KAROLINSKA INSTITUTET

INSTRUCTIONS FOR CLINICAL TRIAL REGISTRATION AND REPORTING

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1. Introduction

Clinical trial transparency is defined as the sharing and use of clinical trial data across global registries. Greater clinical trial transparency leads to improved patient care, research advances and overall better healthcare systems. Failure to report results in clinical trial registries deprives patients and doctors of complete data to gauge the safety and benefit of treatments. Therefore, in an effort to improve clinical trial transparency within open science, the University Director at Karolinska Institutet (KI) has issued a directive to centralize the clinical trial registration and reporting process. This task has been bestowed to the Compliance and Data Office (CDO) within the Research Support Office (RSO) at Karolinska Institutet (KI). As a result, CDO has developed the following instructions to support principal investigators and researchers in registering and reporting clinical trials and clinical studies.

2. Scope

These instructions provide regulatory information and procedures for the registration and reporting of clinical trials and clinical studies in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) and ClinicalTrials.gov registries. These instructions outline available support and guidance for clinical trial registration and reporting based on the requirements and regulations at Karolinska Institutet (KI), clinical trial registries, and national and international institutions.

3. Definition of clinical trials and clinical studies

These instructions describe the registration and reporting procedures at Karolinska Institutet (KI) for both "**clinical trials**" and "**clinical studies**". Not all *clinical studies* qualify as a *clinical trial* under the EU Directive/EU Regulation. The European Union (EU) Directive 2001/20/EC defines a clinical trial as follows[1]:

Clinical Trial

> "*Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining the safety and/or efficacy of those medicinal products.*"

Clinical studies, on the other hand, are more generalizable and can include both interventional and non-interventional studies; however, clinical studies **DO NOT** involve investigational medicinal products (IMPs), as opposed to clinical trials. Clinical studies are defined as follows:

Clinical Study

> *"Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, which include, but are not restricted to drugs, cells and other biological products,*

[1] Directive 2001/20/EC: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc."

For the purposes of these instructions, the term "**clinical trial**" (klinisk läkemedelsprövning) will refer to "trials that are subject to approval by the Medical Products Agency (MPA)", as opposed to the term "**clinical study**" (klinisk studie), which will refer to other "interventional studies" and "non-interventional studies" that do **NOT** require MPA approval.

4. Centralization of clinical trial registration and reporting at KI

CDO has developed detailed strategies and procedures for implementing the centralization of clinical trial registration and reporting. Specific facets in the workplan include, among other things, the development of a database with KI registered trials/studies, establishing a Protocol Registration and Results System (PRS) Administrator account for ClinicalTrials.gov and a Primary Account for EudraCT, developing networks to increase national and international collaboration, and monitoring deadlines for required updates and reporting results for trials/studies in these respective clinical trial registries. In this phase, only ClinicalTrials.gov and EudraCT are included, as the majority of KI trials/studies are registered in these two clinical trial registries. This means that accounts that are registered with KI as a Sponsor will now be tied to a central PRS Administrator account in ClinicalTrials.gov, and a central Primary Account in EudraCT, and both will be maintained by CDO. Through the role as a PRS Administrator at ClinicalTrials.gov, CDO can assist researchers with many issues, including gaining access to information about the trial/study; creating new user accounts; assistance in registration and reporting: and reviewing for errors, required updates, and unreported results. In EudraCT, the KI Primary Account is limited to reporting results only, however, CDO can provide researchers with support for that task. Registering, updating, and reporting results in a clinical trial registry can be a demanding task, however, CDO provides direct support for this endeavor to KI researchers. CDO also provides support to researchers conducting clinical trials with KI as the Sponsor. Researchers with questions or in need of support can contact CDO at compliance@ki.se.

