Clinical trial regulation in Europe

Legal reporting requirements and regulatory strategies in seven key countries

Amsterdam, 26 September 2022

> *"We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner… full transparency on results advances both scientific understanding and timelines for product development and ultimately enables access to essential medicines."*
>
> Dr Tedros Adhanom Ghebreyesus, World Health Organisation

> *"Lack of transparency in clinical trials harms patients. The timely posting of summary results is an ethical and scientific obligation."*
>
> Transparency International and Cochrane

> *"Legislation or supporting regulations [should include] sanctions if a clinical trial is not registered and/or results are not reported."*
>
> WHO Transparency and Accountability Assessment Tool

Report author: Till Bruckner, TranspariMED

EXECUTIVE SUMMARY

Clinical trial transparency benefits patients and taxpayers. This report provides an overview of national clinical trial reporting rules and their implementation across seven European countries.

Key findings – drug trials

- National medicines regulators in seven major European Union countries now have ***legal powers to impose fines of up to EUR 250,000*** on clinical trial sponsors that fail to make the results of drug trials public as required by law. These powers only apply to drug trials launched after January 2022.

- Regulators expect that ***monitoring data*** from the new European CTIS trial registry will enable them to detect and follow up on future violations. However, in practice, the process of ***imposing fines*** is likely to consume considerable regulatory resources.

- Regulators in six countries – ***Austria, Belgium, Denmark, Finland, Germany, and the Netherlands – are actively prompting trial sponsors*** to make the results of their past drug trials public. Their efforts have been remarkably successful.

- Regulators in four countries – ***France, Italy, Spain and Sweden*** – appear to be taking little or no action on missing drug trial results. This threatens to ***undermine European efforts*** to secure the 3,055 drug trial results that are still missing.

Key findings – other trials

- ***Medical device trials.*** It is still unclear whether and how monitoring data from the new EUDAMED database will support national regulators' efforts to ensure that medical device trial results are rapidly reported as required by law.

- ***Other trials.*** There are currently no legal requirements to make the results of other clinical trials public. This regulatory vacuum is perpetuating costly medical research waste.

Policy recommendations

- ***Pre-2022 drug trials.*** National medicines regulators in France, Italy, Spain and Sweden should emulate successful approaches pioneered elsewhere and directly contact trial sponsors to ensure that missing trial results are made public on EudraCT before they are lost forever.

- ***Post-2022 drug trials.*** National medicines regulators in all EU Member States should aim to build a culture of compliance with CTR legal reporting requirements from the very beginning. Specifically, they should develop action plans for how they will respond if and when the first drug trial result within their jurisdiction becomes overdue.

- ***Medical device trials.*** The European Commission and national regulators should jointly define what EUDAMED monitoring data is required to enable national regulators to rapidly detect and respond to instances in which MDR legal reporting requirements are violated.

- ***Other trials.*** National medicines regulators and civil society groups should engage with policy makers at the national level to develop safeguards that ensure that all interventional clinical trials rapidly make their results public. See Annex 1 for a useful model.

ABOUT THIS REPORT

Report aim

This report aims to contribute to improving public health and curbing medical research waste by providing an ***overview of national clinical trial reporting rules and their implementation*** across major European countries.

Report scope and structure

This report provides an overview of legal frameworks and regulatory practices based on information provided by national medicines regulators in **seven major *European Union countries*** with a high level of clinical trial activity: Austria, Belgium, Denmark, Finland, Germany, the Netherlands, and Sweden.

> *Annex 1* of this report provides an overview of the UK model for getting all clinical trials reported.
> *Annex 2* provides details on legal frameworks and regulatory strategies in each of the 7 countries.

Why this matters

A vast body of research shows that many clinical trial results are never made public, or are only made public after a delay of several years. This harms patients, undermines public health, slows down medical progress, and wastes public money.

During the first half of 2022, the legal landscape for clinical trials in the European Union was transformed as two separate European regulations became fully applicable and therefore legally binding in all EU Member States:

- ***Clinical Trial Regulation (CTR)***
- ***Medical Devices Regulation (MDR)***

Each of these regulations introduced new transparency provisions. In the case of the CTR, the requirement to make drug trial results public within 12 months of trial completion – which had already been a requirement since 2014 – became legally binding and therefore enforceable through sanctions, though only for trials launched after January 2022. Meanwhile, the MDR for the first time introduced a wide range of transparency provisions for many new medical device trials.

Responsibility for enforcing these new regulations lies with national regulators within each EU Member State. In other words, the actions of national regulators will largely determine whether the new transparency rules on paper are effectively translated into better clinical trial reporting in practice. The new transparency rules have strong potential to benefit patients, but these benefits will only become reality if national regulators take effective action.

Report methodology

The press offices of eleven national medicines regulators in ten European Union countries with a high volume of trial activity were contacted in May 2022 with a list of detailed questions. Eight out of eleven regulators contacted (Germany has two relevant regulatory agencies) responded substantively to our outreach. This report is not externally funded. We thank all national medicines agencies that responded for the highly detailed information that they provided.

The original questions and the full responses of all responding regulators are included in Annex 2.

KEY FINDINGS

National legislation on drug trials

In all EU Member States, the results of future investigative drug trials ('CTIMPs') must by law be made public within 12 months of trial completion. ***The seven countries covered by this report now have relevant legal frameworks in place.*** Potential fines for violating reporting requirements vary widely between countries, as the table below shows. Regulators in Denmark and Finland indicated that the level of fines will be determined by future court cases.

Table 1: Fines for failing to report the results of drug trials

Country	Fines
Austria	EUR 25,000-50,000
Belgium	EUR 500-250,000
Denmark	To be determined
Finland	To be determined
Germany	EUR 25,000 maximum
Netherlands	EUR 33,500[1]
Sweden	To be determined

Safeguarding the quality of data on drug trials

In the past, many drug trials did not have accurate completion dates on the European trial registry, making it impossible to determine whether their results were due or not. Four regulators (Austria, Belgium, Denmark, and Finland) reported ***efforts to fix the problem***, including central data reviews and direct outreach to trial sponsors.

> *"In total, 337 clinical trials in Belgium have been identified for which the global trial end date has been indicated but not entered. This list was compared to the global trial end dates entered by other Member States for those 337 clinical trials. We are currently in the process of making the necessary adjustments (currently implemented for 25 clinical trials). We also note that a small number of sponsors verify themselves whether the end dates have been entered correctly, because we are sometimes contacted to enter additional data on completed clinical trials in EudraCT."*
> – FAMPH, Belgium

In Germany, the larger regulator (BfArM) did not provide relevant information, but registry records show that trials regulated by BfArM are largely up to date. Meanwhile, the second German regulator (Paul-Ehrlich-Institut) reported that completion dates for all drug trials within its remit are already accurate. The Dutch regulator did not provide relevant information.

[1] "In the Netherlands, it is the Health Inspectorate who can act if a sponsor/investigator does not follow up regulatory requirements. For infringement of article 37 it possible to have an imposition of an order subject to periodic penalty payments. The amount of the penalty must be in reasonable proportion to the gravity of the allegedly infringed interests. The law does not state a maximum. Apart from that, our national law (also article 33) also regulates that our Minister can impose an administrative fine with a maximum of 33.500 Euro to enforce article 37 of CTR." – CCMO, Netherlands

Detecting missing drug trial results

In the past, national medicines regulators did not have monitoring data identifying overdue drug trials within their jurisdictions, limiting their ability to follow up on missing trial results. In recent years, the ***European Medicines Agency*** has started producing relevant datasets for national regulators, allowing them to take action.

> *"Based on the list received from the EMA on 2 May 2022, we contacted the sponsors who should have reported their results on EudraCT by now."*
> *– FAMPH, Belgium*

National regulators reported that in future, they intend to ***use monitoring data from the new European drug trial registry*** (CTIS) to identify violations, in some cases supplemented by national monitoring efforts (Denmark) or GCP inspections (Austria, Belgium, Finland and Germany). However, there appears to be continued uncertainty about what monitoring data CTIS will provide.

> *"Since the EU Clinical Trials Regulation has only been applicable since 31.01.2022 and so far very few (<5) clinical trial applications have been approved in Germany on this basis, the first results reports are not expected before the middle of next year. Therefore, the Paul-Ehrlich-Institut has not yet defined any procedures for the process [of detecting violations] but would first like to gain experience in this regard. At the moment, it is intended to use CTIS data and - if available - data from GCP inspections."*
> *– Paul-Ehrlich-Institut, Germany*

> *"The Swedish MPA foresees to use CTIS data to detect such infringements, as well as GCP inspections. The step-by-step details of the process have not yet been worked out, as the number of authorized trials in CTIS is still very limited and the relevant tools are not yet fully developed."*
> *– LMV, Sweden*

Supporting compliance for pre-2022 drug trials

The European Union first required trial sponsors to make drug trial results public in 2014, but this guidance was not effectively communicated to sponsors, and national regulators failed to follow up with sponsors that violated the rules. As a consequence, many sponsors (especially universities and hospitals) remained ignorant of the rules and were unaware of their growing backlogs of unreported trials. By early 2018, less than half (49.5%) of due trials had reported their results as required.

