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A Global View*

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# Clinical Trial Transparency and Disclosure: A Global View

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## Clinical Trial Transparency and Disclosure: A Global View

### List of Abbreviations and Acronyms

ACT	Applicable Clinical Trial
ANZCTR	Australian New Zealand Clinical Trial Registry
CCI	Commercially Confidential Information
ClinTrials.gov	ClinicalTrials.gov
CSR	Clinical Study Report
CTA	Clinical Trial Application
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU CTD	EU Clinical Trial Directive
EU CTR536	EU Clinical Trial Regulation 536/2014
EU MDR729	EU Medical Device Regulation 2004/729
EU MDR745	EU Medical Device Regulation 2017/745
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOIA	Freedom of Information Act
FSI	First Subject In
IB	Investigator Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trial Registration Platform
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMPD	Investigational Medicinal Product Dossier
IPLD	Individual Patient Level Data
JPMA	Japan Pharmaceutical Manufacturers Associations
LLS	Lay Language Summary (see also TRS)
LSLV	Last Subject Last Visit
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHLW	Ministry of Health, Labour and Welfare
PASS	Post-Authorisation Safety Study
PhRMA	Pharmaceutical Research and Manufacturers of America
PII	Personally Identifiable Information
PIP	Paediatric Investigation Plan
PPD	Protected Personal Data
NIH	National Institutes of Health (US)
SAP	Statistical Analysis Plan
TRS	Trial Results Summary (see also LLS)
US	United States of America
WHO	World Health Organization

## 1. Introduction

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The research community acknowledges that information and data sharing advance the generation of critical scientific knowledge. Traditional methods of sharing are no longer adequate to support the rapid developments in healthcare and the need to make shared information and data digitally available and useful. Globally, the proliferation of disclosure requirements and opportunities has resulted in a network of platforms and venues. The public and researchers need to be aware of these avenues if they are to be useful. This paper was developed by industry experts with the goal of highlighting the evolving global landscape of clinical trial transparency and disclosure with special focus on individual study and submission-related requirements.

This group has also developed/plans to develop complementary material, namely:

- An overview graphic that visually represents many of the topics in this paper, accessible on the [PhUSE website<sup>1</sup>](#).
- A country-level worksheet detailing specific registry requirements, accessible on the [PhUSE website<sup>2</sup>](#).
- A practical guide and a country-specific white paper; links will be provided when these are available.

The intention is that these tools can be used together or separately to assist in understanding a very complex global landscape.

Due to the constantly evolving nature of clinical trial transparency, this paper is intended to be a snapshot in time. While we intend for this paper to include the best information available at the time of writing, we cannot guarantee that it encompasses all requirements. We welcome readers' feedback via an FAQ Forum<sup>3</sup>.

Our focus begins with two significant regulatory arenas, the European Union (EU) and the United States of America (US), along with an overview of other country-specific registers and requirements. Voluntary transparency and disclosure activities that go beyond regulation or may be part of future regulations are also explored.

An overview of the World Health Organization's (WHO) International Clinical Trial Registration Platform (ICTRP)<sup>4</sup> and Primary Registries<sup>5</sup> is also included along with a brief examination of the ethics, guiding principles, and industry references that provide context to the landscape. The role of peer-reviewed publications to disclose clinical trial results is also considered.

As well as disclosure requirements related to study-specific milestones there can be additional disclosure requirements related to submission-level milestones such as submission of new medicine and line extension applications, marketing decisions and withdrawal of application. These submission-level topics are explored in [Section 3 Submission Life Cycle](#).

## 2. Study Specific Requirements

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Across the globe there are many different regulations and requirements depending on the region or country, and the study type/category. This section examines the mandatory requirements of the EU and US whilst also providing an overview of country-specific requirements. As noted above, a supplemental spreadsheet listing the individual country, regional or condition-specific registries is available on the PhUSE website.

This section continues with a review of voluntary activities for individual studies.

After consideration of mandatory and voluntary activities, there is an overview of the WHO ICTRP and a brief discussion of the ethical guidelines and industry principles related to clinical trials, along with a review of publication expectations.

### 2.1 Mandatory Requirements

#### 2.1.1 European Union

The conduct of clinical trials in the EU is currently governed by the Clinical Trials Directive 2001/20/EC (EU CTD)<sup>6</sup>, that was last updated in June 2009. A new regulation, EU Clinical Trial Regulation No. 536/2014 (EU CTR536)<sup>7</sup>, that will replace the current directive is in force, but not yet in application, due to a requirement for a new portal to be completed. It is expected that the new regulation will come into application sometime in 2020 but there have been several delays and the exact timing is not yet confirmed. We have included both the EU CTD and the EU CTR536 in this section to allow readers to prepare for the upcoming regulation which includes additional requirements over the current directive.

##### 2.1.1.1 EU Clinical Trial Directive (EU CTD)

The conduct of clinical trials in the EU is currently governed by the EU CTD. It states that clinical trials are scientifically controlled research undertaken in humans to establish or confirm the safety, efficacy, or clinical uses of investigational medicinal products.

The EU CTD (Article 11) established the EudraCT database for confidential use by the regulators. Article 57 of the [EU Medical Device Regulation 726/2004](#)<sup>8</sup> (EU MDR726) on medicinal products and Article 41 of the [EU Paediatric Regulation 1901/2006](#)<sup>9</sup> required the EMA, which maintains the EudraCT database on behalf of EU member states, to provide information about clinical trials in adults and paediatric populations held in EudraCT to the public, and the EU Clinical Trials Register<sup>10</sup> (EU CTR) puts these requirements into practice.

It is important to remember that if one subject in the trial is under 18 years old during any stage of the trial, the paediatric timelines must be followed.

The EU CTR contains information for interventional clinical trials in medicines conducted in the EU, or the European Economic Area (EEA) which started after 1 May 2004. Clinical trials conducted outside the EU/EEA are included if they:

- form part of an agreed EU paediatric investigation plan (PIP) – see [Guidance on the Information Concerning Paediatric Clinical Trials](#)<sup>11</sup>, or
- are sponsored by a Marketing Authorisation Holder (MAH) and involve the use of a medicine in the paediatric population as part of an EU Marketing Authorisation (MA).

The EU CTR also provides information about older paediatric trials conducted with products covered by an EU MA.

Registration takes place as part of the Clinical Trial Application (CTA) process.

Results are required within 12 months after the end of a clinical trial in the EU (or end of trial globally if otherwise specified in the protocol and scientifically justified) or within six months after the end of trial for trials that include paediatric subjects or trials listed in a PIP.

