Wissenschaftliche Prüfungsarbeit

EMA CLINICAL DATA TRANSPARENCY: A CRITICAL SYNOPSIS

Zur Erlangung des Titels

"Master of Drug Regulatory Affairs"

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von
Manuel Bilke
Aus Roth

München, 2016

Betreuer und 1. Referent: Dr. Ingrid Klingmann
Zweiter Referent: Prof. Dr. Burkhard Sträter

I. Abstract

This thesis aims to answer the question what the current status on EMA clinical data transparency is.

A systematic evaluation of applicable European legislation serves a basis for this synopsis where Directive (EC) 2001/20, Regulation (EC) 1049/2001, Regulation (EC) 536/2014, and Policy 0070 are to be mentioned as the most important. A particular focus is layed on the European databases EudraCT, the EU Clinical Trials Register and the EU Portal.

This comparison eventually results in a comprehensive table that informs about who has to publish clinical data, what is the extent and scope of clinical trial data to be published, when they are to be published and where.

The Clinical Trials Regulation that is planned to come into force in October 2018 introduces clinical data transparency targeted at the lay audience. According to the regulation, a lay summary of study results is to be submitted to the EU Portal. Dependant on how easily accessible this EU Portal will be to the public and to search engines this lay summary will be one influencer of the lay person's shaping of opinion on a drug's properties.

EMA has undergone a fundamental paradigm shift in regards to clinical trial transparency:

- Change from reactive to active clinical data transparency
- Publishing of results regardless of the outcome
- Phase 1 to Phase 4
- Two dominating restricting principles: Protection of personal data and protection of commercially confidential information.

It becomes obvious that there exist clinical data publishing obligations deriving from a multitude of different legislations that coexist in parallel and independently. This greatly impacts the daily work of the Regulatory Affairs Manager and compliance with all publishing legislations adds another layer of responsibility to his or her expertise.

II. Table of Content, List of Tables and Figures and Abbreviations

Table of Content

List of Tables:

List of Figures:

List of Abbreviations:

ACK	Acknowledgment of Receipt
CA	Competent Authority
CCI	Commercially Confidential Information
CTD	Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTA	Clinical Trial Application
CTR	Clinical Trials Regulation EU No 536/2014
EC	European Commission Ethics Committee
EMA	European Medicines Agency
EoT	End of Trial
EU	European Union
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
LVLS	Last Visit Last Subject
MAA	Marketing Authorisation Application
mAB	Monoclonal Antibody
MAH	Marketing Authorisation Holder
NEJM	New England Journal of Medicine
OECD	Organisation for Economic Co-operation and Development
Paediatric Regulation	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Study
PIP	Paediatric Investigation Plan
RA	Regulatory Affairs
SME	Small and medium-sized enterprise
ToU	Terms of Use

III. Introduction

"Transparency of clinical trials" has become a term widely used in the EU in the last few years. It has been the center of a highly controversial debate including a multitude of stakeholders. It is not only regularly covered by scientific journals like the NEJM[1] but also appears in publications of the lay press, often criticising the sponsors' alleged withholding of clinical data[2]. On numerous occasions, interest groups demanded for the extension of data publishing obligations[3].

Dr. Guido Rasi, EMA's Executive Director, coined the agency's guiding agenda at a workshop in 2012[4]:

> *"The European Medicines Agency is committed to proactive publication of clinical-trial data, once the marketing-authorisation process has ended. We are not here to decide if we publish clinical-trial data, but how."*

On the other hand, marketing authorisation holders see commercially confidential information and patient safety jeopardised by extensive publication obligations[5].

This thesis attempts to show to what extent transparency of clinical trial data has been implemented up to this point in time in the EU. It creates a synopsis of what clinical data has to be submitted by whom and when. It provides an overview of the regulatory landscape of data transparency and of the databases set up in the EU.

At the conclusion a sound judgement can be made whether clinical data transparency in the EU lives up to its high claim. Finally, the possible implications of the changed regulatory landscape for CROs, sponsors and marketing authorisation holders are pointed out.

IV. Methods

In this thesis, an overview is provided of the existing legal situation regarding transparency in the European Union by comparing applicable Directives (Directive (EC) 2001/20), Regulations (Regulation (EC), 1049/2001, Regulation (EC) 536/2014), Policies (Policy 0070) and Guidances (i.e. Guidance EMA/90915/2016) in detail. The latter guidance was published on 2 March 2016 and will have far-reaching consequences especially on the redaction of commercially confidential information (CCI) and on the anonymisation of clinical reports and is therefore paid particular attention to. Although the Clinical Trials Regulation 536/2014 has not yet come into force its impact is taken in consideration for this master thesis. Within this context, national pecularities or non-EU legislation and databases like clinicaltrials.gov are disregarded for clarity reasons, however global overarching frameworks like the Declaration of Helsinki are included.

The mentioned laws build the foundation of the databases EU Clinical Trials Register and the EU-Database where results of clinical trials are published. The legislation and databases are examined on the parameters scope, time point of publishing, involved stakeholders and extent of documents. A distinction is made between data that is disclosed on demand and data that is published proactively.

As a centrepiece of this thesis, a comprehensive table containing all examined legislations and databases at a glance is compiled. Judging by these results an answer will be given to the question raised in the thesis on the status of clinical data transparency in the EU.

For the matter of this thesis, transparency does not imply financial transparency as in an investigator's financial disclosure. This thesis does explicitly not discuss possible benefits or downsides of any presented guidelines of data publication for involved stakeholders.
Where appropriate, it is distinguished between public data sharing and non-public data sharing: The former means published data that is accessible to the general public, the latter means published data that is accessible only to a limited group of people like the non-public part of EudraCT.
This thesis will sketch a fictional SME and a fictional investigational medicinal product. It will describe the work of a Regulatory Affairs Manager that is appointed to ensure data transparency compliance according to the legal EMA framework. This happens in support of a candidate, a mAB with anti-inflammatory properties in an allergic asthma third-line indication from the beginning of clinical Phase 1 to several years after marketing authorisation. Due to its biotechnological origin the centralised authorisation procedure is mandatory and due to its novel nature the submission of a paediatric investigation plan is obligatory. The Regulatory Affairs Manager has to determine what directives, regulations, guidelines and policies apply in this case and what clinical data is to be published when and where.

V. Findings

A. Declaration of Helsinki

Although it is not a European particularity, the influence of the Declaration of Helsinki should be described as it functions as an ethical umbrella over the conduct of clinical trials. It states the general ethical principles for medical research on human subjects and was adopted in June 1964. Most recently it was amended in October 2013 and holds two Articles in regards to data transparency:
Article 35:

> *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."*

Article 36:

> *[…] Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. […] Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. […]"*

The requirements are kept very general and are of an ethical nature. It is notable that already at this point, the maxim is introduced that a study result is to be published regardless of its outcome – positive as well as negative.

B. WHO Statement on Public Disclosure of Clinical Trial Results

The WHO Statement on Public Disclosure of Clinical Trial Results which was last stated on April 2015 refers to the Declaration of Helsinki in numerous points:
It demands that the clinical trial should be registered prior to the first treatment of the first subject and that the entry should be kept updated to its current status during the course of

the study. It is required that the results of the study are to be published on a publicly accessible database within 12 months of its completion.

C. Freedom of Information Regulation (EC) 1049/2001

The Maastricht Treaty of 1992 laid the foundation of European efforts to increased transparency by establishing the "Right of Access to Information" in Declaration No 17. In 1997 the Amsterdam Treaty stated in Article 255 that "any citizen of the Union, and any natural or legal person residing or having its registered office in a Member State, shall have a right of access to European Parliament, Council and Commission documents". It is further stated that the Council shall implement "general principles and limits on the grounds of public or private interest".

These principles and limits were eventually set out in Regulation (EC) 1049/2001 in May 2001. It applies to "all documents held by an institution […] in all areas of activity of the European Union". This implies that i.e. documents held by a sponsor of a clinical trial are not eligible by this Regulation.

The documents are not published actively but only "following a written application or directly in electronic form or through a register". The applicant does not have to specify any reason for his request and receives the reply in a short timeframe of 15 working days.

However, Article 4 defines exceptions where disclosure of documents would violate "protection of personal data" and "commercial interests" – two limitations that determine the further development of data transparency until today.

D. Clinical Trial Directive (EC) 2001/20

Directive (EC) No 2001/20 - also called Clinical Trial Directive - lays down the general principles of the conduct of interventional clinical trials in the EU. The Directive was adopted in April 2001 and came into effect in May 2004. For the subject of this thesis, Article 11 is relevant:

a) Article 11

In Article 11 of Clinical Trial Directive (EC) No 2001/20, Member States

> *"in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the Agency and the Commission":*

- Parts from the Clinical Trial Application Form including its amendments in the course of the trial and amendments to the protocol
- The favourable opinion of the Ethics Committee
- End of Trial form
- A reference to the inspections carried out on conformity with GCP

It is noted that this provision by itself does not establish data transparency to the public – it is restricted to the competent authorities. Only by the subsequent Regulation (EC) 726/2004 and its corresponding guidelines the paradigm shift from data that is only accessible to the authorities to data that is accessible to the public took place:

E. Regulation (EC) 726/2004

Regulation (EC) 726/2004 mainly concerns the procedures of centrally authorised medicinal products and became effective in May 2004.