Since then, the European Medicines Agency has started emailing individual investigators whose results are overdue, and many national regulators have additionally begun following up with sponsors (both commercial and non-commercial) that are in violation of the rules. Even in the absence of legal powers to fine trial sponsors, this ***regulatory engagement has been remarkably successful***. As of July 2022, across Europe, 83.6% of due trials have reported results.

Six of the seven regulators who responded to outreach reported directly contacting sponsors of clinical trials whose results are overdue, using data provided by the European Medicines Agency.

> *"[R]esults have been published for 258 clinical trials that were part of last year's list of 577 clinical trials [after the responsible sponsors had been contacted]."*
> *– FAMPH, Belgium*

*"The **CCMO has hired personnel to contact sponsors and investigators** of clinical trials for which no summary of results has been uploaded in EudraCT result database. The European Medicine Agency send us, on a regular basis, an overview of these clinical trials in EudraCT… CCMO is now actively follow up on missing results one year after the end of the clinical trial worldwide."*
– CCMO, Netherlands

"Based on the most recent evaluation from EMA, a final round of contacting sponsors before February 2023 will be planned. Trials for which sponsors cannot be reached then will be marked as 'lost-to-follow-up'."
– BASG, Austria

"[A]s part of the clinical trial application assessment… we ensure sponsors acknowledgement of the required publication policy. Furthermore, we have updated our website and issued press releases to enhance awareness. This have been greatly supported by the public GCP-units (used for GCP monitoring of non-commercial trials) who also released guidance, assisted sponsors technically and boosted the outreach to non-commercial sponsors.
We continuously monitor the required publication of trial results and we reach out to all relevant contact points if publications are lacking and overdue.
Our focus on dialogue with the trial sponsors have been very successful… Approximately 300 trials from year 2017 and onwards had not published trial results, when we intensified our dialogue with the trial sponsors. Now, trial results from around 230 trials have been published and our dialogue and efforts continue for the remainders."
– DKMA, Denmark

"In the past, each time such a list was received [from the EMA]; the Paul-Ehrlich-Institut wrote to all individual sponsors under the responsibility of the Paul-Ehrlich-Institut and insisted on remedial action."
– Paul-Ehrlich-Institut, Germany

Among respondents, only the Swedish regulator had not directly contacted sponsors:

*"**No steps have been taken to contact all sponsors.** Individual sponsors have been approached in relation to GCP inspections. For sponsors who contact the agency with questions related to reporting, individual guidance is provided.*
[Regarding the future:] Subject to resource availability and priorities activities may be initiated to contact sponsors who have clinical trials with unreported results. Assessment of submitted applications will however have a higher priority due to strict legal timelines for the agency to perform those tasks."
– LMV, Sweden

Mechanisms for sanctioning sponsors for unreported post-2022 drug trials

Ideally, national medicines regulators should be able to impose fines rapidly, routinely and efficiently, much like issuing speeding tickets for car drivers. However, regulators report that due to legal constraints, ***the process of sanctioning trial sponsors will likely be complex and time consuming***. This in turn makes it less likely that regulators will impose fines in practice.

While regulators in five countries (Belgium, Finland, Germany, the Netherlands, and Sweden) will be able to impose fines without having to go through the courts, even those regulators will typically have to engage a lengthy process before a fine is actually imposed.

"In practice, if a violation is found for clinical trials… a determination will be made by a good clinical practice (GCP) inspector from the FAMHP, who may then prepare an official report of determinations. This official report, together with the inspection report, will be transmitted to the violator and the FAMHP's official solicitor (the head of the Legislation and Litigation Division). The official solicitor can then, in consultation with the inspection, propose an amicable settlement to the offender (for a minimum amount of 4,000 euros, which is the minimum amount of the fine multiplied by the applicable surcharges). If the offender does not accept the out-of-court settlement, the Public Prosecutor may initiate further proceedings."
– FAMPH, Belgium

"In principle, sponsors must first be heard on the facts of each case before an administrative offence can be imposed. At present, it is planned that the sponsors will be given the opportunity to submit a reasonable extension of time with the hearing letter. If this deadline is not met, BfArM will impose a fine directly, against which, however, each sponsor can file an appeal. If the appeal meets the formal requirements and the BfArM does not want to withdraw the penalty notice, the proceedings must be taken over by the public prosecutor's office... The public prosecutor shall submit the case to the court if he neither terminates the proceedings nor conducts further investigations."
– BfArM, Germany

"If a breach of the publication obligation becomes known, the Paul-Ehrlich-Institut will first contact the sponsor and set a deadline for catching up. If the deadline expires without result, a decision will be made on whether to initiate fine proceedings… This is followed by a hearing… to give the person concerned the opportunity to comment on the accusation. After that, a decision on the imposition of a fine is made by administrative act. The person concerned can appeal against the penalty notice within two weeks. If the appeal meets the formal requirements and the Paul-Ehrlich-Institut does not want to withdraw the penalty notice, the proceedings are handed over to the public prosecutor's office."
– Paul-Ehrlich-Institut, Germany

"The initial step is to approach the sponsor with a request to report the missing data within a given timeframe. If the desired result is not achieved, the agency issues an injunction accompanied by a fine. It is then the court that, at the request of the MPA, imposes the fine."
– LMV, Sweden

The barriers to effective enforcement are even higher in Denmark, where the regulator will have to go through the courts in each and every case before a sponsor can be fined.

"[W]e now have a robust procedure with routine checks if trial results have been published and we will continue the dialogue with the trial sponsors. So far it hasn't been necessary to hand over any cases to the police, but we will do so, if we have to."
– DKMA, Denmark

Regulatory inaction on drug trials in France, Italy, and Spain?

Three major regulators did not respond to repeated requests for information: ANSM/France, AIFA/Italy, and AEMPS/Spain. Registry data show continued weak reporting performance by many sponsors in these countries, and widespread data quality problems.

Across Europe, 12 out of 15 large trial sponsors with very weak reporting records are now concentrated in just two countries: Italy (AIFA) and France (ANSM). These regulators are failing to ensure that sponsors within their jurisdictions upload their share of the remaining ***3,055 drug trial results that are still verifiably missing*** ***across Europe***.

Table 2: Large European trial sponsors with weak trial reporting records

Sponsor	Regulator	Trials total	Due trials with results
Agostino Gemelli	AIFA	193	1
IRCCS Universitaria Di Bologna	AIFA	135	1
Istituto Nazionale Dei Tumori	AIFA	104	1
Fundació Clínic Per A La Recerca Biomèdica	AEMPS	82	2
CHU de Toulouse	ANSM	77	0
Istituto Europeo Di Oncologia	AIFA	70	0
Citta Della Salute Di Torino	AIFA	65	0
CHU Clermont-Ferrand	ANSM	63	0
CHU de Bordeaux	ANSM	59	2
HOVON Foundation	CCMO	58	0
Policlinico San Matteo	AIFA	58	0
AOU Pisana	AIFA	56	0
Fondazione Giovanni Pascale	AIFA	56	0
AOU Policlinico Di Modena	AIFA	53	1
University of Antwerp	FAMPH	50	2

Source: EU Trials Tracker, accessed July 2022. Results counted as per Tracker methodology.

Medical device trials

In all EU Member States, the Medical Device Regulation requires the results of some medical device trials to be made public. Relevant legal frameworks appear to be in place in all countries covered by this report. However, because the European EUDAMED medical device database is still not fully functional, it appears to be ***unclear whether and how national regulators will be able to detect future violations*** of these reporting requirements.

> *"Since EUDAMED is not fully functional yet, infringements will have to be detected based on reports generated from our national database. Such reports can be supplemented with findings from GCP inspections."*
> *– BASG, Austria*

> *"Until Eudamed is fully functional the sponsor shall send the clinical investigation report to the Danish Medicines Agency… If sponsor does not comply with the obligation… the sponsor can be fined… If the sponsor does not comply with the obligation to upload the result in Eudamed after Eudamed is fully functional, the sponsor can be fined or in certain circumstances be punished with imprisonment."*
> *– DKMA, Denmark*

> *"For MDR and IVDR it will be possible to detect missing reports via EUDAMED once it is fully functional. Until then, results reporting is tracked manually at the Swedish MPA."*
> *– LMV, Sweden*

Other clinical trials

The WHO recommends that the results of all interventional clinical trials should be made public on a trial registry within 12 months of trial completion. Existing European Union disclosure rules fail to meet this WHO benchmark because they are limited to (many but not all) clinical trials of drugs and medical devices. In terms of reporting requirements, trials of psychosocial interventions, physiotherapy and surgical techniques (as well as drug and device trials not covered by the CTR and MDR, respectively) continue to operate in a ***regulatory vacuum at the European level***.