##### 2.1.1.2 EU Clinical Trial Regulation (EU CTR536)

The EU CTD will eventually be superseded by the EU CTR536. Although the regulation came into force on the 16 June 2014, the timing of its application depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit. The regulation becomes applicable six

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months after the European Commission publishes a notice of this confirmation. Current estimates predict the EU CTR536 will come into application in 2020.

In 2015, the European Medicines Agency (EMA) issued [additional reference materials<sup>12</sup>](#) that outline the expectations, deadline and specifications of the forthcoming EU clinical trials portal and database.

The EU database will contain information about interventional clinical trials that are conducted in the EU or the EEA and which begin on or after the date that the EU CTR536 becomes effective.

Clinical trials conducted outside the EU/EEA are included if they:

- form part of an agreed EU PIP, or;
- are sponsored by an MAH and involve the use of a medicine in the paediatric population as part of an EU MA.

Submission, including registration, takes place as part of the CTA process and will need to include:

- Main characteristics of the trial
- Subject information sheet/Informed Consent Form (ICF)
- Protocol
- Investigational Medicinal Product Dossier (IMPD) (Safety and Efficacy only)
- Investigator Brochure (IB)
- Regulator requests and assessment reports
- Sponsor responses

Within 12 months after the end of the trial in the EU (or end of trial globally if otherwise specified in the protocol and scientifically justified) or 6 months after the end of trial for trials that include paediatric subjects or trials listed in a PIP, the following results are required for public disclosure:

- Clinical trial result summary including intermediate analysis
- Lay summary

Within 30 days after the MA decision or withdrawal of the application by the applicant, the Clinical Study Report (CSR) is required to be posted to the database.

This timeline is prior to EMA Policy 0070<sup>13</sup> documents being finalized between the sponsor and EMA.

There is the potential to request deferrals of the disclosure publication timelines in the following cases: At the time of registration, a deferral may be requested to delay the publication of registration information submitted to the new EU database.

The following classifications determine the length of time for deferral eligibility:

- Phase 1 or bio-equivalence trials until the earlier date of MA or End of Trial plus 7 years
- Phase 2 and 3 trials until the earlier date of MA or End of Trial plus 5 years
- Phase 4 or low interventional trials until summary results are made public

For clinical trial result summaries and study reports, a potential maximum deferment of 30 months after the end of the trial is available or until MA if earlier.

### 2.1.1.3 EU Post Authorisation Studies

European pharmacovigilance legislation requires the EMA to make public the protocols and abstracts of results of non-interventional post-authorisation safety studies (PASS) imposed as an obligation of MA by a competent authority in accordance with Article 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21 or 22 of

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Directive 2001/83/EC<sup>14</sup>. Annex III of the Commission Implementing Regulation (EU) No 520/2012<sup>15</sup> further specifies that the final report of imposed non-interventional PASS must provide the date of making it public (in the EU PAS Register). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, ENCePP, is a Network established by the EMA. The ENCePP [EU PAS register](#)<sup>16</sup> has a registration guide as well as a frequently asked question guide and a glossary of terms used in this European setting. This is in contrast with US post-authorisation studies conducted on marketed products that are required to be registered on [ClinicalTrials.gov](#)<sup>17</sup> and therefore follow a more harmonized approach. Of note, the ENCePP site also has an FAQ page where part of the information slightly differs from that on the EU PAS site

### 2.1.2 United States

In the US, responsible parties disclose study information on the ClinicalTrials.gov website, mainly via a database managed by the National Library of Medicine at the National Institutes of Health (NIH). The most recent updates to the submission requirements were made as part of the [Food and Drug Administration Amendments Act](#) (FDAAA) 801 Final Rule<sup>18</sup>, which went into effect on 18 January 2017.

#### 2.1.2.1 Applicable Clinical Trials

According to the Final Rule, responsible parties must register and report results information for Applicable Clinical Trials (ACTs) on ClinicalTrials.gov.

To be considered an ACT, a study must meet all the following requirements:

- Study is interventional
- Study evaluates at least one drug, biological, or device product regulated by the Food and Drug Administration (FDA) (see [Section 2.1.4 Requirements Related to Medical Devices](#) for additional information related to medical devices)
- Study is not a Phase 1 study of a drug and/or biological product or a device feasibility study

And at least one of the following requirements:

- At least one US study facility location
- Study conducted under an FDA Investigational New Drug or Investigational Device Exemption application
- Drug, biological, or device product manufactured in and exported from the US

All ACTs must be registered no later than 21 days after enrolment of the first trial participant.

In general, clinical trial registration information must be updated not less than once every 12 months. However, some data elements related to recruitment or site status, or study start and completion dates, must be updated within 30 days of change (or 15 days of change for device studies).

Results must be submitted to ClinicalTrials.gov within 12 months after the primary completion date for the pre-specified primary outcome measures. Results for secondary outcome measures or adverse events data that have not been collected by the primary completion date are due within 12 months after completion of the secondary outcome Last Subject Last Visit (LSLV) date or final data collection date (LSLV) if this is the same.

Submission of results may be delayed for up to two years (i.e., for a total of three years after LSLV) for trials certified to be undergoing commercial product development for initial FDA marketing approval or approval for a new use. Extensions to deadlines for results reporting may also be granted for good cause e.g., if reporting results for the primary outcome measure would require the unblinding of an ongoing (blinded) study.

### 2.1.2.2 Expanded Access Programs

The Final Rule does not consider any expanded access use (such as access under treatment Investigational New Drug or treatment protocols, which provide widespread access, access for intermediate-sized patient populations, or access for individual patients) to be an ACT. However, if the sponsor of an ACT for an investigational product is also the manufacturer of that product and that product becomes available through expanded access, then an expanded access record must also be submitted to the ClinicalTrials.gov database within 30 calendar days of expanded access availability. One record which encompasses all forms of expanded access (individual patient programs, intermediate-size patient populations, and treatment use protocols) must be created for each investigational product. The National Clinical Trial number of the expanded access record is required to be linked to ACTs studying that product.

### 2.1.2.3 Protocols, Statistical Analysis Plans, and Informed Consent Forms

As part of the Final Rule requirements, sponsors are required to submit a copy of the full protocol (including all global and local-US amendments approved by a human subject protection review board) and Statistical Analysis Plan (SAP) at the same time as submission of results information.

Anonymisation of personally identifiable information (PII<sup>a</sup>) and commercially confidential information (CCI) is the responsibility of the sponsor. Guidance for anonymisation techniques is not provided by NIH though see [Section 2.2.3 Sharing IPD with External Researchers](#) for further references on this topic.

