Clinical data publication by the EMA: The challenges facing the pharmaceutical industry

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Abstract

As of October 2016, EMA publishes clinical data on their clinical data website (https://clinicaldata.ema.europa.eu). This new procedure applies to all marketing authorisation applications submitted by pharmaceutical companies under the centralised procedure to the EMA. Before publication of the documents in scope, companies have to ensure that personal data of trial participants and personnel as well as commercially confidential information is protected. This article describes the challenges for sponsors to implement and maintain efficient and up-to-date processes that also take into account the multitude of transparency requirements of other channels, such as ClinicalTrials.gov.

Introduction

Globally, more and more health authorities are establishing regulations to enhance clinical data transparency. Sharing of clinical information is being recognised as beneficial to medical progress; it enhances trust in the authorities' decision-making processes, enables academics and researchers to re-assess the data, and allows healthcare professionals and patients to make more fully informed decisions.[1,2] The European Medicines Agency policy on publication of clinical data for medicinal products for human use, also known as EMA Policy 0070, became effective in January 2015,[3] and its website (https://clinicaldata.ema.europa.eu) went live in October 2016. Other regulatory agencies, such as Health Canada, follow the European approach and also propose the release of clinical information on drugs after the regulatory review process has been completed.[4] Similarly, the US FDA have just started a pilot programme to evaluate the potential benefit of disclosing key

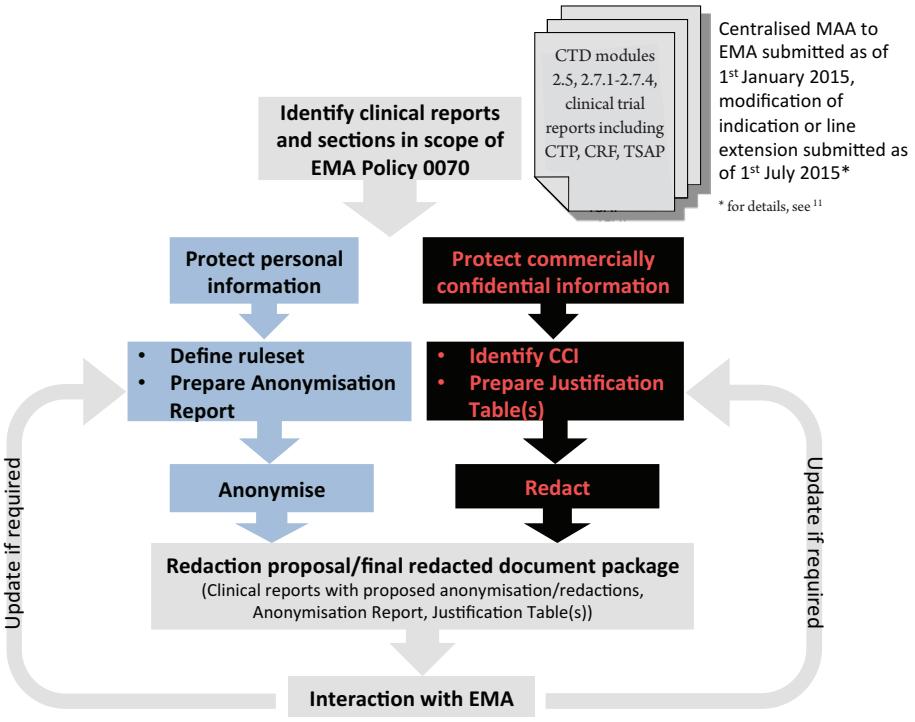

Figure 1. Main sponsor tasks in preparing a document package for publication on EMA's Policy 0070 website

Abbreviations: CCI, commercially confidential information; CRF, case report form; CTD, Common Technical Document; CTP, clinical trial protocol; MAA, marketing authorisation application; TSAP, trial statistical analysis plan.

information included in pivotal clinical trial reports.[5]

All these transparency initiatives have in common that their regulations impose additional and differing obligations with regard to scope, format, and timelines on sponsors. To be compliant, companies need to establish internal processes and increase their capacity to meet the evolving requirements. Whilst the intention of more transparency is acknowledged and supported by the pharmaceutical industry,[6,7] the first year of experience with EMA Policy 0070[8] shows that less than a fifth of all users of this information were registered for academic and other non-commercial research purposes. This is in line with experience from EMA Policy 0043,[9] where more than half of the document requests came from the pharmaceutical industry and law firms.[10]

