An Investigation of Reasons and Potential Solutions for the Low Reporting Rate of Clinical Trial Summary Results in the EudraCT Database among Non-commercial Sponsors in the Northern and Central Region of Denmark: A Questionnaire-based Study in Collaboration with the GCP Unit

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Abstract

Background: Failure to report clinical trial (CT) summary results in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database within 12 months of trial completion is a well-known problem, even though, it has been mandatory for sponsors to report CT summary results since July 2014. In March 2019, the Trialstracker database, a public website presenting reported and non-reported CT summary results, showed that less than 20% of the non-commercial sponsors in the Northern and Central region of Denmark reported summary results. Reporting of summary results entails several advantages, such as decreasing of reporting bias, accurate and robust representation of CT endpoints, and prevention of CT duplication, which all contributes to CT transparency. This can help clinicians, patients, and policy makers to justify safety and benefits of health interventions. Therefore, this study attempted to investigate reasons behind the low reporting rate of summary results in the EudraCT database among non-commercial sponsors in the Northern and Central region of Denmark for CTs completed within the period of 2014 to 2018, and to propose potential solutions that might help increase the reporting rates. Furthermore, investigation of compliance between reported and non-reported CT summary results from the Trialstracker and the GCP unit databases were carried out for non-commercial sponsors in the Northern and Central region of Denmark to examine if the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates.

Methods: In collaboration with the Good Clinical Practice (GCP) unit at Aalborg and Aarhus University Hospitals, a custom-made questionnaire was developed and distributed via SurveyXact to the collected e-mail addresses on non-commercial sponsors or other relevant personnel from the CT team, monitored by the GCP unit. The questionnaire consisted of three parts covering areas related to reasons and potential solutions for the low reporting rates and was open for four weeks in 2019. Descriptive statistics and frequencies were used to identify reasons and potential solutions for the low the reporting rates and to examine if the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates. Fisher's exact tests were carried out to investigate if the ordinal outcome variables for reasons and potential solutions for the low reporting rates were statistically significant associated with the explanatory variables (number of initiated CTs, employment position during the CT, and experience in reporting CT summary results). Further, Fisher's exact tests were carried out to investigate differences between reported and non-reported CT summary results among non-commercial sponsors in the Northern and Central region of Denmark from the Trialstracker and the GCP unit databases.

Results: In total, 39 out of 79 (49.37%) questionnaires were included in the analysis. Here, the majority of the respondents tried to initiate 1 or 2 CTs (48.72%) and were employed as sponsor-investigator (46.15%). Seventeen out of 39 respondents (43.59%) tried to report a CT summary result where 14 out of the 17 respondents succeeded in reporting results. The main reasons behind failure to report summary results were by the majority of the respondents reported as being a time consuming and complicated process and lack of knowledge regarding the European legal framework. The potential solutions to help increase the reporting rates were by the majority of the respondents reported as telephone counseling, creation of a central unit at the university hospitals, and sending out ongoing reminders regarding deadline for

reporting results. Fisher's exact tests showed significant differences (Northern region: $p<.001$ and Central region: $p<.001$) between reported and non-reported CT summary results from the Trialstracker and the GCP unit databases for non-commercial sponsors in the Northern and Central region of Denmark.

Conclusion: The outcome of this study highlighted that reasons behind the low reporting rates were due to a time consuming and complicated process and lack of knowledge regarding the European legal framework. The potential solutions identified to overcome the low reporting rates were telephone counseling, creation of a central unit at the university hospitals, and sending out ongoing reminders regarding deadline for reporting results. The Trialstracker database can be considered as a source to obtain data on sponsors' reporting rates, although it is important to interpret the reporting rates from the Trialstracker database with precaution as the study found a difference between the reported and non-reported CT summary results from the Trialstracker and the GCP unit databases. However, further research is needed to confirm the results of the study and to establish how the potential solutions can be implemented in Denmark.

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List of Abbreviations

CT: Clinical Trial

DMA: Danish Medicines Agency

EC: European Commission

EMA: European Medicines Agency

EU: European Union

EUCTR: European Union Clinical Trials Register

EudraCT: European Union Drug Regulating Authorities Clinical Trials

GCP: Good Clinical Practice

ICH-GCP: International Conference on Harmonization Good Clinical Practice

LPLV: Last Patient Last Visit

SAE: Serious Adverse Event

UAEM: Universities Allied for Essential Medicines

US: United States

1. Introduction

Health research is a major topic worldwide [1], and researchers are constantly trying to generate evidence on new medicinal products, medical devices, and treatment methods to improve health and well-being through Clinical Trials (CTs) [2]. According to the World Health Organization, a CT is defined as: "*Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include, but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials*" [3]. Performing and completion of CTs are therefore a prerequisite for maintaining a high standard of providing accurate and reliable information on treatment options [4]. Likewise, sharing of results from CTs has long been considered as an ethical and scientific imperative [5] because dissemination of these are important for clinicians, patients, and policy makers to justify safety and benefits of health interventions [5]. Without conduction of CTs, no new medicines, no medicinal development, and no positive progression on evidence-based treatments would occur [6].

1.1. European Legal Framework

In order to withheld high standards, safety, and quality during a CT, the European Commission (EC) provides a legal framework on how to conduct clinical research on medicinal products for human use, described in regulations and directives [7]. A directive sets out goals and standards where each member state of the European Union (EU) are responsible for the implementation, generally within two years [7]. Regulations are legal acts that are directly applicable in all member states of the EU, and therefore there is no need to transpose regulations into national law [7]. If a member state does not meet the demands of the legal framework, the EC has the opportunity to initiate infringement proceedings [7].

In 2001, the EC, on behalf of the European Medicines Agency (EMA), issued the 2001/20/EC directive, consisting of several requirements to simplify and harmonize laws and regulations regarding clinical research in the EU [8, 9]. This directive became lawful the 1^{st} of May 2004, and it emphasizes on the importance of following the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guideline. When following the ICH-GCP guideline during CT conduction, different personnel such as a sponsor or an investigator have different areas of responsibilities [10]. An investigator is: "*A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator*" [10]. On the other hand, a sponsor is: "*An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial*" [10]. In some cases, a person can take on the role as both sponsor and investigator [10].

Compliance with the 2001/20/EC directive assures that rights, safety, and well-being of CT participants are protected according to principles of the ICH-GCP guideline originating from the Declaration of Helsinki [9–11].

Reporting of result-related information is also described in the 2001/20/EC directive, and throughout the years, details concerning reporting of result-related information have

been described in various subsequent regulations and directives [12,13]. An important detail regarding reporting of result-related information came into effect the 21^{st} of July 2014 when EMA announced that it became mandatory for sponsors to report summary results in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database [14]. A year before the announcement, sponsors were encouraged to start uploading summary results voluntarily [14]. This was intended for sponsors to familiarize themselves with the new features in order to comply with the new initiative, once it became mandatory [14].

1.2. Reporting of Summary Results

The content of what a CT summary result should encompass (Table 1) is set out in the 2009/C28/01 paediatric commission guideline (Appendix A) [13]. CTs are considered as paediatric if one or more participants are younger than 18 years of age [15]. In 2012, this commission guideline became applicable for both paediatric as well as non-paediatric CTs, simplifying the reporting process [12, 13]. The commission guideline from 2009 designated sponsor as the person responsible for reporting summary results within 12 months from the last patient's last visit (LPLV) completion date for non-paediatric trials and within 6 months from the LPLV completion date for paediatric trials [12, 13, 15]. Furthermore, summary results from phase I-IV trials are mandatory to report in the EudraCT database, whether a trial is completed or terminated prematurely [15]. After summary results are reported in the EudraCT database, they are made public in the European Clinical Trial Register (EUCTR) [5].

Table 1: Content of CT summary results [13]

Content of Summary Results
Administrative information and trial identification
Trial design
Scientific background and explanation of rationale for the trial
Participants in the trial - information on the subject population including inclusion exclusion criteria and demographic information
Interventions - the treatment used
Objective(s) of the trial
Outcome measures
Randomization implementation
Blinding
Statistical method
Patient disposition
Protocol deviations
Recruitment
Baseline data
Trial interruption
Outcomes and estimation
Ancillary analysis
Adverse events
Trial termination
Discussion and interpretation of study results (interpretation of trial results by sponsor, if available and by competent authority, if available)
A declaration of the submitting party on liability for the accuracy of the submitted information

CT: clinical trial

Though, summary results from phase I trials conducted in adults are not made public [15]. An example of a reported summary result from the EUCTR is available in Appendix B.

1.3. Advantages of Reporting Summary Results

Reporting of summary results entails several advantages, allowing to quickly and systematically identify, enter, and share new findings [16]. When results are reported in the EudraCT database, all data becomes visible regardless of positive and negative outcomes, countering the consequences of reporting bias [16]. Therefore, the reporting of summary results can decrease reporting bias because predefined endpoints and actual results can be crosschecked for consistency along with critical evaluation of their validity [16, 17]. Importantly, reporting of summary results gives rise to a more accurate and robust representation of CT endpoints, including Serious Adverse Events (SAEs) [16]. In 2015, a study by *Tang et al.* investigated a random sample of 300 CTs with SAEs from ClinicalTrials.gov, and found that only 11% of the published trials matched the actual number and type of SAEs [18], indicating that reporting of summary results is important as it strengthens CT transparency [5]. Another advantage is that reporting of summary results prevents CT duplication, making it easier for all parties to stop initiating a new CT similar to one already conducted.

Publishing results in academic journals are another way to make results publicly available [5]. These publications are validated in a peer reviewed process, which increases the validity and reliability of the reviewed paper [19]. Though, it can be a time consuming process to search for the academic journals of interest, and journals often have different standardized formats on how to report findings as well as limited word count [5]. Both ways of publishing results are essential for the research community and presents with different advantages, and none of these must therefore be neglected.

1.4. Current Status of Reporting Summary Results in the EU

During CT conduction, participants expose themselves to several risks, such as randomization, untested interventions, and blinding [20]. Because such significant risks are present, and participants not necessarily benefit directly from CT participation, the obligation to report summary results becomes crucial [21]. A study by *Goldacre et al.* investigated 7,274 CTs from the EUCTR in 2018 where summary results were due [5], which showed that 50.5% of the investigated CTs were left unreported [5]. Another study by *Mullard et al.* identified that, even though, all CTs submitted to the EudraCT database were subjected to the European legal framework, around one third of the sponsors failed to report summary results [16]. This shows that member states of the EU, responsible for upholding the European legal framework, are neglecting to efficiently enforce the legal requirements into national law [16].

To support the claims of the low reporting rate of summary results, a group from DataLab at Oxford University established a public non-commercial website called the Trialstracker [22]. The Trialstracker database shows reported and non-reported CT summary results for each sponsor conducting CTs in the EU together with the percentage reporting rate, and retrieves this information from the EUCTR [22]. Furthermore, the Trial-

stracker database shows that CTs with a commercial sponsor generally have a reporting rate of 100% compared to non-commercial sponsors, which often have a reporting rate far below 100% [5,22]. Around 61% out of 4,000 CTs conducted in the EU each year are listed with a commercial sponsor and 39% by non-commercial sponsors, mainly academia [23]. This indicates that non-commercial sponsors are responsible for conducting a great part of the CTs within the EU, and due to the low reporting rates among non-commercial sponsors (<100%), a solution on how to increase the reporting of summary results in the EudraCT database for non-commercial sponsors is needed [19].

