European Federation of Statisticians in the Pharmaceutical Industry

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European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) Position on European Medicines Agency (EMA) Access to Clinical Trial Data Initiative

Executive Summary

EFSPI supports the EMA policy for transparency and is committed to contribute to EMA's access to clinical trial data initiative. EFSPI was instrumental in the establishment of the Committee for Proprietary Medicinal Products (CPMP) Statistical Guidelines that formed the basis for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 document 'Statistical Principles for Clinical Trials'. EFSPI acknowledges it is in the interest of the altruistic nature of patients participating in trials that such data will be used for further development of science as much as possible. It is also in the interest of patients that their data are handled in a strictly confidential manner to avoid misuse under all possible circumstances. EFSPI believes access to clinical trial data should be implemented in a way which supports good research, avoids misuse of such data and fully protects patient confidentiality. EFSPI would like to highlight the following key aspects:

- EFSPI believes allowing different levels of access to data will help to preserve patient confidentiality while optimizing transparency and access to clinical trial data. EFSPI supports open access to aggregate level (summary) data, which is already supported through clinical trial registries, but access to patient level data requires minimum criteria to be met before access is granted. This may be for example only allowing access to data to individuals with an appropriate pre-specified scientific

hypothesis and who are appropriately qualified to conduct the corresponding statistical analyses. If minimum criteria are met, access to patient level data may be controlled, for example, via a secure system although this cannot fully guarantee the data will always remain protected.

- The process of re-analysing data and drawing scientific valid conclusions from it is very complex, and in line with ICH E9 EFSPI believes only qualified and experienced individuals should be granted access to re-analyse data. EFSPI believes individuals wanting to re-analyse patient level data should submit upfront a research protocol and/or statistical analysis plan to verify the scientific integrity of the proposed analyses. EFSPI proposes the protocol, statistical analysis plan (SAP) and the results of the additional analyses are published.
- EFSPI supports opportunities for owners of the data to have a dialogue with individuals proposing additional analyses to align on what analyses can be supported by the data. Such scientific dialogues could facilitate further good research work on such studies.
- EFSPI supports protecting patient confidentiality by data anonymisation however EFSPI wishes to highlight that removing data items that fully protect the identity of patients may prevent results of clinical studies to be reproduced and also may limit further analyses. This is especially true in rare diseases and small populations.
- EFSPI supports that access to data will be granted in the format that data sets were used in the original analysis. Given the focus in recent years by regulators and industry to create data standards, EFSPI anticipates that industry will converge to using the Clinical Data Interchange Standards Consortium (CDISC) data formats.
- Finally, EFSPI supports further guidance is provided on important technical aspects relating to re-analyses and additional analyses of clinical trial data, for example multiplicity, meta-analysis, subgroup analyses and publication bias.

Introduction

EFSPI supports the EMA access to clinical trial data initiative. The new regulation becomes effective 1st January 2014 and will introduce key changes in Europe on the access of clinical trial data included as part of a regulatory submission to EMA. The remit of the initiative is to "enable the independent re-analysis of the benefits and risks to further public health". The implications of open access to potentially both aggregate (summary) level data and patient level data will be far reaching well beyond Europe. While this will facilitate good additional research for the benefit of future patients and will provide more information for the public today on treatment options, such an open access policy is not without risks either.

Ensuring patient confidentiality

EFSPI believes the protection of patient confidentiality is fundamental to the new EMA policy. EFSPI proposes open access to data should only be made to aggregate level (summary) data, for example, summary tables from the clinical study report, and access to patient level data should require some minimum criteria to be met before access is granted. This may be for example only allowing access to data to individuals with an approriate pre-specified scientific hypothesis who are appropriately qualified to conduct the planned statistical analyses. Access to data may also be controlled, for example, via a secure system although this cannot fully guarantee the data will always remain protected. However, researchers may wish to combine sources of data, for example, to conduct an integrated analysis. So these aspects would need to be considered.

