data.	
102	285-292 and 297 (Annex	The Agency takes the view that details of 'investigators and other important participants in the study' are exempt from protection of personal data (PPD) considerations with reference to the 'overriding public interest.' However,	Change access from 'O' to 'C'

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
	II, rows 6 and 16.1.4)	other than stating the obvious that 'these persons have a role and responsibility for public health in ensuring the integrity of trial data and protecting patients' welfare', no rationale or explanation is given as to how the public interest would be served by the pro-active publication of personal data of CT personnel. We do not see a public interest that would be harmed by making such data available through controlled access, nor do we see how controlled access would affect public health in any way. We do see, however, how open access of CT personnel data would pose a risk to medical personnel, for instance, being singled out by activists, patients, survivors, etc.	
103	General	EMA should specifically exclude veterinary medicines from the scope of this document and we refer to IFAH-Europe's previous position submitted to EMA in 2012. In particular this paper pointed out the specific risks in the veterinary sector relating to: - the threat from animal activists; - unfair competition: risk of competitors receiving information on clinical trials that will help them to shorten their product development plans. The conditions and political background for the human medicines industry are entirely different to the veterinary medicines industry; therefore while the basic policies already adopted remain applicable, the method of implementation should be different. It is evident that veterinary trials have not been in the mind of the authors when drafting this document, which specifically refers to human medicines use, human procedures and human organisations. An appropriate balance between public interest and the commercial interests	

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		of a company must be achieved. Unless a clear public health interest can be demonstrated the risk of competitive harm to manufacturers of veterinary medicinal products cannot be balanced with benefits to public health and there is no justification for the publication of clinical trial data relating to veterinary medicinal products.	
103	20	The fields of medicinal products for human and veterinary use are very different. The issues that are driving the implementation of further data disclosure from human clinical trials are simply not evident in the veterinary health field. Applying a policy devised for human clinical trial data to veterinary products would be a step disproportionate to the size and purpose of the veterinary industry. The idea of data being available to "researchers" for purposes of meta-analysis is not realistic for an industry where at very most a handful of trials with typically* a few hundred animals are conducted with any one particular product (*e.g. excluding fish and poultry clinical trials). The current system of reactive disclosure is already sufficient in view of data relating to veterinary medicinal products. Any extension to this current system would be tantamount to seeking to solve a problem that simply does not exist for veterinary medicinal products. In the absence of a clear public health interest there is no justification for publication. Indeed, Policy/0043 section on "General Principles" states "in dealing with requests for access to documents, the Agency will also apply the principle of proportionality in order to avoid that performance of core tasks assigned to the Agency is jeopardized..."	Veterinary medicinal products are removed from the scope of this document.
103	193	It is likely that in some countries, this cannot be monitored or policed.	As above.

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
103	285	Regulation (EC) No 45/2001 paragraph 4, allows for exemptions for certain EU individuals from the rights to personal data protection, where the provision of appropriate safeguards have been made, and only for reasons of substantial public interest. This raises a number of issues when considering animal clinical (field) trials. Firstly the disclosure of details of any personnel involved in animal trials would jeopardize their safety due to the prevalence of animal rights activists. It is difficult to envisage what kind of safeguard could be put in place to offset this risk. Secondly, there is no public interest concern with keeping this information confidential. Lastly, the above mentioned regulation governs the rights of EU citizens, a substantial proportion of personnel involved in trials submitted as part of marketing authorization applications for veterinary medicinal products in the EU are not themselves EU citizens.	As above.
104	General	Humane Society International/Europe (HSI) welcomes the European Medicines Agency's draft policy on "Publication and access to clinical-trial data", with its commitment to proactively open up clinical trial (CT) data into the public domain. We recognise that the benefits of improved transparency and sharing data on clinical trials are far reaching and, among others, include: better accountability of regulators and their decisions; opportunities for independent scrutiny and reanalysis of results; prevention of unnecessary duplication of costly and time consuming trials; better science with quicker results; and, above all, it serves the best interests of patients and the public. We also recognise that tensions exist between these aims and respecting citizens' right to personal data protection and safeguarding commercially sensitive information. However, we believe it is possible to reconcile this tension to establish the European Union as an attractive place to conduct	