Lawmakers within individual European countries appear to have failed to address this gap at the national level. According to information provided by national medicines regulators, existing national legislation in Austria, Belgium, Denmark, Finland, Germany, the Netherlands and Sweden does not require sponsors to make the results of such trials public. Typically, medicines regulators are not responsible for overseeing such trials.

> *"Studies beside interventional clinical trials with medicinal products and… investigations on medical devices is not the DKMAs area of responsibility why we refer to the Research Ethics Committees."*
> *– DKMA, Denmark*

> *"BfArM is only responsible for clinical trials of medicinal products and medical devices. All other clinical studies such as clinical non-drug studies do not fall under the responsibility of BfArM."*
> *– BfArM, Germany*

> *"For interventional clinical studies that are not regulated by the CTR, MDR nor the IVDR, the publication of results could be considered to be required in order to be compliant with article 36 of the Declaration of Helsinki, but this declaration per se is not legally binding. It should be noted that surveillance of such studies are not within the mandate of the Swedish MPA."*
> *– LMV, Sweden*

Existing evidence suggests that these national regulatory gaps are causing widespread research waste. For example, a comprehensive 2021 study found that nearly a third of trials in a cohort largely consisting of non-drug trials run by German universities – many of them publicly funded – had never made their results public. Only 43% of these trials had made their results public within 24 months of completion, a far cry from the WHO benchmark of publishing 100% of results within 12 months.

Addressing these gaps will require national parliaments to adopt new legislation. A new law currently being developed in the United Kingdom, which is supported by a comprehensive monitoring mechanism, provides a strong model that policy makers in other countries could emulate.
See Annex 1 on the following page for more details.

ANNEX 1: THE UK NATIONAL CLINICAL TRIAL TRANSPARENCY SYSTEM

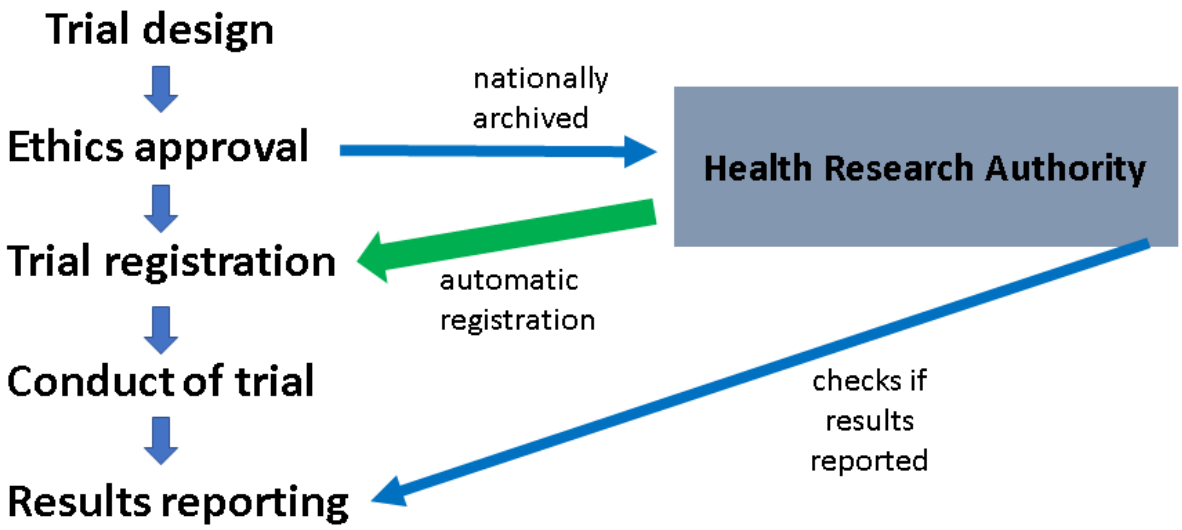
This annex provides an overview of the UK's innovative national trial transparency system. The system will ensure that in future all clinical trials conducted in the UK (drug trials, device trials, and all other interventional trials) are pre-registered and make their results public.

Fixing clinical trial registration

Ethics committees (around 60 countrywide) send the protocols of all studies that they approve to the Health Research Authority in London. Staff at the Health Research Authority (HRA) then ***directly register*** every clinical trial on the ISRCTN registry. After the trial has been registered, the principal investigator of the trial takes over registry management, and is responsible for keeping the registry entry updated and uploading the results.

Fixing clinical trial reporting

Because it directly registers all trials run in the country, the HRA has a comprehensive overview of all clinical research. One year after a trial has been completed, the HRA ***checks on the registry*** to see whether the results have been uploaded there. If not, it sends a reminder to the principal investigator. The HRA also publishes annual trial audits with line-by-line data that shows who has made their trial results public on time, and who has not.



Enforcing the rules

In 2023, the UK will probably adopt a national law requiring ***every*** interventional clinical trial result to be made public (probably within 12 months on a trial registry as recommended by the World Health Organization). It appears likely that ***trial sponsors***, and not individual investigators, will be the party legally responsible for ensuring that results are uploaded. The law will be enforced by the national medicines regulator MHRA. Because the regulator has access to HRA trial audit data (see above), it can easily identify all violations. In practice, the medicines regulator is very likely to effectively enforce the law.

How did this happen?

In 2018, UK parliament's Science and Technology Committee launched an ***enquiry*** into clinical trial transparency. After many heated debates, the Committee published a report recommending that the Health Research Authority (HRA) develop a ***national transparency strategy***.

The HRA set up and led a committee to develop the strategy. The committee included civil servants, industry, academia, transparency groups, and patient representatives. In parallel, the HRA launched a consultation process. After discussion with all stakeholders, the HRA adopted the model outlined above. See here for the strategy.

Throughout this process, a ***coalition of health groups*** including TranspariMED, Cochrane, UAEM and Transparency International kept up the pressure for reform. Discover how they did this here.

Making transparency easy

The motto of the national #MakeItPublic strategy is "make transparency easy, make transparency the norm". The focus is on ***supporting researchers and sponsors***, not on punishing them. The new approach creates a clinical trial workflow that is more streamlined and less bureaucratic than before. There is an ongoing process of integrating the systems of the various players and aligning their transparency requirements. In future, legislation, ethics committees, public research funders, and the ISRCTN registry will all have exactly the same transparency rules. Researchers and trial sponsors benefit from clear and simple rules and workflows, faster study approval, and less paperwork.

Key advantages

- All interventional trials involving UK patients covered
- 100% of trials registered
- 100% of trial results made public
- Faster sharing of results (probably within 12 months via the ISRCTN trial registry)
- Less bureaucracy for researchers and trial sponsors

Supporting measures

The two major public research funders (NIHR and MRC) already actively monitor the registration and reporting of all trials that they fund. The ISRCTN registry already sends out regular emails to remind researchers to update registry data and upload results. All stakeholders are continuously taking steps to improve transparency.

Cost and value for money

The exact cost of developing and implementing the strategy is unclear because it involves work by multiple players. However, the total cost to all players combined is certainly ***less than one million Euros***, a marginal amount compared to the immense costs of medical reseach waste.

ANNEX 2: FULL RESPONSES FROM NATIONAL REGULATORS

This annex reproduces the full responses received from eight regulators across seven major European countries:

- **Austria**
- **Belgium**
- **Denmark**
- **Finland**
- **Germany (two regulators: BfArM and PEI)**
- **Netherlands**
- **Sweden**

Their responses contain detailed information on national laws requiring clinical trial results to be made public within each country, and on regulators' monitoring and enforcement mechanisms.

Responses from three major European regulators could not be included in this annex because they did not respond to repeated requests for information:

- ANSM/France
- AIFA/Italy
- AEMPS/Spain

Austria (BASG)

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

Last report from EMA received on 02.05.2022.
(a) 5
(b) 146
151 in total (103 before 2014)

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

There is a yearly review of our database for ongoing trials that, according to the information entered in EudraCT, should be completed.
Trials that are overdue with the End-of-Trial Notification are notified.
Confirmed by the EMA report above there are no trials under the remit of the BASG that are missing a completion date.

