Examining New Transparency Requirements in the European Union

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CBI Prep Forum for the New EU Clinical Trial Regulation
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Transparency Requirements in the European Union (EU) Are Evolving Rapidly

Regulation (EC) No 1049/2001
• Access to documents

EU Clinical Trial Directive
• EudraCT and EU-CTR

Pediatric Regulation

EudraCT database goes live
EU-CTR registration module goes live

EU Clinical Trial Regulation (May)
• EU Database and Portal

EU Publication Policy (October)
• Phase 1: Clinical documents (effective now)
• Phase 2: Individual patient data (IPD) (deferred)

EU-CTR results module goes live (July)

01 Jan
New MAA
01 Jul
Extensions
Policy 0070 Effective (Phase 1)

EU portal and database live and EU CT Regulation in force?
Policy 0070 individual patient data (IPD) sharing (Phase 2)?
Sponsors Need to Plan to Meet Increased Transparency Requirements

- Have you assessed the impact that Policy 0070 and the EU Clinical Trial Regulation (CT Regulation) will have on your organization?

- What are you doing to prepare?
  - Automated systems?
  - Putting resources in place?

- Do you know whether you are on track to deliver the required data and documents?

- There are multiple mechanisms for release of clinical data and documents
  - Policy 0070 and the CT Regulation are the new mechanisms
  - These have complicated rules which are still in development
Five Mechanisms (Regulation/Directive/Policy) Allow for Disclosure of Clinical Trial Information

   - Herein referred to as the Directive
   - Requires registration and summary results for EU interventional studies
   - Established six-month regulatory timeline
   - Requires registration and summary results for:
     - Pediatric Investigation Plan (PIP) studies (Article 41)
     - Ex-EU pediatric studies in products with marketing authorization (Article 46)
   - Requires publication of CT documents in marketing authorization applications (MAA), line extensions, extension of indication submissions
5. EU Clinical Trial Regulation – Regulation (EU) No 536/2014
   - Herein referred to as the CT Regulation
   - Repeals the Directive
   - Requires registration and summary results
   - Requires publication of study-specific and product-specific CT documents associated with trial authorizations
   - Current estimate: implementation end of 2017
Mechanism 1: Access to Documents (Regulation [EC] No 1049/2001)

- Public access to European Parliament, Council and Commission documents
- Applies to wider range of documents than the policies and regulations that follow, but more time consuming for the requestor
- Documents might include study protocols, clinical study reports (CSR), risk management plans, responses to agency questions, etc.
- Sponsors may have experience working with EMA on what is acceptable for redaction if they have responded to access to documents requests
- Aka Freedom of Information requests
Mechanism 2: EU Clinical Trial Directive
(Directive 2001/20/EC)

• The Directive established:
  – The EudraCT database, in which sponsors can enter information on their studies
  – The EU Clinical Trials Register (EU-CTR), a publicly accessible database, which
displays registration information and summary results for studies
  – Registration is de-centralized through local national competent authority (NCA)

• Impetus for repealing the Directive with the CT Regulation:
  – “The 2001 Clinical Trials Directive has been criticized by patients, researchers
and industry alike for its disproportionate regulatory requirements. High costs
and a lack of harmonization of the applicable rules necessary for multinational
clinical trials are a few examples.

Taken together, these restrictions have contributed to a significant decline in the
number of clinical trials in the EU – a reduction of about 25 % in the last few
years.

The new Regulation aims at restoring the EU’s competitiveness in clinical
research and the development of new and innovative treatments and medicines
by cutting red-tape and bringing patient-oriented research back to Europe.”

Source: Q&A: New rules for clinical trials conducted in the EU. EMA, 02 April 2014
Mechanism 3: Pediatric Regulation
(Regulation (EC) No 1901/2006)

- Expanded registration and results requirements contained in the Directive to include ex-EU pediatric studies in marketed products and PIP studies
- CT Regulation stipulates most requirements contained in the Pediatric Regulation
  - Items not in the CT Regulation, but will remain in effect per Pediatric Regulation:
    - Timing: “The timing of submission of the results of clinical studies which should be without delay and for those referred to by Article 46 of the Pediatric Regulation, within 6 months of the end of the trial”
    - Ex-EU studies: “Additional requirements with regard to non-EU trials included in a pediatric investigation plan (PIP), as per Article 41 or reported in accordance with Article 46 of the Pediatric Regulation continue to apply”