4.1 Information about EudraCT

EudraCT is a web-based database developed by European regulatory authorities for the European Union involving clinical trials conducted throughout the region. EudraCT helps facilitate information and communication of clinical trials between European authorities. EudraCT also provides European authorities with a better oversight of clinical trials and investigational medicinal product development, as well as enhancing protection of clinical trial subjects and patients receiving investigational medicinal products. Directive 2001/20/EC applies to the registration and reporting of all clinical trials conducted on at least one site within the territory of a Member State. The EudraCT database comprises vital information on the study protocol, participants, study outcomes, and adverse events allowing for transparency of the efficacy and effectiveness of investigational medicinal products. It provides researchers and the public with information on clinical trials and PIP (Pediatric Investigation Plan) trials, which have been authorized in the European Economic Area (EEA). It gives users the

ability to search for information on Phase II-IV adult clinical trials and pediatric clinical trials recorded in the database.

4.2 Information about ClinicalTrials.gov

The ClinicalTrials.gov is a web-based database maintained by the National Institutes of Health (NIH) in order to establish a registry of clinical trials and clinical studies. The FDA Amendments Act of 2007 allows more types of clinical studies to be registered and requires additional study registration information to be submitted. The law also requires the submission of results for certain clinical trials. The ClinicalTrials.gov database contains summary information on the study protocol, participants, study outcomes, and adverse events to facilitate transparency in the efficacy and effectiveness of clinical trial and clinical study results. It provides users the ability to search for information on Phase II-IV clinical trials, as well as interventional and non-interventional clinical studies recorded in the database.

5. Regulations for clinical trial registration and reporting

There are number of national and international laws and regulations requiring the registration and reporting of results for clinical trials and clinical studies in a recognized clinical trial registry. In Sweden, regulations for registering clinical trials that test Investigational Medicinal Products (IMP) follows Directive 2001/20/EC of the European Commission[2]. If a study qualifies as a clinical trial in accordance with the EU Directive, then a **Sponsor** must be identified and a **EudraCT number** must be obtained, followed by authorization from the **Medical Products Agency** (**MPA)** and **approval by the Swedish Ethical Review Authority (EPM**). The MPA requires all approved clinical trials conducted in Sweden to be registered in EudraCT. Information about application and registration is available on the Medical Products Agency's website[3].

If a study does not qualify as a *clinical trial*, but qualifies as a ***clinical study***, then approval by the Swedish Ethical Review Authority (EPM) must be obtained. The application will identify the research principals. Authorization from MPA is **NOT** required. **These clinical studies do not have a Sponsor,** as the term is defined in the EU Directive. However, a Sponsor is required for clinical trial registration. In such cases, it is recommended that the research principal stipulated in the ethical approval serve as the responsible 'Sponsor' for registration **(responsible registrant),** unless specified otherwise. Research collaborators can also choose another collaborating organization to serve as the 'Sponsor' (responsible registrant), however, an agreement with the research principal must be ascertained regarding which organization will assume the responsibility for the registration, reporting, funding, and composing all necessary contracts with all collaborating sites.

[2] Directive 2001/20/EC: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

[3] Medical Products Agency: https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials

In terms of reporting results, all clinical trials registered in EudraCT must post trial outcomes. In accordance with the European Commission (EC) guideline 2012/c302/03[4], Sponsors must ensure that all clinical trials registered on EudraCT report their results within 12 months of trial completion.

In the US, Section 801 of the FDA ACT 2007[5] requires all "**applicable clinical trials**" to be registered prior to participant recruitment and results reported within 12 months of trial completion. *Applicable clinical trials* are trials that involve FDA-regulated drug, biological or medical device products that include at least one of the following:

- A study site in the US; or
- A new 'investigational medicinal product'; or
- Funding by the US (e.g., NIH funding); or
- The drug, biological or medical device product is manufactured in the US.

To determine if a study meets the criteria of an "applicable clinical trial", researchers can utilize the PRS ACT checklist[6]. Failure to register and/or report results of an "applicable clinical trial" could lead to noncompliance to which penalties of up to $10,000 daily could occur, or the risk of losing US federally funded grants, such as NIH funding.