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		clinical trials and ensure the overriding priority of public health is upheld.	
104	76-88	2. Scope We feel that the regulation could be strengthened further if, as well as publishing those CT data that are to be submitted to the Agency after the policy comes into effect, data of CT conducted on products that are already authorised and used on the market are made available too (line 79). Evidence-based medicine necessitates that all the evidence about a treatment be made available to fully understand its risks and benefits and make the most appropriate and fully informed clinical decisions for individual patients. Unless the opportunity is taken to make these valuable data available, they will soon be lost forever and could result in repeat, unnecessary costly trials being conducted to re-collate historical trial data as well as poor decision making with unnecessarily adverse outcomes for patients. Old data available for analysis are also important to support and influence future research and scientific decisions by enabling drug researchers and developers to learn from past successes and failures. It will provide the wider scientific community with detailed, high-quality CT data to develop new knowledge in the interest of public health. These benefits are only possible if all the information available is made accessible — past as well as future. The EMA has held a register of Clinical Trials conducted since 2011 on products already market authorised, and we feel these data warrant publication, especially since they have already been collected and are available. To improve trust and confidence in the system, we feel the EMA would also benefit from publicising those medical products that it has authorised, but for which it does not have CT data (line 84), and explain how	

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		these decisions were made and under what circumstances, including those of independent contractors (line 85). Publication of pre-existing CT data of marketed products that will be submitted to the Agency, e.g. in the context of a referral procedure (line 80), would also benefit from publication and be consistent with the overarching aims of openness and transparency. From the date the policy comes into effect, we recommend that the EMA makes it a mandatory requirement that all CT are registered on its register at inception prior to being conducted. This will improve traceability of CT and improve rates of full publication of results in line with the overall aims of the policy. The EMA already has a register in operation, so this would involve minimal additional administrative burden to establish while serving patients' interests by ensuring clinical decisions are as fully informed as possible. Line 86 – The EMA should make it clear to the public and its readers that although Individual Case Safety Reports (ICSRs) are also outside the scope of the policy they are submitted to and dealt with by the MHRA.	
104	128	4.1.1. Category 1 – commercially confidential information Where data are genuinely commercially confidential, we agree that they should not be published as part of the Clinical Study Reports (CSR). However, since CT data are only to be published after a marketing authorisation decision has been made, there is unlikely to be any commercially confidential information (CCI) contained within the CSR and as such it should be published. We bring to your attention the position of the European Parliament's Committee on Environment, Public Health and Food Safety, whose position on the European Commission's proposal noted, among other things, that "in	

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		general the data included in clinical-trial study reports should not be considered commercially confidential once a marketing authorisation has been granted or the decision-making process on an application for marketing authorisation has been completed."	
104	138	4.1.2. Category 2 – open access We agree with the approach set out for 'open access' data and documents where personal protection data are not a concern. Such data should be downloadable 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), or any other outcome of EMA's assessment of CT data. We would like to clarify and ensure that such documents should also be given consideration for concerns of personal protection data relating to non-patient subjects. This includes other citizens such as technicians, clinicians, experts and staff personnel involved in the CT, who are entitled to the same level of identity protection.	
104	155	4.1.3. Category 3 – data with personal data concerns We support the EMA's decision that where documents and data contained within Clinical Study Reports contain 'raw' data concerining individual patients, protection of patient privacy is paramount and should not be proactively published (as category 2 documents are), instead being treated as 'controlled access' data. Such data should first be de-identified according to a recommended minimum scientific standard that prevents retro-identification "even when applying linkages with other data carriers (e.g.	

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		social media)" (line 175). For 'controlled access' data that require the requester to fulfill various requirements, these should be appropriate for the requestor, e.g. a member of the public or an individual patient should be required to upload different documents than an academic research organisation or commercial enterprise. This is to ensure fairness of access and prevent any barriers to access. Paramount importance should be placed upon the requester's ability to justify how access to the data will serve the public interest and provide a clear list of aims and purpose of how the data will be used; this should apply to all requestors. In the case of a non-private individual, a (statistical) analysis plan and/or other relevant documents should be requested; however, interested parties such as individuals and patients should be exempt from these requirements (line 2010). We feel that in order to uphold the credibility of requests, quality of request results and authentic use of data in the public interest, the requirement to submit these documents should be mandatory and not at the discretion of the requester (lines 214-215). We feel that the public interest would be best served if EMA's decision to grant access to data takes into account these documents and how the data request serves the public interest, and where these requirements are inadequate, that revision and resubmission of a request be obligatory before access is granted (lines 210-215). We support the initiative that requires all requestors to sign a legally binding data-sharing agreement (line 181). We feel this is an important requirement to ensure the highest analysis standards are upheld; to ensure protection of personal patient data; to prevent potential misuse of the data, and to ensure	