In addition, a change to the Federal Policy for the Protections of Human Subjects (the Common Rule)<sup>19</sup> for federally-funded clinical trials requires that a copy of the final version of the ICF (legal document approved by a human subject protection review board) must be posted on a “Federal Web site that will be established as a repository for such informed consent forms.” This change is expected to be implemented in early 2019.

### 2.1.3 Additional Country-Specific Requirements

Public disclosure obligations for sponsors conducting clinical trials solely within their country of business operations are normally straightforward as sponsors should be aware of the legal and ethical obligations. However, for multinational clinical trials, the various national obligations as well as the reporting expectations of the [International Conference on Harmonisation \(ICH\) E17](#) General Principles for the planning and design of Multi-Regional Clinical Trials<sup>20</sup>, raise new challenges in the dynamic global registry environment.

A tabulated overview of clinical trial registries worldwide has been developed as a supplement to this white paper and is available on the [PhUSE website](#). Information has been organized with one row for each registry or database as some countries may have multiple registries.

The importance of sponsors tracking national regulatory developments are highlighted by the following examples:

- Russia<sup>21</sup> has indicated the possible implementation of a national database.
- In Croatia, the national database that was being hosted by the University in Split has been discontinued (no reference available). There is a legal requirement for a register of all approved clinical trials since 2010, however, it is understood that the scope of this register is not yet defined<sup>22</sup>.
- A few years ago, the registration of a clinical study in ClinicalTrials.gov was sufficient to meet Brazilian expectations. More recently, there has been a shift to registration in the national Brazilian registry<sup>23</sup>.

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<sup>a</sup> **Personally Identifiable Information (PII):** Any information about an individual maintained by an agency (or group) including but not limited to, education, financial transactions, medical history, and criminal or employment history, which can be used to distinguish or trace an individual's identity, such as name, social security number, date and place of birth, mother's maiden name, biometric records, etc., including any other personal information that is linked or linkable to an individual<sup>24</sup>.

The constantly changing registry environment can lead to uncertainties when planning clinical trials. Additional resources need to be planned by the sponsor to track national requirements. Confusion may result when a country changes or updates its national requirements, especially when data have been publicly posted for a previous study in a clinical development program but not for subsequent trials within the same program. To meet ethical requirements set forth in the [Declaration of Helsinki<sup>25</sup>](#) it is recommended that a sponsor ensures that all clinical trials are registered, and the results made public. This may result in a single centre study requiring registration in an additional clinical trial registry. Additional information related to ethical considerations and industry guidelines is available in [Section 2.4 Guidance, References, and Principles](#).

The tabulated listing of registries discussed earlier has been divided into four categories based upon country requirements at top-level as schematically shown below in *Figure 1*.

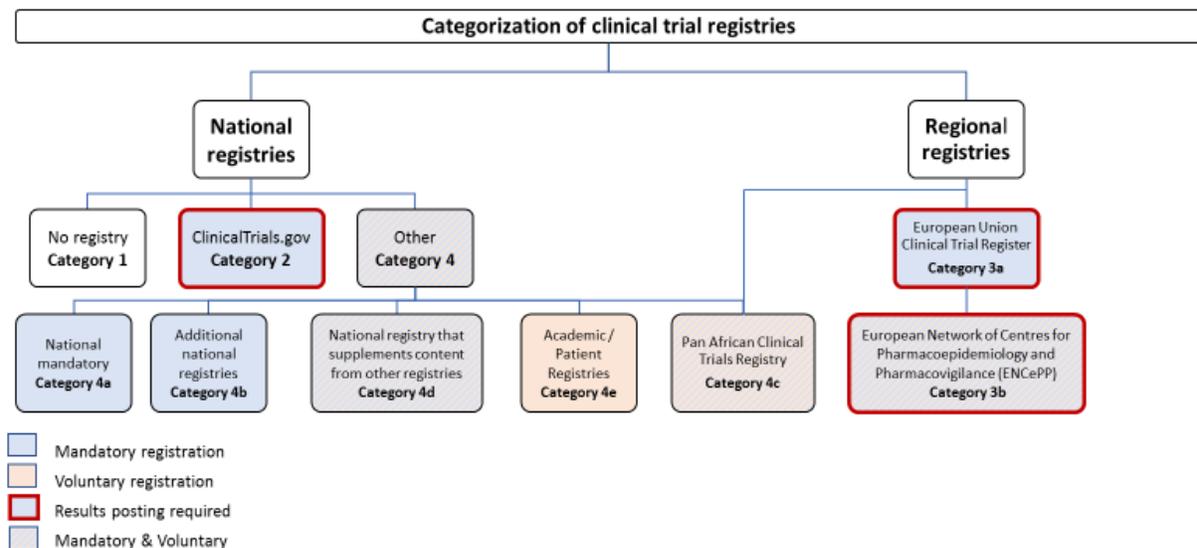


Figure 1: National and regional clinical trial registries have been organized into four main categories.

### Category 1 – Countries with no known public clinical trial database/registry

Category 1 is composed of countries that do not appear to have a national registry. This does not preclude a trial from being required to be registered as such a requirement may be a condition of an ethics or competent authority. The investigator or sponsor may then be free to select a WHO Primary Registry. There are more than 100 countries currently that appear to have no national registry.

### Category 2 – Countries that mandate or accept ClinicalTrials.gov registration

Category 2 has been based on the countries that require registration in ClinicalTrials.gov. These countries have a requirement to register and report results of clinical studies independently of the CTA process within a predefined time period. Category 2 can be mandatory as is the case for ACTs, where the study is being conducted in the US or US territories, such as Puerto Rico, or it can be conditionally mandatory as is the case for Australia.

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In addition, there are numerous countries that pull data from the clinical trial registration records in ClinicalTrials.gov. This includes the UK Clinical Trials Gateway<sup>26</sup>, a UK National Health Service (NHS) platform that expects that all phase I trials conducted in the UK are registered either in ClinicalTrials.gov or in the ISRCTN registry<sup>27</sup>, as well as the Australian New Zealand Clinical Trial Registry (ANZCTR)<sup>28</sup> which populates its own registry as soon as the first site in Australia or New Zealand is entered into the ClinicalTrials.gov record.

### Category 3 – Countries that mandate the use of EU Register

Category 3 is comprised of the 31-member countries of the EEA who have a **common regional register**, the EU CTR. These countries have the CTA submission as part of the registration process and require results to be posted.

