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Subject: Proposal to the Heads of Medicines Agencies to improve harmonisation of access to Clinical Study Reports across National Competent Authorities

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Executive summary

We propose the Heads of Medicines Agencies (HMA) to address important differences in the handling of access to Clinical Study Reports (CSRs) across National Competent Authorities in the European Union. In particular, **we encourage HMA to foster a harmonised access to CSRs from drugs authorised through national and decentralised procedures to mirror the European Medicines Agency's (EMA) transparency policies**.

Recent rejections of independent researchers' requests to access trial data by two European national drug regulatory agencies have made us aware that some National Competent Authorities interpret the legal status of CSRs differently than EMA. Please refer to Appendix 1 for detailed accounts of the rejections.

The European Union legislative framework is configured to ensure access to CSRs, which are included in marketing authorisation applications. CSRs are *not* considered commercial confidential information and the public may access them, e.g. for use in research projects. The European Court of Justice has twice confirmed the validity of the EMA transparency policies 0043 and 0070 (see 'Background Material' for the legislative context)

The HMA also favours access to CSRs. In 2012, the HMA published a guideline with EMA on the identification of commercially confidential information. It was underscored that CSRs are *not* considered commercially confidential and may be shared (see Appendix 2).

This discrepancy between HMA, EMA, and National Competent Authorities creates a loophole since drugs approved through decentralised and national approval routes are not applicable to the same degree of transparency as centrally approved drugs. This has important implications:

(1) clinical data from drugs authorised through national and decentralised routes may be inaccessible,
(2) independent researchers are not able to include important data in research projects with potential detrimental clinical and public health consequences, and
(3) pharmaceutical companies may prefer national rather than EMA's approval route for drug authorisations.

The HMA does not have legal authority to compel National Competent Authorities to adhere to European transparency policies. However, the HMA can foster and promote a joint initiative with the overall goal of ensuring that National Competent Authorities release CSRs upon request. EU Clinical Trial Regulation 536/2014 shall mandate a prospective harmonised access to authorised drugs across Europe. However, **the Trial Regulation will not act in retrospect and immediate actions are therefore needed to ensure access to CSRs from drugs already authorised through decentralised and national routes**.

Our proposal for a joint HMA initiative to ensure access to CSRs:

HMA action point 1: Clarifying the legal status of CSRs and potential roadblocks
The HMA should in collaboration with National Competent Authorities compile a list detailing the confidentiality status of CSRs in each country. The main purpose should be to identify whether agencies grant access to CSRs upon request and to identify areas in which national laws and practices conflict with European transparency policies.

HMA action point 2: Issue a statement on access to CSRs across Europe
The HMA should publish the list and issue a statement setting out its position on access to CSR across Europe. In this context, the HMA may wish to highlight evidence that CSRs contain important information about treatments – including adverse events – that cannot be accessed in other formats (see references to empirical studies in 'Background Material').

National initiatives, such as the German AMNOG law (see Appendix 2), show that is possible to change national legislation to achieve greater transparency. It is our hope that an explicit HMA statement highlighting current barriers could help generating interest on the national level in improving access to CSRs.

A rapid harmonisation and implementation of access to CSRs across European drug regulatory agencies is important for European patients, the medical research community, and national Health Technology Assessment agencies. The HMA should add its voice to those calling for consistent and comprehensive access to CSRs across the entire European Union.

We would greatly appreciate a formal HMA response to the above raised issue.

Yours sincerely,

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Appendix 1: Rejections of access to CSRs

During 2018 and 2019, two researchers, Kim Boesen and Tom Jefferson, submitted Freedom of Information Act requests to national European drug regulators to access Clinical Study Reports (CSRs) included in marketing authorisation applications. The clinical data were intended to be used in research projects on ADHD medications[1] and on statins,[2, 3] respectively. Two National Competent Authorities, the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and the Finnish Medicines Agency (FIMEA) rejected a total of three Freedom of Information Act requests. In contrast, the Dutch Medicines Evaluation Board (MEB) and the British Medicines and Healthcare products Regulatory Agency (MHRA) released some of the requested data.[2] Historically, also other European National Competent Authorities, including the Danish and Swedish regulators, have granted access to CSRs to some of us (summarised in Table 1).