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

Since the combined information campaign by Commission, EMA and NCAs in 2019 the main initiative lies with EMA. EMA sent reminders to the CT contact points at the beginning of May, with a deadline on June 10th. They are also tackling uncompliant sponsors using other email addresses stored in other EMA databases.
Therefore no new steps have been taken on the national level due to priorisation of ongoing trials during the pandemic and the coming into effect of the Regulations (EU) 536/2014, 2017/745 and 2017/746 in 2021 and 2022.

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

Based on the most recent evaluation from EMA, a final round of contacting sponsors before February 2023 will be planned. Trials for which sponsors cannot be reached then will be marked as "lost-to-follow-up".

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

A violation of the EU Clinical Trial Regulation falls under national penalties according to § 84 (1) 18 of the Austrian Medicines Act, as amended,

https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10010441+{color}]
Please note that the EU Clinical Trial Regulation does not apply to clinical trials completed under the Directive 2001/20/EC.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

§§ 48 and 84 (1) 18 of the Austrian Medicines Act

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

The Austrian Medicines Act foresees a fine of up to 25,000 EUR, or up to 50,000 EUR in the event of a repeat offence.
Please note that the Federal Office for Safety in Health Care is only the reporting agency and not the agency that issues the fine, so no further information can be given.

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

For clinical investigations with medical devices or performance studies with IVDs Regulations 2017/745 (Article 77) and 2017/746 (Article 73) apply for studies submitted since 26.05.2021 or 26.05.2022, respectively.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

Infringements will have to be detected based on reports generated by CTIS for the respective Member States. CTIS reports can be supplemented with findings from our own GCP inspections.
Based on such findings Member States can then initiate a corrective measure according to Article 77. This will most likely be coordinated by the Reporting Member State of the trial.
In short, the corrective measure consists of
- an initial assessment by the initiating MSC (most likely the RMS)
- a round of comments by the MSC
- a round of questions to the sponsor
- a coordinated response assessment
- a national decision based on this assessment

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

The Federal Office for Safety in Health Care is only the reporting agency and not the agency that issues the fine, so no further information can be given.

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

Since EUDAMED is not fully functional yet, infringements will have to be detected based on reports generated from our national database. Such reports can be supplemented with findings from GCP inspections. Based on such findings we can then initiate a corrective measure according to Article 76 (MDR) or 72 (IVDR). Further procedure will be as described in Question 10.

Belgium (FAMPH)

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

On 2 May 2022, the European Medicines Agency (EMA) provided all Member States with a list of clinical trials for which results should already have been published. According to this list, results are missing from EudraCT for a total of 358 clinical trials in Belgium: 28 paediatric trials (12 trials with a draft version of the results that is not publicly available and 16 trials without a draft version of the results) and 330 adult trials (98 trials with a draft version of the results that is not publicly available and 232 trials without a draft version of the results).

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

In total, 337 clinical trials in Belgium have been identified for which the global trial end date has been indicated but not entered. This list was compared to the global trial end dates entered by other Member States for those 337 clinical trials. We are currently in the process of making the necessary adjustments (currently implemented for 25 clinical trials).
We also note that a small number of sponsors verify themselves whether the end dates have been entered correctly, because we are sometimes contacted to enter additional data on completed clinical trials in EudraCT.

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

Based on the list received from the EMA on 2 May 2022, we contacted the sponsors who should have reported their results on EudraCT by now. For all 358 clinicals trials listed in our response to question 1, instructions from the EMA templates (one for clinical trials with a draft version of the results and one for clinical trials with no results) were sent to the e-mail address of the sponsor's contact person indicated in the clinical trials application form. These instructions referred to the news item published by the Federal Agency for Medicines and Health Products (FAMHP) on 8 July 2021, calling on sponsors to publish clinical trial results. Unfortunately, after sending this e-mail to the sponsor's contact person, we received many delivery failure notifications. For 319 of the 358 clinical trials mentioned earlier, the sponsor's contact person was also contacted last year on 5 July 2021. 39 out of the 358 clinical trials are therefore "new" compared to last year's list of 577 clinical trials in Belgium without reported results. This also implies that results have been published for 258 clinical trials that were part of last year's list of 577 clinical trials.

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

Please refer to question 3: we have contacted sponsors who did not respond to the obligation to publish results while referring to the news item published on the FAMHP's website. We also answered questions regarding these topics from sponsors.

For clinical trials submitted under Regulation (EU) 536/2014, the FAMHP will have the legal ability to penalise sponsors if clinical trial results are not published in time. This regulation entered into force on 31 January 2022 as did the Belgian Law of 7 May 2017 on clinical trials with medicinal products for human use, in which penalties are included in article 44. Article 44 of the Law of 7 May 2017 provides the following penalties (for your information: article 37 of the Regulation 536/2014 provides for the obligation to publish the results of a clinical trial within one year after the end of the trial):

- *Article 44. Without prejudice to the application of the penalties provided for in other laws and, where appropriate, the application of disciplinary measures, shall be punished by imprisonment from one month to two years and by a fine from €500 to €250,000, or by one of these penalties alone:*

1° whoever violates Articles 3, 4, first paragraph, 15, 28, § 1, 29, §§ 1 to 6, 31, §§ 1 and 2, 32, 33, 35, 36, 37, 38, § 1, 41, 42, 43, § 1, 47, §§ 1 and 2, 49, 51, § 1, 52, § 1, 53, 54, §§ 1 and 2, 55, 56, 57, 58, 59, § 1, 61, § 1, 62, § 1, 63, §§ 1 and 3, 65, 66, 67, 68, 72, § 2, 74, 76, § 2, and 90, para;

2° he who violates Articles 12, § 2, 36, 38 and 40 of this Law;

3° he who buys, possesses, sells, offers for sale, delivers, supplies, distributes, provides, imports or exports tainted, degenerated, expired or counterfeit investigational medicinal products or medicinal products which are not in conformity with the provisions of this Law

4° he who has falsified or counterfeited investigational medicinal products intended to be sold, offered for sale, delivered, distributed, supplied, imported or exported them or has had them falsified or counterfeited

5° he from whom investigational medicinal products are found intended to be sold, offered for sale, delivered, distributed, supplied, imported or exported, and who sells them, offers them for sale, delivers them, distributes them, supplies them, imports them or exports them, knowing that they are perverted, degenerate, expired, counterfeit, or do not conform to the provisions of this Law.

The penalty referred to in paragraph 1, 3°, shall not apply to the possession of medicines for examination in quarantine with a view to their destruction.

Article 46 of the same law provides for the possibility of amicable settlement:

- *Art. 46. Article 17, §§ 1 to 5 and 8, of the Law of March 25, 1964 on Medicines is applicable in case of violation of the provisions of this Law and the decrees taken to implement it.*

In practice, if a violation is found for clinical trials submitted according to the Law of 7 May 2017, a determination will be made by a good clinical practice (GCP) inspector from the FAMHP, who may then prepare an official report of determinations. This official report, together with the inspection report, will be transmitted to the violator and the FAMHP's official solicitor (the head of the Legislation and Litigation Division). The official solicitor can then, in consultation with the inspection, propose an amicable settlement to the offender (for a minimum amount of 4,000 euros, which is the minimum amount of the fine multiplied by the applicable surcharges). If the offender does not accept the out-of-court settlement, the Public Prosecutor may initiate further proceedings.

To be complete, we would like to inform you that the Public Prosecutor can still proceed with the prosecution, even if the out-of-court settlement has been paid. In that case, the Prosecutor must notify the offender of his intention to prosecute, at the latest within one month of

notification of payment of the settlement (See article 17, § 1, fourth paragraph, Medicines Law of 25 March 1964.)

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Article 37(4) of Regulation (EU) 536/2014 has not been incorporated in the Belgian Law but as all regulations it has a direct effect on the national law. However, article 44 of the Belgian Law of 7 May 2017 on clinical trials with medicinal products for human use states the penalties in case of non-compliance with article 37(4) of the Regulation (EU) 536/2014 (see question 4).