But it also contains two Articles that are relevant to clinical data transparency:

a) *Article 57*

In Article 57(1)l EMA is prompted to create a

> *"database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies […]".*

Further on, in Article 57(2) the database is specified to contain

> *"data on clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC. The Commission shall, in consultation with the Member States, issue guidelines on data fields which could be included and which may be accessible to the public."*

b) *Article 80*

In Article 80, EMA shall set out

> *"rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products which is not of a confidential nature".*

This Article builds the foundation of the later discussed Policy 0070 and by "is not of a confidential nature" alludes to its main limitations "commercially confidential information" and "Anonymisation of personal data".

F. Paediatric Regulation (EC) No 1901/2006

The Paediatric Regulation (EC) No 1901/2006 came into force in January 2007. Legislators recognised a lack of authorised medicinal products for paediatric indications and a critical use of paediatric off-label prescriptions. So it "aims to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately."

In order to protect the needs of children as a vulnerable population, it avoids exposing children to unnecessary burdens such as duplicate trials. A way to ensure this protection is to enforce the publication of paediatric clinical trials.

So, in consequence of Article 45, marketing authorisation holders are obliged to submit information of paediatric studies completed by 26 January 2008.

For clinical studies completed after 26 January 2008, Article 46 applies respectively.

In both cases the results are posted in the form of assessment reports; for medicinal products authorised nationally on the Heads of Medicines Agencies website and for centrally authorised medicinal products on the EMA website as European public assessment reports.

In addition, Article 41 requires that the protocol and results are published on the EudraCT database within six month of the completion of the study.

G. Subsequent Guidelines

Subsequent to these general provisions of Directive (EC) 2001/20, Regulation (EC) 726/2004 and Regulation (EC) 1901/2006, the Commission has developed several more specific guidelines:

In the guideline 2008/C168/02, the European Commission has drawn up "the scope, the elements and guidance on implementation of making information contained in EudraCT publicly available". Based on this, the Commission specifies in the guideline ENTR/F/2/SF (2009) 3687 the data fields to be published according to Article 11 of Directive (EC) No 2001/20 and Regulation (EC) No 726/2004 and the time limit of one year for providing this information.[6]

In the same way, guideline 2009/C28/01 sets out the "nature of the information to be entered into EudraCT, the information to be made accessible to the public and the responsibilities of the EMA and related tasks in this context" in accordance with Article 41 of the Paediatric Regulation. Based on this, ENTR/F/2/SF/jr D (2009) 3698 describes in a very detailed manner the specific data fields contained in the clinical trials database for paediatric trials.

a) Comparison Between the Data Fields Required for Non-paediatric and Paediatric Trials

The following table establishes the similarities and differences between the data fields of both guidelines; additional requirements of paediatric trials are underlined:

ENTR/F/2/SF (2009) 3687 non-paediatric trials	**ENTR/F/2/SF/jr D (2009) 3698 paediatric trials**
Protocol-related	
Identification of the clinical trial and its protocol	
Identification of the sponsor (paediatric: status of sponsor – commercial or non-commercial)	
Source of funding	
Contact point for public use	
Identification and description of the treatment arms of the study (IMPs) to be used	
Therapeutic objective of the trial (disease under investigation	
Major objectives and endpoints	
Trial design including the countries in which it is to be conducted (additional paediatric: Human pharmacology (Phase 1), First administration to humans, bioequivalence study)	
Trial population	
Inclusion/exclusion criteria (additional paediatric: Clinical trial sites/investigators in the member state of country concerned, networks to be involved in the trial)	
Review by the Competent Authority of Ethics Committee in the country(ies) concerned Trial status (per country or region as applicable), and paediatric: if refused for ethical reasons the reasons for refusal	
Results related information	
Administrative information and trial identification	
Trial design	

Scientific background and explanation of rationale for the trial
Participants in the trial – information on the subject population including inclusion exclusion criteria and demographic information
Interventions – the treatments used
Objectives of the trial
Outcome measures
Randomisation implementation
Blinding
Statistical methods
Participant flow, Patient disposition
Protocol deviations
Recruitment
Baseline data
Trial interruption
Outcomes and estimations
Ancillary analysis
Adverse events
Discussion and interpretation of study results (interpretation of trial results by sponsor, if available and by competent authority, if available) Paediatric: result reporting within 6 months, in exceptional cases (scientific reasons or trial not in scope of Article 46(1): 12 months)
A declaration of the submitting party on liability for the accuracy of the submitted information
Trial termination

Table 1: Comparison between data fields

From this table it can be followed, that the requirements for both kinds of studies are nearly congruent and differ only in a few minor points:

- In contrast to the provisions of Clinical Trial Directive 2001/20/EC, Regulation 1901/2006 requires that data from clinical trials that are part of a PIP but conducted in third countries are published. The Directive applies only for studies taking place in at least one EU-country.
- Where the Directive only includes data from Phase 2, 3 and 4 clinical trials, the Paediatric Regulation includes data from Phase 1, too.
- The reporting time frame for the Paediatric Regulation is set narrower: Applicants have 6 months for results posting for paediatric trials, for non-paediatric trials 12 months. In this case the end of trial is defined as the notification to EudraCT via “Declaration of the End of Trial Form”
- In paediatric trials, the status of the sponsor has to be presented, in particular commercial or non-commercial.
- In paediatric trials, the applicant has to state the reason for a refusal by a prior ethics committee if it is an ethical reason.

b) Guidance on Posting and Publication of Result-related Information on Clinical Trials in Relation to the Implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

In addition to ENTR/F/2/SF (2009) 3687 and ENTR/F/2/SF/jr D (2009) 3698, the Commission Guideline 2012/C 302/03 was published.

In Chapter 4.7, this guideline also describes the implications for sponsors that do not provide the required data at all or not in time, that is 9 months for paediatric trials and 15 months for other trials after the end of trial: The Commission decided against penalty fees and for a naming and shaming policy by flagging concerned clinical trials and making this information publicly available.

c) Technical Guidance on the Format of the Data Fields of Result-related Information on Clinical Trials Submitted in Accordance with Article 57(2) of Regulation (EC) No 726 and Article 41(2) of Regulation (EC) No 1901/2006

To conclude the guidelines discussed above, the European Commission has published a further technical guidance. In it a graphic display and organisation of the data fields of the EudraCT are provided.

H. EudraCT

EudraCT is the EMA's electronic database of clinical trials that is fed by the provisions of Directive 2001/20/EC, Regulation (EC) No 726/2004 and the Paediatric Regulation (EC) 1901/2006 and was started on 1 May 2004. In its history, it was the subject of several updates and extensions. Most recently on 13 January 2016 it was updated to Version 10 and enables the submitting of summary clinical trials results and subsequently publishing to the EU Clinical Trials Register, based on the regulations and guidelines presented above.

Apart from that, it functions as an interface for registering a study and obtaining a EudraCT-Number at the beginning. The xml and pdf file of a Clinical Trial Application according to the Clinical Trial Directive is created on EudraCT, too.

I. EU Clinical Trials Register

As described above, Article 11 of Directive 2001/20/EC requires the EMA to build up a database for clinical data, EudraCT. Whereas EudraCT is mainly used by applicants and competent authorities, EU Clinical Trials Register represents the publicly accessible part of the database resulting from Article 57 of Regulation (EC) No 726/2004 and Article 41 of the Paediatric Regulation (EC) No 1901/2006.

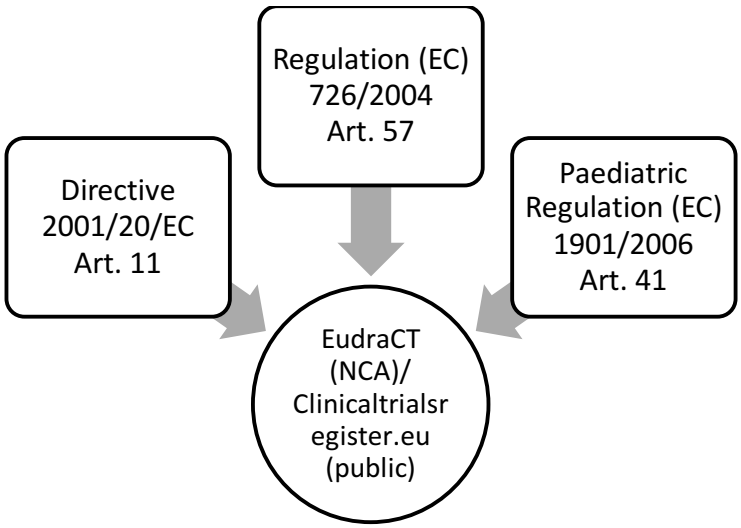


Figure 1: Sources of EudraCT

The register contains data from clinical trials that started after the Directive 2001/20/EC became effective in 2004 and covers[7]:

- The description of any phase 2-4 adult clinical data trial where the investigator sites are in the European Union or the European Economic Area.
- The description of any paediatric clinical trial with the investigator sites in the European Union
- The description of any paediatric trial that is marketing authorisation holder-sponsored and involves the use in the paediatric population of a medicinal product covered by an EU marketing authorisation (Article 46 of Regulation (EC) No 1901/2006
- The description of any trials which form part of an agreed paediatric investigation plan (PIP) including those where the investigator sites are outside the European Union
- Summaries of results of the clinical trials mentioned above (if results have been posted by the sponsor or marketing authorisation holder).
- Summaries of results (with a reduced set of data fields) of paediatric trials that were completed by 26 January in respect of products covered by an EU marketing authorisation (Article 45 of Regulation (EC) No 1901/2006.