Source: Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014 (EMA/228383/2015), Section 3.2.
Mechanism 4: EMA Policy on Publication of Clinical Data for Medicinal Products for Human Use (Policy/0070)

• Scope:
  – Phase 1 of Policy 0070 implementation:
    • Clinical reports contained in MAAs (beginning 01 January 2015)
    • Clinical reports contained in line extension, and extension of indication submissions (beginning 01 July 2015)
    • Publication within 30 days of marketing authorization decision
  – Phase 2 of Policy 0070 implementation:
    • Individual patient data (IPD) listings (not yet in force)
• Limited redaction allowed for commercially confidential information (CCI)
• Policy 0070 Annex 3 describes sections of the clinical report that may contain CCI, and details what is potentially acceptable for redaction
• Policy 0070 Annex 4 describes the process for consultation on redactions between sponsor and EMA and process for publication
• Redaction guidance and consultation process is further described in: *External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070.* (08 Oct 2015) (EMA/471266/2015)
Policy 0070 CCI Redaction Guidance Is in Development

• Detailed guidance contained in:
  – *Guidance to pharmaceutical industry on redacting commercially confidential information (CCI) in clinical reports & Process*, 06 July 2015 stakeholder meeting
  – *Key aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA Policy 0070*, 07 Sept 2015 stakeholder meeting

• Approach to redaction of CCI: must be a type of information described in Policy 0070 Annex 3 as potentially considered CCI
  – “Has to be adequately justified”
  – “Justifications solely based on Annex 3 justification text or referring to Annex 3 information types will not be considered relevant, therefore will be rejected”

• Information not considered CCI: information in the public domain, is common knowledge, does not bear any innovative features, must be disclosed due to overriding public interest, information for which justification is insufficient or irrelevant

• Justification table must be included for each redacted document (EMA provides template)

• Further guidance contained in: *External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070* (08 Oct 2015) (EMA/471266/2015)
  – Guidance on document types in scope, process for submission, process flowcharts, CCI, and anonymization

1 Source: *Guidance to pharmaceutical industry on redacting commercially confidential information (CCI) in clinical reports* (24 June 2015) (presentation material from Stakeholder Webinar)
Individual Patient Data (IPD) Required in Policy 0070, Phase 1

- Patient data listings are not yet in scope (will be in Phase 2)
  - Phase 2 is deferred while standards and infrastructure are being developed
- IPD present elsewhere in the CSR should not be redacted, but rather anonymized
  - Case narratives
  - In-text IPD
  - External guidance on anonymization of clinical reports in development
  - Anonymization report is required, detailing approach and methodology to anonymization of IPD
    - Current approach is to redact
    - Future approach will be to prospectively anonymize data
- EMA vision for sharing of IPD is that reanalysis, further research, and prevention of duplicative research is in the public interest, and must be balanced against the sponsor’s commercial interest
- In contrast, FDA vision for sharing of IPD is to enable increased meta-analyses, but that it should be controlled more closely; they are not the owners of the data and will not act as a publishing house
Mechanism 5: EU Clinical Trial Regulation (Regulation (EU) No 536/2014)

- Anticipated benefits of the CT Regulation \(^1\)
  - Authorization procedure for clinical trials based on a single CTA submission via the EU portal
  - Assessment procedure leading to a single decision on all aspects per member state
  - Rules on the protection of subjects and informed consent
  - Extensive transparency requirements (in the public interest)

Impact of the Evolving Regulatory Landscape

• Mechanisms 1-3 are in effect, sponsors have experience and understanding of them
• Mechanisms 4 (Policy 0070) and 5 (CT Regulation) are new, guidance is still being developed, and sponsors have little experience or understanding of them

Policy 0070 and the CT Regulation, which are in the implementation process, will have a significant impact on the way we do business
Policy 0070 and the CT Regulation Present Major Challenges and Impact to Sponsors

- Confusion while trying to determine requirements
  - Guidance still in development, many criteria for EMA evaluation unknown
- Tracking timing of information release and required sponsor actions
- Expense, resources, and expertise required to create, review, and approve redacted documents for publication
- Potential threat to intellectual property
- Potential for increased litigation
  - EMA requiring disclosure of documents, but will not enforce its own Policy 0070 Terms of Use (ToU)
  - EMA may be unlikely (or unable) to provide identity of requestors to aid sponsors of protecting their intellectual property
- Obstacles to running studies in the EU
  - Directive credited with increase in associated costs, delays, and the administrative and regulatory burdens, and decrease in the number of clinical trials conducted in the EU
  - CT Regulation will not reduce, but rather increase the burden on sponsors with regards to transparency requirements
# EU CT Regulation Has 3 Categories of Studies