If the study does **NOT** meet the criteria of an "applicable clinical trial", but qualifies as a *clinical study*, then the requirements and regulations for reporting results do **NOT** apply to clinical studies registered in ClinicalTrials.gov. Clinical studies are, however, required to be registered by the International Committee of Medical Journal Experts (ICMJE), particularly if the study will be submitted for subsequent publication. ICMJE states that unregistered clinical studies will not be considered for publication in journals that follow ICMJE standards. Although clinical studies are not required to report results in ClinicalTrials.gov, ICMJE does require researchers to meet all results reporting obligations of their funding and regulatory agencies. Karolinska Institutet **strongly recommends** that all clinical studies registered with KI as the Sponsor (responsible registrant) to report results in the respective clinical trial registry.

6. Clinical trials that require registration in EudraCT

Clinical trials testing investigational medicinal products (IMPs) **must be approved** by the MPA and **must be registered** in EudraCT. The MPA defines a clinical trial as the following[3]:

> *"Any study performed on humans to determine or confirm the clinical, pharmacological or pharmacodynamic effects of one or more investigational medicinal products, to identify adverse reactions to one or more investigational medicinal products or to study the absorption, distribution, metabolism and*

[4] Commission Guideline: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012XC1006(01)&from=EN

[5] Section 801 of FDA ACT 2007: https://ClinicalTrials.gov/ct2/manage-recs/fdaaa#:~:text=Section%20801%20of%20FDAAA%20amended,and%2For%20results%20submission%20requirements

[6] PRS ACT Checklist: https://prsinfo.ClinicalTrials.gov/ACT_Checklist.pdf

excretion of one or more investigational medicinal products, in order to ensure the safety or efficacy of those medicinal products".

Trial drugs can be those that are under development or those that are already approved. MPA approval is required if the clinical trial meets at least one of the four criteria:

1. The trial aims to establish or confirm the therapeutic, diagnostic, or preventive effect of one or more trial drugs.
2. The trial aims to identify or map side effects of one or more trial drugs.
3. The trial aims to establish or confirm the pharmacological or pharmacodynamic effect of one or more investigational medicinal products.
4. The trial aims to investigate the absorption, distribution, metabolism, or elimination (pharmacokinetics) of one or more trial drugs.

If the clinical trial does not meet one of the four criteria, then it is considered a non-interventional study, based on the definition and criteria of the MPA, and thus, does not require MPA approval. Additional criteria for determining if the clinical trial requires approval can be found at the Medical Products Agency website[3]. If the study is determined to **NOT** meet the criteria of a clinical trial, then the study should **NOT** be registered in EudraCT.

7. Clinical studies that require registration according to ICMJE

In order to determine if a study requires registration, the ICMJE has developed an expanded definition of a clinical study adopted from the WHO[7] that can be utilized.

> "*Any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes."*

If a study meets one of these criteria, then it is considered a ***clinical study*** and registration is required. In cases where it is uncertain whether if a clinical study meets the expanded ICMJE definition, researchers should verge on the side of registration if the subsequent goal is to seek publication in an ICMJE journal. It is important to note that the clinical trial registry one chooses to register a clinical study is determined by the study design.

7.1 Studies that can be registered in ClinicalTrials.gov[8]

7.1.1 *Interventional study:* A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or

[7] ICMJE: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/
[8] ClinicalTrials.gov Glossary of Common Terms: https://ClinicalTrials.gov/ct2/about-studies/glossary

health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.

7.1.2 Observational Study: A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific interventions/treatment. A patient registry is a type of observational study.

7.2 Studies that can be registered in EudraCT[9]

7.2.1 Interventional study: Includes only interventional clinical trials testing investigational medicinal products (IMP) conducted in the EU/EEA, or outside the EU/EEA if they are part of an agreed PIP (Pediatric Investigation Plan).