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		that trust and confidence in the system is maintained. We also recommend that the names of EMA panel members responsible for evaluating and granting controlled data access be made public together with each member's declaration of interests. The panel should comprise independent representatives from the patient, clinical and scientific fields, along with representatives of the public. This is important to ensure transparency and impartiality of the decision-making process, build trust, and ensure decisions made are in the interests of society and public health at large.	
104	219	Publication of Category 3 data When 'controlled access' data and documents are made available, the information should first be de-identified as per the most appropriate method adopted.	
104	222	Publication of information about requests The EMA should disclose information about the persons who have requested data along with their stated aims for use of the data at the same time that access to data is granted. This will improve efficiency should another person be interested in requesting the same data or be investigating similar aims, improve collaboration of data analysis and results, and be consistent with the overarching aims of openness and transparency. It would aid ease of administration to publish this information on a regular basis rather than a year or more in retrospect. All results of the analysis should be uploaded and made public 'within a reasonable time period,' considered one year from date access to data is granted. We are in agreement with this time period and feel that one year is	

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		reasonable, but if more time is required the reason for this should be published with the results, and if more than a full additional year is required, the requestor should submit an appeal to the EMA panel before the additional year has expired to justify this need and request an extension (line 203-204).	
104	234	4.2. Data standards We agree that wherever technically possible, analysable, de-identified raw CT data shall be made available for downloading in the original format in which they have been analysed by the applicant, submitted and evaluated in searchable PDF form. We encourage standardisation of formats for consistency and to facilitate searchable parameters in raw data.	
104	248	4.3. Date of coming into effect (line 248) We agree that to ensure 'controlled access' data is adequately and effectively de-identified to uphold strict patient confidentiality, this data will be available once appropriate standards and procedures are in place "no later than 31 October 2014."	
104	Other comments	This consultation provides the opportunity to raise a related and highly relevant recommendation that would enable EMA to harness the full potential of data sharing and achieve greater scientific evaluation of medicines and improved safety for patients. Building upon this initiative to improve transparency and clinical trial data sharing by including sharing of preclinical safety and efficacy data would enable the integration and analysis of these data and revolutionise the development of new drugs through	

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		identification of unsuccessful disease models and toxicological test methods. We very much hope that sharing of preclinical data will receive due consideration in future as it provides a logical progression from the current discussion. Combined with clinical data, this large data set would assist scientists in identifying meaningful and non meaningful measures of disease pathways and the models that best serve drug safety. Research endeavours and resources could then be targeted at those methods identified as the more expedient as disease models and for toxicology testing. Additionally, the ability to share both clinical and preclinical data would benefit research by allowing a determination of ineffective products earlier in the drug development process which would help to explain why a high proportion of products fail in clinical trials, presenting the potential to save companies millions of pounds and time by preventing duplication of failure or conducting unproductive preclinical studies. By maximizing the potential of this initiative and developing further new thinking in this area, EMA can build up a repository of medicines data for greater stimulation of innovation and research in the pharmaceutical sector and ensure the Pharmacovigilence Risk Assessment Committee has the most comprehensive data available to protect patients and improve the safety and efficacy of human medicines.	
105	General	The Board of the German affiliate of IPPNW, the International Physicians for the Prevention of Nuclear War, strongly supports the principle of sharing data from clinical trials to revisit and reanalyse the data. This is in the interest of good science and true drug innovation, the health of patients, public health, efficient financing of drug research and health insurance, and in the interest of the trial participants who take risks (and probably would	

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		not have consented if they were told that the results of the trials they take part in might never be published or in a distorted way). For these reasons IPPNW Germany welcomes the European Medicines Agency's "Publication and access to clinical-trial data" policy for the publication of data from clinical trials submitted in support of a marketing authorisation application, after the decision-making process has ended. It is a long overdue step to provide the necessary transparency and access to clinical trial data. However, such a policy- and this is of utmost importance - must guarantee full access to data without any unnecessary restrictions that might hinder or even prevent a scientifically correct interpretation of data. If implemented, it will hopefully help correct and change the malpractice of many studies either not being published at all, or in a biased and often manipulated way, as numerous studies show, thus distorting the evidence for effective, rational and safe drug treatment. As a consequence, doctors can't really know whether the medicines they prescribe their patients really work or are the best choice. This is an intolerable situation for all involved, which should be ended better sooner than later. Without going into details, the policy paper presented by the EMA deserves full support in principle and under the premises mentioned above.	
106	General	Pfizer welcomes the opportunity to comment on the EMA draft Policy 0070 on publication and access to clinical-trial data (EMA/240810/2013, referenced as the 'draft Policy' in this document). Pfizer fully supports the EFPIA-PhRMA *"Principles for Responsible Clinical Trial Data Sharing - Our Commitment to Patients and Researchers"* (announced on 24 July 2013, to take effect from 1 January 2014) and the	