There is a belief that sponsors of clinical trials will be able to ensure patient confidentiality by providing anonymised datasets, where any data fields that have the potential to reveal the identification of patients will be removed. Hence the resulting redacted dataset should maintain data protection in all circumstances. However, this may not be possible in all cases. This is especially true in rare diseases and small populations. EFSPI is concerned of the potential that anonymised patient level data sets are made available to

individuals who wish to mis-use the data and try to re-identify patients, or conduct incorrect analyses. EFSPI proposes the liability of any violation of patient confidentiality after access to data has been granted cannot be with the sponsor of the data. On the other hand EFSPI is concerned that anonymising datasets to fully protect patient confidentiality may prevent the results of clinical studies to be reproduced as key patient level information is no longer available. Anonymising datasets also has the potential to impact the ability to conduct some additional analyses, for example, analyses seeking to incorporate patient characteristics.

EFSPI believes there should be a defined set of rules clearly stated by the regulators about what the requester is allowed to do with the data if they are granted access. For example, EFSPI believes the requester should not be able to share the data with other parties or individuals not listed in the research protocol and/or statistical analysis plan, and the requester should only use the data for the intended pre-specified analyses and not make any attempt to re-identify patients.

EFSPI acknowledges there are a number of secondary databases containing patient level data (e.g. CPRD-UK) where processes are in place that protect patient confidentiality yet allow requesters to ask for specific analyses of the data by the data owners. There are also processes in place that allow third parties to buy data elements for research purposes, and where data access is only granted after reviewing a pre-specified research proposal. EFSPI believes there may be some useful best practices in analyses of secondary databases that would be relevant for consideration in the EMA access to clinical trial data initiative.

Data formats

EFSPI supports the use of existing standards for clinical trial data formats, for example CDISC, when submitting data to the regulators. There have been great efforts in recent years involving industry and regulatory representatives to standardise formats for data collected in clinical trials that can be provided to regulatory authorities that enable them to efficiently review the data. EFSPI

supports developing standards for meta-data, including protocols, annotated case record forms, statistical analysis plans, that would need to be submitted as supportive documentation along with the clinical trial data sets.

Nevertheless, for transparency reasons EFSPI supports a grandfathering principle which allows non-standard data formats to be provided, i.e. datasets would always be provided "as analysed". Standard formats will then become available over time in a prospective manner through the process within industry driving for a standard format for clinical trials. Additional documentation should include the study protocol, analysis plan, annotated case record form (CRF), data structures for all datasets and the clinical study report redacted for confidential information. Actual statistical programming code should not be part of this list as in many companies such code is intellectual property of the individual company. The formats for this information could be anything easily accessible, for example SAS transport files for datasets and PDF files for documents.

Clinical study reports are part of this new process. However given these may contain patient confidential information, for example case study narratives, all patient confidential information would need to be redacted from the report.

Transparency of request and scientific purpose

EFSPI strongly believes that requesters for access to data should submit a research protocol or statistical analysis plan before access to data is granted. A protocol or statistical analysis plan enables the scientific integrity of the proposed analyses to be transparent to the regulators and scientific community before access to data is granted. It will allow the scientific community to better interpret research results when they are published as pre-specification of analyses increases the integrity of analyses. This is especially important when trial data is being re-used while the (primary) results have already been presented. The plan could also include details for how long access to data is requested for. In order to ensure scientific quality of such additional data analyses the same rules should be applied as for any sponsor analysis. EFSPI believes EMA should consider establishing a

committee that reviews and endorses research proposals. At a minimum, a system should be in place allowing the uploading of a protocol and/or statistical analysis plan before a requester is able to access data. There should also be an obligation to publish the results of the additional analyses.

EFSPI believes it would be useful to differentiate access to patient level data for the purpose of conducting an independent re-analysis of the benefits and risks, compared to the purpose of conducting additional analyses of the data, e.g. to address new clinical questions. The first is an essential part of the transparency as noted in the remit of this initiative. The second is an essential principle for conducting further scientific research. The level of access granted could help define the level of governance required.

The protocol and/or statistical analysis plan as well as the results obtained should be fully published, as a minimum for example by posting on a website. Deviations to the planned analyses or additional analyses should be appropriately identified and referenced. A rejoinder by the data owners should also be allowed to be published at the same time.

Qualification

As noted in ICH E9, qualified statisticians are required to be involved in the design, analysis and reporting of clinical trials. Thus any requester wanting access to clinical trial data should also include in their research protocol or statistical analysis plan confirmation of their skills and experience which should be considered before granting access to data. For additional analyses of clinical trial data, the interpretation of results is complex and this should be done in the context of the original trial results. This requires advanced statistical expertise.