Table 1. Historical cases of Freedom of Information Act requests submitted to National Competent Authorities

Project	Regulator	Date	Decision
ADHD[1]	BfArM	July 2019	Rejection
Statins[2, 3]	FIMEA	July 2018	Rejection
Statins[2, 3]	MHRA	July 2018	Release of CSR data
Statins[2, 3]	BfArM	June 2018	Rejection
Statins[2, 3]	MEB	June 2018	Release of CSR data
Antidepressants[4, 5]	MHRA	2010	Release of CSR data
Antidepressants[6]	MEB	2010	Access to CSR data[a]
Antidepressants[6]	MPA	2010	Access to CSR data[a]
Anti-obesity drugs[7]	DKMA	2008	Access to CSR data[b]

[a)] The agencies granted access to the data, but the projects never materialised into published articles. See reference 6, p. 142. [b)] The process behind acquiring this data has been described in a Danish article only.[7] **BfArM**= German Bundesinstitut für Arzneimittel und Medizinprodukte, **DKMA** = Danish Medicines Agency, **FIMEA**= Finnish Medicines Agency, **MEB**= Dutch Medicines Evaluation Board, **MHRA** = the UK Medicines and Healthcare product Regulatory Agency, **MPA** = Swedish Medical Product Agency.

Rejection 1 (Sep 2018)
Jefferson asked The Finnish drug regulatory agency, FIMEA, for access to Clinical Study Reports related to one statin, simvastatin (trade name Zocor, marketed by Merck Sharp Dome) approved by the agency in 1992. FIMEA responded that Clinical Study Reports, "are considered as a classified information due to Finnish administrative legislation (i.e. trade secrets)", without referring to the relevant Finnish legislation.

Rejection 2 (Oct 2018)
Jefferson asked the German drug regulatory agency, BfArM, for access to Clinical Study Reports to three different statins, atorvastatin (trade name Liptor, marketed by Pfizer), fluvastatin (trade name Lescol, marketed by Novartis) and lovastatin (trade name Mevacor, marketed by Merck). BfArM answered that they "can't provide the Clinical Study Reports" and instead referred to articles published in medical journals. The BfArM did not provide a legislative rationale for not providing access to the data.

Rejection 3 (July 2019)
Boesen asked The German drug regulatory agency, BfArM, for access to Clinical Study Reports related to the ADHD medication, extended-release methylphenidate (trade name Medikinet, marketed by Medice), which BfArM approved through a national procedure in 2011. BfArM approached the marketing authorisation holder, Medice, which did not agree to disclose the requested trial data. BfArM stated in their response letter that they were incapable of releasing the requested data without the company's consent as the requested documents contained "company and trade secrets". BfArM referred to the German Freedom of Information Act,[8] Paragraph 6 (Box 1).

Box 1: German Freedom of Information Act

Section 6. Protection of intellectual property and business or trade secrets.

"No entitlement to access to information shall apply where such access compromises the protection of intellectual property. Access to business or trade secrets may only be granted subject to the data subject's consent".[8]

Appendix 2: HMA's stance on access to CSRs

The Heads of Medicines Agencies (HMA) is a network of European National Competent Authorities, i.e. national European drug regulatory agencies. The HMA cooperates its activities with the European Medicines Agency (EMA) and the European Commission. According to the HMA website,[9] its main activities are (Box 2):

Box 2: HMA's activities

1. Addresses key strategic issues for the network, such as the exchange of information, IT developments and sharing of best practices.
2. Focuses on the development, co-ordination and consistency of the European medicines regulatory system.
3. Ensures the most effective and efficient use of resources across the network. This includes developing and overseeing arrangements for work-sharing.
4. Co-ordinates the mutual recognition (MRP) and decentralised procedures (DCP).[9]

The HMA/EMA guidance document

In 2012, the HMA and EMA published together a guidance document entitled "On the identification of commercially confidential information".[10] The guidance document was a consensus document targeting the National Competent Authorities to enable a harmonised understanding of confidential and non-confidential information and to, "facilitate that all members have a harmonised approach to requests for access to marketing authorisation applications" (Box 3).