EMA Policy 0070

The core of EMA Policy 0070 Phase I is the publication of clinical reports after conclusion of the regulatory decision-making process within the centralised marketing authorisation procedure.[11] Thus, the policy applies to marketing authorisation applications for medicinal products derived from biotechnology processes, orphan medicines, and medicines containing a new active substance to treat HIV or AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and other immune dysfunctions, and viral diseases.[12] Clinical documents that are made public include reports summarising clinical data at trial level (e.g., clinical trial reports, etc.) or at submission level (e.g., clinical overview, clinical summaries, etc.).

Before a document package is published on the EMA Policy 0070 website, the sponsor needs to perform several preparatory steps. The main sponsor tasks in preparing a document package are summarised in Figure 1. Within the application dossier, it is first necessary to identify the clinical reports in scope; for clinical trial reports, additionally, the sections in scope have to be determined. Further steps include the identification and protection of commercially confidential information (CCI) and personal data of the trial participants and sponsor- and non-sponsor personnel. Interaction with the EMA starts with the submission of the "redaction proposal document package". Depending on the feedback from the EMA, the proposed package may need to be updated before it is finally submitted and made public.

Protection of personal data and challenges involved

For the protection of personal data, an appropriate anonymisation strategy needs to be developed that balances data utility and the risk of re-identification of trial participants, taking trial-specific factors into account. To achieve this, the sponsor needs to have an overview of the trials and the type of data included in the clinical reports. As cross-referred trial reports submitted in previous procedures may also fall within the scope of EMA Policy 0070, the trial-related clinical documents in question may also include legacy trials completed many years ago. TransCelerate, a non-profit organisation of biopharmaceutical companies, has developed a qualitative approach to anonymisation based on the *rarity of the patient population*, the *number of patients in the study*, and the *number of sites in the study*;[13] see Figure 2. Taking these considerations into account, the sponsor has to define trial- and document-specific anonymisation rules that should ideally be agreed with the responsible data protection officer and possibly also with the competent data protection authority. The anonymisation approach that is applied to the clinical documents of a specific dossier needs to be described in an "anonymisation report", which is also made public. Of note, although several anonymisation techniques exist (e.g., randomisation, generalisation), currently redaction is most frequently used, as shown by the dossiers published within the first year on the EMA's clinical data website.[14]

One challenge when protecting personal data is to ensure consistency of anonymisation across different documents, e.g., clinical reports at trial and submission level. In addition, for the development and maintenance of an appropriate anonymisation strategy, the company's transparency policy has to be aligned with applicable law and data protection regulations at a local and global level. The study of data anonymisation techniques is a vibrant field of research. Therefore, further developments in re-identification and anonymisation techniques have to be monitored and potentially implemented. This requires that companies allocate resources to both the operational dossier-specific tasks and to the maintenance of oversight of scientific and technological progress. For a summary of dossier-specific and general tasks related to the protection of personal data for EMA Policy 0070, see Table 1.

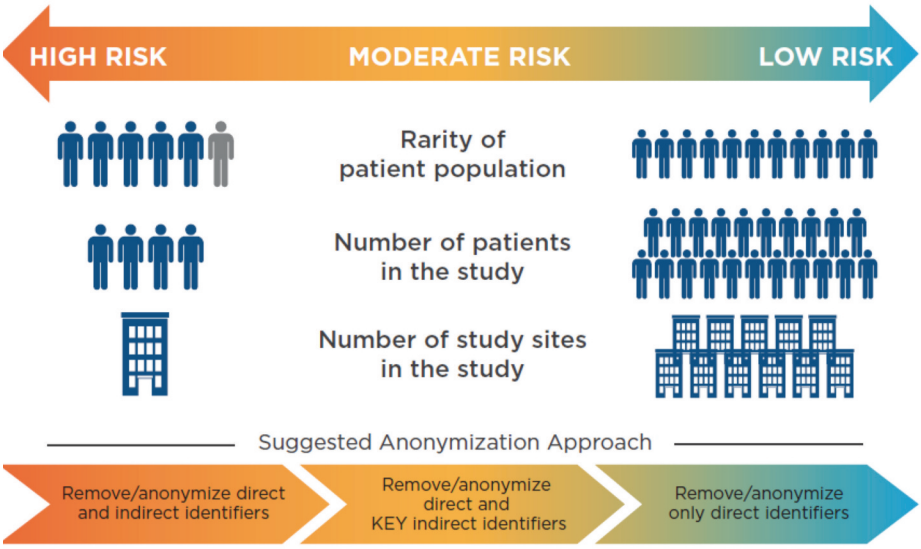

Figure 2. Illustration of a qualitative approach to anonymisation based on the risk level of the study; developed by TransCelerate[13]