- **Category 3a.** There are EEA countries that in addition to the EU CTR also have additional public national registries/databases. The supplemental tabulation to this white paper provides a snapshot overview of these.
- **Category 3b.** In addition, the 31 EEA member countries require that all PASS and post authorization efficacy evaluation studies are registered by the sponsor in the EU PAS Register at ENCePP. Historically these countries have also required additional national requirements at the ethics level, e.g. The Netherlands (the CCMO database<sup>29</sup>) or Norway (REK<sup>30</sup>).

### Category 4 – Countries with their own registries/databases

The final category, category 4, is a collection of countries that either have their own national registry or were created to curate clinical trials conducted in specific diseases, e.g. the ATM Clinical Trials Registry<sup>31</sup>, which focused on clinical trials in HIV/AIDS, Malaria and TB in Africa.

Broadly speaking, these countries require the registration of clinical studies but almost none of these national databases or registries require the posting of results, either due to technical requirements not yet being available or because these are not foreseen. Note, that the requirement to post results is increasing though, in registries in this Category. These countries may include legal requirements as part of an ethical requirements built into the constitution of a country, such as in South Africa, or registration is part of the regulatory process such as in Canada and Peru. Therefore, category 4 countries can be split into several subcategories:

- **Category 4a.** Countries with their **own mandatory national database**. These countries include Australia, Brazil, Peru, India, Iran, Republic of Korea and Switzerland.
- **Category 4b.** Countries where **the national competent authority makes additional information available**, such as Belgium (for phase I studies) and Germany (for pivotal adult studies for market-authorized products with sites in Germany during the Clinical Development Program)
- **Category 4c.** Countries without a national registry that have access to a **regional registry**. This includes countries such as Egypt, Malawi, Zambia that can register their studies in the [PACTR registry](#). The PACTR does not have functionality to post results.
- **Category 4d.** Countries with a **national registry that supplement information from other registry sources**. There are national databases that include information for studies that are recruiting patients not only in their country but also in neighbouring countries, an example is the Swiss National Clinical Trial Portal (SNCTP)<sup>32</sup>.
- **Category 4e.** Besides national databases there are databases that are **hosted by academic institutions and or patient associations**. Thus, a trial may have been registered on ClinicalTrials.gov and additional details may be made available by third parties such as the universities in the US and Canada who will make data available in their disease-specific portals.

### 2.1.4 Requirements Related to Medical Devices

The European Parliament passed legislation, the [EU Medical Device Regulation 2017/745](#) (EU MDR745)<sup>33</sup> to regulate medical devices and will require high risk devices, such as hip implants, to undergo more pre-market testing and assessment. At present the EU CTR does not contain medical device studies. Furthermore, EU CTR745 will require that device studies be made transparent as per EU CTR 536, and it is foreseen that EUDAMED will become public and improve transparency through the establishment of a comprehensive EU database on medical devices. The notifying bodies, responsible at national level, have access to EUDAMED at present. A notified body is an organisation that has been designated by an EU member state to assess whether manufacturers and their medical devices meet the requirements set out in legislation. The Medicines and Healthcare products Regulatory Agency (MHRA) is the designating and competent authority in the UK.

The FDA approves Class III medical devices via the pre-market approval pathway<sup>34</sup>. The studies that are performed following this process are clinical studies that must be registered on ClinicalTrials.gov and are ACTs. Manufacturers can submit incremental device changes via supplemental applications. The pre-market approval process involves reviewing evidence of clinical tests of a new device. A less stringent approach, known as the 510(k) process<sup>35</sup>, is for the approval of devices similar to those already on the market, these trials may be ACT and are then required to be in ClinicalTrials.gov. Once a device has been either approved or cleared by the FDA under one of these routes, it can be marketed. The FDA publishes a list of recalled devices and the regulatory processes they had passed through.

In Japan, on 31 July 2017, the Ministry of Health, Labour and Welfare (MHLW) enacted a new regulatory framework called the fast-break scheme for innovative medical devices aiming to expedite patient access<sup>36</sup> ([reference in Japanese](#)). The new framework is expected to provide greater benefits to patients who require access to new medical devices and to companies via improved transparency and predictability, as well as to reduce the social and medical cost incurred for medical innovation.

Other countries have local registers in which medical device studies must be registered. These are not specifically listed here but the spreadsheet supplement gives an overview of the national registers and further details can be searched at the national level.

## 2.2 Voluntary Activities

With additional transparency requirements being implemented around the world and the addition of external pressure from outside advocates, more sponsors are widening their transparency and disclosure policies to include more voluntary activities, which may include registering and disclosing additional interventional clinical trials or observational trials to a public registry.

Some of these sponsor policy updates are related to non-regulatory guidelines such as the International Committee of Medical Journal Editors (ICMJE) Recommendations<sup>37</sup>, which requires each trial is registered on a WHO Primary Registry before the first participant is enrolled to qualify for publication in an ICMJE journal. Additional discussion regarding external guidelines can be found in [Section 2.4 Guidance, References, and Principles](#).

In some cases, sponsor voluntary activities related to trials in some regions may already be mandatory or strongly encouraged in trials in other countries or regions, either presently or in the future, as in the case with Lay Summaries. For more details, please refer to [Section 2.2.2 Lay Summary \(Plain Language Summary\)](#). It should also be noted that some voluntary activities can prompt additional mandatory requirements, as discussed in [Section 2.2.1 ClinicalTrials.gov](#) below.

### 2.2.1 ClinicalTrials.gov

The FDAAA 801 Final Rule was implemented on 18 January 2017 and stipulates several new required fields, as well as more rapid update requirements. New obligations are also included related to trials that are voluntarily registered or have results disclosed on ClinicalTrials.gov, so called ‘trigger’ and ‘triggered’ trials.

#### Triggered trials on ClinicalTrials.gov

If a non-ACT has been voluntarily registered/has results disclosed, it may “trigger” a requirement to submit the corresponding level of information for additional clinical trials (i.e., registration *or* registration and results disclosure) may be “triggered”. These triggered trials include Phase I trials or ACTs that were initiated prior to FDAAA and completed prior to 26 December 2007. Only ACTs can be triggered by the voluntary registration/results disclosure of a trigger trial, which is a non-ACT that has been voluntarily registered/has results disclosed. Triggering would apply only to other ACTs that are included in the same marketing application for the drug product as the trigger trial, and that were not already registered/had results disclosed.

This requirement means that if a marketing application includes a trial that was voluntarily registered or for which results were disclosed, other ACTs that are included in the same marketing application will also need to be disclosed to the same degree as the voluntarily disclosed trial.