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Belgian Law of 7 May 2017 on clinical trials with medicinal products for human use in which penalties are included in article 44. Article 44 of the Law of 7 May 2017 provides for the following penalties (for your information: article 37 of the Regulation 536/2014 provides for the obligation to publish the results of a clinical trial within one year after the end of the trial):

- *Article 44. Without prejudice to the application of the penalties provided for in other laws and, where appropriate, the application of disciplinary measures, shall be punished by imprisonment from one month to two years and by a fine from €500 to €250,000, or by one of these penalties alone:*

1° whoever violates Articles 3, 4, first paragraph, 15, 28, § 1, 29, §§ 1 to 6, 31, §§ 1 and 2, 32, 33, 35, 36, 37, 38, § 1, 41, 42, 43, § 1, 47, §§ 1 and 2, 49, 51, § 1, 52, § 1, 53, 54, §§ 1 and 2, 55, 56, 57, 58, 59, § 1, 61, § 1, 62, § 1, 63, §§ 1 and 3, 65, 66, 67, 68, 72, § 2, 74, 76, § 2, and 90, para;

2° he who violates Articles 12, § 2, 36, 38 and 40 of this Law;

3° he who buys, possesses, sells, offers for sale, delivers, supplies, distributes, provides, imports or exports tainted, degenerated, expired or counterfeit investigational medicinal products or medicinal products which are not in conformity with the provisions of this Law

4° he who has falsified or counterfeited investigational medicinal products intended to be sold, offered for sale, delivered, distributed, supplied, imported or exported them or has had them falsified or counterfeited

5° he from whom investigational medicinal products are found intended to be sold, offered for sale, delivered, distributed, supplied, imported or exported, and who sells them, offers them for sale, delivers them, distributes them, supplies them, imports them or exports them, knowing that they are perverted, degenerate, expired, counterfeit, or do not conform to the provisions of this Law.

The penalty referred to in paragraph 1, 3°, shall not apply to the possession of medicines for examination in quarantine with a view to their destruction.

- *Article 46 of the same law provides for the possibility of amicable settlement:*

Art. 46. Article 17, §§ 1 to 5 and 8, of the Law of March 25, 1964 on Medicines is applicable in case of violation of the provisions of this law and the decrees taken to implement it.

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

Please refer to our answers on the previous questions.

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

There is no legal obligation to make the results of clinical investigations with or without investigational medicinal products (IMPs) that are not clinical trials or other clinical investigations public (not provided for in the Law of 7 May 2004).

In Belgium, article 77 of Regulation (EU) 2017/745 is applicable to other clinical investigations within the meaning of article 82 of Regulation (EU) 2017/745 (see article 49 of the Royal Decree of 18 May 2021 on the clinical investigation of medical devices).

Article 77 of Regulation (EU) 2017/745 on clinical investigations:
7. The summary and report of the clinical investigation referred to in paragraph 5 of this article shall be publicly accessible through the electronic system referred to in article 73, at the latest when the device is registered in accordance with article 29, and before it is placed on the market. In the case of early termination or temporary discontinuation, the summary and the report shall immediately become publicly accessible after its submission.

Article 73 of Regulation (EU) 2017/746 on performance studies:
7. The summary and report of the performance study referred to in paragraph 5 of this article shall be publicly accessible through the electronic system referred to in article 69, at the latest when the device is registered in accordance with article 26, and before it is placed on the market. In case of early termination or temporary discontinuation, the summary and the report shall immediately become publicly accessible after its submission.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

The technical details of the Clinical Trials Information System (CTIS) are not known yet, so this is still an uncertainty. Business Intelligence reporting trainings will be available in May 2022.

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

The FAHMP can propose a penal transaction, without going through the courts to impose penalties. Payment of the settlement nullifies the public prosecution, unless the Public Prosecutor notifies the offender within one month from the date on which they were notified of the payment, that they intend to bring this action (See Belgian Law of 7 May 2017 on clinical

trials with medicinal products for human use, article 46). In the event of violation of the provisions of this law and the decrees issued in implementation thereof: article 17, §§ 1 to 5 and 8 of the Medicines Law of 25 March 1964 is applicable.

If a penalty is imposed
The verbalizer sends a copy of their report to the alleged offender within twenty days of the establishment of the offence. The original of the report is sent by the verbalizer to the civil servant-lawyer. The civil servant-lawyer, can either send the original of the report directly to the Public Prosecutor, or propose a settlement to the offender, within three months of the date of the report. If the civil servant-lawyer does not propose a transaction to the offender, they will send the original of the report to the Public Prosecutor for the prosecution of the public action. If a transaction is proposed but is not paid within the month of its sending, the civil servant-lawyer informs the Public Prosecutor and sends them the original of the minutes so that they can exercise the public action. If a transaction is proposed and is paid within the month of its dispatch, the civil servant-lawyer informs the public prosecutor of the payment and sends them the original of the report. In this case, however, the Crown Prosecutor still has the right to "cancel" the transaction and pursue public action against the offender.

Please refer to the Medicines Law of 25 March, 1964: article 14, § 3, paragraph 1 to 4 and article 17, § 1, paragraph 1 to 9, § 3 et § 8.

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

Penalties are described in the Law of 22 December 2020 on medical devices. The penalties range from level 1 to 5 as stated in section 6 of the law.
Infringements of article 77 of Regulation (EU) 2017/745, are defined as a penalty of level 2 in the article 87 from the Law on medical devices:

Penalties of level 2 go from a fine between 50 and 5,000 euros (to be multiplied by the applicable surcharges – eight at present) and imprisonment from eight days to one month or only one of these penalties (article 85, § 4 from the Law on medical devices).

Regulation (EU) 2017/746 is currently pending in the House of Representatives and can be consulted via this link.
Article 86, number 6, of this project defines the infringement of article 73 IVDR as penalty of level 2. Penalties of level 2 go from a fine of 50 to 5,000 euros (to be multiplied by the applicable surcharges – eight at present) and imprisonment from eight days to one month or only one of these penalties (article 84, subparagraph 4 of the law IVDR).

For other clinical investigations within the meaning of article 82 of Regulation (EU) 2017/745, there is no sanction up to now. Article 118 of Regulation (EU) 2017/746 will introduce the possibility of sanctions (article 49 of the Royal Decree implements article 61 of the Law of 22 December 2020 on medical devices). The project defines the infringement of article 49 of the royal decree as a penalty of level 3. Penalties of level 3 go from a fine of 200 to 50,000 euros (to be multiplied by the applicable surcharges – eight at present) and imprisonment from one month to one year or only one of these penalties (article 85, subparagraph 5 of Regulation (EU) 2017/746).

Denmark (DKMA)

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

> *Approximately 300 trials from year 2017 and onwards had not published trial results, when we intensified our dialogue with the trial sponsors. Now, trial results from around 230 trials have been published and our dialogue and efforts continue for the remainders. It is not possible to define the number of pediatric trials from this pool.*

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

> *We have the same approach as for publication of trial results, which include continuous monitoring and follow-up dialogue with the trial sponsors. We react upon uncertainties of the trial status and contact the sponsor if the deadline for the end of trial declaration is overdue.*

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

> *A mitigating procedure have been implemented as part of the clinical trial application assessment where we ensure sponsors acknowledgement of the required publication policy. Furthermore, we have updated our website and issued press releases to enhance awareness. This have been greatly supported by the public GCP-units (used for GCP monitoring of non-commercial trials) who also released guidance, assisted sponsors technically and boosted the outreach to non-commercial sponsors.*
>
> *We continuously monitor the required publication of trial results and we reach out to all relevant contact points if publications are lacking and overdue. Our focus on dialogue with the trial sponsors have been very successful with the majority of trial results being published, and our efforts will continue in regards to the remaining ones.*

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

> *Most importantly we now have a robust procedure with routine checks if trial results have been published and we will continue the dialogue with the trial sponsors. So far it hasn't been necessary to hand over any cases to the police, but we will do so, if we have to.*

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

None as the regulation, including article 37.4, is directly applicable in Denmark and all other member states.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Danish Law 620 of 08/06/2016 (in Danish: Lov om kliniske forsøg), § 35.2.

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

Not fulfilling the obligation of publishing results of clinical trials can give an economical penalty or up to 4 months of imprisonment. In practice, the Danish Medicines Agency can lodge a complaint with the police, which would turn the case over to the public prosecutor. About the size of the economical penalty, this is yet unknown, as no court cases has taken place.

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

For clinical investigations on medical devices (investigation on non-CE marked medical devices and investigations where CE marked medical devices are investigated for another purpose than the CE-marked), sponsors has an obligation to publish the results from the investigation in the new European Database for Medical Devices, EUDAMED. This requirement is stated in article 77(5) and (7) in the Medical Device Regulation 2017/745.
Link to legislation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20200424

The regulation for medical devices came into force 26.05.2021, however the module in EUDAMED for clinical investigations, where sponsor shall upload and publish the clinical investigation report and a summary of the report is not available yet. The report and summary shall be made publicly available 1 year after the investigation has terminated, or alternatively when the device is placed on the market. EU COM expects the clinical investigation module in EUDAMED to be ready in 2023.
Link to EUDDAMED: https://ec.europa.eu/tools/eudamed/#/screen/home

Until Eudamed is fully functional the sponsor shall send the clinical investigation report to the Danish Medicines Agency according to section 11 (6) in Executive order no. 957 of 29 April 2021 on medical devices and products without a medical purpose. If sponsor does not comply with the obligation in section 11, (6), the sponsor can be fined, cf. section 14 (1)(1) in Executive order no. 957 of 29 April 2021 on medical devices and products without a medical purpose.