Box 3. The purpose of the HMA/EMA guidance document

"This guidance document is intended to be a consensus document agreed by the whole Network of National Competent Authorities of the EEA for the release of information regarding medicinal products for human use (i.e. not applicable to medicinal products for veterinary use) and lays down practical orientations for national and European authorities in regard to the release of the MA dossier upon request. Notwithstanding this guidance document it should be noted that National Competent Authorities/EMA have to follow their national /European legislation in terms of access to documents and on the protection of personal data (based on the Directive 95/46/EC)." (p. 1)[10]

It is stated in the guidance document (our highlights) that clinical data is not confidential, "In general, the **data included in clinical trial study reports is considered as data that can be released as such data is not considered either commercially confidential or personal data** that should be protected" (Section 3.2 'Non-Clinical and Clinical Information', p. 5).[10]

To clarify further the release status of data submitted to regulatory authorities in marketing authorisation applications, each submodule of the Common Technical Document was categorised into four levels (Guidance Document, p. 2).[10] The four categories were **CCI** = 'commercial confidential information', i.e. cannot be released; **PPD** = 'Protected personal data', i.e. cannot be released; **CBC** = 'Case-by-case analysis', i.e. may or may not be released; **CBR** = 'can be released'. In Table 2 we highlight the classifications of submodules that contain clinical data. We note that all of them are categorised as 'Can be released'.

Table 2. Release status of relevant CTD submodules

Submodule	Title/content	Classification (verbatim text from Guidance Document)
Sub-module 2.5.	Clinical overview – report on clinical data (p. 29)	"**CBR** In accordance with principle 3.2. However, in accordance with principles 2.A, 2.B, 2.C and 2.1 some information in this section may be regarded as **PPD"**.[10]
Sub-module 2.7.3	Summary of clinical efficacy (p. 30)	
Sub-module 2.7.4	Summary of clinical safety (p. 30)	
Sub-module 2.7.6	Synopses of individual studies (p. 31)	
Sub-module 5.3.5	Reports of efficacy and safety studies (p. 40)	"**CBR** However, this section may contain information on bio analytical methods developed/owned (and not publicly available) by the sponsor or CRO. Such information may be regarded as **CCI**. This is in accordance with the principle 3.2.outlined above. If not, this section should be regarded as **CBR**, this is in accordance with the principles 3.2. and 3.4 outlined above In accordance with principles 2.A, 2.B, 2.C and 2.1, some information in this section may be regarded as **PPD**"[10]
Sub-module 5.3.6	Reports of post-marketing experiences (p. 40)	
Sub-module 5.3.7	Case report forms and individual patient listings, when submitted (p. 40)	

Highlights as reported in the guidance document.[10]

HMA and the EMA also published a supplementary document[11] clarifying some of the most important points (Box 4, our highlights).

Box 4: Clarification of HMA/EMA guidance document (our highlights)

Section 18, 'Clinical Data'

"Although there was in general a very positive move towards increasing awareness expressed in the responses received, some stakeholders highlighted concerns towards the release of clinical data and documentation on the basis that this may reveal insights to competitors, and/or may bring disadvantages to researchers when publishing manuscripts from public clinical data and/ or may have an impact on the way intellectual property rights are enforced worldwide.

Approach Agreed:

The concerns about intellectual property and medical journals are addressed separately.

In general, the **data included in clinical trial study reports is considered as data that can be released as such data is not considered either commercially confidential or personal data that should be protected** (see point 5 above). In addition, there are increasing demands from the public to put as much clinical data as possible in the public domain.

It should be noted that **in order to reinforce transparency and public confidence in the European Medicines Regulatory System, NCAs are intending to develop strengthened efforts to release (either on request or proactively) growing amounts of clinical data**" (p. 8).[11]

HMA's approach to the release of clinical data seems unequivocal and reflects EMA's transparency policies. Clinical trial data, including the Clinical Study Reports, are not considered commercially confidential information and should be released upon request.