This is expected to be rarely seen as most trials will have already been registered per FDAAA.

See [Voluntary Submission Flowchart Checklist<sup>38</sup>](#) for further details on how to determine what qualifies as a voluntary submission under Final Rule, and when triggering applies.

### 2.2.2 Lay Summary (Plain Language Summary)

Currently lay summaries are listed as voluntary activities but will be a requirement once EU CTR536 is in application. However, some countries are encouraging provision of lay summaries ahead of this mandatory milestone. For example, The Netherlands, encourages provision of lay summaries for trials conducted in their region, starting from the 15 December 2015.

A lay summary is a brief document that is written with non-technical vocabulary and non-promotional language that accurately describes the study and meets the requirements set forth in the EU CTR536. The aim is a health literacy level for a 12 to 14-year-old with a lower reading age for paediatric trials. It is not intended to replace the label or provide comprehensive information about a product or a condition.

For further details about the EU CTR536, refer to [Section 2.1.1.2 EU Clinical Trial Regulation \(EU CTR536\)](#).

EU CTR536 requires sponsors to provide a lay summary for all completed interventional clinical trials with a site in the EU. An expert group has produced a [guidance and template<sup>39</sup>](#) to help authors writing these lay summaries so that they are more easily accessible or understandable to a non-technical person. The content of the lay summary is specified in Annex V of the EU CTR536.

A summary of the requirements to report results as lay summaries for the EU CTR536 is included below in *Table 1*.

Lay Summaries	
Mandatory	Voluntary
Interventional clinical trials with a site in EU with a CTA submitted under the new EU CTR536 <b>from the date of its applicability</b> .	Interventional clinical trials not conducted in EU Observational clinical trials

Lay Summaries	
Mandatory	Voluntary
Interventional clinical trials started in accordance with the EU CTD, either before or within 1 year after the date of applicability of the Regulation <b>and</b> that are ongoing 3 years after the date of applicability.	

Table 1: On overview of the mandatory and voluntary Lay Summary activities.

Lay summary timelines per the EU CTR536 are presented below in Table 2.

Lay Summaries
Timeframe for Lay Summaries
<p>Lay summaries in English and local language of the EU countries recruiting patients:</p> <ul style="list-style-type: none"> <li>• Within 12 months after the end of the trial in the EU (or end of trial globally if otherwise specified in the protocol).</li> <li>• 6 months for trials that include paediatric subjects or trials listed in a PIP.</li> </ul> <p>Phase 1 / bioequivalence trials: Sponsor may opt to defer the publication of the lay summary for a maximum of 18 months after the due date (usually 12 months after the end of the trial unless paediatric - i.e. in total, a potential maximum of 30 months after the end of the trial) or until the time of MA, if earlier.</p>

Table 2: Timelines associated with the EU CTR536 requirement to publish a lay summary of study results.

Two additional references that can aid understanding the content of these documents and key considerations when creating them, include:

- TransCelerate: [Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results: An Implementation Guide](#)<sup>40</sup>
- The MRCT Center of Brigham and Women’s Hospital and Harvard: [Plain Language Summary Guidance Document](#)<sup>41</sup>

### 2.2.3 Sharing Individual Patient-Level Data (IPD) with External Researchers

In recent years, the broader value of individual patient-level data (IPD) collected within clinical trials has been more widely recognized. Many sponsors have now defined voluntary mechanisms through which to share these data with qualified external researchers. Researchers often pool data from across multiple trials and indeed multiple sponsors, and this provides a rich data pool for these new and novel analyses.

Although there are multiple pathways through which IPD are shared, many share common elements:

- Secondary analyses must be covered under the informed consent provided by the trial participants in the original trial. In recent years, many sponsors have clarified the language in their ICFs to more clearly align with these subsequent data sharing activities, as well as with privacy requirements in new regulations such as the EU General Data Protection Regulation<sup>42</sup>.
- Requests are reviewed by independent review panels, who assess the scientific integrity of the research proposal, as well as confirming the statistical qualifications of the researcher.

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- The IPD are anonymized prior to sharing, and any accompanying trial documents are redacted or anonymized. These steps protect trial participant privacy, and approaches to anonymization have been published by numerous authors including [TransCelerate<sup>43</sup>](#) and [PhUSE<sup>44</sup>](#).
- Data Sharing Agreements are implemented which contain clauses confirming that no deliberate attempts will be made to re-identify trial participants.

The risk of re-identification of trial participants will depend on multiple factors including the anonymisation techniques employed, whether legal or professional safeguards have been implemented and whether an open-access or a secure environment is used to share the data. A careful balance must be maintained when sharing data between protecting the privacy of the trial participants and providing data that has strong clinical utility. If anonymized data are shared within secure platforms, then the analysis tools that the researchers require also need to be available to them there.

Some of the main platforms through which anonymized IPD and associated documents are shared, are listed below:

- [Clinical Study Data Request<sup>45</sup>](#) (CSDR)
- [Yale Open Data Access Project<sup>46</sup>](#) (YODA)
- [Supporting Open Access for Researchers<sup>47</sup>](#) (SOAR)
- [Project Data Sphere<sup>48</sup>](#)
- [Vivli<sup>49</sup>](#)

Alternatively, some individual sponsors make data available via their own platforms or company websites.

### 2.3 WHO International Clinical Trial Registration Platform (ICTRP) and Primary Registries

The ICTRP<sup>4</sup> was developed by the WHO to facilitate clinical trial registration across the globe utilizing a standard dataset. The WHO regards trial registration as the publication of an [internationally-agreed set of information<sup>50</sup>](#) about the design, conduct and administration of clinical trials. This information is to be published on a publicly-accessible website managed by a registry conforming to [WHO standards<sup>51</sup>](#).

In addition, the WHO has developed a list of clinical trial public registries that have met specific criteria to ensure the data collected meets the standards of the ICTRP. These registries are considered the [WHO Primary Registries<sup>5</sup>](#).

The goal of the ICTRP and the WHO Primary Registries is to enable collaboration of registries and allow the public to search a database of multiple registries, rather than searching each registry independently. The WHO is continually working with global registries to establish the criteria as a WHO Primary Registry to expand the ICTRP database.

The criteria that the WHO has established to be a Primary Registry is broken down into six main categories: Content, Quality and Validity, Accessibility, Unambiguous Identification, Technical Capacity, and Administration and Governance.