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical development</strong></td>
<td><strong>Therapeutic exploratory and confirmatory clinical trials</strong></td>
<td><strong>Phase IV (interventional) and low-intervention trials</strong></td>
</tr>
</tbody>
</table>

## Balance of interests

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limited public interest for disclosure at time of decision on the trial</td>
<td>• Economic interests of the sponsor, including preparation for publication or furtherance of development plans, are given protection</td>
<td>• Public interest is of overriding importance as the IMPs are in routine use in medical practice</td>
</tr>
<tr>
<td>• Commercial confidentiality “particularly acute”</td>
<td></td>
<td>• Economic interest of sponsors is confined to the possible novelty of their trial design and hypothesis</td>
</tr>
</tbody>
</table>

## Document Publication Deferral

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Up to 7 years after EOS</td>
<td>• Up to 5 years after EOS</td>
<td>• Up to time of summary results publication</td>
</tr>
</tbody>
</table>

## Types in category

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phase I – healthy volunteers/patients</td>
<td>• Safety and efficacy in patients (or target populations for prophylaxis)</td>
<td>• Phase IV – post-marketing studies to delineate additional information including the IMP’s risks, benefits, and optimal use</td>
</tr>
<tr>
<td>• Phase 0 – healthy volunteers or patients, no therapeutic/prophylactic intent</td>
<td>• Phase II and III during clinical development of a new product, or during exploration of new indications, pharmaceutical forms, strengths and routes of administration for existing products with a marketing authorization</td>
<td>• Low-intervention clinical trials</td>
</tr>
<tr>
<td>• Bioequivalence/bioavailability – innovative products, new formulations of approved products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trials with efficacy endpoints for biosimilarity or equivalence, where pharmacokinetic and/or pharmacodynamic studies are not possible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Appendix, on disclosure rules (EMA/228383/2015), Section 4.3.3, 4.3.4
<table>
<thead>
<tr>
<th>EU CT Regulation: Timing for Release of Data (high-level summary of Table 1 from Appendix, on disclosure rules [EMA/228383/2015])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table</strong> represents trials that are authorized. If a trial is refused the date of decision on the trial will also be the date of the end of the trial; options for deferral will apply.</td>
</tr>
<tr>
<td><strong>1</strong> Includes WHO ICTRP data fields, cover letter, investigator details (including CVs and facility suitability statement)</td>
</tr>
<tr>
<td><strong>2</strong> EU substance/product numbers, INN/other substance/product names; published in Medical Product Dictionary (MPD)</td>
</tr>
<tr>
<td><strong>3</strong> Justification required</td>
</tr>
<tr>
<td><strong>4</strong> Except pediatric</td>
</tr>
<tr>
<td><strong>5</strong> Sponsor selects 1 of 3 publication timing options; may include deferral</td>
</tr>
<tr>
<td><strong>6</strong> See Appendix, on disclosure rules, Section 4.6</td>
</tr>
<tr>
<td><strong>7</strong> If sponsor has deferred on other options, some information may be deferred</td>
</tr>
<tr>
<td><strong>8</strong> Pediatric time line: 6 months</td>
</tr>
<tr>
<td><strong>9</strong> Must be submitted within 12 months (6 months in pediatric) regardless of deferral request</td>
</tr>
<tr>
<td><strong>10</strong> See Appendix, on disclosure rules, Section 4.5</td>
</tr>
<tr>
<td><strong>Category 1</strong></td>
</tr>
<tr>
<td><strong>Main characteristics</strong> 1</td>
</tr>
<tr>
<td><strong>IMP data (w/out MA)</strong> 2</td>
</tr>
<tr>
<td><strong>Notifications during the trial (safety, quality, GMP, etc.)</strong></td>
</tr>
<tr>
<td><strong>Subject information sheet (ICF)</strong></td>
</tr>
<tr>
<td><strong>Protocol and amendments</strong></td>
</tr>
<tr>
<td><strong>Investigational Medicinal Product Dossier (IMPD)-E and IMPD-S</strong></td>
</tr>
<tr>
<td><strong>Substantial modifications</strong></td>
</tr>
<tr>
<td><strong>Requests to sponsor</strong></td>
</tr>
<tr>
<td><strong>Assessment reports</strong></td>
</tr>
<tr>
<td><strong>Conditions for conclusion on Part I or II or decision on the trial</strong></td>
</tr>
<tr>
<td><strong>Sponsor responses on trial aspects</strong></td>
</tr>
<tr>
<td><strong>Conclusion on Part I &amp; Part II</strong></td>
</tr>
<tr>
<td><strong>Conclusion on Part II</strong></td>
</tr>
<tr>
<td><strong>Decision on trial</strong></td>
</tr>
<tr>
<td><strong>Clinical summary (intermediate)</strong></td>
</tr>
<tr>
<td><strong>Clinical summary (final) and layperson summary</strong></td>
</tr>
<tr>
<td><strong>Clinical study report</strong></td>
</tr>
<tr>
<td><strong>Serious breaches, inspections, Union Controls, Corrective Measures</strong></td>
</tr>
</tbody>
</table>