8. Responsibilities of the Sponsor regarding registration

The term "Sponsor" regarding clinical trials is defined by the EU Directive as an individual, company, institution, or an organization, which takes responsibility for the initiation, management and/or financing of a clinical trial[2]. It is illegal to start a clinical trial (IMP trial) without a Sponsor. The Sponsor of a clinical trial is ultimately liable for ensuring ethical and regulatory requirements are adhered to. For clinical trials where KI is the Sponsor, it is KI that assumes responsibility for ensuring the clinical trial is registered, updated, and the results are reported accurately and in a timely fashion. The lead researcher (principal investigator) of the clinical trial is responsible for registering, updating, and reporting results in EudraCT. KI as the Sponsor provides support and monitoring of this task to ensure compliance through CDO.

The term "Sponsor" regarding the 'responsible registrant' for clinical studies (non-IMP clinical trials) in ClinicalTrials.gov refers to the company, institution, or organization responsible for ensuring the clinical study is registered, updated, and results are reported within the allocated timeframe. For clinical studies where KI is the Sponsor (responsible registrant), KI assumes responsibility to ensure researchers comply with the requirements for registering, updating, and reporting results on time. The goal for KI as Sponsor regarding registration and reporting is to increase clinical trial transparency to promote open science. To achieve this goal, registration and results reporting are monitored by CDO and support is provided for researchers to comply with the necessary regulations and requirements.

9. Responsibilities of the research principal regarding registration

For clinical studies where KI is the research principle (non-IMP clinical trials), the lead researcher is responsible for registering the clinical study, maintaining required updates, and reporting results within the allocated timelines stipulated by ClinicalTrials.gov. In cases where there are several research principals for the same clinical study, the collaborating parties must agree in advance upon which organization will assume the responsibility for clinical trial registration and reporting **(responsible registrant)**.

[9] European Medicines Agency (EMA): https://eudract.ema.europa.eu/help/Resources/EudraCT%20FAQ_for%20publication.pdf

When an amendment in the ethical application results in the removal or the inclusion of KI as research principal for a clinical study, the responsibilities regarding registration and reporting of the clinical study should be transferred to the new research principal. For example, if SLL removes KI from the ethical application and becomes the new research principal of the clinical study, then the responsibilities of registration and reporting are transferred to SLL, and the clinical study registration must be transferred from the KI account to the SLL account in ClinicalTrials.gov.

It is important to note that register entries must be complete and accurate. Ensuring register entries are accurate and results are reported must be part of the standard procedure for conducting any clinical study. Moreover, even if the clinical study is published in a peer-reviewed journal, results should still be reported in the clinical trial registry where the study was registered.

10. Preparing to register a new clinical study: choosing the responsible registrant

Prior to registering a new clinical study, it is important to coordinate with all collaborators and other centers, if it is a multicenter or multi-national project, in developing a process for registration and results reporting. This process can start at the planning stages when developing a research proposal for a grant. Many funding agencies, particularly at the European level, allow research proposals to include clinical trial registration and results reporting in the research budget.

10.1 Determining the research principal

It is important to ascertain the research principal of a research project before registering a clinical study. The law (2003:460) concerning the "Ethical Review of Research Involving Humans" defines a research principal as a "state authority or a person or legal person in which research activities are carried out[10]." If there is more than one research principal for the same research project, it is recommended that the clinical study is registered under the name of the institution stipulated in the ethical approval as the "responsible research principal (ansvarig forskningshuvudman) for submitting the ethical application." In cases where KI is not the research principal that is submitting the ethical application, then the parties involved must agree upon who will be the responsible 'Sponsor' for registration and reporting **(responsible registrant)**.