Some countries will allow clinical trials to be registered on a WHO Primary Registry to fulfil their country requirements for public registration and disclosure however there may be other country-specific registries with their own regulations. These regulations can be based on the type of trial (interventional vs. observational), the phase of the trial, the compound and whether it is approved or not, as well as other criteria. We suggest to always check the local regulations when registering a clinical trial.

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The WHO also has a short list of “Partner Registries”<sup>52</sup> that meet the same criteria as a WHO Primary Registry and are included in the ICTRP Network, but that fall under the following categories, and are out of scope to be a WHO Primary Registry because they do not need to:

- Have a national or regional remit or the support of government
- Be managed by a not-for-profit agency
- Be open to all prospective registrants, as in if the register is limited to a single condition or intervention

These WHO Partner Registries must also be affiliated with a WHO Primary Registry, who has the responsibility of ensuring the Primary Registry criteria are met.

ClinicalTrials.gov is a special case since it is not a Primary or Partner Registry but is a data provider to the WHO Network as shown in *Figure 2*.



Figure 2: Data Providers to the WHO International Clinical Trial Registry Platform.

### 2.4 Guidance, References, and Principles

In addition to the aforementioned regulations, there are non-regulatory considerations in the form ethical guidance, industry principles and recommendations that straddle the line between voluntary and mandatory. This section includes a brief overview of some of these guidance documents, references and principles that the reader may find useful, along with links to additional information. Each of these documents has been written from a varying perspective, and together they accomplish a wide range of objectives.

As regulation in these areas continues to evolve, it is even more important to be aware of the larger landscape beyond the regulations. Understanding the many similarities in these documents along with, in some cases significant differences, will allow the reader to better assess the entire clinical trial transparency landscape.

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However, it should be noted that this list is not exhaustive and there may be other documents to consult, especially given the fast pace of change in this landscape.

### 2.4.1 Declaration of Helsinki

First adopted in 1964, the [Declaration of Helsinki](#) is the foundational ethical document for human clinical trials. It includes ethical obligations that every research study involving human subjects must be registered, and the results of all human subject research must be published or disseminated.

### 2.4.2 Good Clinical Practice

[Good Clinical Practice](#)<sup>53</sup> (GCP) is a standard developed by the ICH for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality for trial subjects are protected. These are ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human subjects ensure that the rights, safety and wellbeing of trial subjects are protected. GCP also ensures the credibility of the clinical trial data.

### 2.4.3 EFPIA/PhRMA Principles for Responsible Data Sharing

The pharmaceutical trade associations from the EU, EFPIA (European Federation of Pharmaceutical Industries and Associations) and the US, PhRMA (Pharmaceutical Research and Manufacturers of America), jointly released [principles](#)<sup>54</sup> that oversee topics including sharing data with researchers, public access to clinical study information, information for patients that participate in clinical trials, procedures for sharing clinical trial information and publishing the results of trials.

### 2.4.4 Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases

Four pharmaceutical industry groups, namely, EFPIA, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the Japan Pharmaceutical Manufacturers Association (JPMA), and PhRMA, released guidance related to [public clinical trial registries](#) on 10 November 2009 with minor revisions 15 January 2018<sup>55</sup>.

### 2.4.5 Joint Position on Publications of Clinical Trial Results in the Scientific Literature

The industry position developed by four leading pharmaceutical groups EFPIA, IFPMA, JPMA, and PhRMA for [publication in scientific literature](#) was updated 10 June 2010 with minor revisions 30 October 2017<sup>56</sup>.

### 2.4.6 IFPMA Principles for Responsible Data Sharing

On 15 January 2018, IFPMA adopted [principles](#)<sup>57</sup> that support enhancing data sharing, public access to clinical study information, sharing results with patients, procedures for sharing clinical trial information, and commitments to publish results.

### 2.4.7 International Committee of Medical Journal Editors Recommendations

International Committee of Medical Journal Editors (ICMJE) updated their [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals](#)<sup>58</sup> to include the need for a data sharing statement with manuscript submissions beginning in July of 2018. In addition, studies that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. This is in addition to a previous requirement to register all clinical trials prior to enrolling the first participant for the trial to be eligible for publication in an ICMJE journal.

### 2.4.8 World Health Organization Statement

On 14 April 2015, the [WHO](#) published a new statement<sup>59</sup> on public disclosure of clinical trial results. They reiterated their position on clinical trial registration, results reporting timeframes, reporting past clinical trial results, along with the inclusion of trial identifiers in publications.

## 2.5 Publications

Traditional publication in a peer-reviewed journal has been the preferred way to share scientific information for hundreds of years. Today, it is just one tool in an ever-expanding toolbox of transparency and data sharing activities.

Good Publication Practice defines the term publication “to include the full range of formats published in peer-reviewed journals (for example, original research articles, short reports, reviews, or letters to the editor).” Typically, the main audiences for this type of disclosure are both scientific and medical and include the research community as well as health care practitioners. Peer-reviewed journals allow for clinical research to be put into context and explained. This has immense value for health care practitioners considering prescribing a new medication or a researcher interested in the latest scientific discovery.

Newer trends in the world of publications include electronic publications (ePub), open access models that reduce the need for an expensive subscription to access the articles, and increased requirements related to transparency and data sharing prior to peer-review of submitted publications.

Recent and upcoming recommendations by the ICMJE have expanded their requirements related to clinical trial registration. To publish a manuscript in ICMJE medical journals, each clinical trial must be registered on a public registry prior to enrolling the first participant. In addition, beginning 1 January 2019, a data sharing plan will be required at the time of registration. As of 1 July 2018, a data sharing statement is also required at the time of manuscript submission to inform the reader whether, and if so where and how, the data described in the manuscript are available.

Other emerging trends in publications include:

- Public Library of Science (PLOS)<sup>60</sup> journals require authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception.
- The Journal of the American Medical Association (JAMA)<sup>61</sup>, the New England Journal of Medicine (NEJM)<sup>62</sup> and others require the trial protocol including the complete SAP to be submitted with the publication and posted online.

Further exploration of publications and their best practices will be addressed in a subsequent Practical Guide that is planned as part of this series of information.

## 3 Submission Life Cycle

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In addition to the study-specific requirements already discussed, new medicines and line extensions often have additional disclosure requirements after submissions, marketing decisions, or withdrawal of application, depending on regional requirements. An overview graphic that visually represents many of these topics is accessible on the [PhUSE website](#).

### 3.1 Mandatory Requirements

There are a mix of laws, regulations, policies, and best practices that exist globally. In this section the focus is on the mandatory requirements per laws, regulations, and policies.