Background Material

EMA's transparency policies and access to clinical data

The Common Technical Document and Clinical Study Reports

The Common Technical Document[12] is a highly standardised format that pharmaceutical companies must adhere to when they submit a new marketing authorisation application. Regulatory agencies such the US Food and Drug Administration, Health Canada, Australian Therapeutic Goods Administration, and EMA have adopted this format.

The Common Technical Document is divided into five modules (Figure 1). Module 5 contains clinical data in the form of Clinical Study Reports from the pivotal trials that have been conducted prior to submitting the marketing authorisation application.[12] Empirical studies have demonstrated repeatedly that Clinical Study Reports are more complete and informative compared to other sources of clinical trial data, e.g. publications in medical journals or information on trial registry websites.[13 - 17] In addition, due to the documents' structured format they are also easier to use for research purposes.

Figure 1. The Common Technical Document

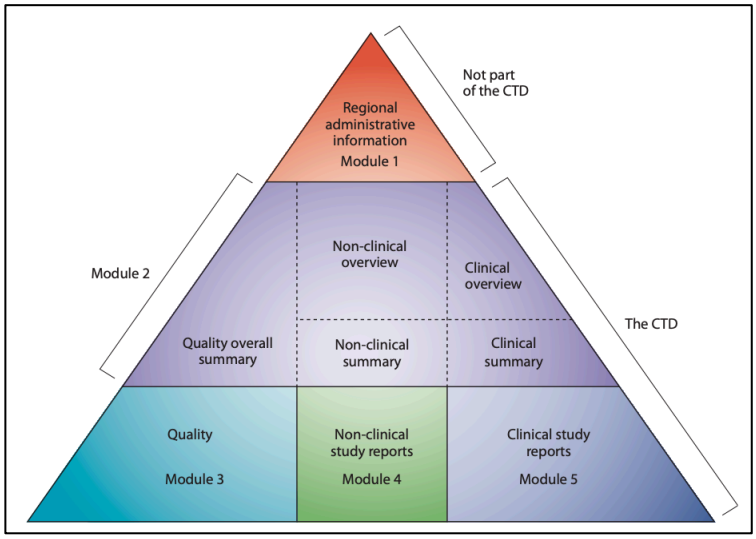

Figure reproduced from https://www.ich.org/page/ctd.

Clinical Study Reports are highly valuable in making reliable assessments of the benefits and harms of drugs and they are considered the gold standard as data source for systematic reviews of healthcare interventions.[18] An important example of using Clinical Study Reports is the systematic reviews of oseltamivir for seasonal flu.[19] The review demonstrated that the inclusion of Clinical Study Reports shifted the benefit harm balance compared to published literature on the drug.[20] As a direct consequence of the systematic review,[19] oseltamivir was downgraded from a "core" to a "complementary" drug on the World Health Organization's list of essential medicines.[21] Increasingly, more systematic reviews and other research projects[4,5,14-17, 22-29] include Clinical Study Reports, demonstrating the added value of Clinical

Study Reports compared to published literature. Most of these projects have relied on Clinical Study Reports obtained from regulatory agencies, whereas some projects also obtained data from pharmaceutical company databases and websites.

Policy 0043

Since 2010, EMA has released Clinical Study Reports upon request of centrally approved drugs,[30, 31] i.e. of drugs approved by the EMA through the centralised procedure. Policy 0043 was the end result of the Nordic Cochrane Centre's complaint to the European Ombudsman after they were denied access to clinical data to two weight loss drugs, rimonabant and orlistat.[32] The Ombudsman found that EMA committed administrative malpractice by not allowing the researchers access to clinical trial data of approved drugs.[33] As a consequence, EMA introduced Policy 0043 on access to documents acknowledging that parts of the documents submitted for regulatory drug approval, the marketing authorisation application, may contain commercially confidential information, but also that the documents are not considered confidential in their entirety.