Protection of CCI and challenges involved

The identification and justification of CCI is a complex and multidisciplinary task requiring review by and input from many different subject-matter experts. As a basis, a company-wide shared understanding of which information constitutes CCI is essential. All clinical reports in scope of EMA Policy 0070 have to be screened for potential CCI. The number of pages that have to be reviewed can be substantial because, in addition to the clinical reports included in the dossier, cross-referenced clinical trial reports submitted with previous applications may also be in scope.

If information considered to be commercially confidential is identified, a sufficient and relevant justification has to be provided in "justification tables" (one per file with CCI). In addition, it has to be checked and confirmed that the CCI proposed for redaction is not yet publicly available. It is extremely challenging to submit a justification that is accepted by the EMA. Based on the first year of experience with EMA Policy 0070, the likelihood that the EMA accepts proposed CCI is very low (success rate: 0.01% of all published pages).[14] For a summary of dossier-specific and general tasks related to CCI protection for EMA Policy 0070, see Table 1.

Organisational steps and further challenges

As described above, the tasks related to protected personal data (PPD) and CCI protection require close cross-functional communication and collaboration of all relevant stakeholders within a company. Firstly, the relevant internal stakeholders need to be identified; then responsibilities, interfaces, and the sequence of interactions need to be determined and agreed cross-functionally. All functional units involved have to be trained in the requirements of EMA Policy 0070 and in their unit-specific roles. For the different tasks outlined in Table 1, the involved functional units may include members from regulatory affairs, medical writing, data transparency, legal and data protection, statistics, programming, publishing, and patents, not to mention subject-matter experts from many different areas for CCI protection. An example of the task allocation and responsibilities of the functional units is provided in Table 1.

The new EMA Policy 0070-related processes have to be incorporated into standard operating procedures or work instructions. Over time, lessons learnt and changes to the guidance have to be implemented into existing processes. Since its first publication in March 2016, the guidance on implementation of EMA Policy 0070 has already been updated three times.[11] Each time, the EMA introduced major changes, affecting the clinical reports in scope or substantially modifying procedural aspects, which required adaptation of established procedures and re-training of the company-internal stakeholders.

Challenges in aligning different channels for clinical data transparency

The establishment of further channels for the public disclosure of clinical documents adds additional complexity to a company's data transparency activities. In addition to EMA Policy 0070, clinicatrials.gov is a key channel for the disclosure of clinical trial information. Through the various channels (see examples summarised in Table 2), different types of clinical data are made available to different audiences at different time points during drug development. The requirements for the publication of clinical documents, such as the clinical trial protocol (CTP) and the trial statistical analysis plan (TSAP), can differ greatly. For the CTP and TSAP of a trial in scope of EMA Policy 0070, the time of publication on EMA's clinical data website is linked to the date of the commission decision or the withdrawal letter.[11] If these trial documents relate to a so-called "applicable clinical trial",[15] they need to be published together with the structured trial results on clinicaltrials.gov[16] at different time points, i.e., 1 year after completion of each of the following milestones: the primary endpoint, the secondary endpoint(s), and the entire trial. Moreover, the public sharing of the CTP and TSAP may be requested when the results of clinical trials are submitted as manuscripts to journals that follow the recommendations of the International Committee of Medical Journal Editors (ICMJE).[17]

Transparency-ready clinical documents

To increase process efficiency and limit workload for the sponsor, transparency-ready clinical documents should be usable for all channels. However, the examples above illustrate that the time of data sharing differs between the various channels. This may lead to inconsistencies in the type and extent of information needing protection. Particularly for CCI, there is a complex relationship between the time of data release and the degree of protection needed. As some initially confidential information may be published during the drug development process, the need for CCI protection usually decreases over time. An approach to tackle this challenge is to already improve the transparency-readiness of clinical documents during writing. For example, cross-references, CCI, and PPD could be limited to the information that is necessary for standard regulatory review. Another possibility is the early identification of CCI and PPD and their mark-up in the documents for later redaction and anonymisation. It appears that the time for such efforts is well spent as there are more transparency initiatives about to be established.[4,5]