1.4.1. Current Status of Reporting Summary Results in Denmark

In Denmark, the low reporting rate of summary results among non-commercial sponsors has also been found [22]. One public non-commercial organization aware of the importance of reporting summary results is the Good Clinical Practice (GCP) unit [24]. There are three GCP units covering all five regions of Denmark. The GCP unit at Copenhagen University Hospital covers Region Zealand and the Capital Region of Denmark, whereas the GCP unit at Odense University Hospital covers the Southern Region of Denmark. Lastly, the GCP unit at Aalborg and Aarhus University Hospitals combined covers the Northern and Central region of Denmark [25]. The GCP unit focuses on monitoring ongoing non-commercial CTs before first visit of the first patient to after the LPLV at University Hospitals in Denmark, including the Regional Hospitals, ensuring all regulatory requirements are fulfilled within the ongoing period of a specific CT [25]. The GCP unit assists sponsors and investigators in laws and regulatory requirements in order to comply with the ICH-GCP guideline, including reminding them to report summary results in the EudraCT database. However, summary results are mandatory to report no later than 12 months after trial completion where no monitoring with the GCP unit is present. Therefore, the GCP unit developed a guideline on how to report CT summary results in the EudraCT database, publicly available on their website [24, 26].

In March 2019, the Trialstracker database stated that 6.7% out of 15 completed CTs at Aalborg University reported summary results in the EudraCT database. Further, the Trialstracker database showed that 18% out of 61 completed CTs at Aarhus University reported summary results [22]. The low reporting rate of summary results indicates that there is a need for more awareness within this area. Thus, investigation of reasons behind the low reporting rates and potential solutions that might help increase the reporting of summary results in the Northern and Central region of Denmark, for CTs completed within the period of 2014 to 2018, will be formed as the focus of the present work.

1.5. Reasons Behind the Low Reporting Rates

The reasons behind the low reporting rates are not classified yet. However, it might be influenced by factors specific to region, culture, or number of initiated trials [5].

One reason behind the low reporting rate of summary results might be due to poor compliance or lack of monitoring and enforcement of the European legal framework by the Danish government. It has been stated in *Mullard et al.* that strengthening of legal rules and frameworks is one of the major milestones needed to increase the reporting rate of summary results [16]. Another reason might be that the

process of entering summary results in the EudraCT database can entail a long and difficult entry procedure. Therefore, improvements of already existing guidelines that assist sponsors in reporting summary results can be necessary [5].

It has not yet been investigated which factors and reasons that influence the low reporting rates in the Northern and Central region of Denmark, though several reasons can be present, why further research is needed.

1.6. Scope and Aim

Collectively, the status presented above indicates that the low ($<100\%$) reporting rate of summary results is a well-defined issue [5, 15, 22, 27]. The focus on how to overcome this issue is less studied, and the need to identify reasons and potential solutions are therefore essential for clinical research throughout the EU, including Denmark [5, 16]. Therefore, this study attempted to investigate reasons behind the low reporting rate of summary results in the EudraCT database among non-commercial sponsors in the Northern and Central region of Denmark for CTs completed within the period of 2014 to 2018, and to propose potential solutions that might help increase the reporting rates. Furthermore, investigation of compliance between reported and non-reported CT summary results from the Trialstracker and the GCP unit databases were carried out for non-commercial sponsors in the Northern and Central region of Denmark to examine if the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates. This study might give Denmark the opportunity to shape the transition to a new framework for the conduction of CTs based on full transparency.

It was hypothesized that the majority of people involved in the CT research teams at the University Hospitals in the Northern and Central region of Denmark (I) agreed that a complicated and time consuming entry procedure was a reason for failure to report summary results in the EudraCT database (II) agreed that counseling from a third party would be the preferred solution to help increase the reporting rates. Additionally, this study hypothesized that (III) the reporting of summary results from CTs extracted from the Trialstracker and the GCP unit databases were in compliance.

2. Methods

This study was performed in collaboration with the GCP unit at Aalborg and Aarhus University Hospitals. According to the National Committee on Health Research Ethics guidelines, no ethical approval was needed when using a questionnaire-based approach [28]. Regulations regarding the General Data Protection Regulation, however, were followed according to the Danish Data Protection Agency for the extracted information on CTs from the GCP unit database [29].

2.1. Data Extracted from the GCP Unit Database

Data on CTs completed in the period of 2014 to 2018, monitored by the GCP unit at Aalborg and Aarhus University Hospitals, were available for both researchers using a two-way secured log-on. In the GCP unit database, separate files for each CT were organized, and from these the following data were extracted; GCP unit number; e-mail on sponsor or other relevant personnel; name of sponsor or other relevant personnel; title; EudraCT number; completion date; location (Northern or Central region of Denmark); population age (adult or paediatric); phase; intervention (medicinal

product or non-medicinal product including medical device); site (single or multi).

The associated EudraCT number to the corresponding protocol was searched in the EUCTR for all CTs to support the findings from the extracted data. Additionally, data extracted by one researcher were verified by the other and vice versa as the researchers extracted data independently.

2.2. The Trialstracker Database

To investigate whether the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates, investigation of the compliance between reported and non-reported CT summary results from the Trialstracker and the GCP unit databases for non-commercial sponsors in the Northern and Central region of Denmark were carried out. The following inclusion and exclusion criteria were outlined in order to achieve the optimal frame of reference for the comparison analysis.

2.2.1. Inclusion and Exclusion Criteria for Comparison of Data Extracted from the Trialstracker and the GCP Unit Databases

CTs within the period of the 21^{st} of July 2014 to the 11^{th} of April 2018 from both the Trialstracker and the GCP unit databases were included in the comparison analysis. The earliest completion date was set on the 21^{st} of July 2014 as EMA announced that from this date, it became mandatory for sponsors to report summary results in the EudraCT database [14]. The latest completion date was set on the 11^{th} of April 2018 to allow 12 months for reporting results [15].

CTs conducted at Regional Hospitals monitored by the GCP unit were included for the comparison analysis as the Trialstracker database also includes CTs conducted at Regional Hospitals.

The Trialstracker database only defines trials as due if a completion date is present, which automatically exclude ongoing trials or trials with no completion date from the reporting rate percentage presented at the Trialstracker database. To match this, CTs from the GCP unit database were also excluded from the comparison analysis if a CT was listed as ongoing or with no completion date. Furthermore, CTs from the GCP unit database should be registered in the EUCTR to be included.

2.2.2. Procedure for Comparison of Data Extracted from the Trialstracker and the GCP Unit Databases

CTs from the GCP unit database were sorted according to the inclusion and exclusion criteria. The EudraCT numbers were entered in the EUCTR to see whether a summary result was reported or not.

In the Trialstracker database, both Aarhus and Aalborg University were searched. For each university, available CTs were selected based on the inclusion and exclusion criteria.

Data were recorded and transferred to an Excel sheet for further analysis. Additionally, data extracted by one researcher were verified by the other and vice versa as the researchers extracted data independently.

2.3. Questionnaire

To investigate reasons and potential solutions to help explain the low reporting rates and increase the reporting of summary results in the EudraCT database, a Danish custom-made questionnaire was developed.

2.3.1. Inclusion and Exclusion Criteria for Receiving the Questionnaire

A prerequisite for receiving the questionnaire was for sponsors to have an available e-mail listed in the CT protocol from the GCP unit database. If a sponsor appeared multiple times, another e-mail address on other relevant personnel included in the CT team was chosen, such as the investigator. If no e-mail address of other relevant personnel from the CT team were found, the CT was excluded. E-mails were checked for availability through a Google search online and corrected according to the findings. E-mails not available here were also excluded.

2.3.2. Structure of the Questionnaire

A three-part questionnaire consisting of 12 questions was developed using SurveyXact (Version 12.6 Rambøll Management, Aarhus N, Denmark) (Figure 1).

In the beginning of the questionnaire, an overview of the content in the different parts was provided. The questionnaire was designed allowing respondents to be directed to different questions, depending on the answers.

Part one of the questionnaire was initiated by asking the respondents how many CTs they have been involved in, followed by their employment position during the CT monitored by the GCP unit. Next, the respondents were asked towards their experience with reporting summary results in the EudraCT database. No experience, lead the respondents to part two of the questionnaire. Part one continued if they stated having experience and were followed with a question regarding their success in reporting summary results. Stating no success, the respondents were asked if they tried reporting summary results in the EudraCT database, but failed due to complications. If respondents either succeeded in reporting or failed due to complications, they were further asked if they used the online guideline provided by the GCP unit for reporting summary results, and the usefulness of it. Further, they could elaborate on suggestions for improvement of the GCP unit guideline on how to report summary results.

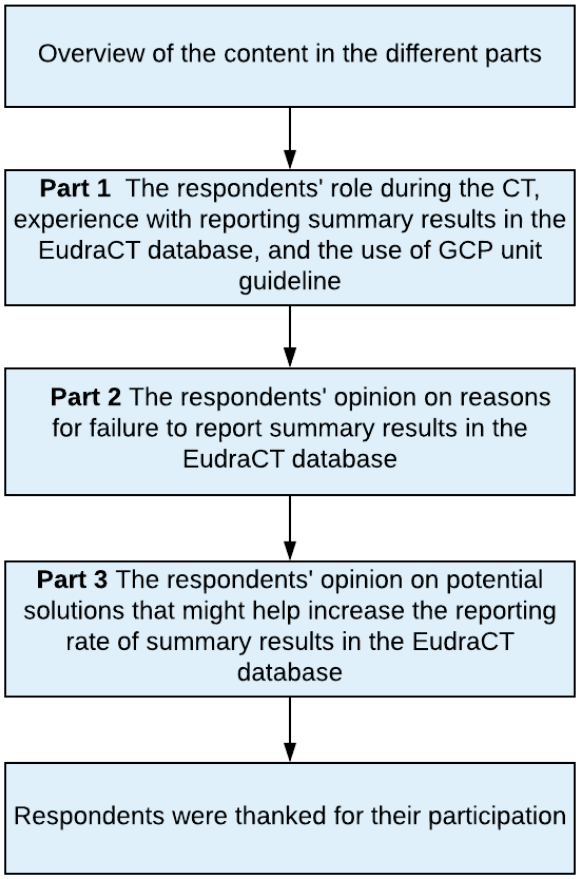

Figure 1: Structure of the Danish custom-made questionnaire

Part two consisted of eight 5-point-likert scale questions, focusing on the respondents' opinion on reasons for non-commercial sponsors' failure to report summary results in the EudraCT database. This was followed by an open-ended question, giving the respondents the opportunity to state their own suggestion on reasons for failure to report summary re-

sults.

Part three consisted of nine 5-point-likert scale questions. Here, the respondents stated their opinion on potential solutions to help increase the reporting of summary results in the EudraCT database. Again, this was followed by an open-ended question where the respondents could elaborate on their own solutions that might help increase the reporting of summary results.

2.3.3. Procedure of Questionnaire Development and Distribution

The questionnaire was compiled based on findings from the literature [5, 15–17], and to ensure reliability and validity of the questionnaire, a profound pretest consisting of three rounds was carried out. Two rounds were performed with experts where one of these rounds was within a focus group to ensure the overall content of the questionnaire. The third round was carried out with laymen to confirm the understanding of the questionnaire. After each round, modifications of the questionnaire were made.

Throughout the development process, efforts were made to create a logical and user-friendly questionnaire to help avoid misconception.

The final version of the questionnaire was distributed via SurveyXact to the e-mail addresses collected from the GCP unit database, including a distribution e-mail. The distribution e-mail included a short elaboration on the thesis of this study, together with information regarding the respondents' anonymity and a link to the questionnaire.

Recipients of the questionnaire had the opportunity to reply the distribution e-mail if any questions occurred. If recipients replied that they were not responsible for reporting the summary results in the EudraCT database, they were encouraged to forward the e-mail with the link to the questionnaire to other relevant personnel from the CT team, or reply to the best of their knowledge and experience.

The questionnaire was available for four weeks from March to April 2019. Reminders were send out four times during this period.

2.4. Statistical Analysis

Processing of data and graphs were carried out by using SurveyXact and Excel 2013 (Microsoft Office Professional Plus 2013, version 15.0.5067.1000, Redmond, Washington, USA). Flowcharts were created using Lucidchart 2018 (Lucid Software Inc., South Jordan, Utah, USA), and data were displayed as numeric or frequencies.

Statistical analyses were performed by using Statistical Package for Social Sciences software (IBM SPSS, version 25, Armonk, New York, USA). $p \leq .05$ was considered statistically significant.