If the sponsor does not comply with the obligation to upload the result in Eudamed after Eudamed is fully functional, the sponsor can be fined or in certain circumstances be punished with imprisonment, cf. section 6 (2) in the Danish Act No. 139 of 15 February 2016 concerning medical devices (with later amendments).

Studies beside interventional clinical trials with medicinal products and the above-mentioned investigations on medical devices is not the DKMAs area of responsibility why we refer to the Research Ethics Committees.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

We will continue the current practice supported by data from the CTIS portal.

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

The DKMA efforts to ensure data transparency have been successful because of dialogue with our stakeholders. Therefore, we will continue to issue reminders and follow-up warnings. As previously mentioned the DKMA cannot impose penalties but instead lodge complaints with the police, which may turn the case over to the public prosecutor.

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

Please be referred to the response for question 8.

Finland (Fimea)

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

> *The Finnish Medicines Agency Fimea follows up only the reporting of clinical trial results to the national health authority. Monitoring the compliance of reporting to EudraCT is a task which is performed EMA. According to the latest available data from EMA (2 May 2022), there are altogether 231 completed trials lacking results at the EudraCT.*

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

> *Fimea transfers the date of completion of clinical trials to EudraCT as reported by the sponsor. Based on the original estimated duration of the trial, which was initially informed by the sponsor upon the authorization of the trial, Fimea actively contacts the sponsor in case the information of the date of completion and/or the results of the trial have not been forwarded to Fimea. EMA sends regular reminders to sponsors who have not been compliant with the reporting requirements and are lacking results at the EudraCT.*

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

> *Fimea issued a newsletter at our webpage in the beginning of July 2019 regarding the requirements for EU reporting. In addition, we have reminded the sponsors of this requirement by e-mail correspondence. In addition, the newest administrative regulation concerning clinical trials 8/2019, effective from 1. January 2020 includes a statement which reminds sponsors of the requirement to post results in the EU Clinical Trials database. Based on the original estimated duration of the trial, which was initially informed by the sponsor upon the authorization of the trial, Fimea actively contacts the sponsor in case the information of the date of completion and/or the results of the trial have not been forwarded to Fimea. In addition, a reminder of the obligation to post results in the EU Clinical trials database, is always included in information events held by Fimea.*

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

> *Fimea will continue the activities mentioned above: i.e., based on the original estimated duration of the trial, which was initially informed by the sponsor upon the authorization of the trial, Fimea actively contacts the sponsor in case the information of the date of completion and/or the results of the trial have not been forwarded to Fimea. In addition, a reminder of the obligation to post results in the EU Clinical trials database is always included in information events held by Fimea. As of May 2022, 3 information events have been held to investigators and sponsors.*

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

There is no national legislation incorporating the CTIMP reporting requirements set out in the Clinical Trial Regulation. Article 37(4) of the Regulation is directly applicable. Please note that the CTR cannot be applied to the results of the trials conducted under the Clinical Trials Directive.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

The Finnish Act on Clinical Trials on Medicinal Products (983/2021) is the main law implementing the Clinical Trials Regulation. Section 31 of said Act concerns infringements in a clinical trial on a medicinal product. According to said Section, a person who intentionally or by gross negligence infringes certain rules set out in the law or the Regulation, shall be sentenced to a fine for an infringement in a clinical trial on a medicinal product, unless a more severe penalty is provided elsewhere in the law. For an act that is punishable under said Section, the penalty is imposed on the person whose obligations the act or negligence infringes.

In Section 32 of the Act on Clinical Trials on Medicinal Products it is stated that Provisions on the penalty for an infringement in a clinical trial on a medicinal product are laid down in chapter 44, section 9a of the Criminal Code of Finland (39/1889). Provisions on the penalty for violating the duty of secrecy laid down in section 38 are contained in chapter 38, section 1 or 2 of the Criminal Code unless the act is punishable under chapter 40, section 5 of the Criminal Code or a more severe penalty is provided elsewhere in the law. The amount of the possible fine that is sentenced for an infringement is decided by the court assessing the infringement.

According to Section 29 of the Act on Clinical Trials on Medicinal Products, to enforce its decision on a corrective measure specified in Article 77 of the CTR, a request for information and documents specified in section 28, and a decision related to fulfilling some other obligation laid down in the CTR, the Implementing Regulation or the national Act, the Finnish Medicines Agency may issue a notice of a conditional fine. Fimea may issue a notice of a conditional fine also in order to enforce its decision related to publishing the results of a trial.

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

The Finnish Act on Clinical Trials on Medicinal Products (983/2021) is the main law implementing the Clinical Trials Regulation. Section 31 of said Act concerns infringements in a clinical trial on a medicinal product. According to said Section, a person who intentionally or by gross negligence infringes certain rules set out in the law or the Regulation, shall be sentenced to a fine for an infringement in a clinical trial on a medicinal product, unless a more severe penalty is provided elsewhere in the law. For an act that is punishable under said

Section, the penalty is imposed on the person whose obligations the act or negligence infringes.

In Section 32 of the Act on Clinical Trials on Medicinal Products it is stated that Provisions on the penalty for an infringement in a clinical trial on a medicinal product are laid down in chapter 44, section 9a of the Criminal Code of Finland (39/1889). Provisions on the penalty for violating the duty of secrecy laid down in section 38 are contained in chapter 38, section 1 or 2 of the Criminal Code unless the act is punishable under chapter 40, section 5 of the Criminal Code or a more severe penalty is provided elsewhere in the law. The amount of the possible fine that is sentenced for an infringement is decided by the court assessing the infringement.

According to Section 29 of the Act on Clinical Trials on Medicinal Products, to enforce its decision on a corrective measure specified in Article 77 of the CTR, a request for information and documents specified in section 28, and a decision related to fulfilling some other obligation laid down in the CTR, the Implementing Regulation or the national Act, the Finnish Medicines Agency may issue a notice of a conditional fine. Fimea may issue a notice of a conditional fine also in order to enforce its decision related to publishing the results of a trial.

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

There's no national legislation requiring to make the results of other interventional trials public. The MD and IVD regulations include the requirement to make the results of medical device and IVD trials public after the EUDAMED IT system supports this functionality.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

The EU CTR implementation and CTIS have only recently started, and Fimea is currently (mid-May 2022) only evaluating the first applications, so there cannot be any results yet reported at CTIS. Fimea will act in line with other EU national competent authorities to develop mechanisms for detecting any compliance issues with reporting requirements. During GCP inspections, the reporting compliance for clinical trials which have been completed is checked as part of normal GCP inspection procedure.

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

To impose a fine or other criminal penalty requires a court process. Issuing a notice of a conditional fine is conducted by Fimea. Act on Conditional Fines (1113/1990) regulates imposing conditional fines. A Conditional Fine may only be issued in order to enforce an administrative decision by Fimea. The decision making process depends on the issue, but in most cases Fimea must ask the sponsor and/or the investigator for their opinion. According to Article 77 of the CTR, the opinion shall be delivered within seven days.

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

Please see the answer for question 8.

Germany (BfArM)

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

> *In response to an enquiry from the BfArM to the EMA regarding the publication figures in EUDRA CT, we received the following answer: The total number of authorised EudraCT trials marked as "completed" by Germany BfArM and also marked as "completed" in all other countries since more than 1 year is 8664. Of those, the number of trials that are uncompliant with the results guideline and that were conducted under Germany BfArM is 1190, of which 57 include paediatric subjects. This data was collected in April 2022. Please note, that this number includes trials that are not publicly available (phase 1 trials conducted solely on adults).*

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

> *In 2020, the BfArM reminded sponsors of clinical trials conducted in the EU with missing EudraCT result reports of their obligation to summarise and publish the results of completed trials. This was done by a database query, as a result of which a total of 1,165 letters were sent to sponsors and applicants. For this database query, a search algorithm was used that compares the presence of so-called end-of-trial reports and missing final reports.*

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

> *Sponsors who have not uploaded their final reports to EudraCT within one year after completion of the study were contacted by BfArM by mail and requested to do so immediately [cf. question 2]. In the bi-annual meetings of the national consultation group with ethics committees, pharmaceutical industry associations, and medical school representatives, which is chaired by BfArM, the issue was addressed and institutions were encouraged to motivate their sponsors to upload reports to EudraCT in a timely manner.*

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

> *It is intended to mail again in the second half of 2022 to all sponsors whose final reports are missing in EudraCT and to ask them again to upload their reports in EudraCT. Additionally, BfArM will provide more information on how to upload result reports to EudraCT on its homepage.*

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

The provisions of the Regulation are directly applicable in each Member State and do not require transposition into national law.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

All offences are subsumed Section 96 and 97 (2d) of the German Medicines Act (AMG). General provisions are laid down in the German Administrative Offences Act (Gesetz über Ordnungswidrigkeiten, OWiG).