Conclusion

To fulfil the EMA Policy 0070 requirements, sponsors need well-defined cross-functional

Table 1. Allocation example of sponsor tasks related to EMA Policy 0070 activities

Dossier-specific tasks	**Functional unit**
Interaction with EMA	Regulatory affairs
Identification of clinical reports and sections in scope for a specific dossier	Regulatory affairs, data transparency, publishing
Development of an anonymisation concept for the protection of PPD, including ● identification of data identifier categories contained in the clinical reports ● assessment of risk level of clinical trials ● definition of trial- and document-specific anonymisation rules ● data utility considerations	Medical writing, data transparency, publishing, legal, data protection officer, statistics and programming
Description of anonymisation approach in anonymisation report	Medical writing, data transparency, legal, data protection officer, statistics and programming
Protection of CCI, including ● review of clinical reports to identify potential CCI ● check and confirmation of public non-availability of information ● justification of CCI in respective table(s)	Medical writing, subject-matter experts, patents
Performance or coordination of redaction/anonymisation	Publishing
Incorporation of EMA feedback on redaction proposal document package (if required) by updating ● anonymisation report ● CCI justification table(s) ● redaction/anonymisation of clinical reports	Medical writing, data transparency, legal, data protection officer, statistics and programming, subject-matter experts, patents, publishing
Tasks unrelated to a specific dossier	**Functional unit**
Follow-up on regulatory and technical developments related to transparency	Data transparency, medical writing, regulatory affairs
Implementation of lessons learnt and new/updated requirements into existing processes	Medical writing, data transparency, publishing, regulatory affairs, statistics and programming
Maintenance of adequate training of all involved functional units in evolving regulatory requirements and their responsibilities for updated processes	Medical writing, data transparency, publishing
Improvement of transparency-readiness of clinical reports	Medical writing, statistics and programming

Abbreviations: CCI, commercially confidential information; PPD, protected personal data

processes with clearly defined responsibilities. In addition, the many stakeholders in a company need to be trained and kept informed of changes to the requirements. Resources need to be allocated to both the maintenance of the operational business and the oversight of regulatory changes and technological developments to ensure up-to-date company strategies and processes. As increasing numbers of national and international transparency initiatives are being established, the key challenge for sponsors is to fulfil all the non-aligned requirements and yet harmonise the data protection processes for the different publication channels. Efficient organisational structures together with increased transparency-readiness of clinical documents from the start will provide an efficient approach to meeting these demanding requirements.

Conflicts of interest and disclaimers

The authors are employed by Boehringer Ingelheim Pharma GmbH & Co. KG. However, the views expressed in this article are those of the authors and do not necessarily reflect those of their employer.

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Table 2. A selection of existing channels for clinical data transparency

Type of clinical data	Channel	Note
Structured results	Clinicaltrials.gov[a]	Together with CTP and TSAP for applicable clinical trials[15,16]
Key findings	Publication in journals	Together with CTP and TSAP
Clinical trial synopsis	EU-CTR (clinicaltrialsregister.eu)	
	Company website	
Clinical trial report, clinical overview and summaries	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of dossiers in scope of EMA Policy 0070[3,11]
Clinical trial protocol	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of clinical trial reports in scope of EMA Policy 0070[3,11]
	Clinicaltrials.gov[a]	To contextualise structured results of applicable clinical trials[15,16]
	Together with a publication in a journal following the ICMJE's recommendations[17]	
Trial statistical analysis plan	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of clinical trial reports in scope of EMA Policy 0070[3,11]
	Clinicaltrials.gov[a]	To contextualise structured results of applicable clinical trials[15,16]
	Together with a publication in a journal following the ICMJE's recommendations[17]	
Other clinical documents	EMA Policy 0043[9]	
	Request via company website	With document sharing agreement

Abbreviations: CTP, clinical trial protocol; ICMJE, International Committee of Medical Journal Editors; TSAP, trial statistical analysis plan

[a] By the United States National Library of Medicine at the National Institutes of Health

for human and veterinary use, POLICY/0043, effective date: 1 December 2010 [cited 2018 Jan 26]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf.

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