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Submission of comments on 'Policy 0070 on publication and access to clinical-trial data'

Comments from:

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Please note that these comments and the identity of the sender (not contact details) will be published unless a specific justified objection is received.

When completed, this form should be sent in Word format (not PDF) to: ctdatapolicy@ema.europa.eu

Comments on text

General remarks

IQWiG strongly supports the improved publication and access to clinical trial information described in EMA's draft policy. Full trial information and results are needed for HTA agencies like IQWiG to be able to provide appropriate and meaningful assessments of drugs within their remit. As drug assessments conducted by HTA agencies support evidence-based decision making in health care systems, improved access to clinical trial data is in the interest of public health.

There is overwhelming evidence, that so far publicly available trial data are insufficient to provide a complete and unbiased picture of a given health care intervention. HTA needs additional independent and high quality data sources. Data submitted to regulatory agencies are therefore required by IQWiG and other HTA agencies. However, the data held by EMA are not only important for HTA agencies but also for other researchers supporting evidence-based decision making in health care and should thus in general be made publicly available.

HTA performed by IQWiG and other agencies specifically is aiming to describe comparative effectiveness. The methodology used by HTA requires

- information on all trials conducted with the intervention under assessment
- full information about clinical trial methods, e.g. for risk of bias assessment
- full information about clinical trial results, e.g. for meta-analysis
- extended information about patient populations included in clinical trials, e.g. to understand to what extent the study results are relevant for real life populations

In addition, comparative effectiveness research increasingly uses indirect comparisons. For this type of analysis full information on study methods including e.g. operationalization of study endpoints and on patient populations is required to allow for assessing assumptions of similarity of studies in a network for indirect comparisons.

IQWiG's own work has shown that clinical trial documentation held by regulatory agencies provides substantial additional information compared to publicly available trial reports. A comparison of clinical study reports (CSR) with publicly available journal publications and reports from study registries has shown, that CSRs provided complete information on 88 % of relevant methods items, while journal publications included complete information only on 40 % of methods items and registry reports only on 31 % of methods items[1]. Concerning clinical trial results, CSRs provided complete information on 86 % of patient-relevant trial outcomes while journal publications and registry reports presented complete information on only 23 % and 22 % of patient-relevant trial outcomes,

[1] Wieseler, B., Kerekes, M. F., Vervoelgyi, V., McGauran, N., Kaiser, T. (2012). "Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications." BMJ 344: d8141.

respectively (39 % in the combined publicly available sources)[2]. This additional information from CSRs can challenge published evidence on a given health care intervention or even reverse conclusions drawn based on publicly available information[3].

These data clearly describe the information gain from one part EMA's draft policy, i.e. making CSRs publicly available. Access to patient-level data will allow further research questions to be addressed. Our studies underline the relevance of improved public access to full clinical trial data according to EMA's draft policy for evidence-based decision making and thus public health. Our studies also show, that alternative proposals like the EFPIA's and PhRMA's recently adopted "Principles for Responsible Clinical Trial Data Sharing" are insufficient to solve the problems associated with an incomplete public record of information on health care interventions, e.g. because they suggest publication of only limited information (synopses of CSRs or journal publications) on a limited range of clinical trials.

Line number(s) *(e.g. 20-23)*	Comment	Proposed changes, if any *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	IQWiG appreciates the opportunity to comment on EMA's draft policy on publication and access to clinical-trial data.	
36 - 43	IQWiG supports protection of personal data. The measures described in the policy are considered sufficient to ensure this protection. According to IQWiG's own experience, patient-level data are required to answer specific questions in HTA and comparative effectiveness assessments. Therefore, patient-level data should be made available.	
49 – 51 Annexes I and II	IQWiG strongly supports the statement that clinical trial data cannot be considered CCI and that the interests of public health outweigh consideration of CCI for clinical trial data. IQWiG also supports the classification of documents with regard to CCI in Annexes I and II of the policy.	

[2] Wieseler B., Wolfram N., McGauran N., Kerekes M.F., Vervölgyi V., Kohlepp P., Kamphuis M., Grouven U. (2013). Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. PLoS Med, in press

[3] Eyding, D., Lelgemann, M., Grouven, U., Harter, M., Kromp, M., Kaiser, T., Kerekes, M. F., Gerken, M., Wieseler, B. (2010). Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 341: c4737.

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77 - 82	Since HTA is comparing new interventions to currently available therapies, full information on study methods and study results is required for all drugs in current use. IQWiG therefore suggests that EMA makes available all clinical study reports available at the agency from past or future submissions for any drug approved in Europe. Restricting the policy to data submitted after the policy comes into effect is insufficient to meet HTA and public health requirements.	
83 - 85	While IQWiG appreciates the fact that EMA can only make available data submitted to the agency, the final goal of EMA's transparency initiative should be availability of all studies on a given drug (or even more on all drugs, devices or other health care interventions). Therefore, IQWiG would like to suggest that EMA expands the trial database to allow for posting of clinical study reports of all studies on a given drug (or even more on all drugs, devices or other health care interventions). The pharmaceutical industry and other trial sponsors could then also release clinical study reports of studies not submitted to EMA in this central database, thus underlining their commitment to transparency.	
116 - 117	Availability of full Clinical Study Reports is of paramount importance to support assessment of a clinical study and its results. To avoid any ambiguity when referring to the ICH E3 document, EMA might want to clarify, that a CSR not necessarily follows the format of the ICH E3 as outlined in Annex II but should meet the requirements of ICH E3 and that the classification of access refers to the CSR-content provided according to the classified sections of ICH E3.	
118 - 123	It is unclear to IQWiG, why "test outputs (if not contained in the statistical analysis plan (SAP))" are considered raw data. According to our understanding, test outputs are outputs from SAS providing the outcome of statistical test procedures. As such, test outputs would be summary data. According to our experience these test outputs include valuable information (e.g. about	

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	treatment by variable interaction) and should be provided as part of summary data.	
150 - 154	IQWiG agrees that the documents classified as “open access” should be made available at the time of publication of the EPAR to allow for timely assessment of a given drug.	
242 - 247	According to our understanding, currently EMA does not require submission of individual patient data sets and associated documentation explaining the structure and content of the data sets. It does not become clear from the policy, if and how these data sets and associated information will be required in the future. The policy should clarify that submission of data sets and associated documentation will be a mandatory requirement after a given date.	
249	IQWiG agrees that the policy should come into effect on 1 January 2014. Since the information that will be provided according to this policy is urgently required, any delay should be avoided.	
Annexes I and II	IQWiG supports the classification of categories of access as provided in Annexes I and II of the policy.	

Please add more rows if needed.