10.2 Contact the Sponsor's PRS Organization in ClinicalTrials.gov

In ClinicalTrials.gov, there is a full list of Sponsors with PRS organizations accounts[11]. Swedish organizations with PRS accounts include, among others, Karolinska Institutet, Region Stockholm (listed as Stockholm County Council), Danderyds Hospital, Stockholm University, and Karolinska University Hospital. Once the full name of the Sponsor on the PRS organization list is identified, researchers must complete a PRS Administrator Contact Request form[12]. Once the request form is submitted, researchers will receive an email from

[10] Law (2003:460): https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2003460-om-etikprovning-av-forskning-som_sfs-2003-460
[11] PRS Organizations: https://ClinicalTrials.gov/ct2/prs-orgs
[12] PRS Administrator Request Form: https://ClinicalTrials.gov/ct2/contact-org-admin

ClinicalTrials.gov that includes contact information for the PRS Administrator at the Sponsor organization. The researcher can then contact that PRS Administrator to create new user accounts and receive information concerning instructions for registration and results reporting. If KI is the Sponsor (responsible registrant), researchers do not have to complete a PRS Administrator Request form. Requests can be sent directly to CDO at compliance@ki.se.

10.3 Informing CDO of new trial/study registrations

KI researchers should inform CDO about their plans to register a new trial/study in EudraCT or ClinicalTrials.gov and provide a copy of the ethical approval/application or other "agreement" to confirm KI is the responsible registrant. This "agreement" can be formalized in the study protocol, application to EPM, MPA, etc. This information can be sent via email to CDO at compliance@ki.se. This process is important for CDO to monitor new trial/study registrations and provide support for registering, updating, and reporting results.

11. Registering a new user account

There are different procedures for registering a new user account for ClinicalTrials.gov and EudraCT. For ClinicalTrials.gov, new user accounts are created through the PRS Administrator at CDO. The researcher must contact CDO and make an official request to open a new user account. Requests can be made via email to compliance@ki.se. Researchers will need to provide the following information in their request email: Full name, email address and telephone number for the researcher requesting a new user account. Regarding EudraCT, new user accounts are registered directly through the EudraCT website. Technical instructions for registering a new user account in both clinical trial registries are available in the Appendix.

12. Registering a new trial/study

The WHO recommends that clinical trials and clinical studies should only be registered once and in only one clinical trial registry. Registering the same study in multiple clinical trial registries must be avoided unless there are specific requirements stipulated by the Sponsor or funding agency.

There are different procedures and requirements for registering a trial/study in ClinicalTrials.gov and EudraCT. Regarding clinical trials for EudraCT, it is important to underscore that IMP clinical trials conducted in Sweden must be approved by the MPA[3] and Swedish Ethical Review Authority[13,14]. This process begins by obtaining a unique EudraCT number and registering the clinical trial on EudraCT. In ClinicalTrials.gov, both interventional and non-interventional clinical studies can be registered prior to Ethics Review Board approval if study participants have not been recruited yet. However, ethical approval must be obtained before participant recruitment begins.

12.1 Requirements for registering a new clinical study in ClinicalTrials.gov

When registering a new clinical study in ClinicalTrials.gov, there are specific requirements that must be underscored. When the researcher starts a 'New

[13] Laws and Regulations: https://www.kliniskastudier.se/english/for-researchers/laws-regulations.html
[14] Swedish Ethical Review Authority: https://etikprovningsmyndigheten.se/

Record' for study registration, a protocol template form will generate. In the protocol registration, there are required fields that must be completed. The following fields (*Record Owner, Unique Protocol ID, Sponsor* and *Responsible Party*) must be completed in accordance with KI instructions. The '*Record Owner*' can be the lead researcher (referred to as principal investigator [PI] in ClinicalTrials.gov), or a researcher assigned by the lead researcher (PI). If the record owner is not the lead researcher (PI), then the lead researcher (PI) must be added to the access list in order to approve and release the study registration to NIH for review. The '*Unique Protocol ID'* can either be a grant number received for the study protocol by the funding agency, the Dnr number from the ethical approval, or the acronym of the study (if the other two identification numbers are unavailable). The '*Sponsor*' must be Karolinska Institutet. The '*Responsible Party*' must be the lead researcher (PI). Technical instructions for completing a clinical study registration are stipulated in the Appendix.