J. Policy 0070: European Medicines Agency Policy on Publication of Clinical Data for Medicinal Products for Human Use

In order to pursue its aim of clinical data transparency, EMA developed Policy 0070. In general, Policy 0070 follows a two-phased approach:

In Phase 1 which came effective on 1 January 2015, only the clinical reports are to be published. In this definition, clinical reports refer to the following parts of the CTD:

- Module 2.5 - the clinical overview,
- Module 2.7 – the clinical summaries
- Module 5 – the clinical study reports, including appendices 16.1.1 – protocol and protocol amendments, 16.1.2 – sample case report form and 16.1.9 documentation of statistical methods

The effective date of Phase 2 is yet to be determined, but its scope is the publishing of individual patient data, IPD. This means the "individual data separately recorded for each participant in a clinical study". Both, IPD and clinical reports, are summarised under the term "clinical data".
Currently, the Policy is in its implementation phase. The first reports are expected to be published in mid of September 2016.

1. Terms of Use

In Annex 1 and Annex 2 of the Policy, the Terms of Use are described. It is important to understand that the data provided by the Policy is not accessed anonymously as is the case with databases like the EU Clinical Trials Register. Here, the user registers by obtaining a user ID and password and accepts the Terms of Use.
The terms of use distinguish between "Terms of Use for general information purposes" and "Terms of Use for academic and other non-commercial research purposes":

- **Terms of Use for general information purposes**

The user is able to view clinical reports in a "view-on-screen-only" mode, that is the documents are not to be saved or distributed in any way.

- **Terms of Use for academic and other non-commercial research purposes**

In addition to a user ID and password, the user has to provide an email address, a place of address in the European Union and a clear personal identification. In this case the user is allowed to download, save or print the Clinical Reports.
In both cases the user confirms that she or he will not use the clinical data for commercial uses like for the support of a marketing authorisation application or attempts to re-identify any study patients.

2. EMA/90915/2016: External Guidance on the Implementation of the European Medicines Agency Policy on the Publication of Clinical Data for Medicinal Products for Human Use

On 2 March 2016, EMA published the "External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use". For this consideration it is important to keep in mind that Policy 0070 is based on Regulation 726/2004 and thus covers clinical data of centrally authorised medicinal products and relates only to Phase 1 of the policy. Consequently, clinical reports are covered:

- *"as part of a marketing authorisation application (MAA) with the exception of informed consent applications […]"*
- *"as part of a procedure under Article 58 of Regulation (EC) No 726/2004 […]"*
- *"submitted by a third party in the context of a MAA […]"*
- *"as part of extension of indication and line extension applications relating to existing centrally authorised medicinal products […]"*
- *"requested by EMA/submitted by the applicant/Marketing Authorisation Holder (MAH) as additional clinical data in the context of the scientific assessment process for the aforementioned situations."*

These requirements apply to clinical data submitted to EMA within a submission under the centralised procedure after 1 January 2015 and within an extension of indication and line extension since 1 July 2015.

a) Procedural Aspects Related to the Submission

In its guidance, EMA gives detailed information about the process of the submission of clinical reports. In case of an initial marketing authorisation application, the applicant will receive three notifications from EMA:

- The validation letter,
- The Day 180 list of outstanding issues or withdrawal notification,
- CHMP Opinion letter

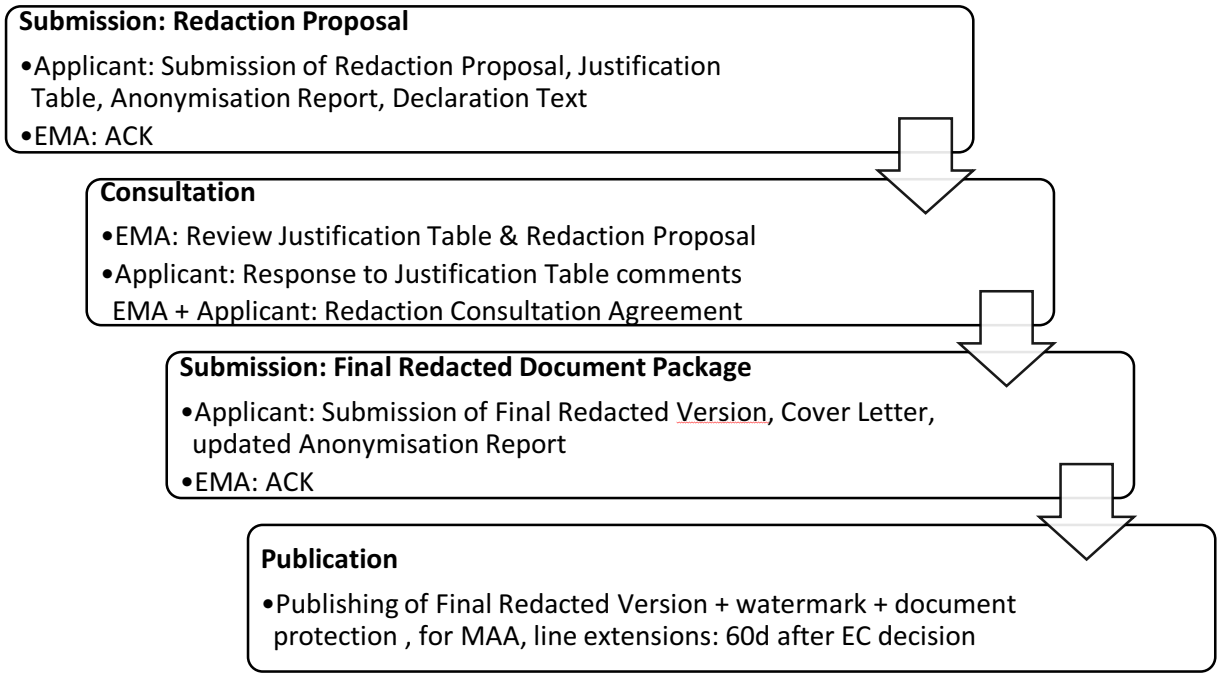


Figure 2: Policy 0070 publishing procedure

The process consists of four parts:

- **Submission of "Redaction Proposal Version"**

The applicant submits the redaction proposal including a justification table, anonymisation report, declaration text.
After that, EMA sends an acknowledgment of receipt.

- **Consultation**

The EMA reviews the redaction proposal and the justification table. The applicant responses to the comments in the justification table. Together, EMA and the applicant reach an agreement on the redaction consultation.

- **Submission: Final Redacted Document Package**

The applicant submits the final redacted version including cover letter and updated anonymisation report.
Again after that, the EMA sends an acknowledgment of receipt.

- **Publication**

The Final Redacted Version including watermark and document protection is posted 60 days after the European Commission decision on the corporate website.
The following table comprises the package components of the "Redaction Proposal Document" and of the "Final Redacted Document" and compares what delineates what parts of the "Final Redacted Document are published" and what not:

Redaction Proposal Document package	**eCTD Module/Section within the eCTD**	**Redaction Proposal Document: Documents published**	**Final Redacted Document: Documents Published**
Cover letter including the declaration confirming that the clinical reports submitted for scientific evaluation are the same as those submitted for publication, except for the proposed redactions/anonymisation. The cover letter templates are at Annex 1.4 and 1.5	1.0	Not published	Not published
A list of documents submitted, annexed to the cover letter. A template for this list is at Annex 1.3	1.0	Not published	Not published
"Redaction Proposal Version" of all clinical reports as follows: "the "Redaction Proposal Version" is an initial version of the clinical reports intended for publication in which proposed redactions are marked			
Clinical overview supplement/amendment/appendix	2.5	Not published	Published
Clinical summary Supplement/amendment/appendix	2.7.1-2.7.4	Not published	Published
Clinical study report – body	5.3	Not published	Published
Clinical study report – Appendices 16.1.1 (protocol and protocol amendments) 16.1.2 (sample case report form) 16.1.9 (documentation of statistical methods)	5.3	Not published	Published
A complete set of justification tables (CCI redactions only) detailing all proposed redactions for each redacted document. Links to downloadable templates are provided in Section 3.3.1.10 and a sample justification table is provided in Annex 1.10	Working document	Not published	Published
Anonymisation Report, the report template is at Annex 1.2	1.9	Not published	Published

Table 2: Content of Redaction Proposal Document and Final Redacted Document

b) Anonymisation of Clinical Reports

Article 2(a) of Regulation (EC) 45/2001 lays the basis for the protection of personal data:

> "'*Personal data*' *shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his/her physical, physiological, mental, economic, cultural or social identity.*"

By this Article alone it would not be possible to publish clinical data containing personal data. But Directive 95/46/EC creates an exception in so far that

> "*the principles of protection shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable[...]*"

This corresponds to the definition of the term anonymisation: Anonymised data must be

> "*processed in such a way that it can no longer be used to identify a natural person by using 'all means likely to be used' by either the controller or a third party*"[8].