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

The maximum fine for an administrative offense based on Section 97 (2d) AMG is limited to 25,000 € according to Section 97 (3) AMG. General criteria for determining the amount of the fine are set out in Section 17 (2-4) OWiG.

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

In relation to the question asked, BfArM is only responsible for clinical trials of medicinal products and medical devices. All other clinical studies such as clinical non-drug studies do not fall under the responsibility of BfArM.

<u>Enforcement mechanisms</u>

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

Since the EU Clinical Trials Regulation is only applicable since 31 January 2022 and until now only very few clinical trial applications have yet been approved in Germany on the basis of the EU Clinical Trials Regulation, the first results reports are not expected before the middle of next year. Therefore, BfArM has not yet defined any exact processes for the procedure but would like to gain experience in this regard. At the moment, it is intended to use CTIS and - if available - data from GCP inspections.

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

In principle, sponsors must first be heard on the facts of each case before an administrative offence can be imposed. At present, it is planned that the sponsors will be given the opportunity to submit a reasonable extension of time with the hearing letter. If this deadline is not met, BfArM will impose a fine directly, against which, however, each sponsor can file an appeal.

If the appeal meets the formal requirements and the BfArM does not want to withdraw the penalty notice, the proceedings must be taken over by the public prosecutor's office (Section 69 (3, 4) OWiG). The public prosecutor shall submit the case to the court if he neither terminates the proceedings nor conducts further investigations (Section 69 (4) OWiG).

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

BfArM is only competent for clinical trials with medicinal products and medical devices [cf. question 8].

Germany (Paul-Ehrlich-Institut)

Please note that the Paul-Ehrlich-Institut's remit only includes vaccines and biomedicines for human use, certain in vitro diagnostic devices and immunological medicines for veterinary use.

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

Answer: In Germany and the EU, there are various sources of clinical trial results.

1. Section 13 (9) GCP-Ordinance (GCP-Verordnung - GCP-V) in the version of 26.01.2022 during the transition period pursuant to Section 148 Medicinal Products Act (Arzneimittelgesetz - AMG), Article 98 of the Regulation (EU) No 536/2014 (EU Clinical Trial Regulation)
The sponsor shall submit to the competent higher federal authority and the competent ethics committee, within one year after the end of the clinical trial, a summary of the clinical trial report covering all essential results of the clinical trial. These reports are not public.

2. Section 42b Medicinal Products Act (AMG)
Publication of the results of clinical trials These reports are publicly available at www.pharmnet.bund.de in the clinical trials module.

3. EudraCT
For EudraCT, according to the legal opinion here, there is no legal basis for the requirement of results reports/results (see below). Guidelines from various organisations, such as EU-COM/EMA/HMA, to enter clinical trial results in EudraCT have an appellative rather than a binding character.

The EudraCT database is hosted and administered by the European Medicines Agency (EMA). Tools that could show in a personnel-efficient way for which clinical trials results reports are existing, missing or in draft mode are not accessible to the EU member states. With several tens of thousands of clinical trials in the EU and over twenty thousand clinical trials in Germany alone, a manual analysis, which would have to be repeated at short intervals, is not feasible by the higher federal authorities.

This lack of a database supported analysis of EudraCT within the existing data warehouse was reported to the European Medicines Agency by the Paul-Ehrlich-Institut on several occasions in meetings of the EMA working groups on EudraCT. The European Medicines Agency sends extensive lists of allegedly overdue results reports to the member states at irregular annual intervals, instead of ensuring the recovery of the reports themselves.

In the past, each time such a list was received; the Paul-Ehrlich-Institut wrote to all individual sponsors under the responsibility of the Paul-Ehrlich-Institut and insisted on remedial action. An effective control of the implementation by the sponsors is not possible due to the above-mentioned lack of adequate analysis tools.

On 02.05.2022, the EMA informed the Paul-Ehrlich-Institut of 138 clinical trials with overdue results compared to the 3,043 completed clinical trials within the remit of the Paul-Ehrlich-Institut. There are no missing completion dates to be entered by the PEI.

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

Answer: The end of a clinical trial must be reported to the Paul-Ehrlich-Institut. The date of completion in Germany and, if applicable, in all countries worldwide is immediately entered in EudraCT by the Paul-Ehrlich-Institut. According to the last notification from the EMA on 02.05.2022, no endings/terminations of clinical trials under the responsibility of the Paul-Ehrlich-Institut are overdue.

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

Answer: As described above, the Paul-Ehrlich-Institut has individually requested defaulting sponsors on several occasions to enter results in EudraCT. Contact possibilities/help at the EMA and the PEI in case of problems were mentioned in each email.

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

Answer: Due to the implementation of EU Clinical Trial Regulation by 31.1.2022 in parallel with the ongoing approvals / amendments of clinical trials pursuant to Directive 2001/20/EC or sections 40 ff Medicinal Products Act (AMG): None.

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Answer: The provisions of the EU Clinical Trial Regulation are directly applicable in each Member State and do not require transposition into national law.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Answer: Penal provisions are found in section 96 numbers 10, 11 and 21 of the Medicinal Products Act (AMG). Fining regulations are found in section 97 (1) and (2d) of the Medicinal Products Act (AMG).

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

Answer: For infringements of CTIMP reporting requirements set out in Article 37 paragraph 4 of the EU Clinical Trial Regulation fines of up to € 25.000 may be imposed (section 97 (2d)

number 2, (3) Medicinal Products Act (AMG)). General criteria for determining the amount of the fine are set out in section 17 (2 - 4) of the German Act on Regulatory Offences (Gesetz über Ordnungswidrigkeiten - OWiG).

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

Answer: Please be aware, that the Paul-Ehrlich-Institut approves primarily clinical trials of medicinal products and only in very rare cases interventional performance studies with special types of in vitro diagnostic medical devices.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

Answer: Since the EU Clinical Trials Regulation has only been applicable since 31.01.2022 and so far very few (<5) clinical trial applications have been approved in Germany on this basis, the first results reports are not expected before the middle of next year. Therefore, the Paul-Ehrlich-Institut has not yet defined any procedures for the process but would first like to gain experience in this regard. At the moment, it is intended to use CTIS data and - if available - data from GCP inspections.

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

Answer: If a breach of the publication obligation becomes known, the Paul-Ehrlich-Institut will first contact the sponsor and set a deadline for catching up. If the deadline expires without result, a decision will be made on whether to initiate fine proceedings under the Act on Regulatory Offences (OWiG). This is followed by a hearing pursuant to sections 55, 9 and/or 30 of the OWiG to give the person concerned the opportunity to comment on the accusation.

After that, a decision on the imposition of a fine is made by administrative act. The person concerned can appeal against the penalty notice within two weeks. If the appeal meets the formal requirements and the Paul-Ehrlich-Institut does not want to withdraw the penalty notice, the proceedings are handed over to the public prosecutor's office. The public prosecutor's office submits the case to the court if it neither discontinues the proceedings nor conducts further investigations. (cf. sections 68 et seq. Act on Regulatory Offences (OWiG)).

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

Answer: See question 8.

Netherlands (CCMO)

Note: CCMO responded in the form of a continuous email text. That text is reproduced fully and verbatim below, but is structured in line with the questions originally sent to Dutch authorities.

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

No information provided.

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

No information provided.

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

The CCMO has hired personnel to contact sponsors and investigators of clinical trials for which no summary of results has been uploaded in EudraCT result database. The European Medicine Agency send us, on a regular basis, an overview of these clinical trials in EudraCT. The work is progressing but for very old clinical trials the contact data as registered in the EudraCT and our own system is not up to date. I think we have to acknowledge that we will never have all results in EudraCT results database. This is unfortunate, but learning from this experience CCMO is now actively follow up on missing results one year after the end of the clinical trial worldwide.

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

CCMO is now actively follow up on missing results one year after the end of the clinical trial worldwide.