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		EFPIA Response to EMA Consultation on the Publication and Access to Clinical-Trial Data (see Stakeholder no. 05 for EFPIA comments). For Pfizer's comments on the draft Policy, we refer to the EFPIA Response, which notes that industry has concerns with several aspects of the draft Policy, the implementation of which, in its current form, we believe would not benefit patients and would even conflict with a number of public health imperatives. Namely, we are concerned that the draft Policy presented could actually (1) weaken safeguards intended to ensure the privacy of patients and other individuals identified, or potentially identified, in MAA dossiers; (2) undermine the trust in the regulatory approval system governing biopharmaceutical products and introduce risks of misinterpretation and misuse of clinical data into the process; and (3) weaken incentives for companies to invest in biomedical research by disclosing companies' commercially confidential information (CCI), without due consideration of the competing interests that may or may not justify disclosure, in each particular case.	
106	General	In addition to the EFPIA Response, Pfizer would like to make the following comments: **1. <u>Pfizer's track record of and continued commitment to responsible clinical trial data sharing</u>** Pfizer has been active in the development of the EFPIA-PhRMA Principles, which we fully support and will adhere to in our policies and practices. We have been and continue to be aligned with these commitments as part of our ongoing efforts to optimize the use of our clinical data to further medical research and improve the quality of health care. Many of our practices	

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		already meet or exceed the standards established by PhRMA and EFPIA. Pfizer's current practices in relation to the different types of clinical trial data are outlined below: Trial Design: Pfizer registers all Pfizer-sponsored interventional studies in human subjects on ClinicalTrials.gov and, as required by EU law, on EudraCT. Trial Results: Pfizer shares clinical trial results in three ways: Pfizer posts basic results from all sponsored interventional studies in patients that evaluate the safety and/or efficacy of a Pfizer product on ClinicalTrials.gov. Pfizer issues press releases to disclose results of the primary endpoints of all Phase 3 studies. Pfizer policy requires a manuscript reporting the results of the primary end point for all completed interventional clinical studies in patients involving a Pfizer product, regardless of their result, to be submitted to a peer-reviewed scientific journal within 18 months. Clinical Study Reports (CSRs): Pfizer currently provides CSRs to regulators as required as part of the MAA assessment process and on a case-by-case basis evaluates and responds to non-regulatory requests for CSRs. In particular, Pfizer has been a leader in making results available and accessible to clinical trial participants and we will continue to expand our sharing of information in meaningful ways to inform and empower patients, including providing "lay language" summaries of trial results and electronic	

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		data to participants. Finally, Pfizer has a long history of precompetitive collaboration where we share clinical trial data to advance medical research and regulatory science. These initiatives have included longstanding consortia under the Foundation for the National Institutes of Health, FDA Critical Path Initiative, European Innovative Medicines Initiative (IMI) and others. In the coming months, Pfizer will expand its policy on data sharing to further facilitate sharing data with appropriately qualified researchers. **2. <u>The potential negative impact of the draft Policy on the innovative industry, especially in markets outside the EU, is of particular concern to Pfizer as a global research-based pharmaceutical company.</u>** Pfizer is concerned that broad dissemination of clinical trial data, disregarding the MA applicant's concerns about CCI, may negatively impact upon industry's commercial opportunities in markets outside the EU which have no or different standards of regulatory data protection, and may prejudice intellectual property rights. Competitors may circumvent Regulatory Data Protection rules or take advantage of their non-existence, especially outside the EU, when detailed, non-public domain data are disclosed in the EU. Disclosure in the EU could in some cases also prevent the MA holder from obtaining patent protection, thus undermining its IP rights. We are particularly concerned about the misuse of clinical trial data by competitors, because the large majority of requests made to the EMA for disclosure of clinical trial data thus far have been from pharmaceutical companies, rather than healthcare professionals or members of the public. This is borne out not only by the EMA's data but by our own experience of	

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		document requests made to the EMA in relation to Pfizer's regulatory filings. In addition to the negative impact that such unfettered disclosure of clinical trial data may have on incentives to invest in research for new treatments, we would note that it could also conflict with the EMA's obligation under Article 39(3) of the WTO TRIPS Agreement to protect the data submitted for MA purposes against unfair commercial use. The EMA's draft Policy also applies to clinical trial data in withdrawn or denied MA applications. Pfizer is very concerned that the release of certain data from these dossiers could prejudice the integrity of the regulatory process for any future re-submission, as well as potential MA submissions in markets outside the EU, and could therefore undermine the future commercial viability of such products. Therefore, we believe that the policy should not apply to withdrawn or denied MA applications. **3. <u>Introduction and implementation of the new Policy</u>** Pfizer believes that the introduction and implementation of the new Policy should be deferred pending the outcome of the ongoing litigation in the General Court of the EU between AbbVie and Intermune and the EMA[28], which cases raise legal issues which are fundamental to the operation of the Policy, requiring determination by the Court. Once those legal actions are resolved, we would urge the EMA to collaborate with key stakeholders, including industry, to ensure that the new Policy and associated new processes are implemented in a manner consistent with the legal principles laid down by the Court.	