In contrast to that, pseudonymisation means the substitution of an attribute with another. The pseudonymisation of clinical data is considered to be inferior to anonymisation in terms of traceability. It must be noticed that pseudonymised data can be traced back under certain circumstances and thus is covered by data protection.

In Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party, criteria are established to benchmark the quality of anonymisation:

> "*(i) is it still possible to single out an individual,*
> *(ii) is it still possible to link records relating to an individual, and*
> *(iii) can information be inferred concerning an individual?*"

A successful anonymisation technique either leads to results that fulfil all three criteria or is tested against an evaluation of identification risks.
EMA acknowledges that data that is processed according to these three criteria may be of little scientific use. Therefore, in most cases the performance of a risk assessment is recommended to achieve a best balanced choice between usability of scientific data and grade of anonymisation.

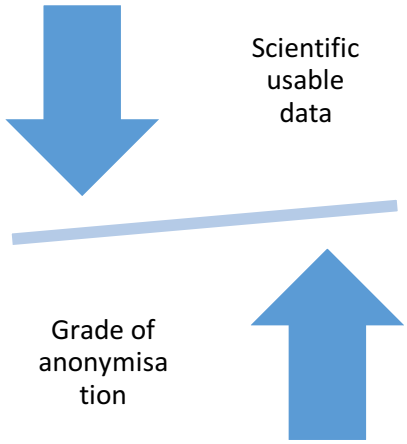


Figure 3: Anonymisation: Best Balanced Choice

Three major anonymisation techniques are described:

- Masking: Predefined variables that refer to identifiable data are removed, either by hand or by software.

- Generalisation: The original value is replaced with a less specific one.
- Randomisation: Removing the connection between the data and the individual by altering the veracity of the data. This could include the technique of noise addition which would be for example the shifting of dates by a couple of days.

c) Redaction of Commercially Confidential Information

The Agency states that clinical data is generally not considered CCI. However, Annex 3 of Policy 0070 identifies information that may potentially be considered CCI.
However, the guidance identifies four types of information that are not considered CCI:

- Information that is already in the public domain or publicly available
- Information that does not bear any innovative features
- Additional information the disclosure of which would be in public interest
    - General or administrative information
    - Quality-related information
    - Non-Clinical-related information
    - Clinical-related information
- Information that lacks sufficient or relevant justification

A table with columns for the text proposed for redaction, the reference according to Annex 3 on which the redaction is based, the justification of the applicant and the Agency's assessment including rationale or redaction code is provided.

K. Clinical Trials Regulation 536/2014

The Clinical Trial Directive originally sought to harmonise the conduct of clinical studies in the European Union by providing a standardised framework to all member states. As a directive is not aimed to be directly binding, the member states implemented national laws leading to a highly diversified regulatory European landscape for clinical trials. This poses a major hurdle especially for sponsors of multinational trials resulting in an increased delay for launching a clinical trial, massively increased costs for the conduct and eventually a severe decline of the number of applications since the directive came into force[9].
As a way to counteract this harmful development, the Clinical Trials Regulation 536/2014 was adopted on 16 April 2014. Its key points are:

- Its legal nature is a regulation, meaning it is directly binding and is not translated into national law. As a consequence, once it comes applicable, the Directive will be repealed.
- It will greatly simplify the application process. Instead of multiple clinical trial applications that are to be submitted to each competent authority and to an enormous number of ethics committees of each concerned European member state each with different national peculiarities and requirements, there will be a single application that is submitted to a single European Portal.

According to Article 82(2), an independent audit has to be performed to prove full functionality as a prerequisite for the regulation to become effective. Therefore, EMA has released a maximum delivery time frame[10]: The audit will be completed by November 2017 and the results will be published in March 2018. The regulation will become applicable 6 months afterwards, in October 2018.
The basis for data transparency in terms of the new Clinical Trials Regulation is laid out in Article 36, 37, 81 and Annex IV and V.

1. Legal Basis

a) Article 37: Technical Summary of Results, Clinical Study Report

Article 37(4) sets out the obligation for publishing of the technical summary of results and the summary of results for laypersons:

> *"Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.*
> *It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V"*

Article 37(8) even extends these obligations by including the publishing of intermediate data analysis where applicable:

> *"[…] where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date."*

This means a fundamental change from freedom of information only available upon request to a proactive publishing of vital study data like study results aimed not only to experts but to every lay person in the European Union.
Besides these obligations during the clinical development phase, the regulation requires the applicant of a MAA to submit the clinical study report to the EU database within 30 days after the European Commission decision in the case the study was used as part of the MAA. In addition, Article 37(4) allows the sponsor to share raw data voluntarily – the related guidelines to be issued by the Commission are in the "Inception phase" at the time of this thesis[11].

b) Article 81(4): Exceptions

Article 81(4) lays down that every information submitted to the clinical trial database is publicly available with four exemptions:

- Protection of personal data,
- Protection of commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest in disclosure,
- Protection of confidential communication between Member States in the preparation of their assessment,
- Protection of the supervision of clinical trials by Member States

c) Annex IV: Content of the Summary of the Results of the Clinical Trial

The following table compares the wording of the information that is required to be posted in the EU Clinical Trials Register according to with the provisions of Annex IV of Regulation (EC) 536/2014:

EU Clinical Trials Register	**Annex IV, Regulation 536/2014**
Trial information:	**Clinical Trial Information**
Study identification	Clinical trial identification (including title of

	the trial and protocol number)
Identifiers	Identifiers (including EU trial number, other identifiers)
Sponsor details	Sponsor details (including scientific and public contact points)
Paediatric regulatory details	Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan)
Result analysis stage	Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product
General Information about the trial	General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used)
Population of trial subjects with actual number of subjects included in the trial	Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).
Subject disposition:	
Recruitment	Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);
Pre-assignment Period	Pre-assignment Period
Post Assignment Periods	Post Assignment Periods
Baseline Characteristics:	
Baseline Characteristics (Required) Age	Baseline Characteristics (Required) Age

Baseline Characteristics (Required) Gender	Baseline Characteristics (Required) Gender
Baseline Characteristics (Optional) Study Specific Characteristic	Baseline Characteristics (Optional) Study Specific Characteristic
End Points:	
Endpoint definitions	Endpoint definitions
End Point #1, Statistical Analysis	End Point #1, Statistical Analysis
End Point #2, Statistical Analysis	End Point #2, Statistical Analysis
Adverse Events:	
Adverse events information	Adverse events information
Adverse event reporting group	Adverse event reporting group
Serious Adverse Events	Serious Adverse Events
Non-serious adverse event	Non-serious adverse event
More Information	
Global Substantial Amendments	Global Substantial Modifications
Global Interruptions and re-starts	Global Interruptions and re-starts
Limitations & Caveats	Limitations, addressing sources of potential bias and imprecisions and Caveats;
	A declaration by the submitting party on the accuracy of the submitted information.

Table 3: Comparison between EU Clinical Trials Register and Annex IV of CTR

Although the specific final data fields for the EU Database have not yet been published, the factual congruency of the items suggests that the data fields and graphic display of the results that are posted to the EU Database will be highly similar to the ones that are currently posted to EudraCT.

d) Annex V: Summary of Results for Lay Persons

In Annex V, the CTR states, which ten elements the summary of the results of the clinical trial for laypersons shall contain:

- Clinical trial identification (including title of the trial, protocol number, EU trail number and other identifiers),
- Name and contact details of the sponsor,
- General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it),
- Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria),
- Investigational medicinal products used,
- Description of adverse reactions and their frequency,
- Overall results of the clinical trial,
- Comments on the outcome of the clinical trial,
- Indication if follow up clinical trials are foreseen,
- Indication where additional information can be found.

In a recent publication, the American Medical Writers Association (AMWA) appreciates this development but raises concern that the reading level target of the lay audience has yet to

be determined[12]. In their opinion, this could lead to divergent levels quality of the summary of results for lay persons.

e) Summary of Clinical Trial Results for Laypersons: Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use

On 1 June 2016, EMA released a consultation document[13] that was open to contribution to stakeholders until 31 August 2016. It further specifies the elements of the Summary of Clinical Trial Results for Laypersons provided by Annex V of the regulation.

- It is emphasised, that the responsibility of the submitting of the lay summary lies with trial sponsor.
- The General Principles are stated:
    - *„Develop the summary for a general public audience and do not assume any prior knowledge of the trial*
    - *Develop the layout and content for each section in terms of style, language and literacy level to meet the needs of the general public.*
    - *Keep the document as short as possible*
    - *Focus on unambiguous, factual information.*
    - *Ensure that no promotional content is included [..].*
    - *Follow health literacy and numeracy principles [...]).*
    - *Consider involving patients, patient representatives, or advocates in the development and review of the summary information to ensure that it truly meets their needs. This won't be feasible for some studies but where it is a possibility, it may enhance the final version. Medical writers with experience of writing in plain language for the public may also be helpful. "*

It is to be noted that EMA discourages promotional language. In "Annex 2 – Neutral language guidance in describing results" numerous specific examples of promotional language are set against the desired neutral language.

- Particular recommendations for readability tests for the European Languages:

While the AMWA asked about the reading level that is to be targeted, this question is now answered by the recommendation in the document: The text is expected to aim at people with a low to average level of literacy, expressed by the literacy proficiency levels 2 to 3 of the OECD Skills Outlook publication. This means that high school level is required by the reader at the least.