12.2 Requirements for registering a new clinical trial in EudraCT

The process of applying and registering a clinical trial should be completed before submitting an application to any of the Member State in which the clinical trial will be conducted. The MPA requires that IMP clinical trials be approved and registered in EudraCT. To register a new clinical trial in EudraCT, the process begins by obtaining a unique EudraCT number. The EudraCT number is created in the EudraCT database where all clinical trials conducted in the EU/EEA region are registered. PIP clinical trials conducted outside of the EU/EEA are also registered in the EudraCT database. The application for a EudraCT number[15] can be accessed from the EudraCT Community Clinical Trial System[16]. To obtain the EudraCT number automatically from the database, the applicant will need to provide a few items of information. A EudraCT number will only be issued once by the system. If a number is issued, but the clinical trial does not proceed, that number is not available for reuse. The EudraCT number is issued via email within 24 hours.

Once an EudraCT number has been obtained for the clinical trial, then researchers must complete the *Clinical Trial Application*. This number identifies the protocol for a trial, whether conducted at a single site or at multiple sites, in one or more Member States. In the Clinical Trial Application (CTA), applicants must complete the required sections and include the unique EudraCT number, the name of NCA (National Competent Authority), which is the Swedish Medical Products Agency, and have access to the EudraCT public or secure application. In the application, it is important to state all Investigational Medicinal Products (IMPs) to be used in the clinical trial, and all participating investigators and trial sites in Sweden. When the mandatory fields in the Clinical Trial Application form have been completed, save the form as an xml-file, and thereafter, as a pdf-file. A "package" will be created containing an xml-file, a pdf-file, and a validation report. The application

[15] EudraCT number application: https://eudract.ema.europa.eu/help/Default.htm#eudract/create_eudract_no.htm
[16] EudraCT access: https://eudract.ema.europa.eu/results-web/

including attachments can be sent to the MPA in Swedish or English and the Swedish Ethical Review Authority. The MPA recommends applications to be sent via Eudralink. Researchers will need an account to access Eudralink, which is accessible at EMA Account Management[17]. Applications can also be submitted via email to: registrator@lakemedelsverket.se. In the email subject field, include "*EudraCT number: Clinical Trial Application*." After the CTA is approved by the MPA and Swedish Ethical Review Authority, the trial will be published on EudraCT as a registered clinical trial. Technical instructions for completing a clinical trial registration are stipulated in the Appendix.

13. Reporting results

Researchers have ethical and legal obligations to report results for both clinical trials and clinical studies. The paramount goal is to ensure summary results are reported timely and accurately in clinical trial registries. With the rise of clinical trial transparency within open science, KI has implemented significant measures to ensure trial/study registrations and results are up-to-date and accurate. CDO provides support for researchers to report their results in both ClinicalTrials.gov and EudraCT.

13.1 Reporting results in ClinicalTrials.gov

The process of submitting results information to ClinicalTrials.gov is conceptually similar to preparing a manuscript for publication in a journal. An individual familiar with the study design and data analysis (e.g., the lead researcher (PI), researcher, or statistician) will need to be involved to accurately summarize the results information in the tabular format required by US law, and to ensure that the results are consistent with the ClinicalTrials.gov review criteria. Scientific information is submitted as four separate modules, including:

1. **Participant Flow:** demonstrates how participants were assigned to the arms or groups of a study and how they progressed through the stages of the study.
2. **Baseline Characteristics:** includes demographics and study-specific measures.
3. **Outcome Measures and Statistical Analyses:** summarizes results data, by arm or comparison group, for each primary and secondary outcome measure assessed in the study.
4. **Adverse Events:** includes three tables summarizing anticipated and unanticipated adverse events.