If the new EMA policy will allow re-analysis of patient level data, EFSPI would be interested to know whether it would be possible for EMA to increase their capabilities including expertise and resources to be able to re-analyse patient level data they receive in a regulatory submission, similar to how some other regulatory authorities review regulatory dossiers.

Re-analysis of clinical trial data

When a requester wishes to independently re-analyse clinical trial data, EFSPI believes there could be many reasons for the results not completely matching the results generated by the owners of the data. For example, the data sets will generally have complex data structures which a requester may not fully understand which could lead to an incorrect re-analysis; specific variables may be unavailable due to anonymising the data sets; and the requester will not have access to the computer software/code used to generate the analyses. EFSPI believes that re-analysis of data and their results may not enable the same conclusions to be drawn. In such situations, EFSPI is not sure who should be the 'arbitrator' and EFSPI proposes this is a consideration in the policy that EMA develops. EFSPI believes that requesters should commit to inform data owners and the regulators in advance of publishing any unexpected findings that inform the safe and effective use of a medicine. EFSPI also believes that it would be best practice for requesters to take reasonable steps to explore with the data owner possible explanations for discrepancies before publishing. If there were any deviations to the planned re-analyses of the data or further analyses conducted that were not pre-specified, these should be identified and appropriately referenced in publications.

Further (post-hoc) analyses of data

Regarding further (post-hoc) analyses of data, requesters may propose to generate additional analyses on the data. Where appropriate, before generating additional new analyses of the data, EFSPI believes it would be useful for the requester to verify results generated by the owner of the data first as this will confirm the requester has sufficiently understood the data structure. EFSPI believes it is also important to check that new clinical questions targeted in further analyses can be supported by the data collected in the clinical trial, as the data collected were targeted to specifically address the original clinical hypotheses stated in the clinical trial protocol. If inappropriate further analyses are conducted EFSPI is not sure who would be the 'arbitrator' and EFSPI proposes this is a consideration in the policy that

EMA develops. EFSPI believes a dialogue between the requester and the owner of the data would enable both parties to explore under what situations new analyses would be supported and which ones would not be supported by the available data.

EFSPI believes there will be a need for further guidance to be provided on important technical aspects for reanalysis of clinical trial data, for example aspects relating to multiplicity, meta-analysis, subgroup analyses and publication bias.

Scope of policy

EFSPI understands that the intention of the new legislation will be forward looking and impacts all regulatory submissions to EMA as of 1st January 2014. EFSPI believes that access to individual patient data should only be made available for the clinical trials included in a regulatory submission on or after the 1st January 2014 and where the patient informed consent allowed for patient level data to be made accessible for re-analysis and/or additional analysis. Access to patient level data for clinical trials beyond this scope should be the responsibility of the individual sponsor who will be accountable for data transparency whilst ensuring patient confidentiality and maintaining scientific integrity.

If access to redacted clinical study reports included in regulatory submissions that were sent to EMA before 1st January 2014 is to be considered in the access to clinical trial data policy, it would be useful if EMA could specify a time limit on how far back in time would be relevant. Current legislation requires sponsors to retain clinical trial archives for at least 15 years. EFSPI suggests it would be beneficial to have a staggered approach for releasing historical data.

Summary

In summary, EFSPI suggests it would not be appropriate to enable open access to patient level anonymised clinical trial data. Valuable scientific investigation relies on the testing of pre-specified hypotheses by experts in the field. EFSPI believes that the access to clinical trial data initiative, which EFSPI supports, will generate more useful insight and fewer spurious findings, by seeking to enforce this principle. At a minimum, this requires a system where requesters can detail their hypothesis, analysis plan and the expertise of their research team before being granted access to data and where this information is publically available. EFSPI believes that independent scientific assessment of requests could further enhance this system. Furthermore, requests for data should address questions within the scope of the original informed consent and requesters should commit to act in the best interests of the patients whose data they use, particularly to protect their confidentiality. At a minimum, this requires a process for screening requests to ensure that this commitment is present and that consent is respected. A system of governance is required, supported either by regulatory bodies or by owners of data (with independent oversight).