Chi-square tests were carried out to investigate if the reported and non-reported CT summary results from the Trialstracker database were associated with the reported and non-reported CT summary results from the GCP unit database.

Additionally, Chi-square tests were carried out to investigate if the ordinal outcome variables for reasons behind the low reporting rates (lack of knowledge regarding rules and regulations, lack of knowledge regarding who is responsible for reporting results, reporting of results is complicated, reporting of results is time consuming, lack of consequences, results are not worth reporting, failure to recruit enough participants and ends before time, lack of founding to proceed and ends before time) and potential solutions to help increase the reporting rates (more awareness from authorities to obey laws and regulations, fine if deadline exceeds, courses regarding how to report results, ongoing reminders about avail-

able guidelines for reporting results, ongoing reminders regarding deadline for reporting results, telephone counseling, a part of the founding requirement is to report results, creation of a central unit at the university hospitals, reporting documentation is a demand to publish in academic journals) were associated with the explanatory variables (number of initiated CTs, employment position during the CT, and experience in reporting CT summary results).

The ordinal outcome variables were measured on an ordered, categorical 5-point-likert scale (disagree, partly disagree, neither disagree nor agree, partly agree, and agree).

An assumption of the Chi-square test is that 80% of the cells in the cross-tab have a value above 5. If this assumption was not met, Fisher's exact test was applied.

3. Results

3.1. Data Extracted from the GCP Unit Database

In total, 216 completed CTs within the period of 2014 to 2018 were available from the GCP unit database (Figure 2).

Here, 88 CTs were excluded due to; non-commercial sponsor not located in the Northern or Central region of Denmark; commercial sponsor; no initiation of the trial, leaving 128 available CTs. Of these, 28 CTs were further excluded due to; non-medicinal product or medical device; completion date before 2014; phase I trial (adults), leaving 100 CTs conducted on medicinal products in the Northern and Central region of Denmark to be included in this study.

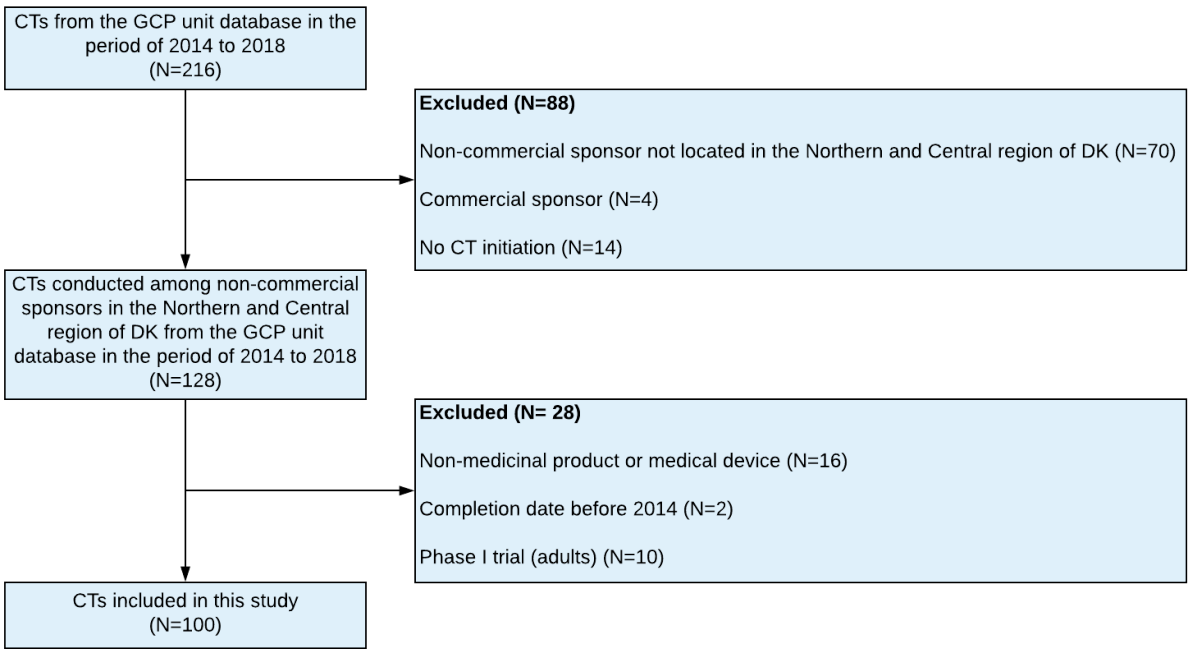

Figure 2: Flowchart of processing data extracted from the GCP unit database in the period of 2014 to 2018. CT: clinical trial, GCP: good clinical practice, N: number, DK: Denmark

Table 2: CTs included from the GCP unit database (N=100)

Variable	Category	2014	2015	2016	2017	2018	N
Total	CTs	12	19	22	28	19	100
Danish region	Central	10	18	19	18	16	81
	Northern	2	1	3	10	3	19
Population age	Adult	11	18	21	27	18	95
	Paediatric	1	1	1	1	1	5
Phase	II	-	11	10	9	6	36
	III	5	1	-	1	1	8
	IV	7	7	12	18	12	56
Site	Single	9	17	18	24	16	84
	Multi	3	2	4	4	3	16

CT: clinical trial, GCP: good clinical practice, N: number

An overview of the 100 included CTs from the GCP unit database is summarized in Table 2. Here, an increase in the conduction of CTs from 12 to 28 was present in the period of 2014 to 2017, where after it decreased in 2018 to 19 CTs. Most sponsors were located in the Central region of Denmark (81%), and the majority of the CTs were conducted on adults (95%). Phase IV (56%) trials were the most common CT design, and 16 out of 100 CTs were a multi-center study.

3.2. Extracted Data from the Trialstracker and the GCP Unit Databases for the Comparison Analysis

The 100 CTs extracted from the GCP unit database were exposed to an additional inclusion and exclusion process in order to meet the criteria for the comparison analysis (Figure 3). Here, 8 CTs from the Northern and Central region of Denmark were excluded due to not having a completion date within the period of the 21^{st} of July 2014 to the 11^{th} of April 2018. Further, 12 CTs were excluded because of being an ongoing trial followed by 11 CTs due to no listed completion date. Additionally, 7 CTs were excluded as they were missing in the EUCTR, resulting in 12 CTs included from the Northern region of Denmark and 50 CTs included from the Central region of Denmark.

From the Trialstracker database, 35 CTs at Aalborg University and 151 CTs at Aarhus University were available and exposed to the inclusion and exclusion process in order to meet the criteria for the comparison analysis (Figure 4). From Aalborg University, 7 CTs were excluded due to a completion date outside the period of the 21^{st} of July 2014 to the 11^{th} of April 2018. Further, 16 CTs were excluded due to being listed as an ongoing trial, and finally 4 CTs were excluded due to a missing completion date. From Aarhus University, 26 CTs were excluded due to a completion date outside the period of the 21^{st} of July 2014 to the 11^{th} of April 2018. Further, 70 CTs due to being listed as an ongoing trial, and finally 18 CTs were excluded due to a missing completion date. This resulted in 8 CTs from Aalborg University and 37 CTs from Aarhus University included for the comparison analysis within the period of the 21^{st} of July 2014 to the 11^{th} of April 2018.

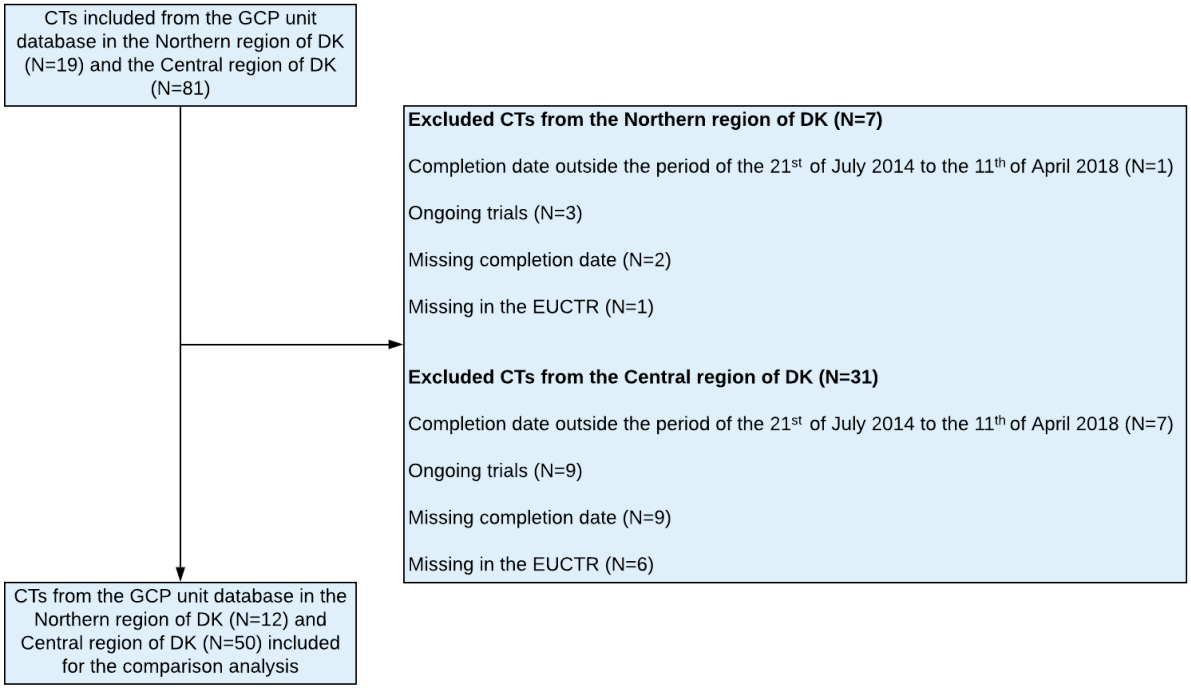

Figure 3: Flowchart of extracted data from the GCP unit database for the Northern and Central region of DK for the comparison analysis. DK: Denmark, CT: clinical trial, N: number, EUCTR: European clinical trial register, GCP: good clinical practice

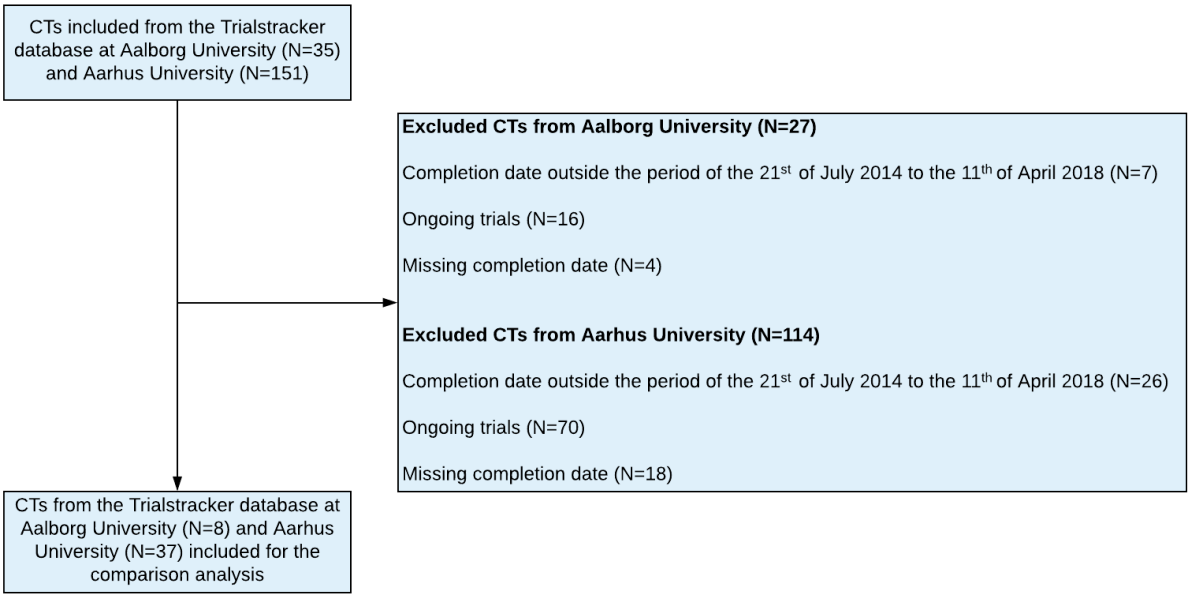

Figure 4: Flowchart of extracted data from the Trialstracker database at Aalborg and Aarhus University for the comparison analysis. CT: clinical trial, N: number