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Many locations have a law which allows citizens to request copies of some documents held by agencies. For example:

- In Europe, [EU Regulation 1049/2001](#)<sup>63</sup> aimed to give the fullest possible right of public access to documents of the European Parliament, Council and Commission, and to lay down the general principles and limits on such access in accordance with Article 255(2) of the EC Treaty. The EMA as an EU institution implemented Policy 0043 as foreseen in this regulation.
- In the US, such requests are handled through the [Freedom of Information Act](#) (FOIA)<sup>64</sup>.
- In Canada, the draft guidance document, [Public Release of Clinical Information](#)<sup>65</sup>, contains a retrospective element whereby “Clinical information from past drug submissions and medical device applications (received by Health Canada prior to the coming into force of the regulations) may be requested through Health Canada’s clinical information portal.”

Each jurisdiction’s approach to these document access policies varies in both mechanics of delivery and as to what information is freely shared versus kept private. For example, in the US, regulators take a more conservative approach to the protection of CCI whereas in EU, more data points may be considered Personal Protected Data (PPD<sup>b</sup>) and thus require masking prior to document sharing. A further difference is that in the US, there is no opportunity for a sponsor to review the proposed redacted documents prior to their release whereas in the EU under EMA P0043, sponsors may review and propose redactions. Note: PII<sup>a</sup> is a more commonly used term in the US, whereas PPD<sup>b</sup> is more commonly used in the EU. While definitions are not identical, the terms have been considered synonymous in this paper, i.e., the variables requiring redaction/anonymization to protect the privacy of trial participants

### 3.1.1 European Union

#### EMA Policy 0070 Phase 1 – Clinical Documents

The EMA launched their [Clinical Data Publication Access Policy 0070](#) in 2014 with an initial outline of the policy, including scope, timelines, and implementation guidelines.

At a high level, this policy requires companies to provide redacted/anonymised clinical documents that include CSRs, key clinical overview documents and an anonymisation report to the EMA after the submission process. This package should protect the privacy of patients and all other study participants (such as investigators, site nurses and sponsor staff), while providing a level of clinical utility to researchers and the public.

Several key reference materials exist that can provide support to this process. Some include:

- [TransCelerate: De-Identification and Anonymization of Individual Patient Data in Clinical Studies](#)
- [PhUSE De-Identification Standards](#)
- [EMA Policy 0070 First Year Report](#)<sup>66</sup>

Companies also have an opportunity to protect CCI with specific and detailed justifications on the impact to the sponsor should the details be released. It is important to note that information cannot be considered CCI if it has been posted in the public domain anywhere in the world. The protection of CCI is based on the EU CCI laws. The EMA is obligated to uphold the current EU definitions of what is and is not CCI. Justification of a potential CCI item is key, and a sponsor must obtain permission from the EMA during the review process to mask such information within these documents. CCI justifications are not made public.

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<sup>b</sup> **Personal Protected Data (PPD):** 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, psychological, mental, economic, cultural or social identity<sup>67</sup>.

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The redacted/anonymised clinical packages are then reviewed by the EMA through a consultation process and subsequently published through the EMA on a [Clinical Data website](#)<sup>68</sup> that is accessible globally after a registration procedure. Note, the requirement for user registration prior to accessing information on this site is different to the approach when accessing data on the EU Register, which does not require any prior registration steps. The implementation of this policy has seen a significant increase in the information from some studies (e.g. phase I and generics) being disclosed publicly.

### European Assessment Report

In 1993 Regulation (EEC) No 2309/93<sup>69</sup> required the EMA to make assessment reports of a medicinal product available on request from any interested person. For further details see [Article 12, pages 137-138](#).

As part of the central submission procedure, EMA also prepares and makes public [European Assessment Report](#)<sup>70</sup> also known as an EPAR, for every medicine granted a central marketing authorization by the EMA. These documents represent the full scientific assessment.

This report contains summary level information but can also contain some PPD and CCI. This document is produced by the EMA and reviewed by sponsors. It is important to recognize that any information that is included in an EPAR (or any other public domain) cannot be considered as CCI by the agency in a Policy 0070 submission or Policy 0043 information request.

### The EU CTR536

As previously discussed, in the EU the application of the EU CTR536 will soon replace the current EU CTD<sup>1</sup>. At a submission level, this means all CSRs included in an MAA will be required to be posted to the EU clinical trials database and published on the EU portal within 30 days of MA.

These deliverables will be produced by the sponsors and reviewed at different levels by authorities in the EU.

### 3.1.2 United States of America

The US has several key study-level clinical transparency requirements, however at the product level, overall transparency deliverables are fewer than in the EU. Key study level documents include the Summary Basis for Regulatory Action, available via the [Drugs@FDA](#) webpage<sup>71</sup>, and the study protocol and SAP now posted on [ClinicalTrials.gov](#) at the time of results reporting (usually 12 months after LSLV) for studies covered under the FDAAA 801 Final Rule.

#### Advisory Committee Briefing Documents or Briefing Summaries

Briefing summaries are created by the Sponsor and describe the results of the panel of experts and patients that were called together to discuss the details of the new medicine and vote on whether it should be approved. These documents can be very extensive, depending on the product. The information contained should be understood as part of the overall disclosure landscape.

#### Summary Basis for Regulatory Action

The current mandatory landscape requires less disclosure once a medicine is approved. Today, the US FDA must publish a Multi Discipline Summary Review also referred to as the Summary Basis for Regulatory Action after the review of every submission. This document is created by the FDA and published by FDA without Sponsor review. It contains extensive information about the drug compound

Per US law, individuals other than patients do not have a right to privacy and their details can be published.

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and clinical studies that led to the agencies decision. During this process the FDA is committed to protecting CCI as required by US Legislation. However, sometimes personal data which Sponsors currently mask as part of EMA Policy 0070 may be disclosed in these FDA assessments.

### 3.1.3 Additional Mandatory Requirements

Transparency requirements are increasing globally. Much of the global transparency landscape is limited to local study registrations and some results publication requirements – see detailed description earlier in [2.1.3 Additional Country-Specific Requirements](#). However, there are a limited number of regions that also have product-level transparency requirements. Those known at the time of publication include but are not necessarily limited to the following.

#### 3.1.3.1 Australia

In Australia, the government prepares a Summary Report after review of all potential drug candidates. Sponsors can review and propose redactions of PPD/CCI prior to publication.

Australia has a regulation supporting the citizens right to ask for private documents to be disclosed which will impact trial and drug information.

The Therapeutic Goods Administration (TGA) provides details on their approach to disclosure of CCI and documents released under [Section 11C of the Freedom of Information Act 1982](#)<sup>72</sup> that are made public in an overview which includes redacted individual case reports.