In the outcome measures and statistical analysis module, studies where data was not collected for all pre-specified *Primary* and *Secondary Outcome Measures* registered in the protocol, describe why data could not be summarized in the data table (e.g., specify zero "0" for the *Number of Participants Analyzed* in each Arm/Group, leave the data fields blank, and provide an explanation in the *Analysis Population Description* for why zero participants were analyzed). In the adverse events module, studies that did not assess or collect adverse events can specify "0"

[17] EMA Account Management: https://register.ema.europa.eu/identityiq/home.html

for the *Number of Participants Affected* and *Number of Participants at Risk* and explain in the *Additional Description* field that adverse events were not collected. All stipulated modules allow for the entry and display of information in a series of data tables with supporting notes, however, narrative conclusions about the results are not required. Once summary results are completed, the lead researcher (PI) must approve and release the study for NIH review. The review can take up to 30-60 days before the study results are approved and made public on the ClinicalTrials.gov database. A full tutorial on reporting results in ClinicalTrials.gov can be accessed on their PRS Guided Tutorials[18].

It is important to note that adding a link of the publication from PubMed does not fulfill the requirements of summary results reporting in ClincalTrials.gov. It is difficult to estimate the time it will take to report the results of a clinical study on ClinicalTrials.gov, as this can vary according to the size and complexity of the study. However, it is estimated that summary results reporting can take from 30 minutes to 2 hours to complete.

13.2 Reporting results in EudraCT

In EudraCT, summary results can be submitted for clinical trials that ended on or before 21 July 2013. For summary results, researchers can upload an abstract, if the clinical trial has been published in a peer-reviewed journal, and a link to the study. Clinical trials completed after the above-mentioned date must complete the full dataset form. The full dataset form includes the following six modules:

1. **Trial Information**: Includes information regarding general information about the trial, Sponsorship, regulatory details, and trial subjects.
2. **Subject Disposition:** Includes the recruitment process of subjects and description of intervention arms.
3. **Baseline Characteristics:** Includes demographic information of study subjects.
4. **End Points:** Includes a description of outcome measures and results.
5. **Adverse Events:** Includes information for adverse events, serious adverse events, and non-serious adverse events.
6. **Additional Information:** Includes information regarding protocol amendments, study limitations, and caveats.

In order to report results in EudraCT, researchers must first create an account and register as a 'results user'. A results form template is generated by the EudraCT system and will be displayed in the secure area after logging in with the secure account. The form will have fixed fields with information from the trial protocol and the six modules mentioned above. This is the full dataset form where results are reported. All fields with asterisk must be completed. Once the full dataset form is completed, researchers have the option to upload their full anonymized database to share their data, however, this is not obligatory. Anonymized

[18] PRS Guided Tutorials: https://prsinfo.ClinicalTrials.gov/tutorial/content4/index.html#/

databases can be uploaded in an xml-file. Once all fields are completed, press the 'post results' button at the top of the page. The results will be processed, and upon approval, EudraCT will post the results to their database. **It is very important to inform the Medical Products Agency (MPA) that the clinical trial has been completed. Otherwise, the clinical trial will incorrectly have the status 'ongoing', when in fact it is 'completed'.** Detailed instructions for reporting results in EudraCT can be accessed on the "*Tutorials on posting results in EudraCT*" page[19].

14. Timeline requirements for registration, updating and reporting results

14.1 Registration

The ICMJE recommends that all medical journal editors require registration of all clinical studies in a public clinical trial registry at or before the time of the first participant enrollment as a condition of consideration for publication. In ClinicalTrials.gov, clinical studies can be registered prior to ethical approval, if no participants have been recruited yet. Ethical approval is required prior to recruitment. FDAAA 801 requires 'applicable clinical trials' to be registered no later than 21 days of enrollment of the first participant. EudraCT requires IMP clinical trials to be registered prior to patient recruitment, and the study must have approval from the MPA and Swedish Ethical Review Authority before the registration can be published on EudraCT.

14.2 Updating

Clinical study registration information submitted to ClinicalTrials.gov must be updated at least once every 12 months. Researchers are required to update the clinical study registration within 30 days of any changes to the protocol, e.g., changes to individual site status or overall recruitment status. When updating a clinical study in ClinicalTrials.gov, the Record Verification Date must always be updated to the month and year the update was performed. It is recommended that the Record Verification Date is updated at least every 6 months for clinical studies not completed. In EudraCT, any changes to the clinical trial must be reported and updated within 30 days.