- Where it is appropriate, the use of visuals like diagrams is encouraged to illustrate the results
- It is clarified that the summary is to be provided in the local languages where the trial was conducted, at least and optional – if not already included – an English version.

2. EU-Portal / EU-Database

The new Clinical Trials Regulation requires the EMA in Article 80 to provide a portal to applicants where clinical data are to be submitted. In Article 81, the EU database is described in which the clinical data is stored. It is stated in Article 82 that EMA has to define functional specifications for both EU portal and EU database before the regulation came

become effective. Additionally, these specifications have to undergo an audit. Up to the date of this thesis, the regulation is planned to come into force not before October 2018.
Figure 4: EU Portal, Workspace and EU Database depicts the procedure of submission of data from the user to the EU Portal through the Workspace and to the EU Database where the data is eventually stored:

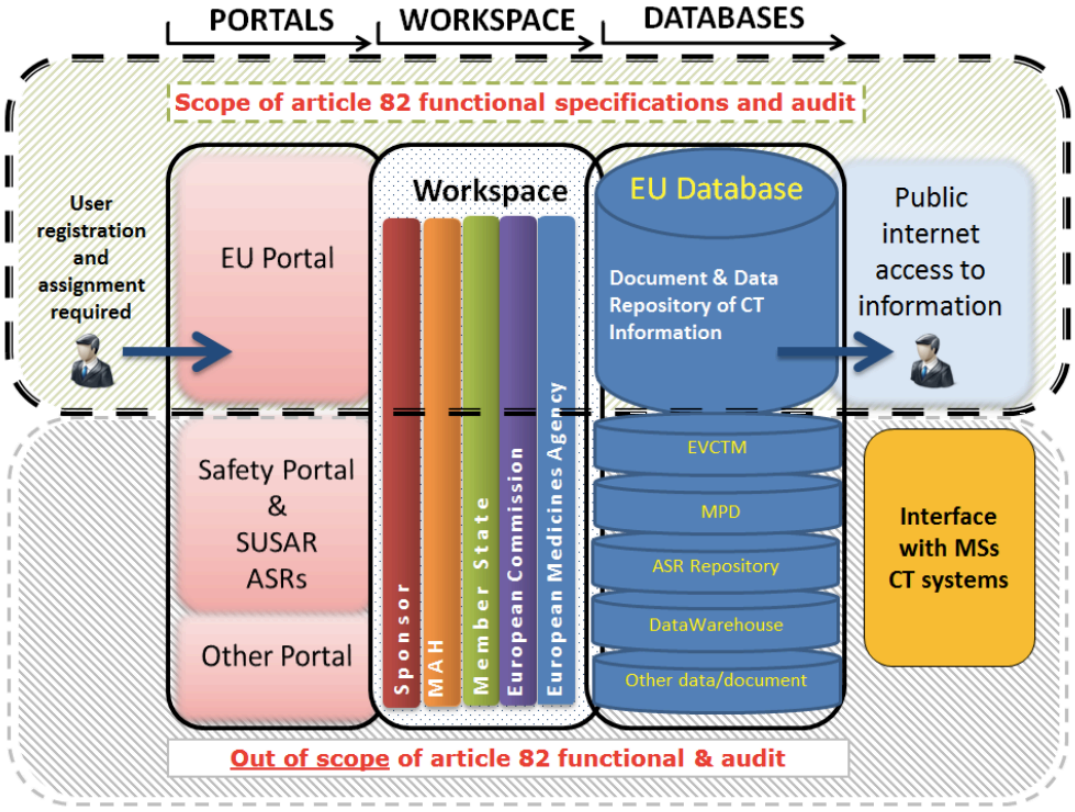


Figure 4: EU Portal, Workspace and EU Database, from "functional specifications for the EU portal and EU database to be audited".

On 25 March 2015, EMA eventually released the "functional specifications for the EU portal and EU database to be audited". For the matter of this thesis, requirements no. 7, 9 and 18 are relevant.
In requirement no. 7 the sponsor is required to upload the CT summary results including lay summary after the end of the trial according to Article 37(4) and after the intermediate analysis date according to Article 37(8). In requirement no. 9 the applicant for marketing authorisation has to submit the clinical study report according to Article 37(4). Requirement 18 refers to Article 81(4) and states that the EU database shall be publicly accessible except for the grounds stated in V.K.1.b) Article 81(4): Exceptions
Based on these requirements the functional specifications are phrased. Table 4 sums up the functional specifications that are related to the publication of clinical data:

4.3 Publication of CT data and information	• Publication via an automated process, manual override only in exemptions • Differentiation between public and non-public data • Determination of timing of publication of each data field
4.4 Search functionality	Advanced search functionality by the use of

	metadata
4.5 Presentation of the information	Allows related information to be grouped together by way of the EU trial number with links or display of data and document of relevance
4.6 Download option	Data can be downloaded as several document formats like XML, PDF or Word
4.7 Public interface	The public interface is planned to be displayed in the official EU languages once the system is fully operational.
4.8 Help and training features	Implements a help and tooltip system to support the understanding of the information published

Table 4: EU Portal and Database, Functional specifications related to the publication of clinical data

3. Possible Consequences of the Clinical Trials Regulation Coming into Effect for the Directive 2001/20/EC

In V.I the legislation was outlined that currently feeds in Clinicaltrialsregister.eu: The Directive 2001/20/EC, the Regulation (EC) No 726/2004 and the Paediatric Regulation (EC) 1901/2006. As already stated Directive 2001/20/EC will be entirely repealed once the Clinical Trials Regulation comes into force.

The Guidance that describes the data fields that the EU Clinical Trials Register contains - Guidance ENTR/F/2/SF (2009) 3687 – is based on Directive 2001/20/EC and Regulation (EC) No 726/2004. Further clarification of Competent Authorities is needed if – as a result of repealing of one of these pillars – the prerequisites of the posting to the database are no longer fulfilled.

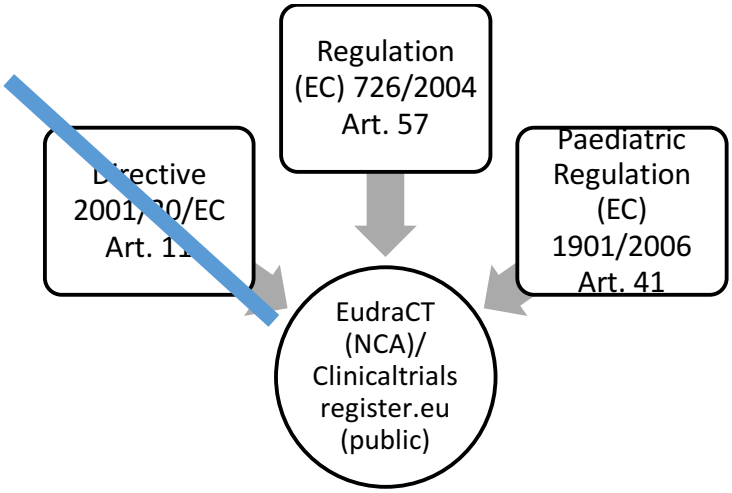


Figure 5: Possible Consequences of the CTR concerning the publication to Clinicaltrailsregister.eu

L. Timeline: Implemention of Guidelines

The applicable legislation is listed chronologically in the following table and visualised in the subsequent timeline:

Legislative	**Entry into force**
Freedom of Information Regulation	May 2001

(EC) 1049/2001	
Directive 2001/20/EC	May 2004
Regulation (EC) No 726/2004	May 2004
Policy 0070	January 2015
Clinical Trials Regulation 536/2004	Expected in October 2018 at the latest

Table 5: Legislative cornerstones

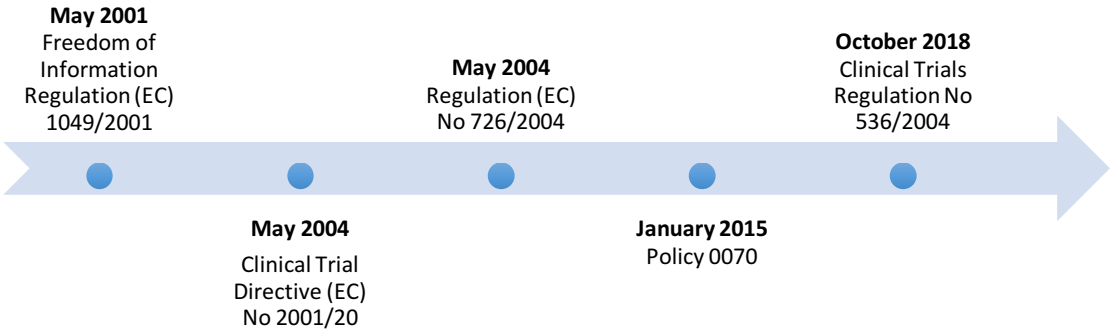


Figure 6: Timeline, Implementation of Guidelines

The mind map in Annex 2 depicts the applicable legislation by breaking down the applicable directives, regulations, adjunct guidelines and communications and related articles that are referenced in this thesis. The red fields mark the place where the data is published – whether it is a dedicated web site or register.

VI. Discussion

A. EFPIA Transparency

Although this thesis aims to investigate transparency set by European law a look at voluntary transparency initiatives established by the pharmaceutical industry will add important aspects to the discussion.