Policy 0043 specifies under section 4.1.1, 'General principles', that, "When only parts of a document contain information that cannot be disclosed, access to the remaining parts of the document shall be granted"[30] and, "Likewise, documents or parts thereof may be redacted before disclosure in order to protect information contained therein that cannot be disclosed (i.e. the need to protect commercial confidential information or personal data)."[30]

EU Clinical Trial Regulation

In 2014, the EU Trial Regulation 536/2014[34] was announced. It will replace the EU Trial Directive 2001/20/EC.[35] According to EMA, the application of the new Trial Regulation has been delayed due to technical challenges of establishing a new EU clinical trial database, the Clinical Trial Information System (CTIS).[36, 37] The CTIS is planned to go online in December 2021.[37]

The EU Trial Regulation, sub-section 68, explicitly states that Clinical Study Reports are not considered commercial confidential information (Box 5, our highlights).

Box 5: The EU Trial Regulation on Clinical Study Reports (our highlights)

EU Trial Regulation 536/2014, Sub-section 68:

"For the purposes of this Regulation**, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted**, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, **and the clinical trial results** including reasons for temporary halt and early termination, in general, **should not be considered confidential**".[34]

Policy 0070

In October 2016, EMA strengthened their policy on access to clinical data with the introduction of policy 0070.[38] This policy meant that Clinical Study Reports from drugs approved centrally by the EMA should be prospectively released on a designated website.[39] In an accompanying guidance document[40] on how to implement the policy it was stated, "As a general rule all clinical reports submitted as part of a regulatory application will be subject to publication" (p. 7).[40]

Following Brexit and EMA's relocation from London to Amsterdam, EMA "suspended the publication of clinical data",[39] and it is unknown when the Agency plans to resume prospective release of trial data for centrally approved drugs. During the current COVID pandemic EMA has, "in line with its exceptional transparency measures for treatments and vaccines for COVID-19", released clinical data from remdesivir's authorisation.[39]

The European Court of Justice's rulings in favour of transparency

The 2018 decision

Three pharmaceutical companies, Pari Pharma, PTC Therapeutics, and MSD, challenged EMA's transparency rules regarding access to data included in marketing applications, such as the Clinical Study Reports.[41] The Court of Justice of the European Union ruled that the marketing applications should not be considered commercially confidential in their entirety, and that release of certain parts, e.g. the Clinical Study Reports, does not violate the companies' commercial interests.[41]

The 2020 decision

In 2019, PTC Therapeutics and MSD again challenged EMA's transparency rules.[42, 43] The European Court of Justice announced their final judgement in January 2020, which - again - ruled in favour of EMA's transparency rules. The Court confirmed that the public have the right to access clinical trial data submitted to the agency for marketing applications.[42, 43]

National initiatives increasing transparency

The European Union have unambiguous policies ensuring access to clinical trial data from Marketing Authorisation Applications. This 'right to access' is stipulated in EMA policies 0043[30] and 0070,[38] the EU Clinical Trial Regulation[34] and in the common HMA/EMA guidance document[10] on the identification of commercially confidential information.

However, we note that that the HMA/EMA guidance document[10] provides leeway for the National Competent Authorities to exempt release of trial data if they find support in national jurisdiction, "Notwithstanding this guidance document it should be noted that National Competent Authorities/EMA have to follow their national /European legislation in terms of access to documents and on the protection of personal data (based on the EU Directive 95/46/EC",[10] see also Box 3.

Until the EU Trial Regulation 536/2014[34] is assumed, National Competent Authorities may choose to follow European policies but they may also, seemingly without contradicting European obligations, deny access to clinical trial data of drugs authorised through decentralised or national routes.

The German and Finnish drug regulatory authorities did not adhere to European transparency policies when they rejected the requests to access Clinical Study Reports included in marketing authorisation applications, see Appendix 1. Explicitly for case 3, the German drug regulator, BfArM, did this with referral to national German legislation.[8]

In this context it is important to mention the Germany national legislation, the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG).[44] This legislation *mandates* companies to submit the Clinical Study Reports of newly approved drugs (both centrally and nationally approved drugs) to the German health authorities, who will then commission independent drug assessments based on the Clinical Study Reports. These assessments are usually conducted by the Institute for Quality and Efficiency in Health Care (IQWiG).[45] This showcases that national European legislations may also *increase* transparency.

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