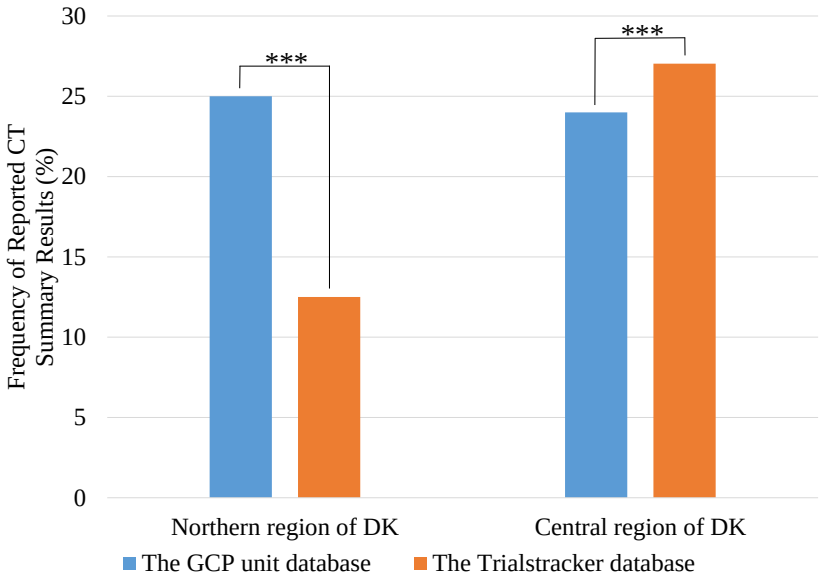

Figure 5: Frequency of reported CT summary results from the GCP unit and the Trialstracker databases for the Northern and Central region of Denmark (N=39). CT: clinical trial, DK: Denmark, GCP: good clinical practice, ***: p<.001 (Fisher's exact test)

3.2.1. Comparison of Data Extracted from the Trialstracker and the GCP Unit Databases

Figure 5 shows the frequency of reported CT summary results from the Trialstracker and GCP unit databases for the Northern and Central region of Denmark.

In the Northern region of Denmark, 3 out of 12 (25%) CTs from the GCP unit database reported summary results. From the Trialstracker database at Aalborg University, 1 out of 8 (12.50%) CTs reported summary results. Here, a Fisher's exact test showed a significant difference (p<.001) of the association between the reported and non-reported CT summary results extracted from the Trialstracker and the GCP unit databases.

In the Central region of Denmark, 12 out of 50 (24%) CTs from the GCP unit database reported summary results. From the Trialstracker database at Aarhus University, 10 out of 37 (27.03%) CTs reported summary results. Here, a Fisher's exact test also showed a significant difference (p<.001) of the association between the reported and non-reported CT summary results extracted from Trialstracker and the GCP unit databases.

3.3. Data Extracted from the Questionnaire

The 100 CTs extracted from the GCP unit included in this study were exposed to an additional inclusion and exclusion process before and after the questionnaire was distributed (Figure 6). Before distributing the questionnaire, 8 e-mails were excluded as sponsor and investigator appeared several times, resulting in 92 recipients eligible to receive the questionnaire. Additionally, 9 e-mails were excluded as SurveyXact stated no availability of these. Four people received the questionnaire twice as they were listed with two different e-mail addresses. Therefore, 4 e-mails were further excluded, leaving 79 recipients of the questionnaire.

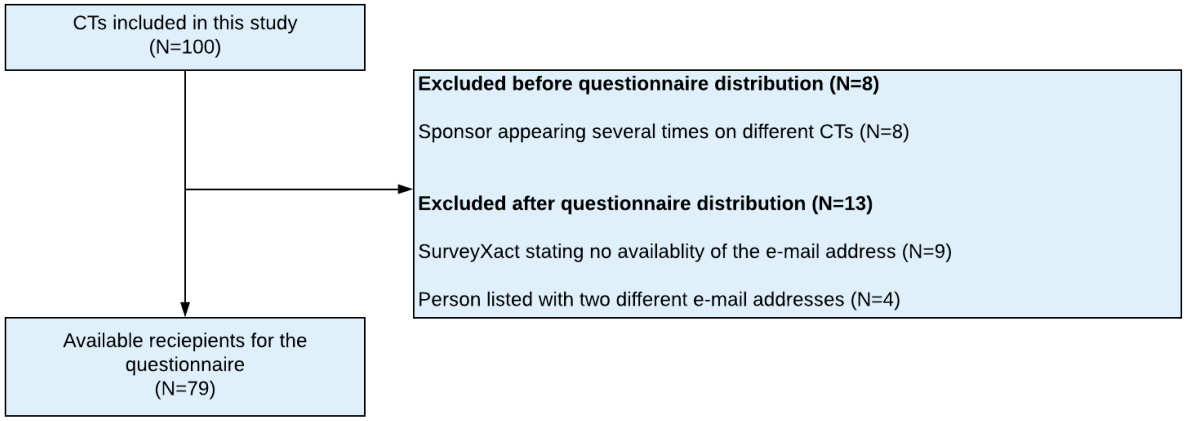

Figure 6: Flowchart of processing elected e-mails to receive the questionnaire before and after questionnaire distribution. CT: clinical trial, N: number

Of the 79 recipients, 6 respondents replied the distribution e-mail, stating that they were not responsible for entering data in the EudraCT database, changed jobs, or that the CT ended years ago, and therefore did not want to respond the questionnaire.

In total, 39 completed the questionnaire (Table 3), resulting in a response-rate of 49.37%.

As summarized in Table 3, the majority of the respondents tried to initiate 1 or 2 CTs (48.72%) and were employed as sponsor-investigator (46.15%). Two respondents stated other employment positions during the CT where one was a clinical research assistant and the other a surgeon. Seventeen out of 39 respondents (43.59%) tried to report a CT summary result where 14 succeeded and 2 tried but failed due to complications. The respondents who tried to report a summary result in the EudraCT database, further, had the opportunity to elaborate on the challenges during the reporting process. Here, 11 out of 39 respondents answered the open-ended question, mentioning that the process was very complicated. This was partly due to a time consuming entry procedure or error messages that they were unable to correct during the reporting process. Of the 17 respondents that tried reporting a CT summary result, 9 used the GCP unit guideline and found it useful.

The respondents had the opportunity to state their opinion towards improvements of the GCP unit guideline, and here it was mentioned that few error messages and how to overcome them were missing in the GCP unit guideline. However, the respondents agreed that the guideline was very useful and helped overcome most of the complications when reporting summary results.

3.3.1. Identified Reasons Behind the Low Reporting Rates

The respondents' rating of the ordinal outcome variables for reasons behind the low reporting rate of summary results is shown in Figure 7 and Appendix C. Here, the ordinal outcome variable "lack of knowledge regarding rules and regulations" showed an equal distribution among the respondents who either disagreed (28.21%) or agreed (28.21%) in this being a reason behind the low reporting rates.

Table 3: Respondents' experience with CTs regarding initiation, employment position, reporting of summary results in the EudraCT database, and the use of the GCP unit guideline (N=39)

Variable	Category	N
Number of initiated CTs	None	3
	1-2	19
	3-4	6
	5+	11
Employment position during the CT	Sponsor	5
	Investigator	14
	Sponsor-investigator	18
	Other	2
Experience in reporting CT summary results	Yes	17
	No	22
Successful reporting of CT summary results	Yes	14
	No	3
Initiated reporting of CT summary results but without success	Yes	2
	No	1
Used the GCP unit guideline	Yes	9
	No	7
Useful GCP unit guideline	Yes	9
	No	0

CT: clinical trial, EudraCT: European union drug regulating authorities clinical trials, GCP: good clinical practice, N: number

The ordinal outcome variable "lack of knowledge regarding who is responsible for reporting results" were rated as not being a reason for the low reporting rates with the majority of the respondents (30.77%). Moreover, most of the respondents agreed that reporting of summary results in the EudraCT database was a complicated and time consuming process (48.72% and 48.72%, respectively).

Further, the majority (35.90%) of the respondents neither disagreed nor agreed that "Lack of consequences" was a reason for the low reporting rates.

When considering "results are not worth reporting", 46.15% of the respondents did not agree with this ordinal outcome variable as being a reason for the low reporting rates. Likewise, "failure to recruit enough participants and ends before time" and "lack of founding to proceed and ends before time" were also not considered as reasons for the low reporting rates among the majority of the respondents (41.03% and 48.72%, respectively).

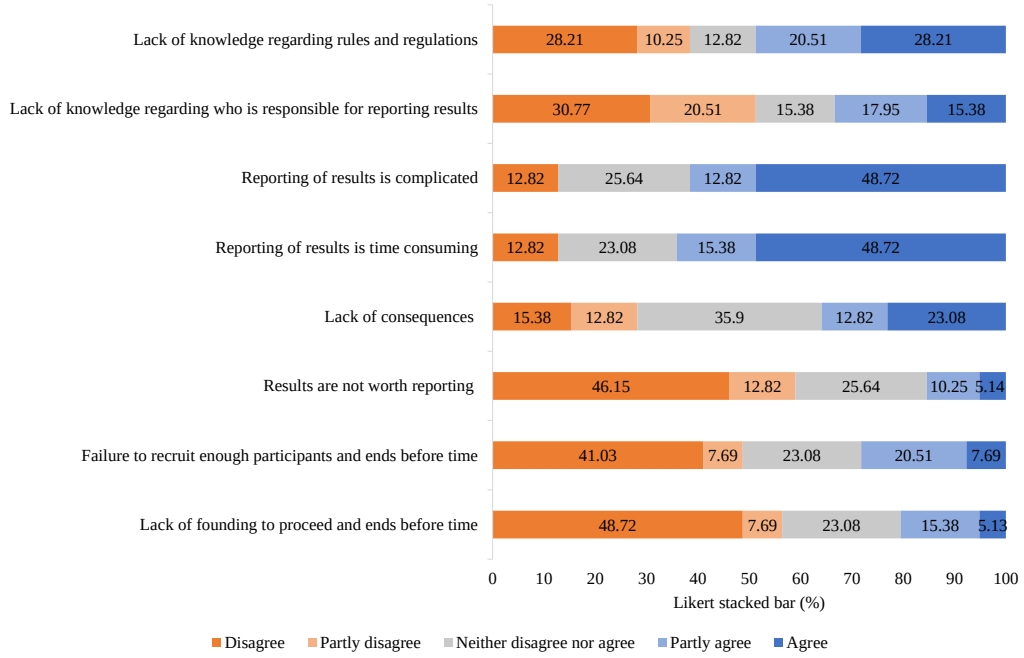

Figure 7: Frequency of respondents' opinion on reasons for non-commercial sponsors' failure to report CT summary results (N=39). CT: clinical trial, N: number

For the ordinal outcome variable "reporting of results is complicated", Fisher's exact tests showed statistically significant associations with the explanatory variables "number of initiated CTs" (p=.050) and "experience in reporting CT summary results" (p=.001), and no statistical significant association with "employment position during a CT" (p=.828). For "reporting of results is time consuming", Fisher's exact tests showed a statistically significant association with the explanatory variable "experience in reporting CT summary results" (p=.002) and no statistically significant associations with "number of initiated CTs" (p=.095) and "employment position during the CT" (p=.868).

Associations between the remaining ordinal outcome variables for reasons behind the low reporting rates and the explanatory variables are seen in Appendix D.