EFPIA – the European Federation of Pharmaceutical Industries and Associations – comprises 33 national associations and 42 pharmaceutical companies. On 18 July 2013, the "Principles for Responsible Clinical Trial Data Sharing" were published. 5 principles are included:

1. Enhancing Data Sharing with Researchers

Upon request from qualified scientific and medical researchers the companies will grant access to patient-level, study-level data and protocols. It is stressed that patient data is anonymised and that the access is restricted in cases where re-identification of study participants is possible.

Several conditions are attached to the use of this data: The company sets up a scientific board that evaluates each applicant and each request by its legitimacy in form a research proposal that includes the description of data being requested, a hypothesis, an analysis plan, a publication plan and qualifications and experience of the concerned team. In

addition, it is to be stated if any competitive conflict of interest would arise by the release of data.
Furthermore, a request is denied if the protection of personal data would be endangered by publication or for legal reasons.

2. Enhancing Public Access to Clinical Study Information

CSR synopses that have been submitted to competent authorities on or after 1 January 2014 will be made publicly available.

3. Sharing Results with Patients Who Participate in Clinical Trials

A summary of study results is made available to its participants.

4. Certifying Procedures for Sharing Clinical Trial Information

The companies declare on a website to implement policies and procedures for these data sharing commitments.

5. Reaffirming Commitments to Publish Clinical Trial Results

The principles apply to trials regardless of their outcome – positive or negative and regardless whether the trial has been ended prematurely. This is in line with the requirements the European legislation sets out.
These principles demonstrate the industry's intention to draw a line between a release of data to the public in form of a CSR synopsis on the one side and limited access to raw clinical trial data to qualified researchers in a controlled environment only.

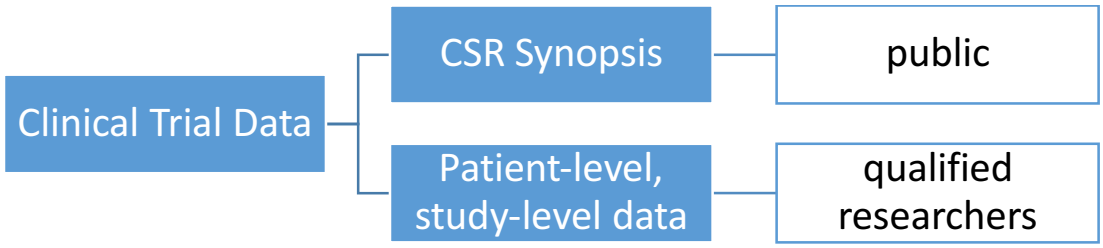


Figure 7: EFPIA Transparency of Clinical Trial Data

EFPIA provides a gateway for available clinical trial data which is a list of links to the participating pharmaceutical companies' transparency websites.
In total, EFPIA's voluntary provisions to provide clinical trial data do not exceed the mandatory provisions set by the European law in terms of grade of detail of data and time point. Whereas under the terms of EFPIA's principles only the CSR synopsis is provided to the public, European law requires that great parts of the full CSR are posted.

B. Fictional Scenario – Publishing Obligations

For the case of this thesis a fictional scenario is drawn up. It shall be noted that this scenario is created to point out possible publishing obligations of a Regulatory Affairs Manager in a biotech company or CRO and not to deliver realistic estimations of time limits in the development of novel drug candidate.
A biotech company develops a monoclonal antibody, so it falls under the mandatory scope of Regulation 726/2004 and is subject to the centralised procedure. Subsequently, the publication according to Policy 0070 is applicable.
The envisaged indication is severe allergic asthma, an indication prevalent in children. So according to Paediatric Regulation 1901/2006 the submission of a Paediatric Investigation Plan is obligatory. Currently, a confirmatory Phase 3 study is planned to evaluate the

efficacy of the antibody. The following table outlines the decisive time points in the development of the IMP in terms of publishing obligations.

Submission of the Clinical Trial Application to the Ethics Committee and Competent Authority	01 July 2016
Last Visit Last Subject, End of Trial as defined in the protocol	18 September 2018
EC decision on marketing authorisation	15 May 2020

Table 6: Decisive time points in the development

The following time line depicts the publishing obligations according to EMA regulations (not to scale) in dependence of the milestones in development stated in Table 6.

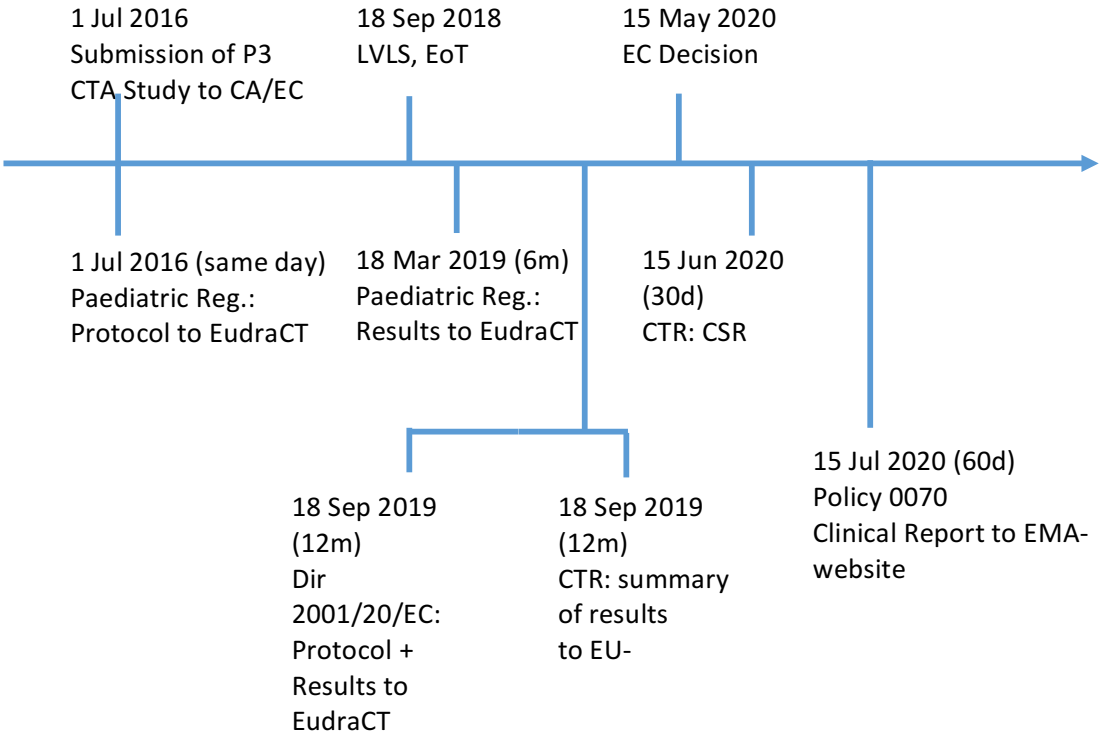


Figure 8: Publishing Obligations

The clinical trial application of the Phase 3 study is submitted to the Competent Authority and Ethics Committee on 1 July 2016. According to the Paediatric Regulation, the protocol is to be uploaded to EudraCT on the same day. On 18 September 2018, the Last Visit Last Subject takes place which is the End of Trial as defined in the study protocol. According to the Paediatric Regulation, the results of the study must be posted within 6 months after that date. Within 12 months after the End of Trial, at the latest on 18 September 2019, the protocol and the results are to be posted to EudraCT according to the Clinical Trial Directive and according to the Clinical Trials Regulation, the summary of results to the EU-database. Then on 15 May 2020, the European Commission releases its positive decision on the marketing authorisation application. 30 days later, on 15 June 2020, the clinical study report is posted to the EU-database and 60 days later, on 15 July 2020, Policy 0070 requires publishing the Clinical Report to the EMA-website.

A Regulatory Affairs Manager has extensive expertise in regulatory databases and holds close contact with National and European Competent Authorities. He functions as an interface between operational departments like data management and the authorities and – in the case of a CRO – the sponsor of the trial. Thus it is evident that while complying with all different regulation represents a challenge, it greatly strengthens the position of the Regulatory Affairs Manager over the course of drug development. It starts with the submission of the first clinical trial application and ends shortly after marketing authorisation. The trend to an increasing number of post marketing studies like PASS or PAES even extends the involvement of RA in this regards.