[28] Cases T-29/13, T-44/13; T-44/13R; T-73/13 and T-73/13R

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107	General	PhUSE (Pharmaceutical Users Software Exchange) supports the principles of the EMA 'Policy 007 on publication and access to clinical-trial data' and is committed to contribute to EMA's access to clinical trial data initiative. A group of PhUSE expert members has extensively reviewed the policy and is submitting herewith the outcome of their discussion as comments. PhUSE is an Independent, Not-for-profit organization run by volunteers. Since its inception in 2005, PhUSE has expanded from its roots as a conference for European Statistical Programmers to a society providing a global platform for the discussion of topics encompassing the work of Statistical Programmers, Data Managers, Biostatisticians, and eClinical IT professionals. Open collaboration and the sharing of information have been central efforts of the society since its foundation. PhUSE established working groups with regulators and across-industry participation. Collaborations have been established on topics such as "Optimizing the use of standards" or "Development of Standard Scripts for Analysis and Programming" etc. (for reference http://www.phuse.eu/WorkingGroup_OverviewCSS.aspx). Other open collaborations are provided via the Society's Wiki page. PhUSE believes that scientific transparency and independent replication of clinical trial results are genuine elements that serve the interest of public health. While it follows the intent of patients participating in clinical trials, it should also foster their interest in that their personal data is being handled in a safeguarded manner to avoid misuse under all possible circumstances. PhUSE would like to highlight the following key aspects that reside in the focus area of the Society and are related to the 'Policy 0070 on publication and access to clinical-trial data'. • Different classification levels of data (Categories 1 to 3) as suggested in	

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		the Policy are an effective mean to define the protection levels required. Patient level data (Category 3) require special attention and it is apparent that substantial considerations are provided in the Policy. In order to make data available for secondary analyses and publication PhUSE anticipates that as a pre-requisite the informed consent given by the patients specifically covers these aspects. • PhUSE suggests that for data access more advanced technologies are considered than the mentioned option via download to each requestor's individual environment. Corresponding technologies are available today. The provision of private and secured environments with available common analytics tools to requestors would enable to better ensure that data would not be further dispersed. Moreover, secondary analyses together with data can be properly archived for later reproduction. • PhUSE supports protecting patient confidentiality by anonymisation. This may require de-identification which subsequently may prevent some results from clinical studies to be reproduced. As suggested above, using a secure environment where analysis can be executed may allow sharing of data in a more comprehensive way. • PhUSE shares the view that raw clinical trial data in this context expands beyond individual data sets. It includes all metadata that is being used for the analyses such as data structure definitions, annotated CRFs, derivation definitions and a detailed description of the intended analysis. We would like to provide some points for consideration regarding statistical analysis software programs and log-files. In particular programs are rarely available in a standalone way but are the result of a nested combination of modular programs. Those have evolved from	

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		standardization efforts within organizations and across the industry. PhUSE has been an active contributor at the forefront in their development and promotion. We see that they provide a great benefit not only from an efficiency point of view but even more as it relates to quality and consistency of analyses. If individual standalone programs have to be compiled. This means substantial efforts while the outcome would still remain difficult to read. Logs thereof are also barely comprehensive for someone who is not familiar in operating these systems. PhUSE believes that in order to independently replicate analyses the detailed intended analysis (SAP) and the end product (CSR), with all other information about the data provide appropriate information for independent verification. Not having the detailed implementation (program code) provides an unbiased mean of verification as generally applied in independent quality control procedures. • PhUSE sees opportunities on the topic of statistical analysis software programs. A technical dialogue between primary provider and requestor could better facilitate the clarification of implementation and contribute to an overall superior professional standard. The PhUSE members participating to this review very much enjoyed to constructively reflect on the “Policy 0070 on publication and access to clinical trial data”. We believe that our suggestions can contribute to establish a manageable practical framework and we would like to express our interest to continue our contribution in the context of the supplemental guidance document referred in the policy [lines: 259,260].	
107	118 /119	De-identification can have an impact on the originally generated listings. Will	If de-identified raw data is made available