In the open-ended question, the respondents had the opportunity to elaborate on their own suggestions regarding reasons for non-commercial sponsors failure to report summary results. Here, the respondents did not add any new reasons, but stated that reminders from authorities and training in how to enter summary results were important to increase the reporting rates.

3.3.2. Potential Solutions to Help Increase the Reporting Rates

The respondents' rating of the ordinal outcome variables on potential solutions to help increase the reporting of summary results is

shown in Figure 8 and Appendix E.

Here, the ordinal outcome variable ”more awareness from authorities to obey laws and regulations” showed an almost equal distribution among the respondents who either disagreed (25.64%) or agreed (23.08%) in this being a potential solution to help increase the reporting rates. Further, 58.97% of the respondents agreed that ”fine if deadline exceeds” should not be a solution to help increase the reporting rates.

The majority of the respondents (33.33%) partly agreed that ”courses regarding how to report results” could be a potential solution to help increase the reporting of summary results.

Additionally, ”ongoing reminders about available guidelines for reporting results” and ”ongoing reminders regarding deadline for reporting results” were also by the majority (30.77% and 33.33%, respectively) of the respondents rated as potential solutions.

”Telephone counseling” was by the majority of the respondents rated as a potential solutions to help increase the reporting rates as 35.9% of the respondents agreed, 30.77% partly agreed, 23.08% neither disagreed nor agreed, 7.69% partly disagreed, and 2.56% disagreed.

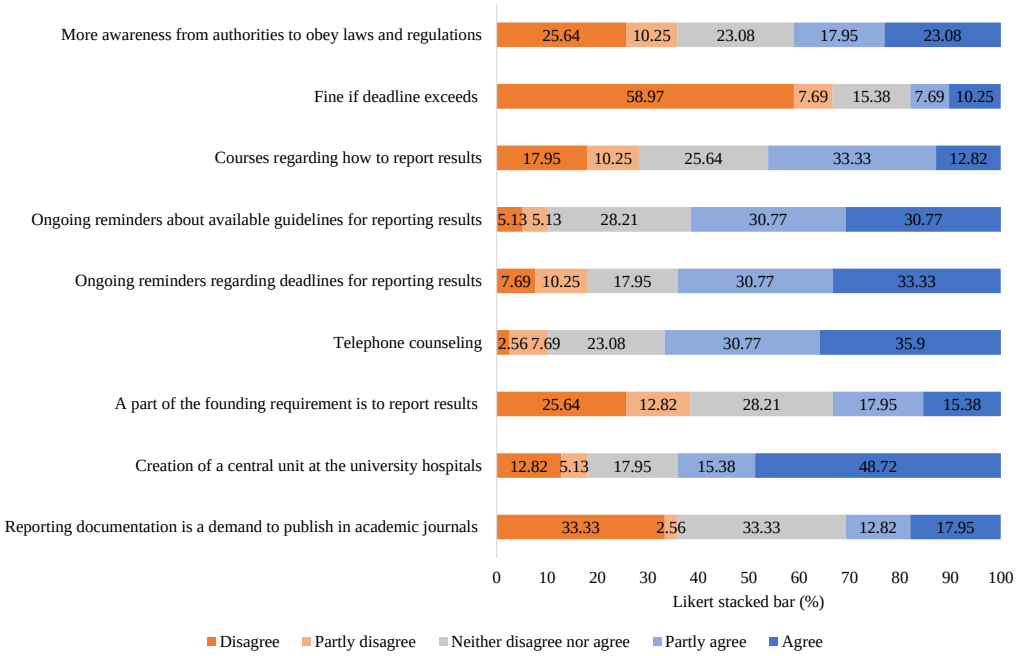

Figure 8: Frequency of respondents' opinion on potential solutions to help increase the reporting rate of CT summary results (N=39). CT: clinical trial, N: number

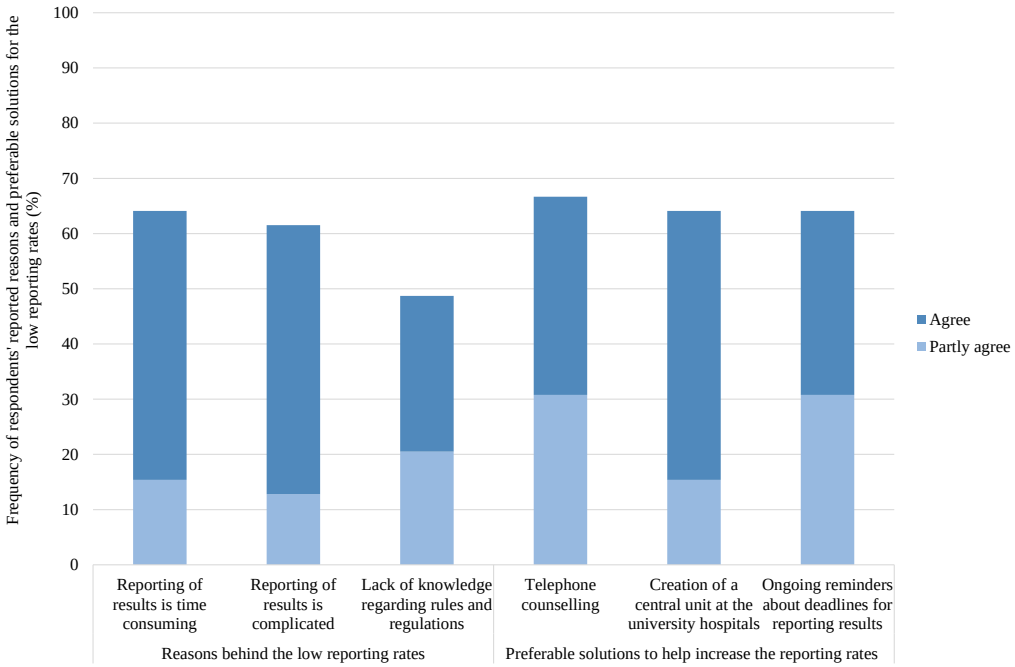

Figure 9: Frequency of respondents' reported reasons and preferable solutions to help explain the low reporting rates and increase the reporting of summary results in the EudraCT database (N=39)

For the ordinal outcome variable "a part of the founding requirement is to report results", most of the respondents neither disagreed nor agreed (28.21%) with this being a potential solution, followed by 25.64% of the respondents who disagreed.

"Creation of a central unit at the university hospitals" was by the majority (48.72%) of the respondents rated as a potential solutions to help increase the reporting rate of CT summary results in the EudraCT database. Lastly, "reporting documentation is a demand to publish in academic journals" were among the respondents equally divided between disagree (33.33%) and neither disagree nor agree (33.33%) as not being a potential solution.

For the ordinal outcome variable "telephone counseling", Fisher's exact tests showed a statistically significant association with the explanatory variable "number of initiated CTs" (p=.034) and no statistically significant associations with "employment position during the CT" (p=.309) and "experience in reporting CT summary results" (p=.492).

For the remaining ordinal outcome variables for potential solutions to help increase the reporting of summary results, no statistically significant associations with the explanatory variables were found (Appendix F).

When giving the respondents the opportunity to elaborate on their opinion on potential solutions to help increase the reporting rates, one respondent commented that: "*Too many authorities are involved*".

3.3.3. Summarized Findings on Reasons and Potential Solutions for the Low Reporting Rates

The respondents' preferred reasons and potential solutions to help explain the low reporting rate and increase the reporting of summary results in the EudraCT database are summarized in Figure 9, which presents a compile of data based on frequencies of respondents' answers indicated as agree and partly agree.

As seen in Figure 9, the respondents agreed that "reporting of results is time consuming", "reporting of results is complicated", and "lack of knowledge regarding rules and regulations" were main reasons for failure to report CT summary results. Additionally, "telephone counseling", "creation of a central unit at the university hospitals", and "ongoing reminders regarding deadline for reporting results" were identified as the preferable solutions to help increase the reporting of summary results.

4. Discussion

The current study attempted to investigate reasons behind the low reporting rate of summary results in the EudraCT database among non-commercial sponsors in the Northern and Central region of Denmark for CTs completed within the period of 2014 to 2018, and to propose potential solutions that might help increase the reporting rates. Furthermore, investigation of compliance between reported and non-reported CT summary results from the Trialstracker and the GCP unit databases were carried out for non-commercial sponsors in the Northern and Central region of Denmark to examine if the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates.

Regardless of the explanatory variables, the main findings of this study showed that reporting of summary results is a time consuming and complicated process and that lack of knowledge regarding the European Legal framework are reasons for failure to report CT summary results. Furthermore, the respondents reported telephone counseling, creation of a central unit at the university hospitals, and sending out ongoing reminders regarding deadline for reporting results as the preferred solutions to help increase the reporting of summary results.

4.1. Comparison of the Trialstracker and the GCP Unit Databases

In this study, it was expected that the Trialstracker database was a reliable source to obtain an overview of non-commercial sponsors' reporting rates. No other studies have yet investigated the trustworthiness of the Trialstracker database in Denmark. This study found that the reporting rate of CT summary results extracted from the Trialstracker database at Aarhus University (27.03%) was somehow similar to data extracted from the GCP unit database in the Central Region of Denmark (24%). A greater difference was seen when comparing data extracted from the Trialstracker database at Aalborg University, showing a lower frequency (12.5%) of reported summary results compared to reported summary results from the GCP unit database in the Northern region of Denmark (25%). Further, the comparison analysis in this study showed significant differences between the reported and non-reported CT summary results obtained from the Trialstracker and the GCP unit databases for the Northern and Central region of Denmark, indicating that the report-

ing rates are not comparable. Similarly to the method in this study, a study by *Powell et al.* also investigated reporting rates from Oxford University through a manual search in the EUCTR and compared it with reporting rates from the Trialstracker database. *Powell et al.* found a compliance between the two databases, contradicting the finding in this study [30]. On the contrary, a study by *Coens et al.* stated some concerns regarding the Trialstracker database being a newly established website and as a result to this, misleading and incomplete representation of the actual reporting rates might occur [31]. This implies that there are some inconsistencies regarding the trustworthiness of using the Trialstracker database to obtain an overview of the reporting rates. Still, the Trialstracker database presents as the first tool to show ongoing public monitoring of sponsors' reporting rates at a lower cost than a manual search. However, the Trialstracker database have shown not to produce results with the accuracy of a manual search [30].

Despite the differences, several articles welcome the Trialstracker database as a new initiative [5, 30–32]. The Trialstracker database can help increase CT transparency and bring awareness to sponsors with low reporting rates, concurrently with being a freely accessible and public website [5, 30]. Therefore, the Trialstracker database can be considered as a reliable source to obtain an overview of non-commercial sponsors' reporting rates, although it is important to interpret the reporting rates with precaution.

4.2. Reasons and Potential Solutions for the Low Reporting Rates

The following sections discuss the identified reasons and potential solutions for the low reporting rates, followed by suggestions on how the potential solutions can be implemented in Denmark.

4.2.1. Reasons Behind the Low Reporting Rates

In compliance with the hypothesis of this study, it was found that a complicated and time consuming entry procedure were identified as the main reasons behind the low reporting rate of summary results in the EudraCT database among non-commercial sponsors. To further support these findings, significant associations among respondents with different experience in reporting CT summary results and number of initiated CTs with the outcome variable "reporting of results is complicated" were found. Additionally, a significant association was found for respondents with different experience in reporting CT summary results and the outcome variable "reporting of results is time consuming". A study by *Goldacre et al.* stated that sponsors initiating a larger number of CTs and with different levels of experience in reporting summary results were more likely to report results in the EudraCT database, influencing the reporting rates positively as the entry procedure might become easier [5]. This might explain the significant differences found in this study as the non-commercial sponsors mostly initiated one or two CTs and therefore might have limited experience in reporting summary results in the EudraCT database, making it a complicated and time consuming procedure. Since CT summary results first became mandatory for sponsors to report in the EudraCT database in July 2014 [33], it might still be considered a new initiative as implementation of new regulations can require an adaption process. However, adaption to complicated entry procedures can be a time consuming process, which might ex-

plain the main reasons for the low reporting rates identified in this study. As the public health care system is often characterized by time limitations [34], it can be difficult for non-commercial sponsors to find the time to acquaint themselves with the reporting procedure, thereby reaching a level where the reporting of summary results becomes a well-known process.