[See Appendix, on disclosure rules, Section 4.6]
Registration and Results Currently on the EU Clinical Trials Register (EU-CTR) will move to EU Portal and Database

- At this time, no change to the content of registration and results records currently in the EU-CTR is anticipated

- Current state:
  - Registration and summary results currently entered on EudraCT and visible to public on EU-CTR
  - Registration is de-centralized through local NCA

- Anticipated future state:
  - The same content currently on the EU-CTR will be entered in the EU database via the EU Portal for future studies, legacy studies will remain on EudraCT/EU-CTR and will be accessible through the EU Portal
  - Documents submitted through Policy 0070 will be accessible through the EU Portal
  - It is anticipated that data/documents/clinical reports required as part of increase in transparency requirements will be accessible through the EU Portal
  - Summary of Clinical Results/Summary of Results for Laypersons are detailed in CT Regulation Annex IV and Annex V, respectively
# Policy 0070 versus CT Regulation – At a Glance

## Policy 0070

The Directive has no provision for prospective publication of Clinical Trial documents/data. Policy 0070 mandates this publication. The EU CT Regulation (when fully implemented) will expand these transparency requirements.

### Scope
- Applies to MAA, line extension, or extension of indication submissions

### Effective
- 01 January 2015: new MAAs
- 01 July 2015: major type 2 variations (label changes) including extension of indication and line extension applications

### Content
- CTD Section 2.5
  - Clinical overview and appendices
- CTD Section 2.7
  - Standard clinical summaries
  - Integrated summary of safety/efficacy
- CTD Section 5.3
  - CSRs (including statistical analysis plan and sample case report form [CRF])
  - Reports of analyses of data from ≥ 1 Study (meta-analyses, pooled analyses)
  - Section 5.3.5.4, Other Study Reports, reports not related to the claimed indication

### CT Regulation ¹

- Applies to individual studies
- 6 months following finalization of EU database and portal
- Current estimate from EMA is in the 1st quarter of 2017.

### Content
- Application dossiers
- Protocols (synopsis and body have different timing rules ²)
- Statistical analysis plans
- Clinical study reports
  - Synopsis, body, tables, figures
  - All appendices except data listings
- Clinical summary (results posting)
- Clinical summary (lay person)
- Investigator brochure
- IMPD-E, IMPD-S
- Assessment reports, inspection reports, Union Control reports, serious breaches and corrective measures, unexpected events and urgent safety measures

### Source
- External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070 (08 Oct 2015) (EMA/471266/2015)

¹ Separate redaction guidance for documents loaded to the EU Database is in development, and will be consistent with that developed for Policy 0070 (Appendix, on disclosure rules [EMA/228383/2015], Section 4.5).

² Source: Functional specifications for the EU portal and EU database to be audited. (25 Mar 2015) (EMA/42176/2014 Rev. 1)

Note: unclear if this is still true, this is not indicated in the recently released Appendix, on disclosure rules (EMA/228383/2015 Endorsed)
### EU versus US: Different Timing for Summary of Clinical Results

- Content and format of the summary of clinical results is similar to current EU-CTR and ClinicalTrials.gov results postings, but the timing is different between EU and US
- Regulation contains requirement for interim summaries (not in the Directive)