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		two separate sets have to be provided, one for agency review and one for sharing purpose? Will technical guidance e.g. related to data file format be provided in the guidance document referred to on line 260/261?	corresponding line listings appear to be redundant as all information is available in the provided data. Reference to the technical guidance as it relates to data file format would be helpful here.
107	121	The expression of “test output” is not precise enough. Does it refer to prototype outputs created on blinded data? Their value is questionable given all final outputs are provided in the CSR and all intended pre-planned analyses are defined in the Statistical Analysis Plan (SAP) prior to unblinding of the data.	Remove the test outputs from the Raw CT data section. It appears sufficient if mentioned that output definitions are expected in the SAP as per ICH guideline E9.
107	122/123	Mentioning of SAS as an abbreviation leads to the immediate association of the proprietary software with the same name. Likely it has not been meant in this way.	Spell out "statistical analysis software", because analysis could be done in other software like R, WinNonlin, etc. and those would be equally valid.
107	122/123	Most Biopharmaceutical R&D organization and CROs have developed validated, semi-automated reporting tools for standard data to operate in a sustainable and efficient fashion. While they are based on common statistical analysis software packages their build is done in a complex modular way and adapted to the computing environments they are deployed. Individual standalone programs are not readily available and if compiled very difficult to read due to the nested macro functionalities used in these systems. Logs thereof are also barely comprehensive for someone who is not familiar in operating these systems. In order to independently replicate analyses the detailed intended analysis (SAP) and the end product (CSR) provides appropriate information for independent verification. Not having the detailed implementation (program code) provides an unbiased mean of verification as generally applied in independent quality control procedures. In case of doubts and discrepancies the mean of a specific dialogue and exchange of	Remove the statistical analysis program code and log from the list of Raw data provided. A valid alternative may be to state that they may have to be made available on specific request. In addition it may be worth considering a dialogue. A technical dialogue between primary provider and requestor could better facilitate the clarification of implementation and contribute to an overall superior professional standard.

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		information can be established as it is common practice between health authority agencies and Bio-pharmaceutical R&D organizations.	
107	168	The Policy mentions: a relevant subset of data may be appropriate e.g. for reduction of indirect identifiers to minimize risk of patient identification. How and who is defining what a relevant subset is?	This part requires more clarity or a reference where more clarity is being provided should be provided, e.g. the guidance document referred to on line 260/261.
107	205	Mentioning that the CT data will be destroyed once the analysis is completed indicates that requestors will be able to receive physical copies of raw de-identified patient data (confirmed by line 243). Destroying the data is understood from a patient protection point of view. Though from a reproducibility point of view it appears contradictory to other aspects aimed at in this guidance. More advanced technologic ways are available today to provide access to data and sets of analytical tools. Requesters can be provided with private and secure environments to perform their analysis, while the means to generate copies of patient level data outside can be restricted. A further advantage is that upon completion of the work all data & analyses can be properly archived. Moreover such solutions can overcome situations where de-identification means that the primary analyses cannot be reproduced (age is a stratification variable). Physical protection of raw data from copying may ensure better patient privacy protection with equal transparency.	The Agency allows for the option that marketing-authorization holders or sponsors either provide themselves or fund such a platform for independent and protected data access and analysis (also from the sponsor).
107	245-246	Data Standards: It is understood that the agency is working on a supplemental guidance with regard to data standards. Is this part of the guidance planned for 31. October 2014?	More clarifying information would be helpful
107	Annex I	5.3.7 – Case Report Forms and Individual Patient Listings should be defined as 'C' - controlled access as it contains by default patient information that is	Change to C,2 from 2

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		sensitive	
107	Annex II	16.1.6 Listings of patients receiving test drug(s)/ investigational product(S) … The content likely contains patient identifiable information and should be classified as 'C'	change to 'C'
107	Annex II	16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used may contain CCI	change to CCI
107	Annex II	16.4 Individual Patient Data Listings (US ARCHIVAL LISTINGS) are generally no longer produced as data is provided in electronic submission	These listings only should apply if no data is submitted. State accordingly in the Annex with a corresponding footnote.
108	General	**Patient perspective** I am making this response to the European Medicines Association draft policy on *Publication and access to clinical-trial data* as a patient advocate and also as immediate past-chair of the International Alliance of Patients' Organizations, Chair of Consumer Advocare Network (a Canadian-based umbrella organization of patient groups) and President of the Canadian Organization for Rare Disorders. I appreciate the EMA requesting public comment on such a massive policy change, which has implications for patients not only in the European Union but also worldwide. Clinical trials are increasingly international, and this is especially the case for rare diseases whereby clinical trial data are combined from sites and patients literally around the world. Moreover, given the influence of the EMA, other jurisdictions will inevitably follow or emulate the EMA policy and therefore comment to the EMA is important for patients	