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

The Dutch Act on medical research is recently been updated to have more instruments for enforcements if sponsors do not comply with the Clinical Trial Regulation (CTR, EU no 536/2014). Article 37 of the CTR on the obligation to submit a summary of results (scientific and laypersons) in CTIS is explicitly mentioned in article 33 of our national law. See: https://wetten.overheid.nl/BWBR0009408/2022-03-15#Paragraaf7

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

> *For infringement of article 37 it possible to have an imposition of an order subject to periodic penalty payments. The amount of the penalty must be in reasonable proportion to the gravity of the allegedly infringed interests. The law does not state a maximum.*

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

> *In the Netherlands, it is the Health Inspectorate who can act if a sponsor/investigator does not follow up regulatory requirements. For infringement of article 37 it possible to have an imposition of an order subject to periodic penalty payments. The amount of the penalty must be in reasonable proportion to the gravity of the allegedly infringed interests. The law does not state a maximum.*
> *Apart from that, our national law (also article 33) also regulates that our Minister can impose an administrative fine with a maximum of 33.500 Euro to enforce article 37 of CTR.*
>
> *[Note by TranspariMED: The relevant article appears to be 33(b)(2): "Our Minister shall be authorised to impose an administrative fine of up to €33,500 to enforce Articles 36, 37, 43(1), 53 and 58(1) of Regulation (EU) No 536/2014."]*

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

> *Apart from that, our national law (also article 33) also regulates that our Minister can impose an administrative fine with a maximum of 33.500 Euro to enforce article 37 of CTR.*
> *This is all applicable for MDR and IVDR studies as well (see article 33 of our national law). However, the administrative fine by Minister for MDR and IVDR studies has a maximum of 150.000 Euro. (to be clear, this article addresses many other infringements of MDR and IVDR as well).*

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

> *CTIS is the new system for clinical trials and will replace EudraCT fully after the three years of transition. EMA develops KPI and BI reports on the clinical trials in CTIS. Together with EMA we will monitor and follow up. Transparancy is key in CTR and CTIS. Only a few clinical trials in CTIS have been authorized and are now ready to start; the first results are expected not earlier than end of next year.*
> *The CCMO supports transparency with respect to clinical trials ongoing and ended (including trial results) for scientific reasons but also for the interest of (future) patients.*

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an

infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

> *For more information on the system of imposing administrative fines or other penalties you have to contact the Dutch Health Inspectorate.*

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

> *For more information on the system of imposing administrative fines or other penalties you have to contact the Dutch Health Inspectorate.*
> *[CCMO provided no information on detection mechanisms for MDR and IVDR studies that fail to report results.]*

Sweden (LMV)

Note: LMV did not respond to the initial outreach, but did respond to later outreach by Cochrane Sweden. Cochrane Sweden shared LMV's responses after securing LMV's permission to do so.

Regulatory strategies (questions apply to CTIMPs registered on EudraCT only)

Question 1: How many CTIMPs for which you are the NCA currently lacking results on EudraCT in violation of reporting obligations? Please break down the figure into (a) paediatric and (b) adult trials. If current data are not available, please provide the latest available data, and the date on which those data were collected.

> *Status as per 2022-08-10:*
> *A total of 637 clinical trials, for which the Swedish Medical Products Agency is the NCA, have been reported as completed or prematurely ended but lack reported results in the EudraCT database even though the timeline for submitting the results has been, or is suspected to have passed.*
> *Of these 637 trials, 53 are recorded as paediatric trials and 584 are recorded as adult trials. 17 and 177 respectively also lack information on actual End of Trial dates, which makes it difficult to determine compliance in relation to the regulatory timeline requirements to report results.*

Question 2: What steps have you taken to ensure that all completed clinical trials are accurately marked as completed and/or their correct completion dates added to the trial protocol on EudraCT?

> *The Swedish MPA has issued provisions requiring reporting in line with the directive requirements. These are published on the website.*
> *Reporting requirements are also communicated during training provided to academic and commercial sponsors by the agency in collaboration with support organisations such as Clinical Research Support offices and Contract Research Organisations.*
> *In relation to GCP inspections, the reporting requirements are also enforced.*

Question 3: What steps have you taken to date to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT? For example, have you contacted investigators or sponsors over missing results, or provided guidance or training on results reporting?

> *No steps have been taken to contact all sponsors. Individual sponsors have been approached in relation to GCP inspections. For sponsors who contact the agency with questions related to reporting, individual guidance is provided.*

Question 4: What steps are you planning to take during 2022 to encourage and/or support sponsors' compliance with their reporting obligation on EudraCT?

> *Subject to resource availability and priorities activities may be initiated to contact sponsors who have clinical trials with unreported results. Assessment of submitted applications will however have a higher priority due to strict legal timelines for the agency to perform those tasks.*

National legislation

Question 5: What national laws and/or regulations incorporate the CTIMP reporting requirements set out in the EU Clinical Trial Regulation, Article 37(4)? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Note that no additional national legislation is expected in addition to the EU regulation 536/2104 (CTR) since the CTR is an EU regulation and as such applies automatically and uniformly to all EU countries as soon as it entered into force. It should therefore not be transposed into national law but should apply in its original form.

Question 6: What national laws and/or regulations define the penalties for infringements of the EU Clinical Trial Regulation, as set out in Article 94? Please provide the exact name and applicable article(s) of all relevant laws and regulations.

Penalties for infringements of the CTR can be found in chapter 14 section 3 and chapter 16 section 1 of the Medicinal Products Act (2015:315) (läkemedelslagen).

Question 7: Going forward, what penalties will you be able to impose for infringements of CTIMP reporting requirements? Please specify the penalties, for example the maximum fine(s) that you will be able to impose.

Chapter 14 section 3 of the Medicinal Products Act provides the legal foundation for the Swedish MPA to issue injunctions and prohibitions necessary for compliance with the CTR and also the former directives legislation in relation to clinical trials. Decisions on injunctions or prohibitions may be accompanied by a fine.
How the size of fines is determined follows from the Act on fines (1985:206) (viteslagen).

[Note by TranspariMED: The Act on fines does not specify amounts. Instead it states that:
"When a fine is imposed, it must be set at an amount which… can be assumed to induce [the fined entity] to comply with the order that is attached to the fine."
Fines may be imposed either as a single fixed fine, or as a running fine that grows until compliance has been achieved.]

Question 8: Are there legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs (including medical device trials and non-drug trials) public? If yes, please provide the exact name and applicable article(s) of all relevant laws and regulations.

Yes.
For clinical investigations of medical devices, results are to be reported and be made publicly available by sponsors via EUDAMED as per article 77 of the EU Regulation 2017/745 (MDR).
For interventional clinical performance studies of in vitro diagnostic medical devices results are to be reported and be made publicly available by sponsors via EUDAMED as per article 73 of the EU Regulation 2017/746 (IVDR).
For interventional clinical studies that are not regulated by the CTR, MDR nor the IVDR, the publication of results could be considered to be required in order to be compliant with article 36 of the Declaration of Helsinki, but this declaration per se is not legally binding. It should be noted that surveillance of such studies are not within the mandate of the Swedish MPA.

Enforcement mechanisms

Question 9: Going forward, what are the *mechanisms for detecting infringements* of CTIMP reporting requirements? For example, will you detect infringements using CTIS data and/or GCP inspections? Please describe the detection process in detail, step by step.

> *The Swedish MPA foresees to use CTIS data to detect such infringements, as well as GCP inspections. The step-by-step details of the process have not yet been worked out, as the number of authorized trials in CTIS is still very limited and the relevant tools are not yet fully developed.*

Question 10: Going forward, what are the *mechanisms for imposing penalties* for infringements of CTIMP reporting requirements? For example, will you impose penalties immediately when an infringement has been detected, or will you first issue a warning notice? Will you be able to impose penalties directly, or will you have to go through the courts to impose penalties? Please describe the penalty imposition process in detail, step by step.

> *The initial step is to approach the sponsor with a request to report the missing data within a given timeframe.*
> *If the desired result is not achieved, the agency issues an injunction accompanied by a fine.*
> *It is then the court that, at the request of the MPA, imposes the fine.*

Question 11: If there are legal and/or regulatory requirements to make the results of interventional clinical trials that are not CTIMPs public [see Question 8], please outline in detail which (a) *mechanisms for detecting infringements* and (b) *mechanisms for imposing penalties* you are currently using and/or plan to put into place going forward.

> *For MDR and IVDR it will be possible to detect missing reports via EUDAMED once it is fully functional. Until then, results reporting is tracked manually at the Swedish MPA.*
> *Chapter 3 section 6 of the Act (2021:600) with Complementary Provisions to EU's Regulations on Medical Devices, (lag (2021:600) med kompletterande bestämmelser till EUs förordningar om medicintekniska produkter) provides the legal foundation for the Swedish MPA to issue injunctions regarding compliance with the MDR and IVDR.*
> *Procedures would be similar as for clinical trials of medicinal products.*

Author: Till Bruckner, TranspariMED
Author contact: @TranspariMED or tillbruckner@gmail.com