- The Role of the (CRO) Regulatory Affairs Manager in Posting Study Results to EudraCT:

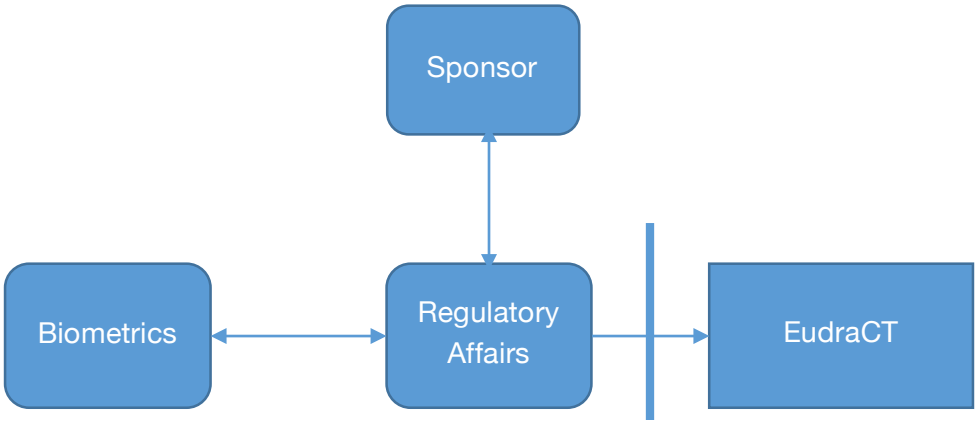


Figure 9: Role of Regulatory Affairs in Publishing to EudraCT

After the Clinical Study Report has been finalised the Regulatory Affairs Manager is assigned to the study as a "delegated preparer" by the Sponsor. The CSR functions as the main source for the data fields to be filled in. Dependant on how complex the protocol is and on how exact the information from the CSR complies with the information required by the EudraCT data fields it can be necessary that further data analyses have to be performed and further data has to be generated by Biometrics. The RA Manager is in close contact with the sponsor of the trial to ensure the content of the data fields meet desired demands. After all mandatory data fields have been filled out, the data set is validated and posted.

C. Layers of Transparency

The author wants to point out another aspect of data transparency:
By the implementation of the Clinical Trials Regulation, EMA, seeks to establish transparency on a lay person level for the first time. To illustrate what clinical data transparency means for a lay person the following example is performed:
A quick, non-representative search for "acetaminophen" on google provides the links to the Wikipedia page, to a Swiss pharmaceutical wiki, several commercial drug databases and to the FDA website.
With this background, the success of EMA's publishing of clinical data will first depend on the accessibility of the summary of results for lay persons to search engines and second on the search engine's algorithm to place the EU-database result amongst the first results of the search. The Functional Specification No 3.10 for the EU portal and database to be audited sets up the search functionalities[14]:

> *"The system should allow the user to search and filter specific topics based on basic search criteria (e.g. CT EU number, product number, product name, RMS, MSC…) Authorised users should be able to query the system from their workspace by use of metadata based on fields present in the information stored in the EU database and be able to retrieve the information requested."*

This leaves room for interpretation if the database will be accessible to the algorithms of search engines.

A lay person seeking information about her or his medicine, i.e. after it was prescribed by a physician, often simply puts the name of his drug into the search engine and bases his estimation on the drug's safety and efficacy on the first few results he receives, be it the drug's Wikipedia page or a yellow press article on the drug's fatal side effects. The average user cannot judge the reliability of a drug's information. Consequently, the success of EMA's agenda to safeguard public health by providing unbiased data of clinical trial results to the public will be measured by the impact of these data on the layperson's opinion shaping process.

This adds an extra layer of transparency:

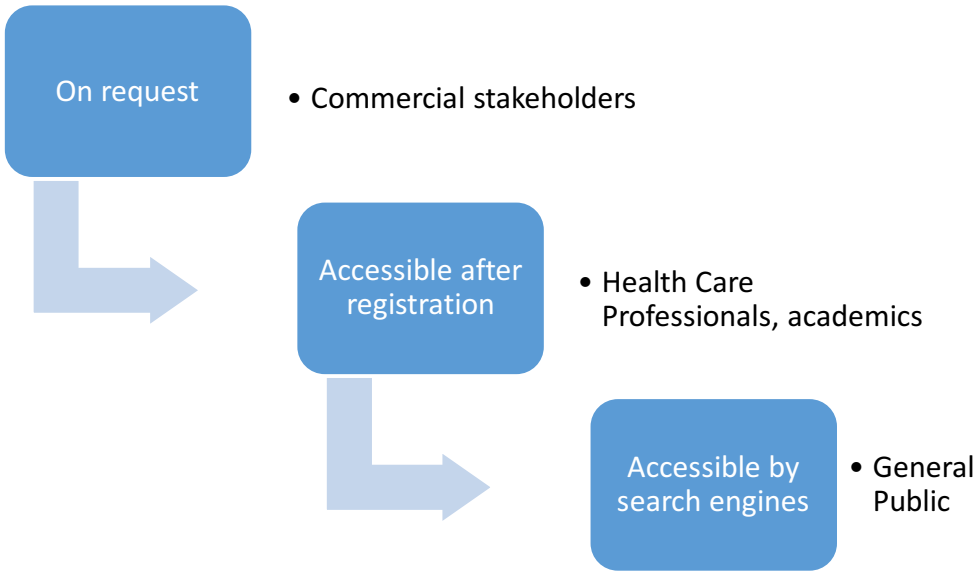


Figure 10: Layers of Transparency

The first layer of transparency, "on request" was established by the Freedom of Information Regulation and is not relevant to general public or health care providers but mainly used for commercial reasons as statistics on the requests show[15].

The second layer, "accessible after registration" as it is established by the Policy 0070 concerns mainly health care professionals as the Terms of Use call explicitly for an "academic and non-commercial use".

The third layer, "accessible by search engines" represents the transparency to the general public as it is the way a patient is informed about clinical data.

D. Tabulated Synopsis

The following table summarises clinical data transparency in the European Union:

It states the legal basis (“Why”), the addressee of the obligation (“Who”), the scope (“What”), the place (“Where”) and the time (“When”) of the publishing obligations. It explicitly includes only the most relevant cases and excludes the exemptions for the sake of clarity.

Why	Who	What	Where	When
Clinical Trial Directive	Sponsor	protocol and result related data of phase 2,3 and 4 studies	EudraCT / EU Clinical Trials Register	within 12 months after End of Trial
Regulation 726/2004	MAH	protocol and result related data of phase 2,3 and 4 studies	EudraCT / EU Clinical Trials Register	within 12 months after End of Trial
Paediatric Regulation	Sponsor, MAH	protocol and result related data of phase 1-4 studies	EMA-website (EPAR), EudraCT / EU Clinical Trials Register	6 months after End of Trial
Policy 0070	MAH	Clinical Reports: Module 2.5, 2.7, 5 incl. appendices	EMA-website	within 60 days after EC decision
Clinical Trials Regulation	Sponsor, MAH	Technical Summary of Results, Summary of Results for Lay Persons, Clinical Study Report	EU-Database / EU-Portal	Summaries of Results: 1 year after End of Trial Clinical Study Report: 30 days after EC decision

Table 7: Synopsis: EMA Publishing Obligations

VII. Conclusions and Outlook

EMA clinical data transparency has come a long way since its first steps with the Freedom of Information Regulation in 2001. The Clinical Trial Directive continued this path with the establishment of a European database which was extended by Regulation (EC) 726/2004 and the Paediatric Regulation from a database accessible only to authorities into a public database. Further guidelines and communications were added to clarify the data fields and timelines incorporated by the regulations. The Clinical Trials Regulation and Policy 0070 which function independently side-by-side represent the latest milestones in the development of European clinical data transparency. Policy 0070 recently became effective and demands comprehensive publishing of clinical data as part of the marketing authorisation application. Not surprisingly, this is the center of a controversial discussion on the anonymisation of personal data and the redaction of commercially confidential information[16]. For the near future, the Clinical Trials Regulation, planned to come in effect in late 2018, will complete the European landscape of clinical data transparency by adding even the most sensitive Phase 1 data of non-paediatric trials to the picture.

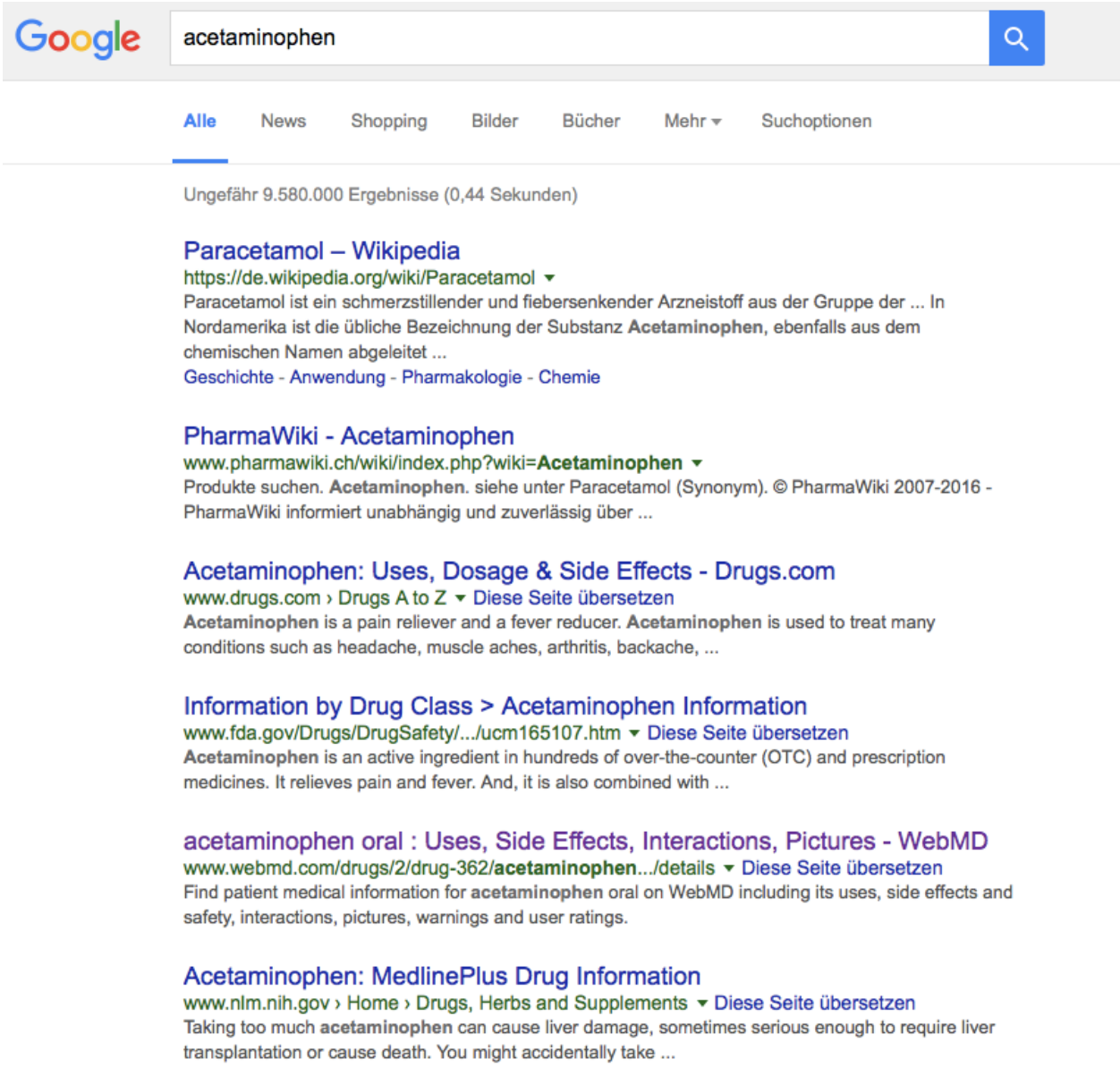
To sum up, EMA transparency of clinical data now comprises Phase 1 to Phase 4, protocol-related and result-related data, negative and positive outcomes and active and not reactive posting of information that is available not only to competent authorities, but to the public, though always redacted for personal data and commercially confidential information.