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		everywhere. I appreciate the EMA putting forth a draft policy on access to clinical trial data that lays out the potential benefits and risks as well as a commitment to mitigating risks. As an informed patient advocate, I have struggled to understand all sides of this debate. Everyone claims to be acting on behalf of the patient (and public) best interest but it is hard not to be wary of the vested interests and political biases, as well as economic and professional implications, implicit in some perspectives. Indeed, patients are the only stakeholders with no hidden agenda and no overriding interest; we are the ultimate beneficiaries or victims in a clinical trial. With respect to clinical trials, patients expect their regulatory bodies to assure safety, quality, scientific value, and validity of findings. We believe the ultimate responsibility is to the patients who are taking part in the clinical trials, and the second responsibility is to the population (public) that may benefit or be adversely affected by the information learned from the clinical trials. With respect to transparency of clinical trials, as patients we have long beseeched for greater transparency, and patients endorse without reservation the publication of all clinical trials and release of findings from all trials. With respect to individual patient data, most patients have been frustrated with the lack of access to their own data as well as the unmasking of clinical trial data that would help them better interpret their own response. At the same time, patients participating in clinical trials are highly concerned that their personal data not be transparent to others, including their family, healthcare providers, insurers, employers, and other researchers without their explicit consent.	
108	General	**Validation of regulatory decisions**	

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		As stated in the introduction, the aim of the EMA is to “protect and foster public health” and to this end, considers a “high degree of transparency” is key. Moreover, the EMA states that the “independent replication of CT data analysis” with “”access to CT data will enable third parties to verify the regulatory authority's positions and challenge them where appropriate.” Really? As a patient, I am not only skeptical but also appalled that I should be expected to rely on secondary parties who may voluntarily, selectively, and randomly access and reanalyze original person-level clinical data to validate the assessment of the EMA or other regulatory agencies. I am not sure what prompts an independent third party to request and reanalyze clinical trial data, but I am sure that this is not the most systematic and rigorous approach to validating regulatory decisions. I would expect that if the regulatory body were not fully convinced of the clinical trial findings, it would ask the manufacturer for reanalysis, additional data or confirmatory trials and/or require on-going data collection post-market and/or any other actions that are necessary to be as certain as possible about its findings.	
108	General	**Protection of personal data:** The EMA states in the draft policy that it “takes a guarded approach to the sharing of patient-level data” and recognizes that “emerging technologies for data mining and database linkage will increase the potential for unlawful retroactive patient identification.” Their solution is “methods of de-identification” … “such that adherence will preclude subject de-identification, even when applying linkages with other data carriers (e.g. social media).” Given the highly unregulated nature of social media (especially internationally), its rapid and continuous evolution, and that fact that, by definition and design, social media is meant to be broadly accessible, I am surprised and certainly not reassured by this assertion. With social media	

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		today, instances of abuse and consequential harm are the prompts to "protective" action, which is tantamount to "closing the barn door after the horse escapes." In terms of potential leakage of personally identifiable clinical trial, the impact of that risk is borne by the patient in the CT. Moreover, we must still be concerned about the sufficiency of the de-identification methods. I do not believe the evidence justifies our exposing all clinical trial data without considerable more research and validation as to quality and adequacy. Moreover, who will assume the responsibility and cost for de-identification? If it is the regulatory agency, will there be a "cost-benefits" analysis to determine the value of de-identification, with the concomitant requirement to safeguard information during the process and validate the data afterwards. Finally, the usual de-identification of personal information may not sufficiently protect patients and families with rare diseases. A constellation of seemingly general information may only too easily lead to identify of individuals within these small patient populations who may already be stigmatized and vulnerable.	
108	General	**Patients' informed consent** In the draft policy, the EMA states the importance of respecting the boundaries of patients' informed consent, that is, to "support the development and assessment of a particular medicine" and to "benefit the advancement of science and public health." Moreover, they state, "any other use of patient data oversteps the boundaries of patients' informed consent, and shall not be enabled by the policy." Frankly, those do not constitute the patients' boundaries. To date, patients believe when they give their informed consent for the use of their personal data it is to the research	