14.3 Reporting results

In ClinicalTrials.gov, results must be reported within 12 months of the Primary Outcome Completion date. In EudraCT, results for non-pediatric clinical trials must be reported within 12 months after completion of the trial. Pediatric clinical trial results must be reported within 6 months after the completion of the trial.

[19] Tutorials for posting results on EudraCT: https://eudract.ema.europa.eu/multimedia_tutorials.html

15. Appendix

15.1 Technical instructions for creating new user account in ClinicalTrials.gov

- Researchers can request a new user account by sending an email to CDO (compliance@ki.se). The following information should be included in the email:
    - The Full Name of the researcher.
    - Email address of researcher.
    - Telephone number of researcher.
- CDO will create a new user account in ClinicalTrials.gov.
- The system will automatically create a new user ID (first initial and last name).
- The researcher will receive an email from ClinicalTrials.gov confirming that they have been registered for a user account.
- The email will include instructions for creating a password and log in information.
- Once completed, the researcher can log in using these credentials.
- The "organization" used for logging in is "KarolinskaI".

15.2 Technical instructions for creating new user account in EudraCT

- Select "Register" at the main log in homepage.
- Select "Create a new EMA account".
- Fill in the fields with red asterisk as these are mandatory and must be entered.
- Once all mandatory information has been entered, review the data protection statement, and select "Register".
- Use the 'drop menu' to select 3 security questions and enter your answers.
- Answer the "Capcha question" and select "Next".
- The researcher will receive an email with a "One Time Token".
- Enter the "One Time Token" in the field and select "Confirm".
- The researcher will then receive an email with registration and log in information.
- The system will automatically create a new user ID (Last name and first initial).
- Use the credentials to log into EudraCT.
- The user can manage the account by selecting on "Manage Account".

15.3 Technical instructions for registering a new clinical study in ClinicalTrials.gov

- A copy of the ethical approval/application or other agreement confirming KI is the responsible registrant for the clinical study should be sent to CDO prior to registration. Copies should be sent to compliance@ki.se.
- Once CDO confirms KI is the responsible registrant, researchers will receive a confirmation email and can then begin registering their study.
- Log into ClinicalTrials.gov using "KarolinskaI" as the organization.
- Select on 'New Record' in the Quick Links on the left side of the page.
- A protocol registration form will generate.
- Complete the necessary fields and select 'Entry Complete' (the green button at the top left under the 'Record Summary' page).
- The lead researcher (PI) must then log in and review the study.
- Once reviewed, the lead researcher (PI) must select 'Approve' (same green button as in the step above).
- The lead researcher (PI) must then select 'Release' (green button).
- The protocol registration will be sent to NIH for review.
- NIH takes 2-5 business days to approve a study registration.
- The clinical study will then receive an NCT ID number from ClinicalTrials.gov.
- If NIH has comments on the protocol registration, the lead researcher (PI) must log in and correct it, and then complete the steps 'Entry Complete', 'Approve' and 'Release' again.

15.4 Technical instructions for registering a new clinical trial in EudraCT

- A copy of the ethical approval/application or other agreement confirming KI is the Sponsor for the clinical trial should be sent to CDO prior to registration. Copies should be sent to compliance@ki.se.
- From the log in page, select EudraCT number.
- Complete all required fields and select 'Get EudraCT number'.
- The EudraCT number will be generated on the page and sent via email.
- A 'Clinical Trial Application' must be completed.
- Select 'Create' and then 'Clinical Trial Protocol'.
- Select 'EEA CTA'.
- A protocol registration will generate.
- Complete all required fields.
- Select 'Create'.
- Review information and select 'Validate'.
- Save the CTA as xml-file and then pdf-file.
- Complete a Submission Package.
- Select 'Package'.
- Create Submission Package for MPA.
- Select 'Save'.
- Create Submission Package for Swedish Ethical Review Authority.
- Select 'Save'.
- Submit CTA package to MPA via Eudralink or email.