It can be noted that the sheer multitude of laws, guidelines and databases, all having different scopes and different timelines presents a great challenge to the Regulatory Affairs Manager or the person who is responsible for compliant posting of clinical data. For a fictional clinical study and a fictional medicinal product this thesis gave a short outline in this respect.

It is likely that the road to actively publishing of data that leads to the marketing authorisation of medicinal products has not come to an end, yet: FDA's commissioner Robert Califf recently expressed his idea[17] for a database of non-clinical results – in vitro and in-vivo. This gives a glimpse to future initiatives that may be started in Europe, too.

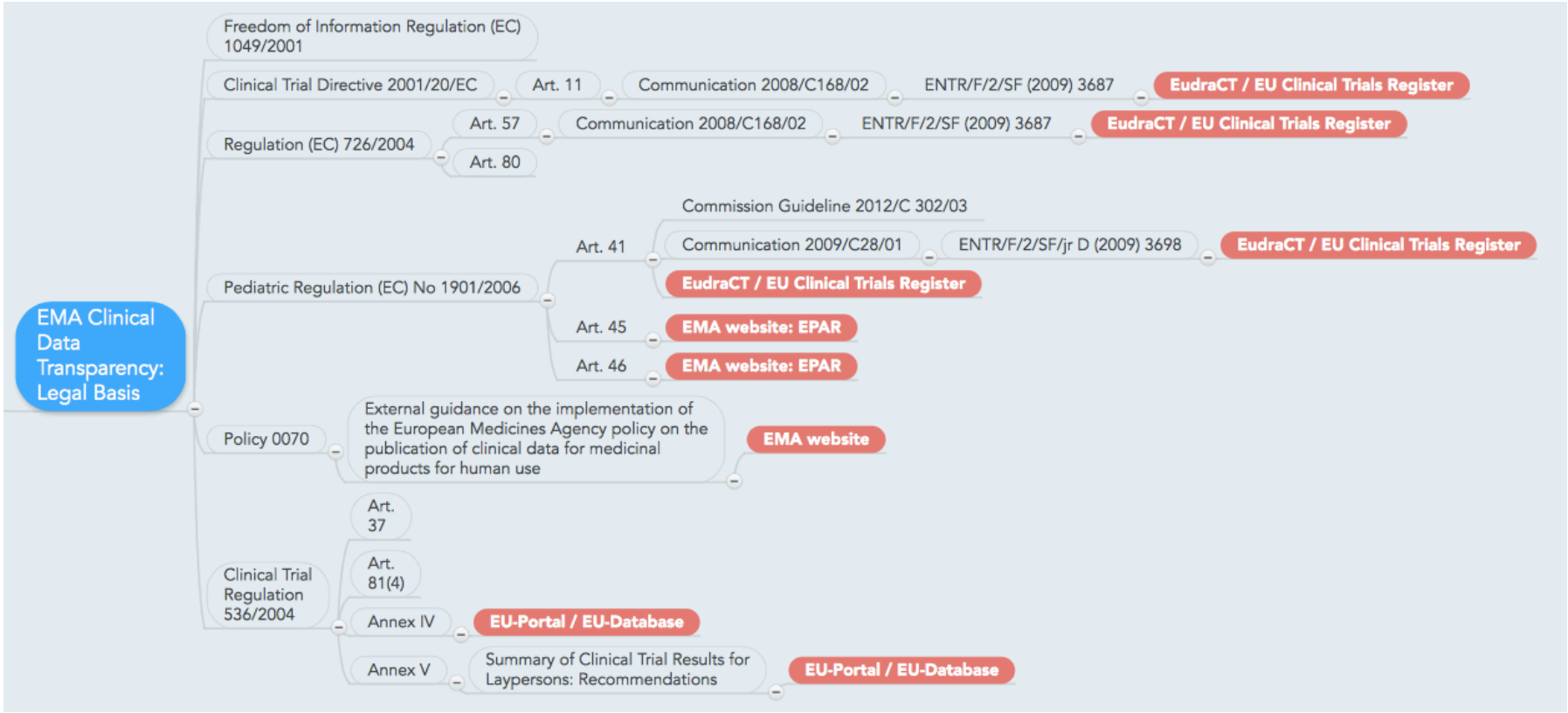
VIII. Annex

A. Annex 1 – google search on “acetaminophen”, performed on 20 June 2016



Annex 1: google search oncetaminophen” , performed on 20 June 2016

B. Annex 2 – mind map depicting applicable legislative



Annex 2, mind map depicting applicable legislative

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

04 Sep 2016 Bilke

IX. References

[1] Sergio Bonini (2014), Transparency and the European Medicines Agency — Sharing of Clinical Trial Data, N Engl J Med, 2014, 371:2452-2455
[2] The Economist, Spilling the Beans (25 Jul 2015) http://www.economist.com/news/science-and-technology/21659703-failure-publish-results-all-clinical-trials-skewing-medical (last downloaded 30 Aug 2016)
[3] Peter C Gøtzsche (2011), We need access to all data from all clinical trials[editorial], Cochrane Database of Systematic Reviews, 2011;(10): 10.1002/14651858.ED000035
[4] EMA Press Release (2012), Workshop on access to clinical-trial data and transparency kicks off process towards proactive publication of data, (23 Nov 2012) http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/11/WC500135088.pdf
[5] BAH – Informationsveranstaltung (2016): Transparenz über alles – gibt es noch Betriebs- und Geschäftsgeheimnisse?, http://www.wachenhausen-law.com/wp-content/uploads/2016/02/Programm-Transparenz.pdf (last downloaded 30 Aug 2016)
[6] Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012) http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf
[7] EU Clinical Trials Register, FAQ (2014) https://www.clinicaltrialsregister.eu/doc/EU_CTR_FAQ.pdf
[8] Data Protection Working Party, Opinion 05/2014 on Anonymisation Techniques (2014) http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf
[9] European Commission, Proposal for a Regulation of the European Parliament and of the council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (2012) http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf
[10] EMA, Delivery time frame for the EU portal and EU database (2015) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199078.pdf
[11] Implementation measures by the Commission in the context of Regulation (EU) No 536/2014 – overview and state of play http://ec.europa.eu/health/files/clinicaltrials/overview_clinical_trials.pdf
[12] Katharina Brauburger (2015), New European Clinical Trial Regulation: The Requirement for Lay Summaries and its Impact on Medical Communicators, AMWA Journal, 2015, V30 N2 http://www.amwa.org/files/2015v30n2_online_RegulatoryInsights.pdf
[13] Public consultation, Summary of Clinical Trial Results for Laypersons: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (2016) http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_3_consult.pdf
[14] EMA, Functional specifications for the EU portal and EU database to be audited (2015) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179339.pdf
[15] Sergio Bonini (2014), Transparency and the European Medicines Agency —Sharing of Clinical Trial Data, N Engl J Med, 2014, 371:2452-2455
[16] efpia, Executive Summary: EFPIA submission of comments on 'Policy 0070 on publication and access to clinical trial data' (2013) http://www.efpia.eu/uploads/Exec_Summary_EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf
[17] statnews, Califf's big idea: Build a database for research done before clinical trials (10 Jun 2016) https://www.statnews.com/2016/06/10/califf-database-preclinical-trials/ (last downloaded 30 Aug 2016)