Stake-holder no.	General/ Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		facility and, by explicit extension, the company caring out the clinical trial. They give consent to have their data used and analyzed but they have not given their informed consent for their personal data to be handed over to the regulatory body and certainly not for the regulatory body to make their individualized information available to any second or third party that the regulatory agency so chooses. Patients enrolled in clinical trials are currently concerned about the lack of control over their individual information. What research has been done to demonstrate that patients would agree to have their personal data shared with any second party, or subsequent third and fourth parties without their explicit knowledge or consent? I believe this presumes too much about the trust of patients. Patients must be asked to provide consent for any and all uses of the personal data; this cannot be in the form of a "blanket" consent to cover any and all circumstances but must be explicit and may, in the future, require re-contacting patients if the use is beyond what was initially intended. Patients should have the right to "opt-out" and their data withheld.	
108	General	**Release of subsequent clinical trial data analyses** The EMA states that re-analysis of original clinical trial data may help to verify or to challenge the EMA's decisions. However, they have also acknowledged that they "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." So what are the patient and public (and even clinicians) to do in the case of contradictory or challenging findings based on a secondary analysis? Without a clearly defined, scientifically based, and rigorously controlled	

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		(implemented) process for reconciling differences in findings and conclusions, the patient will be highly vulnerable. Again and again, patients have experienced uncertainty and distress while experts are debating differences in opinion and the integration of new data with old. How much more distressing when there are conflicting analyses and conclusions of the same data, without clear adjudication. The examples of hormone replacement therapy for menopausal women, vaccines for infants, use of NSAIDs for rheumatoid arthritis, and even seemingly "risk-free" recommendations such a daily aspirin regimen for prevention of cardiovascular diseases and vitamin D supplements for bone health. In clinical trials as in medicine, first do no harm. The lack of evidence of previous harm is not the presumption that no harm will occur, especially in the implementation of such a radical new policy. It would be critical to think through all of the possible scenarios if a policy of access to individual-level clinical trial data were available. What are all of possible situations, and how should these be managed? How would validity of information be determined (peer review, reanalysis by another neutral party if there are conflicts, confirmatory analyses)? At what point should information be offered to the public, and who will provide the protections for potential harm? The manufacturer bears the responsibility for the product and the original data? The regulatory agency that approves has the responsibility to the patient that the information was adequately assessed and the decision rigorous, and the patient has recourse if otherwise. If the secondary analysis leads to harm (for some or all patients, e.g., inappropriate product withdrawal or even reluctance to prescribe or fund), who will be responsible to the patients and the public health system? Finally, patients and providers (and other stakeholders) need to be engaged	

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		in the creation, discussion, and resolution of these scenarios. The proposed date of implementation of policy in January 2014 does not allow for this type of proactive planning and precautionary preparation. Moreover, evaluation in 18 months leaves open too much possibility for harm. If and when such a policy is implemented, each case that comes to the public (and all cases should) must be evaluated on an on-going basis to assure that the public interest is indeed being served and patients adequately protected.	
108	General	**Ensuring future investment in bio-pharmaceutical research and development (R&D)** The EMA has recognized the importance that a "sustained and high level of bio-pharmaceutical research activity is a precondition for future improvements in public health." While the agency states the policy is not intended "to negatively impact on the incentives to invest in future bio-pharmaceutical R&D." The patient community is highly concerned that the reactions of the bio-pharmaceutical industry suggest that it will have a chilling if not halting effect. Certainly, it could reduce clinical trials in Europe and other developed countries that adopt such a policy, which means even more trials taking place in less developed countries with less oversight. For patients with rare and untreated conditions, the continued investment in R&D is critical. We have seen over 425 new drugs for rare diseases since the 1983 US Orphan Drug Act and 70 or more since the 2000 EMA provision. Is there evidence that manufacturers will not diminish their research activities and that patients will not hesitate to enroll in clinical trials if this policy is enacted? I am not requesting that rare diseases be exempted but it is clear that patients with rare diseases are the most vulnerable to the policy and have the most to lose if R&D is negatively impacted.	

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108	General	**Conclusion** In conclusion, we appreciate the EMA bringing this draft policy forward for public consultation. We recognize that this is a large-scale change that will impact patients and other stakeholders not only in the EU but worldwide. We strongly support increased transparency of the findings of clinical trials and the ability of patients to have access to their own data. However, we have considerable concerns about the access to individual-level clinical data as proposed in the policy, especially with regard to the consequences of "unregulated" access and reanalysis with potentially conflicting findings. We are concerned that the draft policy has not adequately analyzed potential scenarios arising from its implementation and strategies for managing potential risks to patients and public and request that a comprehensive consultation, including patients, take place prior to plans for implementation. We have identified concerns over the lack of adequate protection for privacy and personal data as well as the lack of explicit informed consent. We are especially concerned with the possibility that third-party secondary analyses may become public information without adequate vetting, verification, and subsequent reconciliation with existing analyses. We are also not convinced that the proposed policy will have no negative impact on R&D and patient willingness to participate in clinical trials and urge EMA to undertake that research before proceeding.	