Several organizations and authorities, such as the Universities Allied for Essential Medicines (UAEM), Danish Medicines Agency (DMA), and EMA are becoming aware of the low reporting rate of CT summary results, including the complicated and time consuming entry procedure that follows [14, 35, 36].

The organization UAEM were established in 2001, promoting equitable access to medicine for all people around the world [35]. UAEM further took on another key issue promoting CT transparency, and in countries around the world students from different universities including Denmark are joining to advocate and raise awareness towards CT transparency [35]. By welcoming UAEM in Denmark, they can help raise awareness at the university hospitals towards reasons for the low reporting rates in order to help increase the reporting of summary results.

The DMA reported in 2018 that the number of CTs conducted in Denmark increased from 9-10% in 2015 to 12% in 2017 [36]. Since the number of CTs is increasing, the need to report summary results becomes crucial to avoid a further decrease in the reporting rates. To help overcome this, more awareness towards the European legal framework provided by the DMA might be necessary as lack of knowledge regarding rules and regulations was identified as a reason for failure to report summary results. Therefore, better compliance with the legal framework might result in a more open and transparent focus, where society in the future can benefit from and trust the new knowledge gained from CTs [21].

EMA also participates in raising awareness towards the European legal framework, and in connection to this a new regulation (EU no. 536/2014) is in the pipeline [37]. This new regulation is intended to assure a higher level of harmonization of the European legal framework, and to create a favorable environment with high focus on safety standards when conducting CTs [37]. One important change in the EU no. 536/2014 regulation concerns the authorization process for CT approval. To facilitate the authorization process in each member state, a new EU portal is being created in order for sponsors to submit and register CTs in one place [37]. Through this new EU portal, all submission documents are automatically being divided to the applicable authorities in the respective countries. This can help facilitate multi-center CTs [37], which might eventually result in an increase of CTs conducted in the EU. Although, the new regulation (EU no. 536/2014) was enforced in 2014, it is still not applicable for the EU member states as the new EU portal is not fully developed [38]. It is expected that the implementation of the new EU portal can help eliminate some of the identified reasons behind the low reporting rates found in this study, such as the complicated and time consuming entry procedure and lack of knowledge regarding rules and regulations. It is further expected that the new EU portal can result in less contact to multiple authorities, resulting in more surplus energy among the non-commercial sponsors towards reporting CT summary results in the EudraCT database [37].

This study also found that lack of knowledge regarding who is responsible for entering summary results was not a reason for the low reporting rates, which is in compliance with the ICH-GCP guideline [10]. Here, it is

clearly stated who is responsible for entering results in the EudraCT database [10], pointing out there should be no doubt regarding who is responsible. However, it is known that the reporting rates for non-commercial sponsors are low [5], indicating that there actually might be a lack of knowledge regarding who is responsible. This is supported by *Goldacre et al.*, also stating that non-commercial sponsors are not enlightened in who is responsible for reporting results [5]. *Goldacre et al.* further stated that, in reality, this responsibility is sometimes delegated to other personnel within the CT team, such as the principal investigator [5]. There is no doubt that disclosing of CT summary results is important for both ethically and scientific reasons. Therefore, more awareness from authorities regarding who is responsible for reporting summary results is needed to ensure that all sponsors are fully aware of their responsibility.

4.2.2. Potential Solutions to Help Increase the Reporting Rates

The majority of the respondents in this study agreed that telephone counseling and creation of a central unit at the university hospitals could be potential solutions to help increase the reporting rates. This is in agreement with the hypothesis in this study, stating that the majority of the respondents agreed that counseling from a third party was the preferred solution.

A potential solution, involving a third party could be creation of a central unit. This solution has already been carried out at the University of Bristol (United Kingdom) with a small research team, managing and supporting registration and entering of CTs in the EudraCT database [39]. This implementation increased the reporting rate percentage of summary results at Bristol University [39], demonstrating that a central unit can be responsible for reporting CT summary results, and potentially increase the reporting rates.

Further, this study identified that creation of a telephone counseling unit might also be a potential solution to help increase the reporting rates. However, with precaution to that telephone counseling can be less effective than creation of a central unit as it might be difficult to guide sponsors through the reporting process over the phone. To overcome this, the telephone counselors' computer can be connected to the computer of the sponsor by using Remote Desktop Connection or a similar software [40]. Nevertheless, by implementing a telephone counseling unit, sponsors might be more prone to learn how to report summary results themselves as they are guided through the process together with the telephone counselor, and with time decreasing the need to use guidance, thereby also reducing costs.

Another proposal with help from a third party could be performing of external audits. Aberdeen University (Scotland) was the first being exposed to this solution [41]. The aim of these audits was to highlight shortcomings in the reporting procedure, and to remind the non-commercial sponsors to report summary results in order for the university itself to increase the reporting rate [41]. During the external audits, the reporting of CT summary results was investigated through a manual search [37]. Though, this solution turned out being a time consuming and costly process for the university, questioning the effectiveness on the reporting rates in relation to the workload and use of resources [41].

A different solution with the involvement of a third party could include specific founding requirements [42, 43]. The respondents in this study did not find this requirement as a potential solution, though several foundations, such as the Bill and Melinda Gates foundation have already established founding

requirements where a part of the requirement is to report summary results [42]. This is an upcoming requirement among various foundations [42], why sponsors conducting CTs can be compelled to obey such requirements in the future. However, there are already many deadlines to respond to when conducting CTs, thus it can be difficult for the non-commercial sponsors to comply with additional requirements. As the majority of the respondents in this study reported ongoing reminders regarding deadline for reporting results as a potential solution to help increase the reporting rates, implementation of ongoing reminders for the various requirements could therefore be a way to help ease the workload for the non-commercial sponsors.

Commercial sponsors are better in complying with the various deadlines, including reporting of CT summary results as they often have employed staff only focusing on ensuring that they are in compliance with the legal framework [5, 16]. For non-commercial sponsors, it can therefore be suggested that non-profit organizations, such as governmental institutions or the GCP units advocate for the awareness of the importance of complying with the reporting requirements. For this, training-workshops in how to enter results in the EudraCT database could help maintain and reach a reporting rate of 100%. Supporting this solution, the majority of respondents in this study reported courses regarding how to report results as a potential solution, again emphasizing the importance of involvement of a third party.

4.2.3. Implementation of Potential Solutions

Despite numerous efforts to increase the reporting rate of summary results in the EudraCT database, the problem regarding CT transparency still persists [5, 16, 43]. Therefore, this study investigated reasons and potential solutions, trying to overcome this problem.

The findings of this study showed that there is not one reason, but several reasons that could help explain the failure of reporting CT summary results among non-commercial sponsors, indicating that implementation of several solutions might be necessary.

This study recommends creating a telephone counseling unit or a central unit as these potential solutions were rated as the preferable ones. These implementation methods may be costly and time consuming to implement mainly due to training of staff. Though, if a unit is well-established, it can evolve and become an ”on-demand” support unit only running when needed with one person in charge [39], resulting in future low costs and use of resources. If universities and university hospitals are not able to find resources to implement such units, another solution might be to send out ongoing electronic reminders, concerning deadline for reporting summary results, as this is an inexpensive and easy method to implement.

If resources at the universities and university hospitals are not adequate, other institutions can help facilitate the process, such as the DMA and the GCP unit as these organizations might have more resources and staff with already experience in reporting summary results. For the DMA, ongoing automatically reminders regarding deadline for reporting summary results in the EudraCT database could be implemented. This could also be implemented at the GCP unit for their monitored CTs, though this would extend the monitoring period for the non-commercial sponsors until the results have been reported in the EudraCT database. In addition to sending out reminders regarding deadline for reporting results, guidelines on how to report summary results could be included. These guidelines

should be available in both English and the native language in format of both a text document and a video.

If further solutions are needed in order to increase the reporting rates even more, sanctions might become necessary to implement. However, this study found that the majority of the respondents did not report fines as a potential solution if the deadline of reporting summary results exceeds 12 months. Therefore, implementation of sanctions should be carried out with precaution to a negative outcome such as an unwanted decrease of CTs conducted in the EU.

Even though, sponsors are responsible for reporting CT summary results, the entire responsibility should reflect on all parties involved in CT conduction as CT transparency influences the entire society. Therefore, awareness and action from all parties involved are required, including a strong political support from the authorities as well as adequate legal powers to increase the low reporting rates.

4.3. Limitations and Strengths

4.3.1. Databases Used in This Study

In the GCP unit database, it was not always easy for the researchers to identify the EudraCT number for all CTs as the EudraCT numbers were not consistently placed uniformly in the folders. To strengthen this weakness, both researchers independently searched all folders in the GCP unit database to avoid missing EudraCT numbers. For some of the identified EudraCT numbers, a search in the EUCTR showed no results. This might have been due to a typing error of the non-commercial sponsors when filling out the legal documents. Therefore, the title of the corresponding CT was entered in the EUCTR. For these, some CTs still showed no results and were therefore excluded from this study. Another possible solution to explain the missing CTs in the EUCTR might also be lack of registration by the DMA.

For the Trialstracker database, the researchers of this study did not have any requisite on how this database technically works. A software engineer understanding the logarithm of the Trialstracker database could be an advantage, proposing different inclusion and exclusion criteria in order to equalize data used for the comparison analysis even more. However, data extracted from the Trialstracker and the GCP unit databases both obtain reporting of CT summary results from the EUCTR, forming a good frame of reference for the comparison analysis.

4.3.2. Questionnaire

A custom-made questionnaire-based approach was chosen for this study, as it is a fast and efficient method to obtain data. Though, it relies on the respondents to answer correctly, and it has proven a challenge as respondents might perceive the questions different than the researchers intended [44]. Pretests were therefore carried out to ensure reliability and validity of the questionnaire.

Data from the costum-made questionnaire were collected through non-probability sampling. The advantages are that this way of collecting data is inexpensive, simple, and efficient [45]. A disadvantage of this sampling method is the lack of generalizability as the population is selected based on accessibility [46]. Therefore, a high response rate is recommended to legitimize data of the questionnaire [46].

Furthermore, questionnaires developed for physicians are an important and cost-effective source of information in health care research [47]. It was found from the CTs monitored by the GCP unit database that most sponsors

and investigators were listed as physicians. A study by *Wiebe et al.* investigated physicians' response rate to a questionnaire, and found that 76 out of 542 (14%) physicians responded to the distributed questionnaire where three reminders were send [48]. It is recommended that a response rate of at least 60% would be optimal to provide a valid questionnaire with a low response bias [48]. This study achieved a response rate of 49.37%, not reaching the optimal response rate. As web-based questionnaires with physicians in the literature have shown a lower response rate, this might clarify the occurrence of the low response rate in this study [47, 48]. Throughout this study, individual personalized e-mails to the respondents were distributed together with reminders. Additional initiatives could entail a draw for a gift card, which has shown to increase the interest of responding web-based questionnaires [47, 49]. Though, the effect of other initiatives to increase the response rate to 60% is uncertain as one of the main reasons for why physicians do not answer is due to a busy and time limited working schedule [47].

5. Conclusion

This study investigated reasons and potential solutions for the low reporting of summary results in the EudraCT database for non-commercial sponsors in the Northern and Central region of Denmark.

It was found that respondents agreed that reporting of CT summary results is a time consuming and complicated process and that lack of knowledge regarding the European legal framework can be considered main reasons for failure to report summary results.

The preferable solutions to help increase the reporting rates were telephone counseling, creation of a central unit at the university hospitals, and sending out ongoing reminders regarding deadline for reporting results.