<table>
<thead>
<tr>
<th>ClinicalTrials.gov</th>
<th>EU Portal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope</strong></td>
<td>Intervventional EU studies</td>
</tr>
<tr>
<td></td>
<td>Ex-EU pediatric studies as provided in the Pediatric Regulation</td>
</tr>
<tr>
<td><strong>Triggers for results posting</strong></td>
<td>Protocol-specified interim analysis LPLV date</td>
</tr>
<tr>
<td>- Primary endpoint last patient/last visit (LPLV) date</td>
<td>End of study in EU ¹</td>
</tr>
<tr>
<td>- LPLV dates for secondary endpoints</td>
<td></td>
</tr>
<tr>
<td>(per ClinicalTrials.gov Notice of Proposed Rulemaking [NPRM])</td>
<td></td>
</tr>
<tr>
<td><strong>Default timing</strong></td>
<td>12 months from LPLV</td>
</tr>
<tr>
<td></td>
<td>(6 months in pediatric)</td>
</tr>
<tr>
<td><strong>Delay mechanisms</strong></td>
<td>Category 1</td>
</tr>
<tr>
<td>- Seeking initial approval</td>
<td></td>
</tr>
<tr>
<td>- Currently indefinite delay</td>
<td>18 months (total 30 months from LPLV)</td>
</tr>
<tr>
<td>- 2-year delay proposed in NPRM (total 3 years from LPLV)</td>
<td>Category 2</td>
</tr>
<tr>
<td>- Seeking approval for new use</td>
<td>No delay (12 [or 6] months from LPLV)</td>
</tr>
<tr>
<td>- 2-year delay (total 3 years from LPLV)</td>
<td>Category 3</td>
</tr>
<tr>
<td></td>
<td>No delay (12 [or 6] months from LPLV)</td>
</tr>
</tbody>
</table>

¹ Source: Appendix, on disclosure rules (EMA/228383/2015), Table 1 (page 18)
EU Portal and Database

- The EU Portal and Database will replace EudraCT and EU-CTR
- During 3-year transition period, studies may be submitted using the EU Portal and Database, or using EudraCT
- After transition, EU-CTR and EudraCT become legacy databases, still accessible through the EU Portal
- *Draft appendices to draft transparency addendum* (EMA/768628/2014) describes all of the fields that will be visible to the public prior to posting summary of clinical results
  - Final version of the Draft Appendices is pending, which will incorporate provisions for deferral of publication according to the 3 categories described in the *Appendix, on disclosure rules* (EMA/228383/2015)
- Annex V of the Regulation describes the content to be included in the summary of clinical results
  - Same content as currently required on the EU-CTR
“All guidance documents should be considered ‘living’ documents that will be updated in light of experience obtained.”
Questions?

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Multiple Systems to Be Integrated

**Source:** Draft Functional specifications for the EU portal and EU database to be audited. (10 Oct 2014) (EMA/42176/2014 Corr.) Section 3

**Figure 1:** High level overview of the clinical trial systems
24 June 2015: Current status of European Medicines Agency policy on publication of clinical data - Stakeholder webinar

- Multimedia: Webinar broadcast – Guidance to pharmaceutical industry on redaction of CCI in clinical reports
- Documents:
  - Implementation update
  - Guidance on redaction and anonymization
  - Redaction consultation process
  - Submission process

06 July 2015: Meeting on redacting commercially confidential information (CCI) in clinical reports and anonymising clinical reports for the purpose of publication

- Guidance on redaction and anonymization

07 September 2015: Second stakeholder meeting on the implementation of the European Medicines Agency's policy on publication of clinical data for human medicines

- External guidance on implementation of Policy 0070
- Key aspects related to the submission of clinical reports
References

Overview

• Wright E et al. Making sense of clinical trial data disclosure in the EU. (Apr 2015) Scrip Regulatory Affairs

Policy 0070

• European Medicines Agency policy on publication of clinical data for medicinal products for human use. (02 Oct 2014) (EMA/240810/2013)
• External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070. (08 Oct 2015) (EMA/471266/2015)

EU Clinical Trial Regulation

• Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014.” (02 Oct 2015) (EMA/228383/2015 Endorsed)
• Draft Functional specifications for the EU portal and EU database to be audited. (10 Oct 2014) (EMA/42176/2014 Corr.)
• Functional specifications for the EU portal and EU database to be audited. (25 Mar 2015) (EMA/42176/2014 Rev. 1)
• Draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014.” (20 Jan 2015) (EMA/641479/2014)
• Draft Appendices to Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited” EMA/641479/2014 (20 Jan 2015) (EMA/768628/2014)
  Note: update to this is forthcoming, incorporating the rules in “Appendix, on disclosure rules” (02 Oct 2015) (EMA/228383/2015)
• Sweeney F. The Clinical Trials Regulation EU No 536/2014: and Phase I trials. (20 May 2015) Presented at EUFEMED, Brussels
• White Paper, The EU Clinical Trials Regulation – Main Changes and Challenges (Feb 2015) CROM Source