#### 3.1.3.2 Germany

In Germany, the BfArM provides information on medicinal products for healthcare professionals and consumers. The [Public Assessment Reports](#)<sup>73</sup> state the background for scientific evaluations, discussions, and decisions regarding a medicinal product. The completed forms are published on the [CMDh](#)<sup>74</sup> website.

The Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. It issues directives for the benefit catalogue of the statutory health insurance funds (GKV) for more than 70 million insured persons and thus specifies which services in medical care are reimbursed. The G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG) conduct benefit assessments of newly authorized pharmaceuticals in accordance with the German law “SGB V, section 35a.” Since 2011, the G-BA / IQWiG findings form the basis of decisions on the prices statutory health insurance providers pay for new pharmaceuticals with new active ingredients. See here for more details.

The Act for Restructuring the Drug Market (AMNOG) in 2011 required manufacturers to submit a dossier to the G-BA for an early benefit assessment of new drugs in Germany details are available ([in German](#))<sup>75</sup>. Dossier assessments are published in German and English<sup>76</sup> and G-BA decisions are published in [German](#)<sup>77</sup>.

#### 3.1.3.3 Japan

JPMA released [Information on Japanese Regulatory Affairs](#)<sup>78</sup> in 2018 which includes a description of requirements related to Public Disclosure of Information on New Drug Development. These requirements include the publication of Module 1 and 2 from the New Drug Applications since 2013. These are primarily published in Japanese, but some are published in English for key disease areas under expedited review such as submissions related to HIV medicines.

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### 3.1.4 Future Requirements

As the landscape for clinical trial transparency continues to evolve, it is important to consider those policies that are in draft as well as those that are in force. This section describes key global policies that are in review, in a pilot phase, or on the horizon.

#### Health Canada

Health Canada has stated its intention to begin publishing the information used to make decisions on new and existing medicines. The policy has many similarities to EMA Policy 0070; however, the stated intention is to also take a retrospective approach to publication. The current guideline is in draft form. Health Canada has taken a global view of clinical transparency and attempts to align with Policy 0070, where possible. Health Canada strongly endorses quantitative risk assessment.

The [draft guidelines on the Public Release of Clinical Information](#) were released for public comment in April 2018 and expected to be effective January 1, 2019.

#### US FDA Clinical Data Study Pilot Program

In early 2018, FDA launched a [Clinical Data Summary Pilot Program](#)<sup>79</sup> for disclosure of redacted versions of CSRs for up to 9 products. There are several key differences between the approach of this pilot and that of Policy 0070, as follows:

- The Agency performs redaction of the CSRs following practices and procedures established for FOIA requests. These practices and procedures determine what information is redacted and is based on US legislation. No review opportunity is provided to the sponsors.
- Only pivotal CSRs are published.
- No line listings or associated study data are made public.

The Agency is working with sponsors on this pilot process and may take feedback late in 2018.

#### EMA Policy 0070 Phase 2

Under Phase 2 of EMA Policy 0070, some patient-level data would be anonymized and publicly posted. The scope and approach of Phase 2 have not been disclosed and an effective date has not been established.

#### Summary Key Aspects of Clinical Document Disclosure

The following table summarises key aspects of clinical document disclosure per current understanding of the FDA Clinical Data Summary Pilot, EMA Policy 0070 (Part I), and Health Canada's and Japan's guidelines on the subject.

Submission Drive Clinical Data Publication				
	FDA - pilot	EMA - policy 0070	Health Canada	Japan
Language published in	English	English	English	Japanese [if expedited review, e.g., HIV submissions, then published in English]
Who redacts the PII and CCI?	FDA	Sponsor	Sponsor	Sponsor
Who makes the final decision on PII?	FDA	Sponsor <i>(but must justify to EMA)</i>	Health Canada	PMDA
Who makes the final decision on CCI?	FDA	EMA	Health Canada	PMDA
Who owns the legal responsibility for information they publish?	FDA	Sponsor	Health Canada has a role, specific details are unclear	Sponsor
Technical requirements (related to PII)	Redaction ONLY	Redaction accepted Anonymisation encouraged	Anonymisation strongly encouraged, but redaction may be accepted with justification	Redaction and Anonymisation
IPD	Not in scope No plan to release	Will be considered in Part 2 of Policy 0070	Yes, but TBD	No <i>(mini-narratives included in Module 2)</i>
Is there a penalty for sponsors?	No <i>(Not for pilot)</i>	Yes <i>(If identified as a result)</i>	General provision, but specifics unclear	General provision, but specifics unclear
Which modules are made public?	Pivotal studies module 5 only No listings	Module 2.5, 2.7.1-2.7.4 Most of module 5 with appendices	Module 2.5, 2.7.1-2.7.4 Most of module 5 with appendices	Review report including module 1.15-1.10 and 1.12 (different to EU module1) and all Module 2 <i>(Plus, additional requirements including CSR synopses and mini-narratives for serious adverse events)</i>
Policy effective Dates	Pilot started in 2018	Submissions from 01 January 2015 onwards	Expected to be for Opinions from 01 January 2019 onwards	Original requirement from November 1999, with subsequent revisions

Table 3: Key Aspects of Clinical Document Disclosure (post-submission)

## 4 Conclusion

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The world of clinical trial transparency and disclosure continues to evolve and expand. While this paper seeks to share the state of the world as it is today we know that it will not stay this way for long. The regulatory landscape will continue to grow with new disclosure requirements, and with additional countries or regions implementing requirements.



Each piece of the disclosure puzzle is increasingly interconnected. It can be thought of as an expanding network that includes registration and results disclosure, publications, voluntary disclosure activities, lay summaries, and sharing of patient-level data for research, among others. The global and interconnected nature of this expanding puzzle means that sponsors must be fully aware of the landscape and monitor any new developments.

It is also important to note that compliance with all regulations is the 'baseline' expectation, not an aspiration. There are an increasing number of opportunities where public disclosure of information can bring increased value to stakeholder groups such as patients, patient groups, carers, researchers and the public.

The next deliverable of this group will examine some practical applications to assist sponsors and others meet these ever-expanding requirements, expectations and opportunities. This will include considering an holistic approach, planning with the end in mind.

As noted previously, due to the constantly evolving nature of clinical trial transparency, this paper is intended to be a snapshot in time. While we intend for this paper to include the best information available at the time of writing, we cannot guarantee that it encompasses all requirements. We welcome readers' feedback and questions via the PhUSE FAQ Forum.

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