Identification of reasons behind the low reporting rate of summary results are important to help locate where to start initiate solutions. Eventually, this will lead to promotion and improvement of CT transparency, patient outcomes, efficient use of healthcare resources, and new medicinal treatments. As several reasons were identified, a combination of the preferable solutions might also be beneficial to consider, as one solution might not be enough.

It is too soon to generalize the findings obtained in this study. Therefore, further research is needed to substantiate the findings and to establish how the potential solutions can be implemented in Denmark.

6. Future Perspectives

Extensive data on the prevalence of the low reporting rates are already well established in the literature [5, 16, 43]. Instead of repeating similar retrospective prevalence studies, the next step should focus on further determining reasons and potential solutions to help explain the low reporting rates and increase the reporting of summary results.

This study provides a foundation for expanding the research to all regions of Denmark. The first step could therefore be a re-distribution of the questionnaire to non-commercial sponsors at the GCP units at Odense and Copenhagen University Hospitals. Such a nation-wide questionnaire-based observational cross-sectional study might substantiate the findings and provide additional knowledge on different views and opinions.

Another important step is to investigate the possibility of accommodating some of the potential solutions identified in this pilot study. Interviews performed on non-

commercial sponsors at the University Hospitals in Denmark within a focus group might confirm or bring new knowledge into the searchlight to see if implementation of the identified potential solutions, such as telephone counseling, creation of a central unit at the university hospitals, and ongoing reminders regarding deadline for reporting results could be a reality to implement in the daily work routines at a clinical research site.

If further knowledge regarding the implementation of the preferable solutions among non-commercial sponsors in Denmark should be obtained, a larger randomized parallel study could be initiated. Such a prospective study could incorporate three preferable solutions, such as telephone counseling, creation of a central unit at the university hospitals, and ongoing reminders regarding deadline for reporting results. Furthermore, a control group containing no implementation method could help getting a more powerful study design. This approach seems beneficial in order to move towards validation of a potential solution to implement in Denmark.

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Appendices

A. Content of Summary Results

II

(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS AND BODIES

COMMISSION

Communication from the Commission — Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006

(2009/C 28/01)

1. **INTRODUCTION AND SCOPE**

Regulation (EC) No 1901/2006 on medicinal products for paediatric use ([1]) (hereafter the 'Paediatric' Regulation) entered into force on 26 January 2007. Article 41(3) of the Regulation requires the Commission to draw up guidance on the nature of the information on paediatric clinical trials to be entered into the database of clinical trials (EudraCT ([2])), on which information shall be made available to the public, on how clinical trials results shall be submitted and be made public and on the European Medicines Agency (EMEA)'s responsibilities and tasks in this regard.

This obligation aims to increase the availability of information on the use of medicinal products in the paediatric population and to avoid unnecessary repetition of studies. The information is aimed at the public which includes lay persons, patients and families, health professionals, researchers and academics as well as industry and regulators.

This guidance sets out the nature of the information to be entered into EudraCT, the information to be made accessible to the public, the paediatric clinical trial results to be submitted and made public and on the responsibilities of the EMEA and related tasks in this context.

The information referred to in this guidance comprises paediatric clinical trial protocol-related information and paediatric trial results. Such information is to be entered into EudraCT in cases where the respective paediatric trial has at least one investigator site in the European Economic Area (EEA), and/or is part of an agreed Paediatric Investigation Plan (PIP ([3])). It concerns paediatric trials planned, ongoing or completed in the EEA and those that are planned, ongoing or completed in any other country ('third countries') provided these latter trials are included in a PIP. The status of each paediatric trial will be identified (e.g. under assessment, authorised or refused, ongoing, prematurely ended or completed). This status will be listed for each Member State.

The EudraCT data fields are for the most part consistent with international initiatives relating to clinical trial registries, e.g. WHO International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE). Although EudraCT may have additional fields, the convergence of the information to be made public with the WHO ICTRP facilitates the work of sponsors and researchers submitting information to different registries for different purposes, and facilitates access to this information.

The Commission's Directorate-General for Enterprise and Industry (DG ENTR) ([4]) will make available the list of the specific data fields to be included in EudraCT, and those to be made public.

([1]) OJ L 378, 27.12.2006, p. 1.
([2]) http://eudract.emea.europa.eu/
([3]) See point 2, Article 2 of the Paediatric Regulation.
([4]) http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

2. NATURE OF THE INFORMATION TO BE ENTERED INTO EUDRACT AND TIMING

2.1. Nature of the information

The nature of the required information to be entered into EudraCT is based on its importance to clinical trials contained in an agreed PIP. Two sets of information are required:

— paediatric trial protocol related information — supplied prior to the start of the trial and updated if needed during the trial describing the trial protocol, investigational medicinal products (IMPs), therapeutic indication, trial population, the trial authorisation and the current status of the trial,

— paediatric trial results related information — supplied after the completion of the trial and containing a summary of the results and conclusions.

2.2. Timing of entering of the information into EudraCT

2.2.1. *Protocol related information*

All interventional paediatric clinical trials with at least one site in the EEA are required to be entered into EudraCT no later than at the time of the valid application for authorisation of a clinical trial to the National Competent Authorities (NCA).

All clinical trials that are included in an agreed PIP should also be included, whether the trials are planned, ongoing, or completed.

In particular, all paediatric trials conducted with at least one site in a third country and included in an agreed PIP, should be entered into EudraCT no later than one month after, either, the EMEA decision agreeing a PIP, or, the first approval/positive opinion of the trial by a third country competent authority and/or third country ethics committee, whichever is the latest.

2.2.2. *Result related information*

Result-related information for paediatric trials should be submitted to the EMEA, for entry into EudraCT, no more than six months after the trial has ended, whether the trial has been completed or prematurely terminated, whichever occurs first.

However, notwithstanding the above, if

— the clinical trial does not fall within the scope of Article 46(1) of the Paediatric Regulation, and

— it is for objective scientific reasons not possible to submit the result-related information within six months, which has been demonstrated by the submitting party,

result-related information for paediatric trials may be submitted to the EMEA, for entry into EudraCT, at the latest within twelve months after the trial has ended, whether the trial has been completed or prematurely terminated, whichever occurs first.

For the purpose of submitting result-related information, a trial is considered completed when the last visit of the last patient has occurred, as foreseen in the latest version of the protocol. This means that, for the purpose of submitting result-related information for inclusion into EudraCT, open trial extensions, e.g. for maintenance treatment, are not considered as part of the trial.

2.2.3. *Submission of the information into EudraCT*

The sponsor, PIP holder or Marketing Authorisation Holder (MAH) submits the information electronically to the EudraCT staging area, once such a staging area is operational.

In the interim, the information is submitted in electronic format.

3. INFORMATION TO BE MADE AVAILABLE TO THE PUBLIC

3.1. Protocol related information

The information to be included in EudraCT and to be made public will include details of the following elements:

— identification of the clinical trial and its protocol,

— sponsor,

— source of funding,

— contact point for public use,

— identification and description of the treatment arms of the study (IMPs) to be used,

— therapeutic objective of the trial (disease under investigation),

— major objectives and endpoints,

— trial design including the countries in which it is to be conducted,

— trial population,

— inclusion/exclusion criteria,

— trial status (per country or region as applicable), and if refused for ethical reasons the reasons for refusal.

3.2. **Results related information**

The information to be included in EudraCT and to be made public should take into account the format for summary of results set out in the ICE E3 guideline [1]. It will cover the following elements:

— administrative information and trial identification,

— trial design,

— scientific background and explanation of rationale for the trial,

— participants in the trial — information on the subject population including inclusion exclusion criteria and demographic information,

— interventions — the treatments used,

— objective(s) of the trial,

— outcome measures,

— randomisation implementation,

— blinding,

— statistical methods,

— patient disposition,

— protocol deviations,

— recruitment,

— baseline data,

— trial interruption,

— outcomes and estimation,

— ancillary analysis,

— adverse events,

— trial termination,

— discussion and interpretation of study results (interpretation of trial results by sponsor, if available and by competent authority, if available),

— a declaration of the submitting party on liability for the accuracy of the submitted information.

[1] http://www.ich.org/

3.3. **Timing of making information accessible to the public**

Protocol-related information will be made public automatically, once the data has been entered into EudraCT and the trial bas been approved by the NCA concerned. Where a negative opinion bas been issued by an Ethics Committee, the information on the trial will still be published, together with a field indicating the reason for the negative opinion.

Public release of result-related information takes places automatically once this information has been included by the EMEA in the EudraCT database.

3.4. **How information is made public**

The information will be made available through a dedicated public website containing a subset of information regularly updated from EudraCT. Appropriate disclaimers will be included to reflect the stage of regulatory evaluation of the trial.

Studies not registered in EudraCT and for which protocol-related information is not available, e.g. because the conduct of the studies predated requirements for inclusion in EudraCT, should be specifically identified.

Result-related information is not validated prior to its inclusion into EudraCT. Responsibility for the result-related information lies with the sponsor, PIP holder or MAH submitting the results.

EudraCT will contain a disclaimer to this effect.

If and when the results are submitted for assessment (e.g. in a marketing authorisation application), a link to the public assessment report will be made.

4. **RESPONSIBILITIES OF THE EMEA AND TASKS IN THIS REGARD**

4.1. **The EMEA's responsibilities**

The EMEA should:

— make public the protocol-related information on paediatric clinical trials in accordance with this guideline and the lists of data fields made public by DG ENTR,

— make public the result-related information on trials included in EudraCT and on any paediatric studies submitted according to Article 45 and 46 of the Paediatric Regulation,

— coordinate the exchange of information,

— manage the EudraCT database.

4.2. **The related tasks**

The responsibility for the initiation of the process, electronic submission of protocol and result related data, and maintenance of data lies with:

— the MAH, in the case of provision of the results of an authorised medicinal product in accordance with the obligations in Articles 45 and 46 of the Paediatric Regulation,

— the sponsor of trials referred to by Article 41, whether or not it is the MAH,

— the PIP addressee.

The EMEA should:

— enter into EudraCT the protocol information received electronically for third-country trials including their authorisation status and information regarding the end of trial status,

— enter the result information received electronically into EudraCT,

— make public data from the protocol-related and result-related information in accordance with Section 3.4.

The NCAs should:

— enter the protocol information received electronically into EudraCT,

— enter information concerning the review and oversight of the paediatric trial,

— exchange information with the EMEA on the studies submitted,

— enter additional data relating to the review and authorisation, amendment and end of the trial, to be recorded directly into EudraCT by the NCAs or by transmission of the information from national clinical trial databases.

5. **IMPLEMENTATION**

The guidance set out in this Communication applies:

— as regards the protocol-related information, as soon as the programming of EudraCT has been finalised,

— as regards the result-related information, once the detailed guidelines for the reporting format have been published and the related programming has been finalised.

Finalisation of the programming will be publicly announced.

B. Example of a Summary Result

EU Clinical Trials Register

Clinical trial results:
Intestinal Inflammation in Ankylosing Spondylitis assessed by Fecal Calprotectin, Capsular Endoscopy and Colonoscopy and the effects of Adalimumab on mucosal healing

Summary

EudraCT number	2009-018085-35
Trial protocol	DK
Global end of trial date	11 March 2014
Results information	
Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

Trial information

Trial identification	
Sponsor protocol code	4682724
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01174186
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Regionshospitalet Silkeborg
Sponsor organisation address	Falkevej 1, Silkeborg, Denmark, 8220
Public contact	Studieledelse, Regionshospitalet Silkeborg, +45 87222360, henngler@rm.dk
Scientific contact	Studieledelse, Regionshospitalet Silkeborg, +45 87222360, henngler@rm.dk

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage	
Analysis stage	Final
Date of interim/final analysis	09 March 2016
Is this the analysis of the primary	Yes

completion data?	
Primary completion date	11 March 2014
Global end of trial reached?	Yes
Global end of trial date	11 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the proportion of otherwise intestinally low-symptomatic patients with intestinal ulcers in patients diagnosed with active spondyloarthritis and to illustrate the healing rate following treatment with the TNF-alpha inhibitor adalimumab

Protection of trial subjects:

The patients were informed orally and in writing. During the trial the patients could call a phone number day and night with questions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the rheumatologic outpatient clinics in the Central and North Denmark Regions on the basis of SpA activity. Patients ≥18 years with active SpA defined by expert opinion and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 (and thus candidates for anti-TNF treatment) were eligible for inclusion and were a

Pre-assignment

Screening details:

Because NSAID can elevate fecal calprotectin, patients were subjected to a 4-week NSAID washout period, after which fecal calprotectin was measured. Depending on the fecal calprotectin level the patients were grouped into either a "calprotectin normal" (<50 mg/kg) or "calprotectin high" (≥100 mg/kg) category.