Layperson summaries (part of EU Clinical Trial Regulation)

• Proceedings, Harvard Multi-Regional Clinical Trials Center (MRCT), 3rd Annual Meeting (03 Dec 2014)
• MRCT Website: mrctcenter.org, search for layperson summary, return of results
• Northam, J. Writing a lay summary is easy, right? Bournemouth University Research Blog
### Lay Summary – Potential Issues/Proposals for Implementation

**Table 1: Requirements for Lay Summaries, According to the European Regulation EU No. 536/2014: Identification of Potential Issues and Proposal for Implementation**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Issue</th>
<th>Proposal for Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical trial identification (including title of the trial)</td>
<td>The trial title is usually written for a specialist audience in a technical language.</td>
<td>Devise an additional lay title that is shorter and simpler than the full trial title and provide it along with the full trial title.</td>
</tr>
<tr>
<td>3. Main objectives and rationale of the trial</td>
<td>Objectives and rationale are usually described in the trial protocol for a specialist audience in a technical language.</td>
<td>Provide a simplified description avoiding specialist terms, but also provide important medical terminology (like disease stages) to maintain specificity.</td>
</tr>
<tr>
<td>4. Inclusion and exclusion criteria</td>
<td>The clinical trial protocol usually contains many inclusion and exclusion criteria written for a specialist audience in a technical language.</td>
<td>Reduce the lists of inclusion and exclusion criteria from the trial protocol to the most important ones, like age, body mass index, and indication-specific criteria.</td>
</tr>
<tr>
<td>5. Investigational medicinal product</td>
<td>Depending on the product development stage, different drug identifiers are usually available, such as internal compound code, international non-proprietary name, or trade names. In addition, trade names often differ among countries or regions.</td>
<td>Provide the compound code for early trials and all available identifiers for later stages. If feasible, all available identifiers for comparator medication(s) should be given. Provide information if a placebo was used.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
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<th>Proposal for Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Description of adverse reactions and their frequency</td>
<td>By definition, the term adverse reactions refers to the concept of drug–related adverse events. Especially in early drug development programs, this concept might not be appropriate, and it would be reasonable to report all adverse events. In addition, there are several levels of granularity in frequencies of adverse events and in reporting of adverse events (e.g., MedDRA preferred terms and system organ class).</td>
<td>To keep consistency with other sources, provide adverse events using MedDRA preferred terms as default and system organ class level only if useful. The medical terms may need an additional explanation in lay terms. Provide frequencies of all adverse events, deaths (if any), adverse events leading to trial discontinuation. Provide clinical laboratory data only if considered useful for the reader.</td>
</tr>
<tr>
<td>7. Overall results of the trial</td>
<td>Because clinical trials usually have several different endpoints (primary, secondary, further), it is not clear if this section should contain all efficacy and safety data, and to what extent numerical data should be presented. Quality of Life data might be of special interest for patients, but these are often not included as primary/secondary endpoints.</td>
<td>Focus on the primary and the key secondary endpoints. Provide numerical results to make the data comparable to other resources (clinical trial reports, publications, trial results databases). Include Quality of Life data, if relevant results were obtained in the trial.</td>
</tr>
</tbody>
</table>
## Lay Summary – Potential Issues/Proposals for Implementation

### Table 1: Requirements for Lay Summaries, According to the European Regulation EU No. 536/2014: Identification of Potential Issues and Proposal for Implementation

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<thead>
<tr>
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<th>Proposal for Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Comments on the outcome of the trial</td>
<td>This item might refer to the trial objective or the primary endpoint, but it is not clear on what the sponsor is supposed to comment. Because reporting of the trial results is already mentioned above, this might require qualitative statements. However, qualitative summary statements are easily perceived as promotional.</td>
<td>Provide a high-level factual statement on whether the trial fulfilled its objective.</td>
</tr>
<tr>
<td>9. Follow-up trials</td>
<td>Whereas the terms trial and study are precisely defined in the regulation, a definition of what should be considered a follow-up trial is missing. All planned trials investigating the same product might be mentioned. Likewise, already recruiting trials only, or any planned future trials could be reported as well. However, this might be perceived as advertising future studies conducted by the same sponsor.</td>
<td>Only true extension trials related to the trial in question should be reported.</td>
</tr>
</tbody>
</table>

*Items 2 and 10 can be readily implemented and are therefore not included in this table. MedDRA=Medical Dictionary for Regulatory Activities*