Pre-assignment period milestones

Number of subjects started	31[1]
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient gave consent to join the study but withdrew his consent before completing NSAID wash-out period

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Calprotectin high

Arm description:

calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Loading dose of 80 mg. Hereafter 40 mg every other week

Arm title	Calprotectin normal

Arm description:

Faecal calprotectin <50 mg/kg after wash-out period

Arm type	Active comparator

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg every other week

Number of subjects in period 1	Calprotectin high	Calprotectin normal	
Started	15	15	
Repeat endoscopy	15	15	
Follow-up	15	15	
Completed	15	12	
Not completed	0	3	
Lost to follow-up	-	3	

Baseline characteristics

Reporting groups	
Reporting group title	Calprotectin high
Reporting group description:	
calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description:	
Faecal calprotectin <50 mg/kg after wash-out period	

Reporting group values	Calprotectin high	Calprotectin normal	Total
Number of subjects	15	15	30
Age categorical			
Age at baseline			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	15	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	34	32	
full range (min-max)	18 to 45	18 to 43	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	12	11	23
HLA-B27 positive			
Positive meaning having MHC-class 1 allele B27			
Units: Subjects			
Positive	15	10	25
Negative	0	5	5
Disease duration			
Time from first symptom to inclusion			
Units: Years			
median	7	7	
full range (min-max)	1 to 24	1 to 26	-

Subject analysis sets	
Subject analysis set title	Follow-up baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Follow-up endoscopy in patients with intestinal inflammation or elevated calprotectin at baseline

Subject analysis set title	Follow-up 20 weeks
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with either elevated calprotectin at baseline or intestinal inflammation after 20 weeks of treatment

Subject analysis set title	Follow-up 12 weeks
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with elevated calprotectin at baseline or intestinal inflammation at endoscopy

Reporting group values	Follow-up baseline	Follow-up 20 weeks	Follow-up 12 weeks
Number of subjects	16	16	16
Age categorical			
Age at baseline			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	16		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			
HLA-B27 positive			
Positive meaning having MHC-class 1 allele B27			
Units: Subjects			
Positive			
Negative			
Disease duration			
Time from first symptom to inclusion			
Units: Years			
median			
full range (min-max)			

End points

End points reporting groups	
Reporting group title	Calprotectin high
Reporting group description:	
calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description:	
Faecal calprotectin <50 mg/kg after wash-out period	
Subject analysis set title	Follow-up baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Follow-up endoscopy in patients with intestinal inflammation or elevated calprotectin at baseline	
Subject analysis set title	Follow-up 20 weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with either elevated calprotectin at baseline or intestinal inflammation after 20 weeks of treatment	
Subject analysis set title	Follow-up 12 weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with elevated calprotectin at baseline or intestinal inflammation at endoscopy	

Primary: Intestinal inflammation	
End point title	Intestinal inflammation
End point description:	
Number of subjects at baseline with any intestinal ulceration	
End point type	Primary
End point timeframe:	
Baseline	

End point values	Calprotectin high	Calprotectin normal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Subject				
Present	12	1		
Absent	3	14		

Statistical analyses

Statistical analysis title	Intestinal inflammation between groups
Comparison groups	Calprotectin high v Calprotectin normal
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence

P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Lewis score at follow-up	
End point title	Lewis score at follow-up
End point description:	
Follow-up endoscopy in patients with intestinal inflammation or elevated faecal calprotectin at baseline	
End point type	Primary
End point timeframe:	
After 20 weeks of treatment	

End point values	Follow-up baseline	Follow-up 20 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: unit(s)				
arithmetic mean (full range (min-max))	398 (112 to 608)	33 (0 to 180)		

Statistical analyses

Statistical analysis title	Follow-up endoscopy
Statistical analysis description:	
Comparison of Lewis score from baseline to 20 weeks after treatment onset	
Comparison groups	Follow-up baseline v Follow-up 20 weeks
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

Primary: Fecal calprotectin changes	
End point title	Fecal calprotectin changes
End point description:	
Changes in koncentration of calprotectin in faces	
End point type	Primary
End point timeframe:	
Baseline, 12 weeks and 20 weeks of treatment	

End point values	Follow-up baseline	Follow-up 20 weeks	Follow-up 12 weeks	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: mg/kg				
arithmetic mean (standard deviation)	285 (± 186)	48 (± 33)	83 (± 67)	

Attachments (see zip file)	F-calpro.png

Statistical analyses

Statistical analysis title	Faecal calprotectin
Statistical analysis description: Change in calprotectin koncentration over time	
Comparison groups	Follow-up baseline v Follow-up 20 weeks v Follow-up 12 weeks
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	ANOVA

Secondary: MRI inflammation

End point title	MRI inflammation
End point description:	

End point type	Secondary
End point timeframe: Baseline to 52 weeks of follow-up	

End point values	Calprotectin high	Calprotectin normal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: units				
arithmetic mean (inter-quartile range (Q1-Q3))	6.6 (2 to 12)	3.5 (0 to 4)		

Attachments (see zip file)	MRI intasah.png

Statistical analyses

Statistical analysis title	MRI score between groups
Statistical analysis description: Analysis of MRI scores between groups	
Comparison groups	Calprotectin normal v Calprotectin high
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	MRI score over time
Statistical analysis description: Comparison of MRI scores before and after treatment	
Comparison groups	Calprotectin high v Calprotectin normal
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Report for serious adverse events made annually. Here reported for entire study period	
Assessment type	Systematic
Dictionary used	
Dictionary name	ICD
Dictionary version	10
Reporting groups	
Reporting group title	Calprotectin high
Reporting group description:	
calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description:	
Faeacal calprotectin <50 mg/kg after wash-out period	

Serious adverse events	Calprotectin high	Calprotectin normal	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Dizziness	Additional description: 10 days after the start she gets dizziness and malaise. The patient goes to the family doctor, who admits patient. At the hospital examined with blood tests and physical examination. Discharged after 4 hours of stay in hospital.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastro intestinal bleeding	Additional description: 20 year old man wknown previous episodes that bleeding episodes from the gut hospitalized with nausea and dizziness. At the hospital found bleeding from the intestine surgically burned.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Calprotectin high	Calprotectin normal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	2 / 15 (13.33%)	
Skin and subcutaneous tissue disorders			
Dry skin	Additional description: Patients reporting dryness of skin after use of adalimumab		
subjects affected / exposed	3 / 15 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2011	A comparator group (calprotectin normal) was added to the study. Based on included subjects inclusion number was changed to n=15 in each group

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

C. Respondents' Opinion on Reasons for the Low Reporting Rates

Table 4: Respondents' opinion on reasons for the low reporting rates (N=39)

Ordinal outcome variable	Disagree	Partly disagree	Neither disagree nor agree	Partly agree	Agree
Lack of knowledge regarding rules and regulations	11	4	5	8	11
Lack of knowledge regarding who is responsible for reporting results	12	8	6	7	6
Reporting of results is complicated	5	0	10	5	19
Reporting of results is time consuming	5	0	9	6	19
Lack of consequences	6	5	14	5	9
Results are not worth reporting	18	5	10	4	2
Failure to recruit enough participants and ends before time	16	3	9	8	3
Lack of founding to proceed and ends before time	19	3	9	6	2

N: number

D. Associations Between Reasons Behind the Low Reporting Rates and the Explanatory Variables

Table 5: Associations between the ordinal outcome variables for reasons behind the low reporting rates and the explanatory variables (N=39)

Ordinal outcome variable	Explanatory variable	p
Lack of knowledge regarding rules and regulations	Number of initiated CTs	.822
	Employment position during the CT	.461
	Experience in reporting CT summary results	.539
Lack of knowledge regarding who is responsible for reporting results	Number of initiated CTs	.292
	Employment position during the CT	.850
	Experience in reporting CT summary results	.264
Reporting of results is complicated	Number of initiated CTs	.050*
	Employment position during the CT	.828
	Experience in reporting CT summary results	.001***
Reporting of results is time consuming	Number of initiated CTs	.095
	Employment position during the CT	.868
	Experience in reporting CT summary results	.002*
Lack of consequences	Number of initiated CTs	.833
	Employment position during the CT	.669
	Experience in reporting CT summary results	.573
Results are not worth reporting	Number of initiated CTs	.770
	Employment position during the CT	.622
	Experience in reporting CT summary results	.067
Failure to recruit enough participants and ends before time	Number of initiated CTs	.034*
	Employment position during the CT	.021*
	Experience in reporting CT summary results	.645
Lack of founding to proceed and ends before time	Number of initiated CTs	.461
	Employment position during the CT	.153
	Experience in reporting CT summary results	.819

N: number, *: statistically significant at p$\leq$ .05 (Fisher's exact test), ***: statistically significant at p$\leq$ .001 (Fisher's exact test)

E. Respondents' Opinion on Potential Solutions to Help Increase the Reporting Rates

Table 6: Respondents' opinion on potential solutions to help increase the reporting rates (N=39)

Ordinal outcome variable	Disagree	Partly disagree	Neither disagree nor agree	Partly agree	Agree
More awareness from authorities to obey laws and regulations	10	4	9	7	9
Fine if deadline exceeds	23	3	6	3	4
Courses regarding how to report results	7	4	10	13	5
Ongoing reminders about available guidelines for reporting results	2	2	11	12	12
Ongoing reminders regarding deadline for reporting results	3	4	7	12	13
Telephone counseling	1	3	9	12	14
A part of the founding requirements is to report results	10	5	11	7	6
Creation of a central unit at the university hospitals	5	2	7	6	19
Reporting documentation is a demand to publish in academic journals	13	1	13	5	7

N: number

F. Associations Between Potential Solutions for the Low Reporting Rates and the Explanatory Variables

Table 7: Associations between the ordinal outcome variables for potential solutions to increase the reporting rates and the explanatory variables (N=39)

Ordinal outcome variable	Explanatory variable	p
More awareness from authorities to obey laws and regulations	Number of initiated CTs	.197
	Employment position during the CT	.512
	Experience in reporting CT summary results	.406
Fine if deadline exceeds	Number of initiated CTs	.439
	Employment position during the CT	337
	Experience in reporting CT summary results	.832
Courses regarding how to report results	Number of initiated CTs	.916
	Employment position during the CT	.984
	Experience in reporting CT summary results	.502
Ongoing reminders about available guidelines for reporting results	Number of initiated CTs	.718
	Employment position during the CT	.524
	Experience in reporting CT summary results	.716
Ongoing reminders regarding deadline for reporting results	Number of initiated CTs	.856
	Employment position during the CT	.082
	Experience in reporting CT summary results	.375
Telephone counseling	Number of initiated CTs	.034*
	Employment position during the CT	.309
	Experience in reporting CT summary results	.492
A part of the founding requirements is to report results	Number of initiated CTs	.647
	Employment position during the CT	.887
	Experience in reporting CT summary results	.604
Creation of a central unit at the university hospitals	Number of initiated CTs	.729
	Employment position during the CT	.632
	Experience in reporting CT summary results	.826
Reporting documentation is a demand to publish in academic journals	Number of initiated CTs	.151
	Employment position during the CT	.467
	Experience in reporting CT summary results	.859

N: number, *: statistically significant at p$\leq$ .05 (Fisher's exact test)